Barton Journal

Vol. 1, Issue 1
Spring 2026
ISBN: 979-8-234-11525-6
ISSN: 3071-0898

A publication of the Center for Undergraduate Research and Scholarship at Barton College
Home of the Whitehurst Family Honors Program

Cover Art
***The Outer Eye*, oil on panel, 12 x 12 inches**
Jasper Carpenter, class of 2024

Lead Article

Demystifying Nervous System Regeneration: A Comprehensive Review

Taylor Medlock-Lanier, class of 2020

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BARTON COLLEGE

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The *Barton Journal* is a multidisciplinary academic journal focused on undergraduate research and scholarship, and is produced entirely by undergraduate students with the oversight of an advisory board. Funding for the journal is provided through the Office of the Vice President of Academic Affairs and the generous support of college donors, alumni, and the board of trustees.

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DOCUMENTATION

References in this publication are formatted according to APA 7, with the exception of author names that appear in their entirety in order to avoid de-gendering and cultural erasure of the authors' identity.

Launching an Academic Journal for Barton College

At the 2026 Day of Scholarship and Engagement (DOSE) on April 20, Barton College, through its Center for Undergraduate Research and Scholarship, launched the inaugural issue of the *Barton Journal*. This publication has the primary goal of advancing the academic impact of the college through the work of its students, closely guided by faculty mentors. Writings by Barton College students are the central focus of the inaugural issue, particularly drawing from research completed in fall 2025 and spring 2026, along with conference abstracts for work presented at the 2026 DOSE. These writings are outward-facing carrying with them the name and reputation of the college, the faculty, and the students. In year three of the implementation plan, the journal will become outward-reaching, accepting submission from other institutions.

In an effort to be representative of all academic disciplines, the journal has adopted a four category, 18 article type submission structure. Category 1 (3000–5000 words) includes full-length articles, review articles, and technical reports. Category 2 (1500–3000 words) includes case studies, creative scholarship (an accompanying essay), critical essays, data papers, methodology papers, replication studies, research notes, and short articles. Category 3 (750–1000 words) includes book/media reviews, briefs, commentaries, letters, and perspectives. Category 4 is for abstracts including extended abstracts (300–700 words) and conference abstracts (150–300 words). Categories 1, 2, and 3 also include a brief abstract in the word count, but references do not affect the word count. Definitions of all article types are provided in the journal and submission processes.

The scope of the journal is broad, but well-researched planning has led to an inclusive structure. To that end, the journal follows APA 7 formatting (required for all submissions, across all disciplines), with one exception. References in the publication present author names in their entirety in order to avoid de-gendering and cultural erasure of the authors' identities. Adopting this variation of APA aligns with three of the Barton College core values: integrity, creativity, and inclusivity.

Special thanks for the development of the journal is owed to students Emma Davis and Berkley Ann Hicks, who spent many hours working on a meta-analysis of undergraduate research journals from institutions across the U.S. These two students co-authored a white paper on the findings that included a proposed structure and design of the journal. In the spring, these two students also served as founding junior editors.

Gerard C. Lange,
Director of the Center for Undergraduate Research and Scholarship
Director of Whitehurst Family Honors Program

Submission Categories and Article Types

CATEGORY 1 (3000–5000 words)

Full-Length Article. Comprehensive, original research study; presents research questions, methods, findings, and implications in full detail.

Review Article. Critical synthesis of existing scholarship across a discipline or subfield; identifies debates, trends, and gaps in the literature.

Technical Report. Detailed account of applied research, development, or project-based work; emphasizes procedures, data, and practical results.

CATEGORY 2 (1500–3000 words)

Case Study. An in-depth examination of a single event, individual, organization, or community; used to illustrate broader concepts.

Creative Scholarship. Explanatory text accompanying scholarly work grounded in artistic, literary, or creative practices.

Critical Essay. An argument-driven analysis of a text, issue, or concept; prioritizes interpretation, critique, and original perspective.

Data Paper. Documentation-focused article describing a data set collection, structure, and potential uses.

Methodology Paper. Focused exploration of research methods, designs, or analytical tools; emphasizes innovation or refinement of methods.

Replication Study. Study that reproduces prior research to test reliability and validity; applicable to all research disciplines.

Research Note. Short report presenting preliminary findings, emerging questions, or early-stage results to share timely insights.

Short Article. Condensed research piece that presents a focused analysis, small study, or partial findings.

CATEGORY 3 (750–1000 words)

Book/Media Review. Evaluative overview of a recent book, film, performance, or digital media.

Brief. Concise report summarizing key findings, updates, or policy relevant information.

Commentary. Short, argument-based reflection on a current issue, debate, or publication.

Letter. Short communication addressing a specific study, idea, or data set.

Perspective. Reflective or viewpoint-driven piece offering an informed disciplinary interpretation of an issue, trend, or method.

CATEGORY 4 (Abstracts)

Extended Abstract (300–700 Words). A more detailed, mini-article format including background, methods, and preliminary findings.

Conference Abstract (150–300 Words). Concise summary of conference ready research, outlining the question, approach, and significance.

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*Student author, +Faculty mentor

Barton Journal

Demystifying Nervous System Regeneration: A Comprehensive Review

LEAD ARTICLE

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CITATION

Medlock-Lanier, Taylor. (2026). Demystifying nervous system regeneration: A comprehensive review. *Barton Journal, 1*(1), 1–46. https://bartonjournal.org/vol-1-no-1/2026-lead-article-no-001

Abstract

Uncovering mechanisms that govern successful nervous system regeneration will help inform future development of treatments for neurodegenerative disease and brain injury. There are organisms capable of robust nervous system regeneration, but the ability to functionally repair the entire brain is rare. Planarians are freshwater flatworms capable of whole-body regeneration after nearly any injury, including that of their nervous system. Planarians were used as a model to study how successful nervous system regeneration occurs. In this thesis research, six transcription factor-encoding genes were found that are required for the regeneration and maintenance of dopaminergic neurons in the planarian central, peripheral nervous system, and pharyngeal nervous system. Work was done to develop planarians as a model for neurodegenerative disease research through targeted studies and an unbiased screen. The work reviewed here centers around one goal: demystifying nervous system regeneration.

Keywords: regeneration, dopamine, nervous system, planarian, regenerative neurogenesis, neuronal cell fate, specification, transcriptional regulation, differentiation, body patterning, neurodegeneration

Nervous System Development

Development is the process by which a single cell transforms into a complex, multicelled organism. The key stages of development typically include fertilization, cleavage, blastula formation, gastrulation, and organogenesis. Fertilization is when gametes fuse to form a zygote, which will undergo rapid cell division (cleavage) and form the blastula (Gilbert, 2000a, 2000c). During gastrulation, the cells in the blastula will spatially rearrange into three germ layers: the endoderm, mesoderm, and ectoderm (Muhr et al., 2023; Purves et al., 2001b). After gastrulation, the three germ layers will continue to divide and become specialized cell types that form all the inner organs of an organism (Muhr et al., 2023; Purves et al., 2001b). One event critical for organogenesis in vertebrates is neurulation – the process that begins development of the nervous system (Gilbert, 2000b; Purves et al., 2001b).

The vertebrate nervous system is composed of the brain and spinal cord, which make up the central nervous system (CNS), as well as the peripheral nervous system (PNS), which includes all nerves that exist outside of the CNS (Bazira, 2021). In humans, the PNS is split into two subsystems: autonomic and somatic (Bazira, 2021). The autonomic nervous system controls involuntary processes like heartbeat and blood pressure (Bazira, 2021; Gibbons, 2019). Sensory and motor neurons of the somatic PNS, by contrast, are used to carry signals to the brain or carry out commands from the brain, respectively (Bazira, 2021; Ju, 2020). The brain relies on information from the PNS to monitor the internal and external environment and then uses that information to respond to its surroundings. In humans, the enteric nervous system (ENS) is part of the autonomic nervous system in the PNS and innervates the gastrointestinal tract. The ENS acts independently of the CNS, though the ENS and CNS are interconnected through the vagus nerve (Purves et al., 2001a).

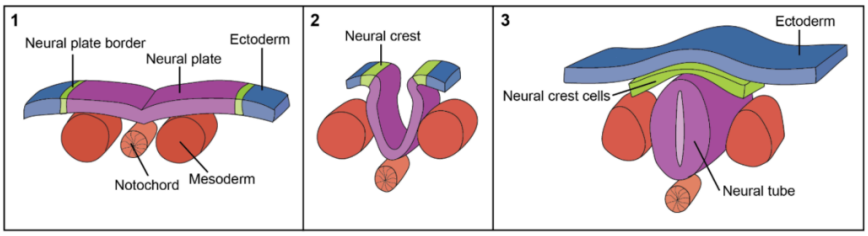
However, other animals organize their nervous systems in other ways. Cnidarians have a simple nervous system and are thought to descend from some of the first animals to possess a nervous system, along with Ctenophores (Burkhardt, 2022; Grimmelikhuijzen & Westfall, 1995; Hiroshi Watanabe, Fujisawa, et al., 2009). The basic Cnidarian nervous system organization is that of a nerve net, in which some locations can be condensed to form more complex structures (Grimmelikhuijzen & Westfall, 1995; Hiroshi Watanabe, Fujisawa, et al., 2009). Echinoderms, in contrast, have three main components to their nervous systems—ectoneural, hyponeural, and endoneuroal systems (Cobb, 1987; García-Arrarás et al., 2001). The ectoneural system has both sensory and motor functions and is composed of the nerve ring surrounding the mouth and the radial nerve cords (Cobb, 1987; Formery et al., 2021; García-Arrarás et al., 2001). The hyponeural system is primarily motor and is composed of the radial nerve cords associated with the skeletal muscle system (Cobb, 1987; Formery et al., 2021; García-Arrarás et al., 2001). Less is known about the entoneural system, which is only present in asteroids and crinoids (García-Arrarás et al., 2001; Haugh, 1975; Mercurio et al., 2024).

In vertebrate development, the nervous system begins to form early, starting with a process called neurulation (Colas & Schoenwolf, 2001; Gilbert, 2000b; Purves et al., 2001b). Neurulation in humans begins in weeks 3-4 of gestation (Chhetri & Das, 2023). During neurulation, the ectoderm is induced to become a neural plate following signals from the mesoderm (Chhetri & Das, 2023; Colas & Schoenwolf, 2001; Gilbert, 2000b). The

neuroectoderm inverts to give rise to the neural tube and, nearby, the neural crest (Chhetri & Das, 2023; Gilbert, 2000b; Purves et al., 2001b). The neural tube, which provides cells for the central nervous system, is the source of CNS neurons, oligodendrocytes (which myelinate neurons in the CNS), astrocytes, and ependymal cells (Chhetri & Das, 2023; Gilbert, 2000b; Rasband, 2015). In the neurula stage, areas of the neural tube are also further specialized into three distinct regions: the forebrain, midbrain, and hindbrain vesicles (Cowan, 1978, 1979). These three regions give rise to all the structures in the developed brain (Cowan, 1978, 1979). The neural crest gives rise to the PNS as well as a variety of other cell types and tissues, including pigment cells, cartilage, and smooth muscle (Mayor & Theveneau, 2013). The neural crest provides cells for the PNS, including PNS neurons, Schwann cells (which myelinate neurons in the PNS), and other glia (Mayor & Theveneau, 2013; Rasband, 2015). Sensory, motor, and enteric nervous systems each develop from the neural crest through distinct but interrelated processes (Mayor & Theveneau, 2013).

Figure 1

Schematic Overview of Neurulation



Note. Adapted from Development of the Central Nervous System – Spinal Cord, TeachMeAnatomy.

The nervous system is formed by neural progenitors, also called neuroblasts, that are characterized by their structure, pattern of differentiation, and transcriptional profiles (David J. Anderson, 2001; Le Douarin & Teillet, 1974). Several factors are known to influence neuroblasts to regulate the mature neuron population. After the establishment of the neurectoderm, basic helix-loop-helix transcription factors are upregulated in pro-neural clusters of neurectodermal cells, promoting the developmental program of neuroblasts (Hartenstein & Wodarz, 2013; Huang et al., 2014; Powell & Jarman, 2008; Quan & Hassan, 2005). Conserved mammalian SoxB family transcription factors are critical for defining cell populations that will become neuroblasts (Sasai, 2001). Transcriptional regulators like *Six3/6, Pax6, Pax3/7*, and *Nkx2.1/2.2* are also expressed early and are restricted to specific locations in the neurectoderm. These genes play active roles in triggering neurogenic potential while inhibiting neural differentiation, thereby maintaining each cell's proliferative state (Arendt et al., 2016; Bylund et al., 2003; Elkouris et al., 2011; Sasai, 2001). Induction and patterning of early neural determinants is achieved through signaling through conserved pathways like Wnt and BMP, as well as their inhibitors (Darras et al., 2011; Marlow et al., 2013; Niehrs, 2010; Sinigaglia et al., 2013). Notch signaling also helps mediate an inhibitory feedback loop that is activated by pro-neural genes, temporally and spatially restricting formation of neural progenitors (Hartenstein & Wodarz, 2013; Kageyama et al., 2009). Neural progenitors proliferate and differentiate variably depending on the type of neural cells they will become and the

region of the nervous system in which they will be located.

Further, temporal patterning is required for proper nervous system development (Blackshaw & Cayouette, 2025; El-Danaf et al., 2023). The underlying factors controlling temporal patterning have been best studied in *Drosophila* (El-Danaf et al., 2023; Grosskortenhaus et al., 2005; Isshiki et al., 2001; Ulvklo et al., 2012). In flies and vertebrates, neuroblasts divide several times asymmetrically to self-renew, to generate intermediate progenitors, and to generate neurons of distinct fates (Doe, 2017; Holguera & Desplan, 2018). Temporal identity factors were first characterized in the *Drosophila* ventral nerve cord, where sequential expression of *hunchback, krüppel, pdm, castor,* and *grainyhead* maps out the temporal steps of neuroblast division and differentiation into specific neuronal subtypes (Grosskortenhaus et al., 2005; Ulvklo et al., 2012). While *Drosophila* temporal identity factors are conserved in vertebrates, specific roles in regulating the timing of neural development are mostly conserved in the eye (Elliott et al., 2008; Javed et al., 2020, 2023).

After neuronal birth, axons and dendrites must extend out along specific routes to create a network of connections between different parts of the nervous system, and connections must be adjusted and refined (Alberts et al., 2002). Typically, a neuron will have one long axon and several shorter dendrites that project toward target cells, though cell morphology can vary by species and neuronal cell type (Alberts et al., 2002). Extension of axons is driven by a growth cone that is present at the tip of the process (Alberts et al., 2002; Maloney & Bamburg, 2011; Pérez-Ferrer & Herrera, 2025; Sousa & Sousa, 2021). Axons and dendrites connect neurons to other neuronal or non-neuronal cells to form synapses (Alberts et al., 2002; Qi et al., 2022). In development, some organisms create an abundance of synapses during synaptogenesis, then use synaptic pruning to create the highly precise network of connections that is seen in the adult nervous system (Alberts et al., 2002; Faust et al., 2021; Qi et al., 2022; Sakai, 2020; Wolterhoff & Hiesinger, 2024).

Neural Diversity

Through neural development, a broad range of neurons are specified and mature, each with its own structure, function, and connections. Recent studies have shown that the human brain has over 3000 cell types, with each cell type possessing a unique transcriptional identity (Ament et al., 2023; Siletti et al., 2023). Heterogeneity in the brain is in part due to different neuron types, often identified by their neurotransmitters (Cizeron et al., 2020; Que et al., 2019; Sugino et al., 2019). In addition to several different types of neurons, the brain has a highly heterogeneous population of glial cells that vary in location, gene expression, and structure (Bisht et al., 2016; Butt & Verkhratsky, 2018; Khakh & Deneen, 2019; Oberheim et al., 2012; Silvin & Ginhoux, 2018; Stratoulias et al., 2019; Tan et al., 2020; Westergard & Rothstein, 2020). Neural diversity extends beyond the central nervous system into all parts of the peripheral nervous system, with various neuronal and glial cell types found in the nervous system throughout the body.

Recent breakthroughs in bar-coding technologies and single-cell sequencing have allowed for lineage tagging and analysis of gene expression profiles to better understand how cellular diversity arises within the nervous system (Alemany et al., 2018; Bowling et al., 2020; McKenna et al., 2016; Raj et al., 2018). During nervous system development, neural progenitor cells initially divide symmetrically to expand the progenitor pool, followed by

frequent asymmetric division to create an intermediate progenitor pool (Ge et al., 2022; Taverna et al., 2014). It is widely accepted that neuronal fate decisions occur at the progenitor level, with more recent evidence suggesting environmental and wiring factors contribute to neuronal identity and diversification post-mitotically (Lodato et al., 2011; Lodato & Arlotta, 2015; Pla et al., 2006; Poliak et al., 2016; Pouchelon et al., 2014). Further, neurogenesis is driven by temporal and spatial patterning, with the possibility that these codes are coordinated to precisely control neuronal production (Briscoe et al., 2000; Sagner & Briscoe, 2019; Telley et al., 2019).

Dopaminergic Neurogenesis

Dopaminergic neurons are specialized neurons located in the CNS and PNS that produce and release the neurotransmitter dopamine (Chinta & Andersen, 2005; Klein et al., 2018). The identification and location of dopaminergic neurons was first confirmed in rodent tissue samples utilizing histofluorescence methods (Falck et al., 1962). Mature dopaminergic neurons are also characterized by their expression of tyrosine hydroxylase (TH), an enzyme involved in the dopamine biosynthesis pathway, though norepinephrinergic neurons also express TH (Blanchard et al., 1993; Moore & Bloom, 1979; Raisman-Vozari et al., 1991; Walkers & Holden-Dye, 1989). In the human CNS, the main source of dopamine is midbrain dopaminergic neurons, though dopaminergic neurons are also found in the diencephalon and olfactory bulb (Björklund & Lindvall, 1984). In the midbrain, several factors promote the development of dopaminergic neurons from stem cells and early progenitors. Sonic hedgehog (Shh) and fibroblast growth factor 8 (FGF8) signals provide essential cues for early dopaminergic progenitor cells (Hynes & Rosenthal, 1999; Rosenthal, 1997). Several early transcription factors help regulate early patterning in the ventral midbrain, including basic Helix-Loop-Helix transcription factors Hes1 and Nato3 (Kameda et al., 2011; Ono et al., 2010). Homeodomain transcription factors like Lmx1a, Lmx1b, and Msx1 help establish the identity of ventral midbrain dopamine neural precursors (Andersson et al., 2006; Failli et al., 2002; Smidt et al., 2000). Ngn2 and Nurr1 are then expressed in more specialized cells that go on to become dopaminergic neurons (Andersson et al., 2006; Hyun Jung Kim et al., 2007; Law et al., 1992; Zetterström et al., 1996).

All dopaminergic neurons in the PNS, including those in the ENS, arise from the neural crest (R. B. Anderson et al., 2013; Hao et al., 2013; Mayor & Theveneau, 2013). While little work has been done to explore the development of dopamine-producing cells in the non-enteric PNS, we do know that dopamine in the body periphery originates from a few different sources: noradrenergic neuronal fibers; neuroendocrine cells; and the adrenal medulla (Fan & Katz, 1993; Goldstein & Holmes, 2008; Katz et al., 1983; Pearse, 1969; Wahbe et al., 1982). ENS neurons come from precursors derived from the neural crest known as enteric neural crest-derived cells (ENCDC) (Le Douarin & Teillet, 1973, 1974; Yntema & Hammond, 1954, 1955). Several factors are required for ENCDCs to enter the gut and migrate through the entire organ, including PHOX2B, RET, and SOX10 (Jaesang Kim et al., 2003; Z. S. Li et al., 2004; Marcos & Pachnis, 1996; Pattyn et al., 1999; Taraviras et al., 1999). SOX10 also works with ZEB2 to maintain the potency of ENCDCs and inhibit neuronal differentiation through EdnrB signaling (Jaesang Kim et al., 2003; Yuli Watanabe et al., 2017). Ascl1 is critical for both enteric gliogenesis and enteric neurogenesis, specifically for dopaminergic neurons (Memic et al., 2016).

In addition to vertebrate dopaminergic neurogenesis, research in invertebrates has provided insights into the mechanisms through which dopaminergic neurons arise during development. For example, identification and lineage tracing of heterogeneous populations of dopaminergic neurons in both embryonic and larval stages of *Drosophila melanogaster* have been completed (Hartenstein et al., 2016). While many factors required for dopaminergic neuron development are conserved, *Drosophila* dopaminergic neurons also require expression of genes like *sim*, *wingless*, and *gooseberry,* which encode transcription factors (*sim* and *gooseberry*) or Wnt family members (*wingless*) (Bhat, 2007; Duman-Scheel et al., 1997; X. Li & Noll, 1993; Nambu et al., 1990; Richter et al., 1998; Skeath et al., 1995).

Further, hermaphroditic *Caenorhabditis elegans* have 302 neurons, eight of which are dopaminergic (J. Sulston et al., 1975; White et al., 1986). Of these eight dopaminergic neurons, there are four different classes that arise at different times during development, are located in different regions of the nervous system, and come from distinct cell lineages (J. E. Sulston et al., 1983; J. E. Sulston & Horvitz, 1977; White et al., 1986). Though these populations of neurons are distinct, several factors impact all 8 *C. elegans* dopaminergic neurons, including AST-1 (an ETS domain transcription factor), CEH-43 (a distal-less ortholog), and several Pbx genes (Doitsidou et al., 2008; Flames & Hobert, 2009; Siehr et al., 2011). Lin-32, which is a basic helix-loop-helix transcription factor, and a PAX6 homolog also regulate dopaminergic neuron identity and cell number, respectively (Doitsidou et al., 2008, 2013). Because *C. elegans* has distinct dopaminergic neuron populations, there are likely factors that are necessary for specific sets of dopaminergic neuron populations. At least one such factor has been identified. *ztf-6* is a gene encoding a zinc finger transcription factor that regulates dopaminergic neurons in a lineage-specific manner, impacting distinct dopamine neuron-producing lineages differently (Doitsidou et al., 2018).

Dopaminergic Neurons & Parkinson's Disease

Loss or dysfunction of dopaminergic neurons is associated with neurological diseases and disorders like Alzheimer's Disease (Nobili et al., 2017), Huntington's Disease (Bédard et al., 2011; Rangel-Barajas et al., 2015), Multiple Sclerosis (Rangel-Barajas et al., 2015), and most commonly Parkinson's Disease (Bédard et al., 2011; Damier et al., 1999; Hirsch et al., 1988; Parkinson, 2002). Parkinson's Disease is a neurodegenerative disease that impacts motor and non-motor systems through loss of dopaminergic neurons in a section of the midbrain, the substantia nigra, that provides dopamine to the basal ganglia (Damier et al., 1999; Hirsch et al., 1988). Motor dysfunction is one of the earliest symptoms, with patients exhibiting tremors, hypokinesia, and rigidity (Parkinson, 2002). Parkinson's Disease was initially thought to be a sporadic neurodegenerative disorder that had greater prevalence depending on certain environmental factors; genetic mutations have been identified in some familial forms of Parkinson's Disease (Duvoisin, 1984; Lesage & Brice, 2009). The first gene mutation associated with Parkinson's Disease was a mutation in the *alpha-synuclein* (*SCNA*) gene (Polymeropoulos et al., 1997). One pathological hallmark of Parkinson's Disease is the presence of alpha-synuclein aggregates in Lewy bodies or Lewy neurites in affected neurons. Aggregates also include other components like phosphorylated neurofilaments and ubiquitin (Srinivasan et al., 2021). The genetic mutation that conveys the greatest risk of Parkinson's Disease occurs in a gene that encodes a lysosomal enzyme, *glucocerebrosidase* (*GBA*) (Sidransky et al.,

2009; Sidransky & Lopez, 2012). Other genes implicated in Parkinson's Disease include *LRRK2* and *parkin* (or *PARK2*), which contribute to the most common forms of inherited Parkinson's Disease (Matsumine et al., 1998; Paisán-Ruíz et al., 2004; Zimprich et al., 2004). While there have been several genetic risk factors identified for Parkinson's Disease, the vast majority of cases (85%) arise sporadically with no known hereditary cause (Matsumine et al., 1998; Paisán-Ruíz et al., 2004; Polymeropoulos et al., 1997; Sidransky et al., 2009; Sidransky & Lopez, 2012; Srinivasan et al., 2021; Trevisan et al., 2024; Zimprich et al., 2004). In these cases, environmental toxins and brain trauma may contribute to some, but not all, sporadic cases.

Many neurodegenerative diseases, like Parkinson's Disease and Amyotrophic lateral sclerosis, have been associated with the accumulation of protein aggregates (e.g., alpha-synuclein aggregates in Parkinson's Disease) in degenerating and dying neurons (Koszła & Sołek, 2024; Polymeropoulos et al., 1997; Sweeney et al., 2017). Whether these protein aggregates are causative or correlated with neuronal decline remains controversial, but the evidence showing the presence of abnormal protein accumulation across neurodegenerative diseases is indisputable. Cells mount defenses to help fix proteostasis problems that may arise, including protein dysfunction and misfolding (Barmaki et al., 2023; Díaz-Villanueva et al., 2015). Neuronal chaperones are proteins that aid in several processes to help prevent neuronal death due to protein aggregation (Ellis, 1988; Hartl et al., 1992; Hartl, 1996). Chaperones assist in the folding of nascent or misfolded proteins into their correct three-dimensional structures and bind to misfolded proteins to prevent harmful aggregation. When chaperones are not successful, misfolded proteins are targeted to the ubiquitin-proteasome system for degradation (Satapathy & Wilson, 2022; Heather L. Smith et al., 2015). Because of their neuroprotective roles, neuronal chaperones and components of the ubiquitin-proteasome system could be a target for treatment of neurodegenerative diseases (Luo et al., 2010; Sharma et al., 2024). Increasing activity of key proteostasis factors could slow disease progression.

Parkinson's Disease is most commonly attributed to defects in the central nervous system, but dopaminergic neurons also exist outside the CNS in the peripheral nervous system, including the enteric nervous system (Chalazonitis et al., 2022; Chinta & Andersen, 2005). The majority of research on Parkinson's Disease has focused on loss of dopamine in the CNS, specifically the substantia nigra (Barker et al., 2017; Björklund & Stenevi, 1979; Brundin et al., 1988; Damier et al., 1999; Freed et al., 2001; Nagarajan et al., 2014; Yang et al., 2008). However, as early as 1931, researchers noticed Lewy bodies in neurons outside of the CNS (den Hartog Jager & Bethlem, 1960; Hechst & Nussbaum, 1931). Braak's 6-stage theory proposes that Parkinson's Disease-associated neurodegeneration begins in the PNS (specifically the ENS) and progresses to the CNS through the vagus nerve (Braak et al., 2003; Braak & Del Tredici, 2017). The Braak staging system is based on the progression of alpha-synuclein structures in over 100 Parkinson's Disease patients presenting with alpha-synuclein aggregates (Braak et al., 2005, 2003). According to this model, the disease begins in the dorsal motor nucleus of the vagus nerve, eventually progressing and extending into and throughout parts of the brain (Braak et al., 2005, 2003). Though the clinical progression of Parkinson's Disease cannot yet be fully explained, data support a spread of the disease between different parts of the nervous system. For example, several studies demonstrated accumulation of alpha-synuclein in the enteric nervous system before the CNS (Iranzo et al., 2014; Kupsky et al., 1987; Qualman et al., 1984; Wakabayashi et al., 1988).

Parkinson's Disease has been studied for over a century, yet there is no cure, and treatment options for Parkinson's Disease revolve around managing symptoms through drugs that help increase dopamine synthesis and uptake. Levodopa has been considered the "gold standard" for treating symptoms of Parkinson's Disease, however long-term use of the drug, which is the immediate precursor for dopamine synthesis in the substantia nigra, causes adverse side effects (Fahn, 2005; Grandas et al., 1998; Melamed, 1979; Salat & Tolosa, 2013; Sethi, 2010; Tolosa et al., 1975). Alternatively, dopamine agonists can be used to activate dopamine receptors, but they also have negative side effects (Calne et al., 1974; Cotzias et al., 1970). In the past several decades, research on stem cell-based therapies emerged, with stem cells posing an attractive treatment option for introducing functioning dopaminergic neurons in affected areas. Dopaminergic neuron transplants in animal models began as early as the 1970s, with transplantation of rat fetal neurons into injured rodents (Björklund et al., 1976; Björklund & Stenevi, 1979). Pioneering work demonstrated that fetal dopamine neurons from rodents could be incorporated into a dopamine-deficient rodent brain and restore dopamine pathways, paving the way for experiments transplanting human fetal neurons in the same manner (Björklund et al., 1980, 1981; Ungerstedt et al., 1974). Grafting human fetal brain tissue into rodent models allowed functional recovery, though development and innervation of these cells took longer than the previously tested rodent cells (24 weeks opposed to 8 weeks) (Brundin et al., 1988). Not only are human dopamine neurons able to functionally recover in the immediate location of the graft, but they also extend axons over long distances to relevant cortical areas and the striatum of the transplanted rodent (Grealish et al., 2014; Moriarty et al., 2022; Wictorin et al., 1992; Xiong et al., 2021).

Early clinical trials based on grafting human fetal ventral mesencephalic tissue into human patients reported variable results and no significant changes in Parkinson's Disease patients, especially for recipients over 60 years old (Freed et al., 2001; Olanow et al., 2003). Further, a few subjects who received grafts were examined 11-24 years later, and researchers found that grafted dopamine neurons displayed alpha-synuclein pathology similar to diseased neurons (Kordower et al., 2008; Jia Yi Li et al., 2008). The presence of Lewy bodies in transplanted cells suggested that Parkinson's Disease can propagate from host cells to grafted cells, though the majority of the grafted cells were unimpaired after over a decade (Kordower et al., 2008; Jia Yi Li et al., 2008).

In the 2010s, there were breakthroughs in human pluripotent stem cell therapies, including human embryonic stem cells (Thomson, 1998) and human induced pluripotent stem cells (Takahashi et al., 2007). The first protocols for generating dopamine neurons from human pluripotent stem cells were adapted from mouse protocols and included induction of neural differentiation and exposure of cells to morphogens and growth factors like Shh, FGF8, brain-derived neurotrophic factor, and glial cell line-derived neurotrophic factor (Sánchez-Pernaute et al., 2001; Sonntag et al., 2007; Zhang et al., 2001). Surprisingly, embryonic stem cell- and induced pluripotent stem cell-derived dopaminergic neurons performed poorly post transplantation and midbrain identity was not confirmed (Jong Hoon Kim et al., 2002; Sánchez-Pernaute et al., 2001; Yang et al., 2008). Because midbrain dopamine neurons arise from floorplate progenitors marked by coexpression of FOXA2 and LMX1A, alternate protocols were then developed (Bonilla et al., 2008; Joksimovic et al., 2009; Ono et al., 2007). These adjustments, in combination with SMAD inhibition, early exposure to Shh, and Wnt pathway activation, allowed for the development of midbrain dopamine neurons that could functionally replace

disease-impacted cells after transplantation (Grealish et al., 2014; Kirkeby et al., 2012; Kriks et al., 2011). Clinical trials for dopamine cell therapy in humans began in the late 2010s and early 2020s, with two groups recently publishing results from their Phase I and/or Phase II trials (Sawamoto et al., 2025; Tabar et al., 2025). Emerging data suggest that dopaminergic cell therapies derived from either human pluripotent stem cells (Sawamoto et al., 2025) or human embryonic stem cells (Tabar et al., 2025) could be safe and could produce clinical benefits for Parkinson's Disease, including improved motor symptoms (Sawamoto et al., 2025; Tabar et al., 2025). While treatments for Parkinson's Disease have improved over the past five decades, the most recent trials still indicate modest benefits, and long-term studies will still need to confirm the efficacy and persistence of cell-based therapies. Thus, additional interventions will likely be needed for a Parkinson's Disease cure.

Regenerative Capabilities Across the Animal Kingdom

One possible approach to functionally restore cells in the case of nervous system injury could be inducing new production of neurons in the brain to replace diseased and dying cells. The ability to regenerate cells is common throughout non-human members of the animal kingdom, with many species repairing and healing neural tissue after injury through limited cell birth or de/transdifferentiation (Arenas Gómez et al., 2020; Iismaa et al., 2018; Tanaka & Reddien, 2011). Most mammals regenerate poorly, but some mammals are capable of regeneration limited to some tissues or developmental stages (Iismaa et al., 2018; Storer & Miller, 2020). For example, humans regenerate parts of organs like the liver, skin, and uterine lining (Cousins et al., 2022; Ferenczy et al., 1979; Gargett & Ye, 2012; He et al., 2021; Rowlatt, 1979; Takeo et al., 2015; Wei et al., 2021). However, there are limitations to human regenerative ability, especially when it comes to the nervous system (Iismaa et al., 2018; Varadarajan et al., 2022). While humans can repair the peripheral nervous system to an extent, the ability to recover after central nervous system injury is extremely limited (Contreras et al., 2022; Gordon, 2020; Varadarajan et al., 2022; Widodo et al., 2025). Thus, brain injuries and diseases of the CNS are often incurable. Treatments for these debilitating diseases focus on prolonging life, rehabilitation, and palliative care or symptom reduction rather than a true cure (Fahn, 2005; Grandas et al., 1998; Shusharina et al., 2023; Tolosa et al., 1975).

In contrast, some remarkable animals complete successful regeneration throughout the nervous system. Axolotls and zebrafish regenerate cells within the brain and spinal cord, though neither organism can fully reestablish perfect neuronal diversity and connectivity after injury (Amamoto et al., 2016; Caldwell et al., 2019). Zebrafish utilize a population of resident progenitors that give rise to mature cells in the locations where they are needed after injury (Grandel et al., 2006). While zebrafish and axolotls do possess incredible regenerative capabilities, the ability to regrow an entire nervous system *de novo* after injury is rare and limited to a small number of animals, including *Hydra* (a cnidarian) and planarian flatworms (Umesono & Agata, 2009; Hiroshi Watanabe, Hoang, et al., 2009). To answer questions specific to successful, whole-brain regeneration, I sought to use planarians due to their robust regeneration of the entire body, including all parts of the nervous system.

Planarians As a Model for Regeneration

Planarians are non-parasitic, freshwater flatworms of the phylum Platyhelminthes that are known for their remarkable regenerative capabilities. Though several species of planarians exist, scientists most often use two

species to study regeneration: *Dugesia japonica* and *Schmidtea mediterranea*. I used the asexual strain of *S. mediterranea* to answer questions about how successful nervous system regeneration occurs. *S. mediterranea* undergoes robust, whole-body regeneration and replenishes all tissues after nearly any injury, including the creation of the nervous system *de novo* (Inoue et al., 2004; Reddien & Sánchez Alvarado, 2004; Ross et al., 2017). Planarians accomplish great regenerative feats through a population of adult pluripotent stem cells, called neoblasts, that give rise to all mature cell types in the planarian body (Baguñà et al., 1989; Morita et al., 1969; Wagner et al., 2011a; Wenemoser & Reddien, 2010). Stem cells produce new cells that differentiate to populate all mature organs in the body, as well as the connective tissue. Planarian pluripotent stem cells are found throughout the body and are only absent from the most anterior part of the head and the pharynx, the feeding organ, which are the only two parts of the animal that cannot regrow the rest of the body when isolated (Reddien et al., 2005).

Pluripotent stem cells make up approximately 20% of all cells within the planarian body and respond to signals after injury (Hayashi et al., 2006; Reddien et al., 2005; Wagner et al., 2011b). In the instance of lost tissue, stem cells respond by dividing and moving to the location of injury to replenish lost cells and tissue (Baguñà et al., 1989; Takeda et al., 2009; Wagner et al., 2011b; Wenemoser & Reddien, 2010). Planarians do not have resident progenitor cells within organs, so it is necessary for stem cells and their progeny to migrate to locations where they are needed. Planarian pluripotent stem cells respond to injury with two proliferative bursts, the first of which occurs at 6 hours and the second at 48 hours post-injury (Baguñà, 1976; Saló & Baguñà, 1984; Wenemoser & Reddien, 2010). Pluripotent stem cells divide to replenish the stem cell population and to create cells that differentiate and eventually mature into specified cell types.

Planarian pluripotent stem cells, or neoblasts, were originally thought to be a relatively homogeneous population of cells defined by morphological characteristics like a large nucleus-to-cytoplasmic ratio, expression of *Smedwi-1*, and location in the mesenchymal tissue (Baguñà, 2012; Baguñà et al., 1989; Reddien et al., 2005). However, many studies have shown that the neoblast population is heterogeneous and that many neoblasts express specific markers of restricted cell fates (Molinaro & Pearson, 2016; Raz et al., 2021; van Wolfswinkel et al., 2014). Pluripotent neoblasts capable of repopulating the animal's tissue and giving rise to all cell types are termed clonogenic neoblasts, though this is a functional definition rather than a molecular one (Reddien et al., 2005). Four subpopulations have been identified that express *Smedwi-1* as well as transcription factor-encoding genes that are tissue-specific. These neoblast populations—ζ-, σ-, γ-, and ν-neoblasts—are thought to be specialized progenitors with narrower fate (van Wolfswinkel et al., 2014). ζ-neoblasts are considered specialized cells that help maintain and give rise to the epidermal lineage, and they express high levels of genes like *egr-1*, *fgfr-1*, *soxP-3*, and *zfp-1* (van Wolfswinkel et al., 2014). σ-neoblasts have a broad role in producing cells of several different lineages, including other neoblast types, like ζ-neoblasts (van Wolfswinkel et al., 2014). σ-neoblasts are characterized by high expression of genes such as *soxP-1*, *soxB-1*, *fgfr-4*, and *nlk-1* (van Wolfswinkel et al., 2014). In this same study, a third population of neoblasts, considered to be a subclass of σ-neoblasts, was identified: γ-neoblasts. This population is likely an intestine-specific progenitor pool, and it is characterized by elevated expression of genes like *gata4/5/6*, *hnf4,* and *nkx2.2* (van Wolfswinkel et al., 2014). Finally, a fourth population of neural-specific progenitors was identified and termed the ν-neoblasts. This neural-committed population of

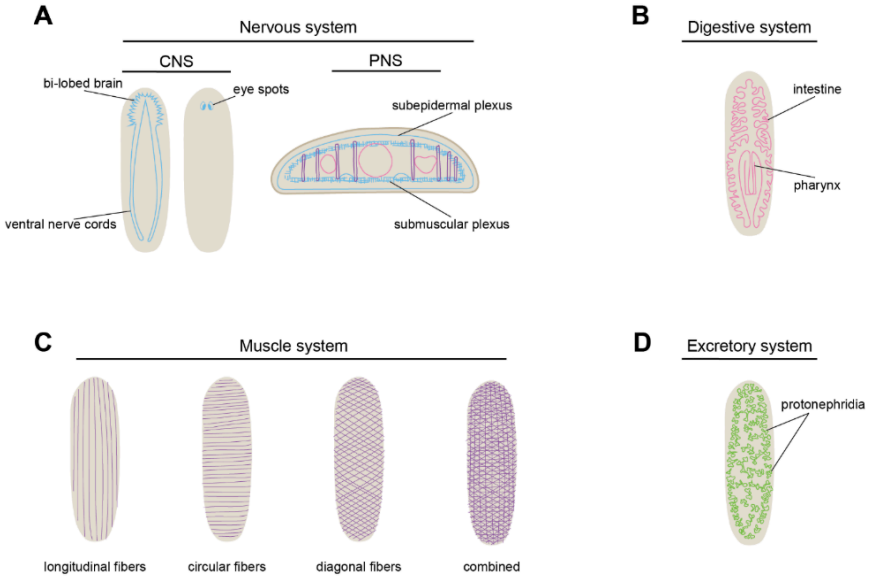
neoblasts expresses high levels of genes, including *ston-2*, *elav-1*, and *ptprd-9* (Molinaro & Pearson, 2016). Importantly, recent work indicates that stem cells with lineage-specific markers retain their potency and can return to a less specialized state after division, suggesting that pluripotency is not linked to a unique stem cell class in planarians (Raz et al., 2021). Additionally, work continues to reveal factors necessary for stem cell maintenance and function, as well as signals that tell a stem cell to differentiate and specialize into each mature cell type (Benham-Pyle et al., 2023; King et al., 2024).

Planarian Organ Systems

Planarians have complex organ systems, including nervous, muscle, digestive, epidermis, excretory, and reproductive systems that are held together by connective tissue called the parenchyma (Roberts-Galbraith & Newmark, 2015) (Figure 2A-D). For this work, I focus on the planarian nervous system, which is made up of a central nervous system, a peripheral nervous system found throughout the body, and a pharyngeal nervous system (PhNS) found in the planarian feeding organ (Roberts-Galbraith & Newmark, 2015; Ross et al., 2017) (Figure 2A-B). The central nervous system is composed of a bi-lobed brain, two nerve cords on the ventral side of the animal, and two eyespots on the dorsal side of the planarian (Agata et al., 1998; Carpenter et al., 1974; Krugelis MacRae, 1964) (Figure 2A). The brain also has brain branches that reach out laterally from the brain and relay chemosensory signals (MacRae, 1967) (Figure 2A). The peripheral nervous system is composed of nerve plexuses that sit between and around different organ systems (Figure 2B). The subepidermal nerve plexus innervates the space between the epidermis and the body wall musculature, and likely functions in sensory processes or in the regulation of epidermal motile cilia (Baguñà & Ballester, 1978) (Figure 2B). The submuscular nerve plexus is located below the muscle wall, and the gastrodermal nerve plexus surrounds the intestine (Baguñà & Ballester, 1978) (Figure 2B). The pharyngeal nervous system, composed of two ring-like nerve plexuses, is found solely within the pharynx and is important for pharyngeal movement in feeding behavior. While characterization of the CNS in planarians has been a focus of the field, the PNS remains poorly characterized, with sparse molecular and genetic information about the identities and developmental processes for PNS or PhNS neurons. The planarian nervous system contains dozens of neuron types, which have been defined by their gene expression and—less commonly—function. Planarian neurons produce several different neurotransmitters including acetylcholine, dopamine, GABA, octopamine, serotonin, norepinephrine, and over 50 neuropeptides (Clay et al., 2025; Collins et al., 2010; Nishimura et al., 2010; Nishimura, Kitamura, Umesono, et al., 2008; Nishimura, Kitamura, Inoue, et al., 2008; Nishimura, Kitamura, Inoue, Umesono, Sano, et al., 2007; Nishimura, Kitamura, Inoue, Umesono, Yoshimoto, et al., 2007; Ong et al., 2016).

Figure 2

Planarian Organ Systems



Notes. A) Diagram of the planarian nervous system. Central nervous system (CNS) on left, peripheral nervous system (PNS) on right. B) Diagram of the digestive system. C) Diagram of planarian musculature. D) Diagram of the planarian excretory system.

While we do not know the entire mechanism through which any neuron type is specified and differentiated, we do know some key regulators of the planarian nervous system. For example, *soxB1-2*, *coe*, and *sim* are required for broad nervous system regeneration (Cowles et al., 2013, 2014; Ross et al., 2017). *ets-1* and *hedgehog* signaling are required for proper regeneration and patterning of planarian glia, neuronal support cells (Chandra et al., 2023; Wang et al., 2016). Finally, there has been substantial work to uncover mechanisms that allow specification and maturation of serotonergic neurons, including identification of *pitx* and *lhx1/5-1* as terminal differentiation factors for neurons producing serotonin (Currie & Pearson, 2013; März et al., 2013). Importantly, additional factors required for determining the exact spatial and regional localization of neurons, and establishing neurons in the correct numbers, types, and ratios, have yet to be elucidated. Uncovering the mechanisms required for proper neuronal regeneration in the correct contexts for a single mature neuron type will likely provide critical information for differentiation pathways for other mature cell types in the planarian.

Within the nervous system, we do know the entire pathway from a pluripotent stem cell to mature eye cells, including pigment cup cells and photoreceptor cells (Atabay et al., 2018; Emili et al., 2019; Lapan & Reddien, 2011, 2012a). Planarians have two eyespots with mature cells, and a trail of eye progenitors that lead toward them (Agata et al., 1998; Carpenter et al., 1974; Inoue et al., 2004; Lapan & Reddien, 2011, 2012b). To determine the order in which transcription factors need to be active for proper eye formation, scientists completed a combination of fluorescent *in situ* hybridization experiments labeling stem cells, mature eye cells,

and transcription factor-encoding mRNAs that were thought to act in the process (Lapan & Reddien, 2011). Transcription factor-encoding genes expressed with the stem cell marker were determined to mark early progenitors, and those expressed with the mature cell type marker were determined to act later in the lineage (Lapan & Reddien, 2011).

We also know the entire pathway from a planarian pluripotent stem cell to mature epidermal cells, and we understand many of the factors at work in between (Eisenhoffer et al., 2008; Tu et al., 2015; Zhu & Pearson, 2016). The combination of 5-bromo-2′-deoxyuridine labeling with *in situ* hybridization experiments allowed lineage tracing in planarians and created a guide for determining lineage for other cell types as well (Eisenhoffer et al., 2008). Other factors have been identified in pathways of specification for different mature cell types in the planarian, including muscle, gut, and protonephridia. Proper expression of genes such as *myoD, foxF-1, nk4, gata4/5/6-2,* and *gata4/5/6-3* is required for proper planarian muscle regeneration (Cebrià, 2016; Lucila Scimone et al., 2017; Scimone et al., 2018). Regeneration and/or maintenance of cells in the intestine requires proper expression of genes like *gli-1, RREB2, lhx2/9-1, lhx1/5-2, LDB1, SSDP2,* and *gata4/5/6* (Flores et al., 2016; Forsthoefel et al., 2020; Medlock-Lanier et al., 2024; Molina et al., 2023). The planarian excretory system is governed by transcription regulators like *six1/2-2, hunchback, eya, sall, and POU2/3* (Scimone et al., 2011). Additionally, an EGF receptor, EGFR-5, is required for proper branching morphogenesis and maturation of planarian protonephridia (Rink et al., 2011).

Planarian Polarity and Body Plans

In addition to replenishing all missing cells after injury, planarians faithfully reproduce the body plan with predictable patterning, using critical polarity signals that govern the body axes. Planarians have anterior-posterior, dorsal-ventral, and medial-lateral axes that are governed by distinct mechanisms. In planarians, the anterior-posterior axis is governed by posterior Wnt signaling proteins, similar to other metazoans (Hardin & King, 2008; Logan & Nusse, 2004; Marikawa, 2006; Schier & Talbot, 2005). β-catenin functions downstream of canonical Wnt signaling and inhibits anterior pole identity. Knockdown of *β-catenin* through RNA interference (RNAi) results in ectopic head growth and regeneration (Gurley et al., 2008; Iglesias et al., 2008; Petersen & Reddien, 2008), indicating a negative regulation of brain regeneration.

The planarian dorsal-ventral axis is governed by bone morphogenetic protein (BMP) and anti-dorsalizing morphogenetic protein (ADMP) signals. *bmp4* is expressed dorsally and represses ventral *admp* (Gaviño & Reddien, 2011). In planarians, *bmp4* is expressed in clusters of cells along the dorsal midline, as well as a small number of neurons in the brain and ventral nerve cords (Molina et al., 2007; Orii et al., 1998). After knockdown of *bmp4*, planarians experience ectopic eye expression, indented blastemas, and ultimate failure of regulation at the dorsal midline (Molina et al., 2007; Reddien et al., 2007). *bmp4*(RNAi) also causes increased *admp* expression, leading to the conclusion that *bmp4* regulates *admp* through inhibitory mechanisms (Gaviño & Reddien, 2011). *admp* is expressed in cells along the ventral midline and cells at the lateral edges of the animal (Gaviño & Reddien, 2011). *admp*(RNAi) animals form indented blastemas and decreased regenerative abilities after a sagittal amputation. Knockdown of *admp* also led to decreased *bmp-4* expression, suggesting that *admp*

activates expression of *bmp-4* (Gaviño & Reddien, 2011). The dorsoventral regulators *bmp* and *admp* are also regulated by several other factors, including an expanded *noggin* family (Molina et al., 2007; Ogawa et al., 2002; William C. Smith & Harland, 1992).

Planarians' bodies are also organized along a medial-lateral axis. The medial-lateral axis is regulated by *slit* at the midline and lateral *Wnt5* through reciprocal patterning (Cebrià et al., 2007; Gurley et al., 2010). *slit* is expressed along the midline of both the dorsal and ventral sides of the planarian (Cebrià et al., 2007), and knockdown of *slit* causes misexpression of *wnt5* into the planarian midline (Gurley et al., 2010). In contrast, *wnt5* is expressed lateral to the ventral nerve cords and peripherally around the planarian body (Gurley et al., 2010). *wnt5*(RNAi) leads to expression of *slit* outside the midline and towards the lateral edges of the animal (Gurley et al., 2010).

Planarians faithfully regenerate their entire body, including their complex nervous system, after nearly any injury. Not only do planarians make the right cell types, but they do so in the correct locations, patterning, and ratios. Because of their remarkable regenerative capabilities, planarians are an ideal model with which to uncover mechanisms underlying successful nervous system regeneration. Revealing the factors required for regeneration and maintenance of their complex nervous system will not only further elucidate how planarians regrow without consequence, but could also inform research into therapies for neurological conditions, including brain injury and neurodegenerative disease.

Specification of Dopaminergic Neurons in Planarians

One of the larger goals of my thesis work was to determine the entire genetic pathway from a pluripotent stem cell to a mature dopaminergic neuron in planarians. I proposed a model in which combinatorial mechanisms specify regional location and neurotransmitter identity of dopaminergic neurons concurrently (Clay et al., 2025). However, there is likely some sort of hierarchy to dopaminergic neuron specification, even if there is overlap in the transcriptional regulation. In an effort to parse out the order in which transcription factors are turned on to create dopaminergic neurons in the peripheral nervous system, orthogonal approaches could be used to determine whether *fli1-2, irx-4/6,* and *soxB1-2* are expressed in the early or late progenitors. I found that *fli1-2, irx-4/6,* and *soxB1-2* are all co-expressed with a broad stem cell marker, *smedwi-1*, and are therefore all expressed in at least some progenitor cells (Clay et al., 2025; Eisenhoffer et al., 2008). In irradiated animals, less specialized stem cells will go away first, followed by early progenitors, late progenitors, and finally mature cell types (Eisenhoffer et al., 2008). Looking at the expression of *fli1-2, irx-4/6,* and *soxB1-2* in irradiated animals over a seven-day timeline will show which of these populations dies off first, providing insight into which of these transcription factor-encoding genes is expressed earliest within progenitors.

In addition to determining the order of expression of the genes I have identified, there are likely other genes that are critical for regeneration and maintenance of dopaminergic neurons in planarians. My current hypothesis is that the genes I have identified are likely enriched for the middle of the specification pathway for dopaminergic neurons. Utilizing available single-cell transcriptomic data, it will be interesting to examine transcripts that are expressed in predicted early neural progenitor populations, especially those that express high levels of *smedwi-1* mRNA (Fincher et al., 2018). Another reverse genetic screen examining transcription factors at this stage could

provide insight into the earliest fate choices in the dopaminergic neuron pathway. Further, the bulk RNA sequencing I completed will provide information as to what genes may be working downstream in the pathway of dopaminergic neuron specification. Conducting a smaller-scale screen using the bulk RNA sequencing data will help identify additional genes required for the maintenance and maturation of dopaminergic neurons.

Factors Influencing Planarian Neuronal Placement

In my thesis work, I proposed a model in which combinations of transcription factor-encoding genes help specify dopaminergic neurons, both in their neurotransmitter identity and in their regional location (Clay et al., 2025). However, there are likely other factors at play that help regulate both processes. One example is the consistent and robust body-patterning system that planarians possess (Reddien, 2018). Planarians have anterior-posterior, dorsal-ventral, and medial-lateral axes that are strictly regulated (Reddien, 2018). IRX family genes play conserved roles in vertebrates and invertebrates in mediating the dorsoventral axis (Glavic et al., 2002; Gómez-Skarmeta & Modolell, 2002; Itoh et al., 2002; Lecaudey et al., 2004). Interestingly, planarian *irx-like* has a polarized expression pattern and is only expressed on the ventral side of the animal. This raises the question of whether there are distinct factors regulating dopaminergic neurons in the dorsal and ventral PNS. *IRX-like* is a likely candidate in helping regulate ventral dopaminergic neurons, but how is this influenced by polarity signaling? Several factors have been identified as regulating polarity axes in planarians (Cebrià et al., 2007; Gaviño & Reddien, 2011; Gurley et al., 2008, 2010; Iglesias et al., 2011; Molina et al., 2007; Ogawa et al., 2002; Orii & Watanabe, 2007; Petersen & Reddien, 2008). Further characterizing the polarity of PNS cells will likely determine other factors impacting dopaminergic neuron fate and regionalization.

Planarians As a Future Model for Neurodegeneration

Unfortunately, there are currently no cures for neurodegenerative diseases, and treatment options available are used to manage symptoms (Cascione et al., 2020; Durães et al., 2018). Several models are being used to model neurodegeneration and identify potential pathways for investigation, including *in vivo, in vitro,* and *in silico* models (Dawson et al., 2018; Jones et al., 2022; Valadez-Barba et al., 2020). While these models have provided critical information in understanding the molecular mechanisms behind neurodegenerative diseases, with some studies resulting in clinical trials, more progress is needed. I reasoned that the use of another model system that already possesses perfect regenerative capabilities, including that of its complex nervous system, might provide complementary information and could reveal new molecular mechanisms underlying neurodegeneration.

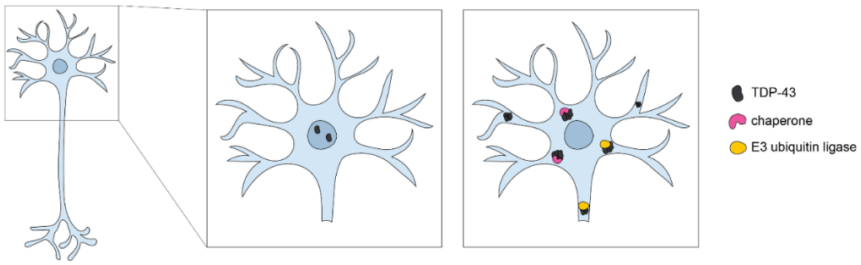
One approach I employed to model neurodegeneration in planarians was by identifying and characterizing planarian TAR DNA-binding proteins (TARDBPs). Protein aggregates are implicated in several neurodegenerative diseases, including Parkinson's Disease, Alzheimer's Disease, and amyotrophic lateral sclerosis (ALS) (Koszła & Sołek, 2024; Polymeropoulos et al., 1997; Sweeney et al., 2017). TDP-43 aggregates are specifically implicated in sporadic and genetic forms of ALS (Sreedharan et al., 2008; Suk & Rousseaux, 2020). However, the exact cause of neuron death after TDP-43 aggregation has yet to be elucidated. In one model, neurons with TDP-43 protein aggregates die due to toxicity when the protein becomes mislocalized and aggregated. In an alternate model, cellular health is primarily compromised due to the loss of healthy TDP-43

protein function. Planarians present a unique organism with which to study the cellular roles of TARDBP because planarians have five homologs of TDP-43. In other organisms with only one TDP-43 homolog, like mice, loss of TDP-43 is embryonic lethal (Kraemer et al., 2010). Because planarians have five TDP-43 homologs, we are able to knock down individual isoforms in the adult animal to examine the subfunctionality of TDP-43. Indeed, I was able to knock down each planarian homolog of TDP-43 and assess whether regeneration of the brain was impaired. I found that *tdp-4* is required for proper planarian brain regeneration. Loss of planarian *tdp-4* eventually led to animal death through lysis, which led me to examine whether *tdp-4* regulated planarian stem cells. I found that *tdp-4* causes a reduction in planarian stem cell abundance compared to controls, and I concluded that planarian TARDBPs regulate both brain regeneration and stem cell maintenance.

Currently, most planarian researchers induce regeneration through tissue amputation or other drastic injury. However, this is not physiologically relevant for modeling neurodegeneration. I hypothesized that I might be able to model neurodegeneration in planarians in a manner that is more physiologically relevant to humans. I started by looking at the literature where dysfunction in neuronal chaperones and proteasomal subunits has been implicated in neurodegenerative disease (Ellis, 1988; Hartl et al., 1992; Hartl, 1996; Satapathy & Wilson, 2022) (Figure 3). Using available single-cell transcriptomic data, I identified planarian homologs of chaperones and proteasomal subunits with enriched expression in the nervous system (Fincher et al., 2018). I narrowed this list down to twenty transcripts (e.g., *heat shock factor, E3 ubiquitin ligase*), which could be used for an RNAi screen to assess their impact on maintenance of brain size and function. Next, I would suggest investigating whether these RNAi conditions lead to neuronal death via protein aggregation. Utilizing TUNEL to examine cell death by apoptosis could help address the first possibility, and I have worked to develop this protocol in the lab (Kyrylkova et al., 2012). Further, a protein dye like Proteostat could be used to quantifiably examine protein aggregates in control compared to knockdown conditions (Navarro & Ventura, 2014). Developing planarians as a future model for studying neurodegeneration could prove pivotal in the field and would allow us to investigate neural loss in a system that is capable of robust regeneration to inform new approaches to tackling old questions.

Figure 3

Proteostasis Mechanisms for Neuronal Survival



Note. Protein aggregates (black) accumulate in the cytoplasm, causing toxicity to neurons. Proteins involved in proteostasis (yellow and pink) work to prevent and break up protein aggregates.

Conclusion

Throughout the body of my thesis work, I uncovered molecular mechanisms of planarian nervous system regeneration and proposed the development of planarians as a future model for neurodegeneration. Specifically, I showed that combinatorial mechanisms specify neuronal neurotransmitter identity and cellular regionalization for planarian dopaminergic neurons. For the first time in planarians, I examined the cellular roles of the five planarian TDP-43 homologs and determined their importance in brain regeneration, stem cell maintenance, and function. Finally, I provided the starting point for a fascinating avenue to develop planarians as a model with which to study neurodegeneration in a physiologically relevant manner.

References

Agata, Kiyokazu; Soejima, Yukihiro; Kato, Kentaro; Kobayashi, Chiyoko; Umesono, Yoshihiko; & Watanabe, Kenji. (1998). Structure of the Planarian Central Nervous System (CNS) Revealed by Neuronal Cell Markers. *Https://Doi.Org/10.2108/Zsj.15.433*, *15*(3), 433–440. https://doi.org/10.2108/ZSJ.15.433

Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; & Walter, Peter. (2002). *Neural Development*. https://www.ncbi.nlm.nih.gov/books/NBK26814/

Alemany, Anna; Florescu, Maria; Baron, Chloé S.; Peterson-Maduro, Josi; & Van Oudenaarden, Alexander. (2018). Whole-organism clone tracing using single-cell sequencing. *Nature*, *556*(7699), 108–112. https://doi.org/10.1038/nature25969

Amamoto, Ryoji; Huerta, Violeta Gisselle Lopez; Takahashi, Emi; Dai, Guangping; Grant, Aaron K.; Fu, Zhanyan; & Arlotta, Paola. (2016). Adult axolotls can regenerate original neuronal diversity in response to brain injury. *ELife*, *5*(MAY2016). https://doi.org/10.7554/ELIFE.13998

Ament, Seth A.; Cortes-Gutierrez, Marcia; Herb, Brian R.; Mocci, Evelina; Colantuoni, Carlo; & McCarthy, Margaret M. (2023). A single-cell genomic atlas for maturation of the human cerebellum during early childhood. *Science Translational Medicine*, *15*(721). https://doi.org/10.1126/SCITRANSLMED.ADE1283

Anderson, David J. (2001). Stem cells and pattern formation in the nervous system: The possible versus the actual. *Neuron*, *30*(1), 19–35. https://doi.org/10.1016/S0896-6273(01)00260-4

Anderson, R. B.; Newgreen, D. F.; & Young, HM. (2013). *Neural Crest and the Development of the Enteric Nervous System*. https://www.ncbi.nlm.nih.gov/books/NBK6273/

Andersson, Elisabet; Tryggvason, Ulrika; Deng, Qiaolin; Friling, Stina; Alekseenko, Zhanna; Robert, Benoit; Perlmann, Thomas; & Ericson, Johan. (2006). Identification of Intrinsic Determinants of Midbrain Dopamine Neurons. *Cell*, *124*(2), 393–405. https://doi.org/10.1016/J.CELL.2005.10.037

Arenas Gómez, Claudia M.; Sabin, Keith Z.; & Echeverri, Karen. (2020). Wound healing across the animal kingdom: Crosstalk between the immune system and the extracellular matrix. *Developmental Dynamics*, *249*(7), 834. https://doi.org/10.1002/DVDY.178

Arendt, Detlev; Tosches, Maria Antonietta; & Marlow, Heather. (2016). From nerve net to nerve ring, nerve cord and brain-evolution of the nervous system. *Nature Reviews Neuroscience*, *17*(1), 61–72. https://doi.org/10.1038/NRN.2015.15

Atabay, Kutay Deniz; LoCascio, Samuel A.; de Hoog, Thom; & Reddien, Peter W. (2018). Self-organization and progenitor targeting generate stable patterns in planarian regeneration. *Science*, *360*(6387), 404–409. https://doi.org/10.1126/SCIENCE.AAP8179

Baguñ, Jaume. (2012). The planarian neoblast: the rambling history of its origin and some current black boxes. *The International Journal of Developmental Biology*, *56*(1-2–3), 19–37. https://doi.org/10.1387/ijdb.113463jb

Baguñà, Jaume. (1976). Mitosis in the intact and regenerating planarian Dugesia mediterranea n.sp. II. Mitotic studies during regeneration, and a possible mechanism of blastema formation. *Journal of Experimental Zoology*, *195*(1), 65–79. https://doi.org/10.1002/jez.1401950107

Baguñà, Jaume; & Ballester, Rafael. (1978). The nervous system in planarians: Peripheral and gastrodermal plexuses, pharynx innervation, and the relationship between central nervous system structure and the acoelomate organization. *Journal of Morphology*, *155*(2), 237–252. https://doi.org/10.1002/JMOR.1051550208

Baguñà, Jaume; Saló, Emili; & Auladell, Carme. (1989). Regeneration and pattern formation in planarians. III. Evidence that neoblasts are totipotent stem cells and the source of blastema cells. *Development*, *107*, 77–86.

Barker, Roger A.; Parmar, Malin; Studer, Lorenz; & Takahashi, Jun. (2017). Human Trials of Stem Cell-Derived Dopamine Neurons for Parkinson's Disease: Dawn of a New Era. *Cell Stem Cell*, *21*(5), 569–573. https://doi.org/10.1016/j.stem.2017.09.014

Barmaki, Haleh; Nourazarian, Alireza; & Khaki-Khatibi, Fatemeh. (2023). Proteostasis and neurodegeneration: a closer look at autophagy in Alzheimer's disease. *Frontiers in Aging Neuroscience*, *15*, 1281338. https://doi.org/10.3389/FNAGI.2023.1281338

Bazira, Peter J. (2021). An overview of the nervous system. *Surgery (Oxford)*, *39*(8), 451–462. https://doi.org/10.1016/J.MPSUR.2021.06.012

Bédard, Catherine; Wallman, Marie Josée; Pourcher, Emmanuelle; Gould, Peter V.; Parent, André; & Parent, Martin. (2011). Serotonin and dopamine striatal innervation in Parkinson's disease and Huntington's chorea. *Parkinsonism and Related Disorders*, *17*(8), 593–598. https://doi.org/10.1016/j.parkreldis.2011.05.012

Benham-Pyle, Blair W.; Mann, Frederick G.; Brewster, Carolyn E.; Dewars, Enya R.; Vuu, Dung M.; Nowotarski, Stephanie H.; Guerrero-Hernández, Carlos; Malloy, Seth; Hall, Kate E.; Maddera, Lucinda E.; Chen, Shiyuan; Morrison, Jason A.; McKinney, Sean A.; Slaughter, Brian D.; Perera, Anoja; & Alvarado, Alejandro Sánchez. (2023). Planarians employ diverse and dynamic stem cell microenvironments to support whole-body regeneration. *BioRxiv*, 2022.03.20.485025. https://doi.org/10.1101/2022.03.20.485025

Bhat, Krishna Moorthi. (2007). Wingless activity in the precursor cells specifies neuronal migratory behavior in the Drosophila nerve cord. *Developmental Biology*, *311*(2), 613–622. https://doi.org/10.1016/J.YDBIO.2007.09.004

Bisht, Kanchan; Sharma, Kaushik P.; Lecours, Cynthia; Gabriela Sánchez, Maria; El Hajj, Hassan; Milior, Giampaolo; Olmos-Alonso, Adrián; Gómez-Nicola, Diego; Luheshi, Giamal; Vallières, Luc; Branchi, Igor; Maggi, Laura; Limatola, Cristina; Butovsky, Oleg; & Tremblay, Marie Ève. (2016). Dark microglia: A new phenotype predominantly associated with pathological states. *Glia*, *64*(5), 826–839. https://doi.org/10.1002/GLIA.22966

Björklund, A.; Dunnett, S. B.; Stenevi, U.; Lewis, M. E.; & Iversen, S. D. (1980). Reinnervation of the denervated striatum by substantia nigra transplants: Functional consequences as revealed by pharmacological and sensorimotor testing. *Brain Research*, *199*(2), 307–333. https://doi.org/10.1016/0006-8993(80)90692-7

Björklund, A.; & Lindvall, O. (1984). Dopamine-containing systems in the CNS. *Handbook of Chemical Neuroanatomy : Classical Transmitters in the CNS*, *2*, 55–122. https://cir.nii.ac.jp/crid/1571417125170103296

Björklund, A.; Stenevi, U.; Dunnett, S. B.; & Iversen, S. D. (1981). Functional reactivation of the deafferented neostriatum by nigral transplants. *Nature*, *289*(5797), 497–499. https://doi.org/10.1038/289497A0

Björklund, Anders; & Stenevi, Ulf. (1979). Reconstruction of the nigrostriatal dopamine pathway by intracerebral nigral transplants. *Brain Research*, *177*(3), 555–560. https://doi.org/10.1016/0006-8993(79)90472-4

Björklund, Anders; Stenevi, Ulf; & Svendgaard, Niels Aage. (1976). Growth of transplanted monoaminergic neurones into the adult hippocampus along the perforant path. *Nature*, *262*(5571), 787–790. https://doi.org/10.1038/262787A0

Blackshaw, Seth; & Cayouette, Michel. (2025). Timing neural development and regeneration. *Current Opinion in Neurobiology*, *91*, 102976. https://doi.org/10.1016/J.CONB.2025.102976

Blanchard, Veronique; Raisman-Vozari, Rita; Savasta, Marc; Hirsch, Etienne; Javoy-Agid, France; Feuerstein, Claude; & Agid, Yves. (1993). Cellular Quantification of Tyrosine Hydroxylase in the Rat Brain by Immunoautoradiography. *Journal of Neurochemistry*, *61*(2), 617–626. https://doi.org/10.1111/J.1471-4159.1993.TB02166.X

Bonilla, Sonia; Hall, Anita C.; Pinto, Luisa; Attardo, Alessio; Götz, Magdalena; Huttner, Wieland B.; & Arenas, Ernest. (2008). Identification of midbrain floor plate radial glia-like cells as dopaminergic progenitors. *GLIA*, *56*(8), 809–820. https://doi.org/10.1002/GLIA.20654

Bowling, Sarah; Sritharan, Duluxan; Osorio, Fernando G.; Nguyen, Maximilian; Cheung, Priscilla; Rodriguez-Fraticelli, Alejo; Patel, Sachin, Yuan; Wei Chien; Fujiwara, Yuko; Li, Bin E.; Orkin, Stuart H.; Hormoz, Sahand; & Camargo, Fernando D. (2020). An Engineered CRISPR-Cas9 Mouse Line for Simultaneous Readout of Lineage Histories and Gene Expression Profiles in Single Cells. *Cell*, *181*(6), 1410-1422.e27. https://doi.org/10.1016/j.cell.2020.04.048

Braak, H.; Rüb, U.; Jansen Steur, E. N. H.; Del Tredici, K.; & De Vos, R. A. I. (2005). Cognitive status correlates with neuropathologic stage in Parkinson disease. *Neurology*, *64*(8), 1404–1410. https://doi.org/10.1212/01.WNL.0000158422.41380.82

Braak, Heiko; & Del Tredici, Kelly. (2017). Neuropathological Staging of Brain Pathology in Sporadic Parkinson's disease: Separating the Wheat from the Chaff. *Journal of Parkinson's Disease*, *7*(s1), S73–S87. https://doi.org/10.3233/JPD-179001

Braak, Heiko; Del Tredici, Kelly; Rüb, Udo; De Vos, Rob A. I.; Jansen Steur, Ernst N. H.; & Braak, Eva. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*, *24*(2), 197–211. https://doi.org/10.1016/S0197-4580(02)00065-9

Briscoe, James; Pierani, Alessandra; Jessell, Thomas M.; & Ericson, Johan. (2000). A homeodomain protein code specifies progenitor cell identity and neuronal fate in the ventral neural tube. *Cell*, *101*(4), 435–445. https://doi.org/10.1016/S0092-8674(00)80853-3

Brundin, P.; Strecker, R. E.; Widner, H.; Clarke, D. J.; Nilsson, O. G.; Åstedt, B.; Lindvall, O.; & Björklund, A. (1988). Human fetal dopamine neurons grafted in a rat model of Parkinson's disease: immunological aspects, spontaneous and drug-induced behaviour, and dopamine release. *Experimental Brain Research*, *70*(1), 192–208. https://doi.org/10.1007/BF00271860

Burkhardt, Pawel. (2022). Ctenophores and the evolutionary origin(s) of neurons. *Trends in Neurosciences*, *45*(12), 878–880. https://doi.org/10.1016/J.TINS.2022.09.001

Butt, Arthur; & Verkhratsky, Alexei. (2018). Neuroglia: Realising their true potential. *Brain and Neuroscience Advances*, *2*. https://doi.org/10.1177/2398212818817495

Bylund, Magdalena; Andersson, Elisabeth; Novitch, Bennett G.; & Muhr, Jonas. (2003). Vertebrate neurogenesis is counteracted by Sox1-3 activity. *Nature Neuroscience*, *6*(11), 1162–1168. https://doi.org/10.1038/NN1131

Caldwell, Lindsey J.; Davies, Nick O.; Cavone, Leonardo; Mysiak, Karolina S.; Semenova, Svetlana A.; Panula, Pertti; Armstrong, J. Douglas; Becker, Catherina G.; & Becker, Thomas. (2019). Regeneration of dopaminergic neurons in adult zebrafish depends on immune system activation and differs for distinct populations. *Journal of Neuroscience*, *39*(24), 4694–4713. https://doi.org/10.1523/JNEUROSCI.2706-18.2019

Calne, D. B.; Teychenne, P. F.; Claveria, L. E.; Eastman, R.; Greenacre, J. K.; & Petrie, A. (1974). Bromocriptine in parkinsonism. *British Medical Journal*, *4*(5942), 442–444. https://doi.org/10.1136/BMJ.4.5942.442

Carpenter, K. S.; Morita, M.; & Best, J. B. (1974). Ultrastructure of the photoreceptor of the planarian Dugesia dorotocephala – I. Normal eye. *Cell and Tissue Research*, *148*(2), 143–158. https://doi.org/10.1007/BF00224579

Cascione, Mariafrancesca; De Matteis, Valeria;, Leporatti, Stefano; & Rinaldi, Rosaria. (2020). The new frontiers in neurodegenerative diseases treatment: Liposomal-based strategies. *Frontiers in Bioengineering and Biotechnology*, *8*, 566767. 566767. https://doi.org/10.3389/fbioe.2020.566767

Cebrià, Francesc. (2016). Planarian body-wall muscle: Regeneration and function beyond a simple skeletal support. *Frontiers in Cell and Developmental Biology*, *4*(FEB), 174749. https://doi.org/10.3389/fcell.2016.00008

Cebrià, Francesc; Guo, Tingxia; Jopek, Jessica; & Newmark, Phillip A. (2007). Regeneration and maintenance of the planarian midline is regulated by a slit orthologue. *Developmental Biology*, *307*(2), 394. https://doi.org/10.1016/J.YDBIO.2007.05.006

Chalazonitis, Alcmène; Rao, Meenakshi; & Sulzer, David. (2022). Similarities and differences between nigral and enteric dopaminergic neurons unravel distinctive involvement in Parkinson's disease. *NPJ Parkinson's Disease*, *8*(1), 50. https://doi.org/10.1038/S41531-022-00308-9

Chandra, Bidushi; Voas, Matthew G.; Davies, Erin L.; & Roberts-Galbraith, Rachel H. (2023). Ets-1 transcription factor regulates glial cell regeneration and function in planarians. *Development (Cambridge)*, *150*(18). https://doi.org/10.1242/dev.201666

Chhetri, Parvat Kuwar; & Das, Joe M. (2023). Neuroanatomy, Neural Tube Development and Stages. *StatPearls*. https://www.ncbi.nlm.nih.gov/books/NBK557414/

Chinta, Shankar J.; & Andersen, Julie K. (2005). Dopaminergic neurons. *The International Journal of Biochemistry & Cell Biology*, *37*(5), 942–946. https://doi.org/10.1016/J.BIOCEL.2004.09.009

Cizeron, Mélissa; Qiu, Zhen; Koniaris, Babis; Gokhale, Ragini; Komiyama, Noboru H.; Fransén, Erik; & Grant, Seth G. N. (2020). A brainwide atlas of synapses across the mouse life span. *Science*, *369*(6501). https://doi.org/10.1126/SCIENCE.ABA3163

Clay, Kendall B.; Medlock-Lanier, Taylor; Grimes, Rachel N.; Oke, Olabamibo O.; Filipov, Nikolay M.; & Roberts-Galbraith, Rachel H. (2025). Combinatorial mechanisms specify cellular location and neurotransmitter identity during regeneration of planarian neurons. *BioRxiv*, 2025.05.23.655781. https://doi.org/10.1101/2025.05.23.655781

Cobb, J. L. S. (1987). Neurobiology of the Echinodermata. In *Nervous Systems in Invertebrates* (pp. 483–525). Springer US. https://doi.org/10.1007/978-1-4613-1955-9_17

Colas, Jean François; & Schoenwolf, Gary C. (2001). Towards a cellular and molecular understanding of neurulation. *Developmental Dynamics*, *221*(2), 117–145. https://doi.org/10.1002/DVDY.1144

Collins, James J.; Hou, Xiaowen; Romanova, Elena V.; Lambrus, Bramwell G.; Miller, Claire M.; Saberi, Amir; Sweedler, Jonathan V.; & Newmark, Phillip A. (2010). Genome-Wide Analyses Reveal a Role for Peptide Hormones in Planarian Germline Development. *PLoS Biology*, *8*(10), e1000509. https://doi.org/10.1371/journal.pbio.1000509

Contreras, Estefania; Bolívar, Sara; Navarro, Xavier; & Udina, Esther. (2022). New insights into peripheral nerve regeneration: The role of secretomes. *Experimental Neurology*, *354*, 114069. https://doi.org/10.1016/J.EXPNEUROL.2022.114069

Cotzias, George C.; Papavasiliou, Paul S.; Fehling, Clas,;Kaufman, Barry; & Mena, Ismael. (1970). Similarities between Neurologic Effects of L-Dopa and of Apomorphine. *New England Journal of Medicine*, *282*(1), 31–33. https://doi.org/10.1056/NEJM197001012820107

Cousins, Fiona L.; Filby, Caitlin E.; & Gargett, Caroline E. (2022). Endometrial Stem/Progenitor Cells–Their Role in Endometrial Repair and Regeneration. *Frontiers in Reproductive Health*, *3*, 811537. https://doi.org/10.3389/FRPH.2021.811537

Cowan, W. M. (1978). Aspects of neural development. *International Review of Physiology*, *17*, 149–191.

Cowan, W. M. (1979). The development of the brain. *Scientific American*, *241*(3), 113–133. https://doi.org/10.1038/SCIENTIFICAMERICAN0979-112

Cowles, Martis W.; Brown, David D. R.; Nisperos, Sean V.; Stanley, Brianna N.; Pearson, Bret J.; & Zayas, Ricardo M. (2013). Genome-wide analysis of the bHLH gene family in planarians identifies factors required for adult neurogenesis and neuronal regeneration. *Development (Cambridge)*, *140*(23), 4691–4702. https://doi.org/10.1242/DEV.098616

Cowles, Martis W.; Omuro, Kerilyn C.; Stanley, Brianna N.; Quintanilla, Carlo G.; & Zayas, Ricardo M. (2014). COE Loss-of-Function Analysis Reveals a Genetic Program Underlying Maintenance and Regeneration of the Nervous System in Planarians. *PLoS Genetics*, *10*(10). https://doi.org/10.1371/journal.pgen.1004746

Currie, Ko W.; & Pearson, Bret J. (2013). Transcription factors lhx1/5-1 and pitx are required for the maintenance and regeneration of serotonergic neurons in planarians. *Development*, *140*(17), 3577–3588. https://doi.org/10.1242/dev.098590

Damier, P.; Hirsch, E. C.,; Agid, Y.; & Graybiel, A. M. (1999). The substantia nigra of the human brain: II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. *Brain*, *122*(8), 1437–1448. https://doi.org/10.1093/BRAIN/122.8.1437

Darras, Sébastien; Gerhart, John; Terasaki, Mark; Kirschner, Marc; & Lowe, Christopher J. (2011). β-Catenin specifies the endomesoderm and defines the posterior organizer of the hemichordate Saccoglossus kowalevskii. *Development*, *138*(5), 959–970. https://doi.org/10.1242/DEV.059493

Dawson, Ted M.; Golde, Todd E.; & Lagier-Tourenne, Clotilde. (2018). Animal Models of Neurodegenerative Diseases. *Nature Neuroscience*, *21*(10), 1370. https://doi.org/10.1038/S41593-018-0236-8

den Hartog Jager, W. A.; & Bethlem, J. (1960). The distribution of Lewy bodies in the central and autonomic nervous systems in idiopathic paralysis agitans. *Journal of Neurology, Neurosurgery, and Psychiatry*, *23*(4), 283–290. https://doi.org/10.1136/JNNP.23.4.283

Development of the Central Nervous System – Spinal Cord – TeachMeAnatomy. (n.d.). Retrieved 28 March 2026, from https://teachmeanatomy.info/the-basics/embryology/central-nervous-system/

Díaz-Villanueva, José Fernando; Díaz-Molina, Raúl; & García-González, Victor. (2015). Protein Folding and Mechanisms of Proteostasis. *International Journal of Molecular Sciences 2015, 16*(8), 17193–17230. https://doi.org/10.3390/IJMS160817193

Doe, Chris Q. (2017). Temporal Patterning in the Drosophila CNS. *Annual Review of Cell and Developmental Biology*, *33*, 219–240. https://doi.org/10.1146/ANNUREV-CELLBIO-111315-125210

Doitsidou, Maria; Flames, Nuria; Lee, Albert C.; Boyanov, Alexander; & Hobert, Oliver. (2008). Automated screening for mutants affecting dopaminergic-neuron specification in C. elegans. *Nature Methods*, *5*(10), 869–872. https://doi.org/10.1038/nmeth.1250

Doitsidou, Maria; Flames, Nuria; Topalidou, Irini; Abe, Namiko; Felton, Terry; Remesal, Laura; Popovitchenko, Tatiana; Mann, Richard; Chalfie, Martin; & Hobert, Oliver. (2013). A combinatorial regulatory signature controls terminal differentiation of the dopaminergic nervous system in C. elegans. *Genes & Development*, *27*(12), 1391–1405. https://doi.org/10.1101/gad.217224.113

Doitsidou, Maria; Minevich, Gregory; Kroll, Jason R.; Soete, Gwen; Gowtham, Sriharsh; Korswagen, Hendrik C.; van Zon, Jeroen Sebastiaan; & Hobert, Oliver. (2018). A Caenorhabditis elegans zinc finger transcription factor, ztf-6, required for the specification of a dopamine neuron-producing lineage. *G3: Genes, Genomes, Genetics*, *8*(1), 17–26. https://doi.org/10.1534/G3.117.300132/-/DC1

Duman-Scheel, Molly; Li, Xuelin; Orlov, Irena; Noll, Markus; & Patel, Nipam H. (1997). Genetic separation of the neural and cuticular patterning functions of gooseberry. *Development*, *124*(15), 2855–2865. https://doi.org/10.1242/DEV.124.15.2855

Durães, Fernando; Pinto, Madalena; & Sousa, Emília. (2018). Old Drugs as New Treatments for Neurodegenerative Diseases. *Pharmaceuticals 2018, Vol. 11, Page 44*, *11*(2), 44. https://doi.org/10.3390/PH11020044

Duvoisin, Roger C. (1984). Is Parkinson's Disease Acquired or Inherited? *Canadian Journal of Neurological Sciences*, *11*(S1), 151–155. https://doi.org/10.1017/S031716710004631X

Eisenhoffer, George T.; Kang, Hara; & Alvarado, Alejandro Sánchez. (2008). Molecular Analysis of Stem Cells and Their Descendants during Cell Turnover and Regeneration in the Planarian Schmidtea mediterranea. *Cell Stem Cell*, *3*(3), 327–339. https://doi.org/10.1016/J.STEM.2008.07.002

El-Danaf, Rana N.; Rajesh, Raghuvanshi; & Desplan, Claude. (2023). Temporal regulation of neural diversity in Drosophila and vertebrates. *Seminars in Cell & Developmental Biology*, *142*, 13–22. https://doi.org/10.1016/J.SEMCDB.2022.05.011

Elkouris, Maximilianos; Balaskas, Nikos; Poulou, Maria; Politis, Panagiotis K.; Panayiotou, Elena; Malas, Stavros; Thomaidou, Dimitra; & Remboutsika, Eumorphia. (2011). Sox1 maintains the undifferentiated state of cortical neural progenitor cells via the suppression of Prox1-mediated cell cycle exit and neurogenesis. *Stem Cells*, *29*(1), 89–98. https://doi.org/10.1002/STEM.554

Elliott, Jimmy; Jolicoeur, Christine; Ramamurthy, Vasanth; & Cayouette, Michel. (2008). Ikaros Confers Early Temporal Competence to Mouse Retinal Progenitor Cells. *Neuron*, *60*(1), 26–39. https://doi.org/10.1016/J.NEURON.2008.08.008

Ellis, John. (1988). Proteins as molecular chaperones. *Nature*, *328*(6129), 378–379.

Emili, Elena; Pallarès, Macià Esteve; Romero, Rafael; & Cebrià, Francesc. (2019). Smed-egfr-4 is required for planarian eye regeneration. *International Journal of Developmental Biology*, *63*(1–2), 9–15. https://doi.org/10.1387/IJDB.180361FC

Fahn, Stanley. (2005). Does levodopa slow or hasten the rate of progression of Parkinson's disease? *Journal of Neurology*, *252*(SUPPL. 4). https://doi.org/10.1007/S00415-005-4008-5

Failli, Vieri; Bachy, Isabelle; & Rétaux, Sylvie. (2002). Expression of the LIM-homeodomain gene Lmx1a (dreher) during development of the mouse nervous system. *Mechanisms of Development*, *118*(1–2), 225–228. https://doi.org/10.1016/S0925-4773(02)00254-X

Falck, B.; Hillarp, N. Å.; Thieme, G.; & Torp, A. (1962). Fluorescence of Catechol Amines and Related Compounds Condensed with Formaldehyde. *Journal of Histochemistry & Cytochemistry*, *10*(3), 348–354. https://doi.org/10.1177/10.3.348

Fan, Guoping; & Katz, David M. (1993). Non-neuronal cells inhibit catecholaminergic differentiation of primary sensory neurons: role of leukemia inhibitory factor. *Development*, *118*(1), 83–93. https://doi.org/10.1242/DEV.118.1.83

Faust, Travis E.; Gunner, Georgia; & Schafer, Dorothy P. (2021). Mechanisms governing activity-dependent synaptic pruning in the mammalian CNS. *Nature Reviews. Neuroscience*, *22*(11), 657. https://doi.org/10.1038/S41583-021-00507-Y

Ferenczy, Alex; Bertrand, Gracia; & Gelfand, Morrie M. (1979). Proliferation kinetics of human endometrium during the normal menstrual cycle. *American Journal of Obstetrics and Gynecology*, *133*(8), 859–867. https://doi.org/10.1016/0002-9378(79)90302-8

Fincher, Christopher T.; Wurtzel, Omri; de Hoog, Thom; Kravarik, Kellie M.; & Reddien, Peter W. (2018). Cell type transcriptome atlas for the planarian Schmidtea mediterranea. *Science*, *360*(6391). https://doi.org/10.1126/science.aaq1736

Flames, Nuria; & Hobert, Oliver. (2009). Gene regulatory logic of dopamine neuron differentiation. *Nature*, *458*(7240), 885–889. https://doi.org/10.1038/nature07929

Flores, Natasha M.; Oviedo, Néstor J.; & Sage, Julien. (2016). Essential role for the planarian intestinal GATA transcription factor in stem cells and regeneration. *Developmental Biology*, *418*(1), 179. https://doi.org/10.1016/J.YDBIO.2016.08.015

Formery, Laurent; Orange, François; Formery, Antoine; Yaguchi, Shunsuke; Lowe, Christopher J.; Schubert, Michael; & Croce, Jenifer C. (2021). Neural anatomy of echinoid early juveniles and comparison of nervous system organization in echinoderms. *The Journal of Comparative Neurology*, *529*(6), 1135–1156. https://doi.org/10.1002/CNE.25012

Forsthoefel, David J.; Cejda, Nicholas I.; Khan, Umair W.; & Newmark, Phillip A. (2020). Cell-type diversity and regionalized gene expression in the planarian intestine. *ELife*, *9*. https://doi.org/10.7554/ELIFE.52613

Freed, Curt R.; Greene, Paul E.; Breeze, Robert E.; Tsai, Wei-Yann; DuMouchel, William; Kao, Richard; Dillon, Sandra; Winfield, Howard; Culver, Sharon; Trojanowski, John Q.; Eidelberg, David; & Fahn, Stanley. (2001). Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease. *New England Journal of Medicine*, *344*(10), 710–719. https://doi.org/10.1056/NEJM200103083441002

García-Arrarás, José E.; Rojas-Soto, Michelle; Jiménez, Luis B.; & Díaz-Miranda, Lucy. (2001). The enteric nervous system of echinoderms: unexpected complexity revealed by neurochemical analysis. *The Journal of Experimental Biology*, *204*(Pt 5), 865–873. https://doi.org/10.1242/JEB.204.5.865

Gargett, Caroline E.; & Ye, Louie. (2012). Endometrial reconstruction from stem cells. *Fertility and Sterility*, *98*(1), 11–20. https://doi.org/10.1016/J.FERTNSTERT.2012.05.004

Gaviño, Michael A.; & Reddien, Peter W. (2011). A Bmp/Admp regulatory circuit controls maintenance and regeneration of dorsal-ventral polarity in planarians. *Current Biology*, *21*(4), 294–299. https://doi.org/10.1016/j.cub.2011.01.017

Ge, Mengmeng; Sheikhshahrokh, Amirhossein; Shi, Xiang; Zhang, Yu Hong; Xu, Zhiheng; & Wu, Qing Feng. (2022). A Spacetime Odyssey of Neural Progenitors to Generate Neuronal Diversity. *Neuroscience Bulletin*, *39*(4), 645. https://doi.org/10.1007/S12264-022-00956-0

Gibbons, Christopher H. (2019). Basics of autonomic nervous system function. *Handbook of Clinical Neurology*, *160*, 407–418. https://doi.org/10.1016/B978-0-444-64032-1.00027-8

Gilbert, Scott F. (2000a). *An Introduction to Early Developmental Processes*. https://www.ncbi.nlm.nih.gov/books/NBK9992/

Gilbert, Scott F. (2000b). *Formation of the Neural Tube*. https://www.ncbi.nlm.nih.gov/books/NBK10080/

Gilbert, Scott F. (2000c). *Principles of Development: Life Cycles and Developmental Patterns*. https://www.ncbi.nlm.nih.gov/books/NBK10125/

Glavic, Alvaro; Gómez-Skarmeta, José Luis; & Mayor, Roberto. (2002). The homeoprotein Xiro1 is required for midbrain-hindbrain boundary formation. *Development*, *129*(7), 1609–1621. https://doi.org/10.1242/DEV.129.7.1609

Goldstein, David S.; & Holmes, Courtney. (2008). Neuronal Source of Plasma Dopamine. *Clinical Chemistry*, *54*(11), 1864. https://doi.org/10.1373/CLINCHEM.2008.107193

Gómez-Skarmeta, José Luis; & Modolell, Juan. (2002). Iroquois genes: genomic organization and function in vertebrate neural development. *Current Opinion in Genetics & Development*, *12*(4), 403–408. https://doi.org/10.1016/S0959-437X(02)00317-9

Gordon, Tessa. (2020). Peripheral Nerve Regeneration and Muscle Reinnervation. *International Journal of Molecular Sciences*, *21*(22), 8652. https://doi.org/10.3390/IJMS21228652

Grandas, Francisco; Martínez-Martín, Pablo; & Linazasoro, Gurutz. (1998). Quality of life in patients with Parkinson's disease who transfer from standard levodopa to sinemet CR: The STAR study. *Journal of Neurology, Supplement*, *245*(1). https://doi.org/10.1007/PL00007736,

Grandel, Heiner; Kaslin, Jan; Ganz, Julia; Wenzel, Isabell; & Brand, Michael. (2006). Neural stem cells and neurogenesis in the adult zebrafish brain: Origin, proliferation dynamics, migration and cell fate. *Developmental Biology*, *295*(1), 263–277. https://doi.org/10.1016/j.ydbio.2006.03.040

Grealish, Shane; Diguet, Elsa; Kirkeby, Agnete; Mattsson, Bengt; Heuer, Andreas; Bramoulle, Yann; Van Camp, Nadja; Perrier, Anselme L.; Hantraye, Philippe; Björklund, Anders; & Parmar, Malin. (2014). Human ESC-derived dopamine neurons show similar preclinical efficacy and potency to fetal neurons when grafted in a rat model of Parkinson's disease. *Cell Stem Cell*, *15*(5), 653–665. https://doi.org/10.1016/j.stem.2014.09.017

Grimmelikhuijzen, C. J.; & Westfall, J. A. (1995). The nervous systems of cnidarians. *EXS*, *72*, 7–24. https://doi.org/10.1007/978-3-0348-9219-3_2

Grosskortenhaus, Ruth; Pearson, Bret J.; Marusich, Amanda; & Doe, Chris Q. (2005). Regulation of Temporal Identity Transitions in Drosophila Neuroblasts. *Developmental Cell*, *8*(2), 193–202. https://doi.org/10.1016/J.DEVCEL.2004.11.019

Gurley, Kyle A.; Elliott, Sarah A.; Simakov, Oleg; Schmidt, Heiko A.; Holstein, Thomas W.; & Alvarado, Alejandro Sánchez. (2010). Expression of secreted Wnt pathway components reveals unexpected complexity of the planarian amputation response. *Developmental Biology*, *347*(1), 24–39. https://doi.org/10.1016/J.YDBIO.2010.08.007

Gurley, Kyle A.; Rink, Jochen C.; & Alvarado, Alejandro Sánchez. (2008). β-catenin defines head versus tail identity during planarian regeneration and homeostasis. *Science*, *319*(5861), 323–327. https://doi.org/10.1126/science.1150029

Hao, Marlene M.; Bornstein, Joel C.; Vanden Berghe, Pieter; Lomax, Alan E.; Young, Heather M.; & Foong, Jaime P. P. (2013). The emergence of neural activity and its role in the development of the enteric nervous system. *Developmental Biology*, *382*(1), 365–374. https://doi.org/10.1016/J.YDBIO.2012.12.006

Hardin, Jeff; & King, Ryan S. (2008). The long and the short of Wnt signaling in C. elegans. *Current Opinion in Genetics and Development*, *18*(4), 362–367. https://doi.org/10.1016/j.gde.2008.06.006

Hartenstein, Volker; Cruz, Louie; Lovick, Jennifer K.; & Guo, Ming. (2016). Developmental analysis of the dopamine-containing neurons of the Drosophila brain. *The Journal of Comparative Neurology*, *525*(2), 363. https://doi.org/10.1002/CNE.24069

Hartenstein, Volker; & Wodarz, Andreas. (2013). Initial neurogenesis in Drosophila. *Wiley Interdisciplinary Reviews. Developmental Biology*, *2*(5), 701–721. https://doi.org/10.1002/WDEV.111

Hartl, F. U.; Martin, J.; & Neupert, W. (1992). Protein Folding in the Cell. *Annual Review of Biophysics and Biomolecular Structure*, *21*, 293–322. https://doi.org/10.1146/ANNUREV.BB.21.060192.001453

Hartl, F. Ulrich. (1996). Molecular chaperones in cellular protein folding. *Nature*, *381*(6583), 571–580. https://doi.org/10.1038/381571A0

Haugh, Bruce N. (1975). Nervous systems of Mississippian camerate crinoids. *Paleobiology*, *1*(3), 261–272. https://doi.org/10.1017/S0094837300002529

Hayashi, Tetsutaro; Asami, Maki; Higuchi, Sayaka; Shibata, Norito; & Agata, Kiyokazu. (2006). Isolation of planarian X-ray-sensitive stem cells by fluorescence-activated cell sorting. *Development, Growth and Differentiation*, *48*(6), 371–380. https://doi.org/10.1111/j.1440-169X.2006.00876.x

He, Lingjuan; Pu, Wenjuan; Liu, Xiuxiu; Zhang, Zhenqian; Han, Maoying; Li, Yi; Huang, Xiuzhen; Han, Ximeng; Li, Yan; Liu, Kuo; Shi, Mengyang; Lai, Liang; Sun, Ruilin; Wang, Qing Dong; Ji, Yong; Tchorz, Jan S.; & Zhou, Bin. (2021). Proliferation tracing reveals regional hepatocyte generation in liver homeostasis and repair. *Science*, *371*(6532). https://doi.org/10.1126/science.abc4346

Hechst, B.; & Nussbaum, L. (1931). Beiträge zur Histopathologie der sympathischen Ganglien. *Archiv Für Psychiatrie Und Nervenkrankheiten*, *95*(1), 556–583. https://doi.org/10.1007/BF01819126

Hirsch, Etienne; Graybiel, Ann M.; & Agid, Yves A. (1988). Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. *Nature*, *334*(6180), 345–348. https://doi.org/10.1038/334345a0

Holguera, Isabel; & Desplan, Claude. (2018). Neuronal specification in space and time. *Science*, *362*(6411), 176–180. https://doi.org/10.1126/SCIENCE.AAS9435

Huang, Carol; Chan, Jennifer A.; & Schuurmans, Carol. (2014). Proneural bHLH Genes in Development and Disease. *Current Topics in Developmental Biology*, *110*, 75–127. https://doi.org/10.1016/B978-0-12-405943-6.00002-6

Hynes, Mary; & Rosenthal, Arnon. (1999). Specification of dopaminergic and serotonergic neurons in the vertebrate CNS. *Current Opinion in Neurobiology*, *9*(1), 26–36. https://doi.org/10.1016/S0959-4388(99)80004-X

Iglesias, Marta; Almuedo-Castillo, Maria; Aboobaker, A. Aziz; & Saló, Emili. (2011). Early planarian brain regeneration is independent of blastema polarity mediated by the Wnt/β-catenin pathway. *Developmental Biology*, *358*(1), 68–78. https://doi.org/10.1016/j.ydbio.2011.07.013

Iglesias, Marta; Gomez-Skarmeta, Jose Luis; Saló, Emili; & Adell, Teresa. (2008). Silencing of Smed-βcatenin1 generates radial-like hypercephalized planarians. *Development*, *135*(7), 1215–1221. https://doi.org/10.1242/DEV.020289

Iismaa, Siiri E.; Kaidonis, Xenia; Nicks, Amy M.; Bogush, Nikolay; Kikuchi, Kazu; Naqvi, Nawazish; Harvey, Richard P.; Husain, Ahsan; & Graham, Robert M. (2018). Comparative regenerative mechanisms across different mammalian tissues. *Npj Regenerative Medicine*, *3*(1), 1–20. https://doi.org/10.1038/s41536-018-0044-5

Inoue, Takeshi; Kumamoto, Hiroshi; Okamoto, Keiji; Umesono, Yoshihiko; Sakai, Masaki; Alvarado, Alejandro Sánchez; & Agata, Kiyokazu. (2004). Morphological and Functional Recovery of the Planarian Photosensing System during Head Regeneration. *Zoological Science*, *21*(3), 275–283. https://doi.org/10.2108/zsj.21.275

Iranzo, Alex; Gelpi, Ellen; Tolosa, Eduard; Molinuevo, José Luis; Serradell, Mónica; Gaig, Carles; & Santamaria, Joan. (2014). Neuropathology of prodromal Lewy body disease. *Movement Disorders*, *29*(3), 410–415. https://doi.org/10.1002/MDS.25825

Isshiki, Takako; Pearson, Bret; Holbrook, Scott; & Doe, Chris Q. (2001). Drosophila Neuroblasts Sequentially Express Transcription Factors which Specify the Temporal Identity of Their Neuronal Progeny. *Cell*, *106*(4), 511–521. https://doi.org/10.1016/S0092-8674(01)00465-2

Itoh, Motoyuki; Kudoh, Tetsuhiro; Dedekian, Michael; Kim, Cheol Hee; & Chitnis, Ajay B. (2002). A role for iro1 and iro7 in the establishment of an anteroposterior compartment of the ectoderm adjacent to the midbrain-hindbrain boundary. *Development*, *129*(10), 2317–2327. https://doi.org/10.1242/DEV.129.10.2317

Javed, Awais; Mattar, Pierre; Lu, Suying; Kruczek, Kamil; Kloc, Magdalena; Gonzalez-Cordero, Anai; Bremner, Rod; Ali, Robin R.,; & Cayouette, Michel. (2020). Pou2f1 and Pou2f2 cooperate to control the timing of cone photoreceptor production in the developing mouse retina. *Development (Cambridge, England)*, *147*(18). https://doi.org/10.1242/DEV.188730

Javed, Awais; Santos-França, Pedro L.; Mattar, Pierre; Cui, Allie; Kassem, Fatima; & Cayouette, Michel. (2023). Ikaros family proteins redundantly regulate temporal patterning in the developing mouse retina. *Development (Cambridge, England)*, *150*(2). https://doi.org/10.1242/DEV.200436

Joksimovic, Milan; Yun, Beth A.; Kittappa, Raja; Anderegg, Angela M.; Chang, Wendy W.; Taketo, Makoto M.; McKay, Ronald D. G.; & Awatramani, Rajeshwar B. (2009). Wnt antagonism of Shh facilitates midbrain floor plate neurogenesis. *Nature Neuroscience*, *12*(2), 125–131. https://doi.org/10.1038/NN.2243

Jones, D.; Lowe, V.; Graff-Radford, J.; Botha, H.; Barnard, L.; Wiepert, D.; Murphy, M. C.; Murray, M.; Senjem, M.; Gunter, J.; Wiste, H.; Boeve, B.; Knopman, D.; Petersen, R.; & Jack, C. (2022). A computational model of neurodegeneration in Alzheimer's disease. *Nature Communications*, *13*(1), 1–13. https://doi.org/10.1038/s41467-022-29047-4

Ju, Dr William. (2020). *1.4 The Somatic Nervous System*. https://pressbooks.claremont.edu/neurosciencecdn2/chapter/anatomy-physiology-the-somatic-nervous-system/

Kageyama, Ryoichiro; Ohtsuka, Toshiyuki; Shimojo, Hiromi; & Imayoshi, Itaru. (2009). Dynamic regulation of Notch signaling in neural progenitor cells. *Current Opinion in Cell Biology*, *21*(6), 733–740. https://doi.org/10.1016/j.ceb.2009.08.009

Kameda, Yoko; Saitoh, Takayoshi; & Fujimura, Takao. (2011). Hes1 regulates the number and anterior–posterior patterning of mesencephalic dopaminergic neurons at the mid/hindbrain boundary (isthmus). *Developmental Biology*, *358*(1), 91–101. https://doi.org/10.1016/J.YDBIO.2011.07.016

Katz, D. M.; Markey, K. A.; Goldstein, M.; & Black, I. B. (1983). Expression of catecholaminergic characteristics by primary sensory neurons in the normal adult rat in vivo. *Proceedings of the National Academy of Sciences of the United States of America*, *80*(11 I), 3526–3530. https://doi.org/10.1073/PNAS.80.11.3526

Khakh, Baljit S.; & Deneen, Benjamin. (2019). The Emerging Nature of Astrocyte Diversity. *Annual Review of Neuroscience*, *42*(Volume 42, 2019), 187–207. https://doi.org/10.1146/annurev-neuro-070918-050443

Kim, Hyun Jung; Sugimori, Michiya; Nakafuku, Masato; & Svendsen, Clive N. (2007). Control of neurogenesis and tyrosine hydroxylase expression in neural progenitor cells through bHLH proteins and Nurr1. *Experimental Neurology*, *203*(2), 394–405. https://doi.org/10.1016/J.EXPNEUROL.2006.08.029

Kim, Jaesang; Lo, Liching; Dormand, Emma; & Anderson, David J. (2003). SOX10 Maintains Multipotency and Inhibits Neuronal Differentiation of Neural Crest Stem Cells. *Neuron*, *38*(1), 17–31. https://doi.org/10.1016/S0896-6273(03)00163-6

Kim, Jong Hoon; Auerbach, Jonathan M.; Rodríguez-Gómez, José A.; Velasco, Iván; Gavin, Denise; Lumelsky, Nadya; Lee, Sang Hun; Nguyen, John; Sánchez-Pernaute, Rosario; Bankiewicz, Krys; & McKay, Ron. (2002). Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. *Nature*, *418*(6893), 50–56. https://doi.org/10.1038/NATURE00900,

King, Hunter O.; Owusu-Boaitey, Kwadwo E.; Fincher, Christopher T.; & Reddien, Peter W. (2024). A transcription factor atlas of stem cell fate in planarians. *Cell Reports*, *43*(3). https://doi.org/10.1016/j.celrep.2024.113843

Kirkeby, Agnete; Grealish, Shane; Wolf, Daniel A.; Nelander, Jenny; Wood, James; Lundblad, Martin; Lindvall, Olle; & Parmar, Malin. (2012). Generation of Regionally Specified Neural Progenitors and Functional Neurons from Human Embryonic Stem Cells under Defined Conditions. *Cell Reports*, *1*(6), 703–714. https://doi.org/10.1016/j.celrep.2012.04.009

Klein, Marianne O.; Battagello, Daniella S.; Cardoso, Ariel R.; Hauser, David N.; Bittencourt, Jackson C.; & Correa, Ricardo G. (2018). Dopamine: Functions, Signaling, and Association with Neurological Diseases. *Cellular and Molecular Neurobiology*, *39*(1), 31. https://doi.org/10.1007/S10571-018-0632-3

Kordower, Jeffrey H.; Chu, Yaping; Hauser, Robert A.; Freeman, Thomas B.; & Olanow, C. Warren. (2008). Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nature Medicine*, *14*(5), 504–506. https://doi.org/10.1038/nm1747

Koszła, Oliwia; & Sołek, Przemysław. (2024). Misfolding and aggregation in neurodegenerative diseases: protein quality control machinery as potential therapeutic clearance pathways. *Cell Communication and Signaling 2024 22:1*, *22*(1), 1–23. https://doi.org/10.1186/S12964-024-01791-8

Kraemer, Brian C.; Schuck, Theresa; Wheeler, Jeanna M.; Robinson, Linda C.; Trojanowski, John Q.; Lee, Virginia M. Y.; & Schellenberg, Gerard D. (2010). Loss of murine TDP-43 disrupts motor function and plays an essential role in embryogenesis. *Acta Neuropathologica*, *119*(4), 409. https://doi.org/10.1007/S00401-010-0659-0

Kriks, Sonja; Shim, Jae Won; Piao, Jinghua; Ganat, Yosif M.; Wakeman, Dustin R.; Xie, Zhong; Carrillo-Reid, Luis; Auyeung, Gordon; Antonacci, Chris; Buch, Amanda; Yang, Lichuan, Beal, M. Flint; Surmeier, D. James; Kordower, Jeffrey H.; Tabar, Viviane; & Studer, Lorenz. (2011). Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson's disease. *Nature*, *480*(7378), 547–551. https://doi.org/10.1038/NATURE10648

Krugelis MacRae, Edith. (1964). Observations on the fine structure of photoreceptor cells in the planarian Dugesia tigrina. *Journal of Ultrastructure Research*, *10*(3–4), 334–349. https://doi.org/10.1016/S0022-5320(64)80013-7

Kupsky, W. J.; Grimes, M. M.; Sweeting, J.; Bertsch, R.; & Cote, L. J. (1987). Parkinson's disease and megacolon: Concentric hyaline inclusions (lewy bodies) in enteric ganglion cells. *Neurology*, *37*(7), 1253–1255. https://doi.org/10.1212/wnl.37.7.1253

Kyrylkova, Kateryna; Kyryachenko, Sergiy; Leid, Mark; & Kioussi, Chrissa. (2012). Detection of Apoptosis by TUNEL Assay. *Methods in Molecular Biology*, *887*, 41–47. https://doi.org/10.1007/978-1-61779-860-3_5

Lapan, Sylvain W.; & Reddien, Peter W. (2011). dlx and sp6-9 Control Optic Cup Regeneration in a Prototypic Eye. *PLoS Genetics*, *7*(8), e1002226. https://doi.org/10.1371/journal.pgen.1002226

Lapan, Sylvain W.; & Reddien, Peter W. (2012a). Transcriptome analysis of the planarian eye identifies ovo as a specific regulator of eye regeneration. *Cell Reports*, *2*(2), 294. https://doi.org/10.1016/J.CELREP.2012.06.018

Lapan, Sylvain W.; & Reddien, Peter W. (2012b). Transcriptome Analysis of the Planarian Eye Identifies ovo as a Specific Regulator of Eye Regeneration. *Cell Reports*, *2*(2), 294–307. https://doi.org/10.1016/j.celrep.2012.06.018

Law, Simon W.; Conneely, Orla M.; DeMayo, Franco J.; & O'Malley, Bert W. (1992). Identification of a new brain-specific transcription factor, NURR1. *Molecular Endocrinology*, *6*(12), 2129–2135. https://doi.org/10.1210/MEND.6.12.1491694,

Le Douarin, N. M.; & Teillet, M. A. (1973). The migration of neural crest cells to the wall of the digestive tract in avian embryo. *Development*, *30*(1), 31–48. https://doi.org/10.1242/DEV.30.1.31

Le Douarin, Nicole M.; & Teillet, Marie Aimée M. (1974). Experimental analysis of the migration and differentiation of neuroblasts of the autonomic nervous system and of neurectodermal mesenchymal derivatives, using a biological cell marking technique. *Developmental Biology*, *41*(1), 162–184. https://doi.org/10.1016/0012-1606(74)90291-7

Lecaudey, Virginie; Anselme, Isabelle; Rosa, Frédéric; & Schneider-Maunoury, Sylvie. (2004). The zebrafish Iroquois gene iro7 positions the r4/r5 boundary and controls neurogenesis in the rostral hindbrain. *Development (Cambridge, England)*, *131*(13), 3121–3131. https://doi.org/10.1242/DEV.01190

Lesage, Suzanne; & Brice, Alexis. (2009). Parkinson's disease: from monogenic forms to genetic susceptibility factors. *Human Molecular Genetics*, *18*(R1), R48–R59. https://doi.org/10.1093/HMG/DDP012

Li, Jia Yi; Englund, Elisabet; Holton, Janice L.; Soulet, Denis, Hagell, Peter; Lees, Andrew J.; Lashley, Tammaryn; Quinn, Niall P.; Rehncrona, Stig; Björklund, Anders; Widner, Håkan; Revesz, Tamas; Lindvall, Olle; & Brundin, Patrik. (2008). Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nature Medicine*, *14*(5), 501–503. https://doi.org/10.1038/NM1746

Li, X.; & Noll, M. (1993). Role of the gooseberry gene in Drosophila embryos: maintenance of wingless expression by a wingless–gooseberry autoregulatory loop. *The EMBO Journal*, *12*(12), 4499–4509. https://doi.org/10.1002/j.1460-2075.1993.tb06139.x

Li, Z. S.; Pham, T. D.; Tamir, H.; Chen, J. J.; & Gershon, M. D. (2004). Enteric Dopaminergic Neurons: Definition, Developmental Lineage, and Effects of Extrinsic Denervation. *The Journal of Neuroscience*, *24*(6), 1330. https://doi.org/10.1523/JNEUROSCI.3982-03.2004

Lodato, Simona; & Arlotta, Paola. (2015). Generating Neuronal Diversity in the Mammalian Cerebral Cortex. *Annual Review of Cell and Developmental Biology*, *31*(Volume 31, 2015), 699–720. https://doi.org/10.1146/annurev-cellbio-100814-125353

Lodato, Simona; Rouaux, Caroline; Quast, Kathleen B.; Jantrachotechatchawan, Chanati; Studer, Michèle; Hensch, Takao K.; & Arlotta, Paola. (2011). Excitatory Projection Neuron Subtypes Control the Distribution of Local Inhibitory Interneurons in the Cerebral Cortex. *Neuron*, *69*(4), 763–779. https://doi.org/10.1016/j.neuron.2011.01.015

Logan, Catriona Y.; & Nusse, Roel. (2004). The Wnt signaling pathway in development and disease. *Annual Review of Cell and Developmental Biology*, *20*(Volume 20, 2004), 781–810. https://doi.org/10.1146/annurev.cellbio.20.010403.113126

Lucila Scimone, M.; Cote, Lauren E.; & Reddien, Peter W. (2017). Orthogonal muscle fibres have different instructive roles in planarian regeneration. *Nature*, *551*(7682), 623–628. https://doi.org/10.1038/NATURE24660

Luo, Wenjie; Sun, Weilin; Taldone, Tony; Rodina, Anna; & Chiosis, Gabriela. (2010). Heat shock protein 90 in neurodegenerative diseases. *Molecular Neurodegeneration*, *5*(1), 24. https://doi.org/10.1186/1750-1326-5-24

MacRae, Edith Krugelis. (1967). The fine structure of sensory receptor processes in the auricular epithelium of the planarian, Dugesia tigrina. *Zeitschrift Für Zellforschung Und Mikroskopische Anatomie*, *82*(4), 479–494. https://doi.org/10.1007/BF00337119/METRICS

Maloney, Michael T.; & Bamburg, James R. (2011). Mechanisms of neuronal growth cone guidance: an historical perspective. *Developmental Neurobiology*, *71*(9), 795. https://doi.org/10.1002/DNEU.20908

Marcos, C.; & Pachnis, V. (1996). The effect of the ret- mutation on the normal development of the central and parasympathetic nervous systems. *The International Journal of Developmental Biology*, *Suppl 1*, 137S-138S.

Marikawa, Yusuke. (2006). Wnt/β-catenin signaling and body plan formation in mouse embryos. *Seminars in Cell and Developmental Biology*, *17*(2), 175–184. https://doi.org/10.1016/j.semcdb.2006.04.003

Marlow, Heather; Matus, David Q.; & Martindale, Mark Q. (2013). Ectopic activation of the canonical wnt signaling pathway affects ectodermal patterning along the primary axis during larval development in the anthozoan Nematostella vectensis. *Developmental Biology*, *380*(2), 324–334. https://doi.org/10.1016/j.ydbio.2013.05.022

März, Martin; Seebeck, Florian; & Bartscherer, Kerstin. (2013). A pitx transcription factor controls the establishment and maintenance of the serotonergic lineage in planarians. *Development (Cambridge)*, *140*(22), 4499–4509. https://doi.org/10.1242/DEV.100081

Matsumine, Hiroto; Yamamura, Yasuhiro; Hattori, Nobutaka; Kobayashi, Tomonori; Kitada, Tohru; Yoritaka, Asako; & Mizuno, Yoshikuni. (1998). A microdeletion of D6S305 in a family of autosomal recessive juvenile parkinsonism (PARK2). *Genomics*, *49*(1), 143–146. https://doi.org/10.1006/geno.1997.5196

Mayor, Roberto; & Theveneau, Eric. (2013). The neural crest. *Development*, *140*(11), 2247–2251. https://doi.org/10.1242/DEV.091751

McKenna, Aaron; Findlay, Gregory M.; Gagnon, James A.; Horwitz, Marshall S.; Schier, Alexander F.; & Shendure, Jay. (2016). Whole-organism lineage tracing by combinatorial and cumulative genome editing. *Science*, *353*(6298). https://doi.org/10.1126/science.aaf7907

Medlock-Lanier, Taylor; Clay, Kendall B.; & Roberts-Galbraith, Rachel H. (2024). Planarian LDB and SSDP proteins scaffold transcriptional complexes for regeneration and patterning. *Developmental Biology*, *515*, 67. https://doi.org/10.1016/J.YDBIO.2024.06.021

Melamed, Eldad. (1979). Early-Morning Dystonia: A Late Side Effect of Long-term Levodopa Therapy in Parkinson's Disease. *Archives of Neurology*, *36*(5), 308–310. https://doi.org/10.1001/ARCHNEUR.1979.00500410086014

Memic, Fatima; Knoflach, Viktoria; Sadler, Rebecca; Tegerstedt, Gunilla; Sundström, Erik; Guillemot, Francois; Pachnis, Vassilis; & Marklund, Ulrika. (2016). Ascl1 Is Required for the Development of Specific Neuronal Subtypes in the Enteric Nervous System. *The Journal of Neuroscience*, *36*(15), 4339. https://doi.org/10.1523/JNEUROSCI.0202-16.2016

Mercurio, Silvia; Gattoni, Giacomo; Scarì, Giorgio; Ascagni, Miriam; Barzaghi, Benedetta; Elphick, Maurice R.; Croce, Jenifer C.; Schubert, Michael; Benito-Gutiérrez, Elia; & Pennati, Roberta. (2024). A feather star is born: embryonic development and nervous system organization in the crinoid Antedon mediterranea. *Open Biology*, *14*(8), 240115. https://doi.org/10.1098/RSOB.240115

Molina, M. Dolores; Abduljabbar, Dema; Guixeras, Anna; Fraguas, Susanna; & Cebrià, Francesc. (2023). LIM-HD transcription factors control axial patterning and specify distinct neuronal and intestinal cell identities in planarians. *Open Biology*, *13*(12), 230327. https://doi.org/10.1098/RSOB.230327

Molina, Ma Dolores; Saló, Emili; & Cebrià, Francesc. (2007). The BMP pathway is essential for re-specification and maintenance of the dorsoventral axis in regenerating and intact planarians. *Developmental Biology*, *311*(1), 79–94. https://doi.org/10.1016/j.ydbio.2007.08.019

Molinaro, Alyssa M.; & Pearson, Bret J. (2016). In silico lineage tracing through single cell transcriptomics identifies a neural stem cell population in planarians. *Genome Biology*, *17*(1), 1–17. https://doi.org/10.1186/s13059-016-0937-9

Moore, R. Y.; & Bloom, F. E. (1979). Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. *Annual Review of Neuroscience*, *2*(Volume 2, 1979), 113–168. https://doi.org/10.1146/annurev.ne.02.030179.000553

Moriarty, Niamh; Gantner, Carlos W.; Hunt, Cameron P. J.; Ermine, Charlotte M.; Frausin, Stefano; Viventi, Serena; Ovchinnikov, Dmitry A.; Kirik, Deniz; Parish, Clare L.; & Thompson, Lachlan H. (2022). A combined cell and gene therapy approach for homotopic reconstruction of midbrain dopamine pathways using human pluripotent stem cells. *Cell Stem Cell*, *29*(3), 434-448.e5. https://doi.org/10.1016/j.stem.2022.01.013

Morita, M.; Best, J. B.; & Noel, J. (1969). Electron microscopic studies of planarian regeneration. I. Fine structure of neoblasts in Dugesia dorotocephala. *Journal of Ultrastructure Research*, *27*(1), 7–23.

Muhr, Jeremy; Arbor, Tafline C.; & Ackerman, Kristin M. (2023). Embryology, Gastrulation. *StatPearls*. https://www.ncbi.nlm.nih.gov/books/NBK554394/

Nagarajan, Archana; Ning, Ye; Reisner, Kaja; Buraei, Zafir; Larsen, Jan Petter; Hobert, Oliver; & Doitsidou, Maria. (2014). Progressive degeneration of dopaminergic neurons through TRP channel-induced cell death. *Journal of Neuroscience*, *34*(17), 5738–5746. https://doi.org/10.1523/JNEUROSCI.4540-13.2014

Nambu, John R.; Franks, Robert G.; Hu, Song; & Crews, Stephen T. (1990). The single-minded gene of Drosophila is required for the expression of genes important for the development of CNS midline cells. *Cell*, *63*(1), 63–75. https://doi.org/10.1016/0092-8674(90)90288-P

Navarro, Susanna; & Ventura, Salvador. (2014). Fluorescent dye ProteoStat to detect and discriminate intracellular amyloid-like aggregates in Escherichia coli. *Biotechnology Journal*, *9*(10), 1259–1266. https://doi.org/10.1002/BIOT.201400291

Niehrs, Christof. (2010). On growth and form: A Cartesian coordinate system of Wnt and BMP signaling specifies bilaterian body axes. *Development*, *137*(6), 845–857. https://doi.org/10.1242/DEV.039651

Nishimura, K.; Kitamura, Y.; Taniguchi, T.; & Agata, K. (2010). Analysis of motor function modulated by cholinergic neurons in planarian *Dugesia japonica*. *Neuroscience*, *168*(1), 18–30. https://doi.org/10.1016/j.neuroscience.2010.03.038

Nishimura, K.; Kitamura, Y.; Umesono, Y.; Takeuchi, K.; Takata, K.; Taniguchi, T.; & Agata, K. (2008). Identification of glutamic acid decarboxylase gene and distribution of GABAergic nervous system in the planarian Dugesia japonica. *Neuroscience*, *153*(4), 1103–1114. https://doi.org/10.1016/J.NEUROSCIENCE.2008.03.026

Nishimura, Kaneyasu; Kitamura, Yoshihisa; Inoue, Takeshi; Umesono, Yoshihiko; Sano, Shozo; Yoshimoto, Kanji; Inden, Masatoshi; Takata, Kazuyuki; Taniguchi, Takashi; Shimohama, Shun; & Agata, Kiyokazu. (2007). Reconstruction of dopaminergic neural network and locomotion function in planarian regenerates. *Developmental Neurobiology*, *67*(8), 1059–1078. https://doi.org/10.1002/dneu.20377

Nishimura, Kaneyasu; Kitamura, Yoshihisa; Inoue, Takeshi; Umesono, Yoshihiko; Yoshimoto, Kanji; Takeuchi, Kosei; Taniguchi, Takashi; & Agata, Kiyokazu. (2007). Identification and distribution of tryptophan hydroxylase (TPH)-positive neurons in the planarian Dugesia japonica. *Neuroscience Research*, *59*(1), 101–106. https://doi.org/10.1016/J.NEURES.2007.05.014

Nishimura, Kaneyasu; Kitamura, Yoshihisa; Inoue, Takeshi; Umesono, Yoshihiko; Yoshimoto, Kanji; Taniguchi, Takashi; & Agata, Kiyokazu. (2008). Characterization of tyramine β-hydroxylase in planarian Dugesia japonica: Cloning and expression. *Neurochemistry International*, *53*(6–8), 184–192. https://doi.org/10.1016/j.neuint.2008.09.006

Nobili, Annalisa; Latagliata, Emanuele Claudio; Viscomi, Maria Teresa; Cavallucci, Virve; Cutuli, Debora; Giacovazzo, Giacomo; Krashia, Paraskevi; Rizzo, Francesca Romana; Marino, Ramona; Federici, Mauro; De Bartolo, Paola; Aversa, Daniela; Dell'Acqua, Maria Concetta; Cordella, Alberto; Sancandi, Marco; Keller, Flavio; Petrosini, Laura; Puglisi-Allegra, Stefano; Mercuri, Nicola Biagio; ... D'Amelio, Marcello. (2017). Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer's disease. *Nature Communications 2017 8:1*, *8*(1), 1–14. https://doi.org/10.1038/ncomms14727

Oberheim, Nancy Ann; Goldman, Steven A.; & Nedergaard, Maiken. (2012). Heterogeneity of astrocytic form and function. *Methods in Molecular Biology*, *814*, 23–45. https://doi.org/10.1007/978-1-61779-452-0_3

Ogawa, Kazuya; Ishihara, Shogo; Saito, Yumi; Mineta, Katsuhiko; Nakazawa, Masum;, Ikeo, Kazuho; Gojobori, Takashi; Watanabe, Kenji; & Agata, Kiyokazu. (2002). Induction of a noggin-Like Gene by Ectopic DV Interaction during Planarian Regeneration. *Developmental Biology*, *250*(1), 59–70. https://doi.org/10.1006/DBIO.2002.0790

Olanow, C. Warren; Goetz, Christopher G.; Kordower, Jeffrey H.; Stoessl, A. Jon; Sossi, Vesna; Brin, Mitchell F.; Shannon, Kathleen M.; Nauert, G. Michael; Perl, Daniel P.; Godbold, James; & Freeman, Thomas B. (2003). A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Annals of Neurology*, *54*(3), 403–414. https://doi.org/10.1002/ANA.10720,

Ong, Ta Hsuan; Romanova, Elena V.; Roberts-Galbraith, Rachel H.; Yang, Ning; Zimmerman, Tyler A.; Collins, James J.; Lee, Ji Eun; Kelleher, Neil L.; Newmark, Phillip A.; & Sweedler, Jonathan V. (2016). Mass spectrometry imaging and identification of peptides associated with cephalic ganglia regeneration in Schmidtea mediterranea. *Journal of Biological Chemistry*, *291*(15), 8109–8120. https://doi.org/10.1074/jbc.M115.709196

Ono, Yuichi; Nakatani, Tomoya; Minaki, Yasuko; & Kumai, Minoru. (2010). The basic helix-loop-helix transcription factor Nato3 controls neurogenic activity in mesencephalic floor plate cells. *Development*, *137*(11), 1897–1906. https://doi.org/10.1242/DEV.042572

Ono, Yuichi; Nakatani, Tomoya; Sakamoto, Yoshimasa; Mizuhara, Eri; Minaki, Yasuko; Kumai, Minoru; Hamaguchi, Akiko; Nishimura, Miyuki; Inoue, Yoko; Hayashi, Hideki; Takahashi, Jun; & Imai, Toshio. (2007). Differences in neurogenic potential in floor plate cells along an anteroposterior location: Midbrain dopaminergic neurons originate from mesencephalic floor plate cells. *Development*, *134*(17), 3213–3225. https://doi.org/10.1242/DEV.02879

Orii, Hidefumi; Kato, Kentaro; Agata, Kiyokazu; & Watanabe, Kenji. (1998). Molecular Cloning of Bone Morphogenetic Protein (BMP) Gene from the Planarian *Dugesia japonica*. *Https://Doi.Org/10.2108/Zsj.15.871*, *15*(6), 871–877. https://doi.org/10.2108/ZSJ.15.871

Orii, Hidefumi; & Watanabe, Kenji. (2007). Bone morphogenetic protein is required for dorso-ventral patterning in the planarian *Dugesia japonica*. *Development Growth and Differentiation*, *49*(4), 345–349. https://doi.org/10.1111/J.1440-169X.2007.00931.X,

Paisán-Ruíz, Coro; Jain, Shushant; Evans, E. Whitney; Gilks, William P.; Simón, Javier; Van Der Brug, Marcel; De Munain, Adolfo López; Aparicio, Silvia; Gil, Angel Martínez; Khan, Naheed; Johnson, Janel; Martinez, Javier Ruiz; Nicholl, David; Carrera, Itxaso Marti; Peňa, Amets Saénz; De Silva, Rohan; Lees, Andrew; Martí-Massó, José Félix; Pérez-Tur, Jordi; ... Singleton, Andrew B. (2004). Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron*, *44*(4), 595–600. https://doi.org/10.1016/j.neuron.2004.10.023

Parkinson, James. (2002). An Essay on the Shaking Palsy. https://doi.org/10.1176/JNP.14.2.223

Pattyn, Alexandre; Morin, Xavier; Cremer, Harold; Goridis, Christo; & Brunet, Jean François. (1999). The homeobox gene Phox2b is essential for the development of autonomic neural crest derivatives. *Nature*, *399*(6734), 366–370. https://doi.org/10.1038/20700

Pearse, A. G. (1969). The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept. *The Journal of Histochemistry and Cytochemistry : Official Journal of the Histochemistry Society*, *17*(5), 303–313. https://doi.org/10.1177/17.5.303

Pérez-Ferrer, Isabel; & Herrera, Eloísa. (2025). Novel insights into the mechanisms of growth cone dynamics during axon pathfinding. *Current Opinion in Neurobiology*, *93*, 103073. https://doi.org/10.1016/J.CONB.2025.103073

Petersen, Christian P.; & Reddien, Peter W. (2008). Smed-βcatenin-1 is required for anteroposterior blastema polarity in planarian regeneration. *Science*, *319*(5861), 327–330. https://doi.org/10.1126/science.1149943

Pla, Ramón; Borrell, Víctor; Flames, Nuria; & Marín, Oscar. (2006). Layer Acquisition by Cortical GABAergic Interneurons Is Independent of Reelin Signaling. *Journal of Neuroscience*, *26*(26), 6924–6934. https://doi.org/10.1523/JNEUROSCI.0245-06.2006

Poliak, Sebastian; Norovich, Amy L.; Yamagata, Masahito; Sanes, Joshua R.; & Jessell, Thomas M. (2016). Muscle-type Identity of Proprioceptors Specified by Spatially Restricted Signals from Limb Mesenchyme. *Cell*, *164*(3), 512–525. https://doi.org/10.1016/j.cell.2015.12.049

Polymeropoulos, Mihael H.; Lavedan, Christian; Leroy, Elisabeth; Ide, Susan E.; Dehejia, Anindya; Dutra, Amalia; Pike, Brian; Root, Holly; Rubenstein, Jeffrey; Boyer, Rebecca; Stenroos, Edward S.; Chandrasekharappa, Settara; Athanassiadou, Aglaia; Papapetropoulos, Theodore; Johnson, William G.; Lazzarini, Alice M.; Duvoisin, Roger C.; Di Iorio, Giuseppe; Golbe, Lawrence I.; & Nussbaum, Robert L. (1997). Mutation in the α-synuclein gene identified in families with Parkinson's disease. *Science*, *276*(5321), 2045–2047. https://doi.org/10.1126/SCIENCE.276.5321.2045

Pouchelon, Gabrielle; Gambino, Frédéric; Bellone, Camilla; Telley, Ludovic; Vitali, Ilaria; Lüscher, Christian; Holtmaat, Anthony; & Jabaudon, Denis. (2014). Modality-specific thalamocortical inputs instruct the identity of postsynaptic L4 neurons. *Nature 2014 511:7510*, *511*(7510), 471–474. https://doi.org/10.1038/nature13390

Powell, Lynn M.; & Jarman, Andrew P. (2008). Context dependence of proneural bHLH proteins. *Current Opinion in Genetics & Development*, *18*(5), 411. https://doi.org/10.1016/J.GDE.2008.07.012

Purves, Dale; Augustine, George J.; Fitzpatrick, David; Katz, Lawrence C.; LaMantia, Anthony-Samuel; McNamara, James O.; & Williams, S. Mark. (2001a). *The Enteric Nervous System*. https://www.ncbi.nlm.nih.gov/books/NBK11097/

Purves, Dale; Augustine, George J.; Fitzpatrick, David; Katz, Lawrence C.; LaMantia, Anthony-Samuel; McNamara, James O.; & Williams, S. Mark. (2001b). *The Initial Formation of the Nervous System: Gastrulation and Neurulation*. https://www.ncbi.nlm.nih.gov/books/NBK10993/

Qi, Cai; Luo, Li Da; Feng, Irena; & Ma, Shaojie. (2022). Molecular mechanisms of synaptogenesis. *Frontiers in Synaptic Neuroscience*, *14*, 939793. https://doi.org/10.3389/FNSYN.2022.939793

Qualman, S. J.; Haupt, H. M.; Yang, P.; & Hamilton, S. R. (1984). Esophageal Lewy bodies associated with ganglion cell loss in achalasia. Similarity to Parkinson's disease. *Gastroenterology*, *87*(4), 848–856.

Quan, X. J.; & Hassan, B. A. (2005). From skin to nerve: flies, vertebrates and the first helix. *Cellular and Molecular Life Sciences: CMLS*, *62*(18), 2036. https://doi.org/10.1007/S00018-005-5124-1

Que, Lin; Winterer, Jochen; & Földy, Csaba. (2019). Deep survey of GABAergic interneurons: Emerging insights from gene-isoform transcriptomics. *Frontiers in Molecular Neuroscience*, *12*, 459023. https://doi.org/10.3389/fnmol.2019.00115

Raisman-Vozari, Rita; Hirsch, Etienne; Javoy-Agid, France; Vassort, Cecile; Savasta, Marc; Feuerstein, Claude; Thibault, Jean; & Agid, Yves. (1991). Quantitative Autoradiography of Tyrosine Hydroxylase Immunoreactivity in the Rat Brain. *Journal of Neurochemistry*, *57*(4), 1212–1222. https://doi.org/10.1111/J.1471-4159.1991.TB08282.X

Raj, Bushra; Wagner, Daniel E.; McKenna, Aaron; Pandey, Shristi; Klein, Allon M.; Shendure, Jay; Gagnon, James A.; & Schier, Alexander F. (2018). Simultaneous single-cell profiling of lineages and cell types in the vertebrate brain. *Nature Biotechnology 2018 36:5*, *36*(5), 442–450. https://doi.org/10.1038/nbt.4103

Rangel-Barajas, Claudia; Coronel, Israel; & Florán, Benjamín. (2015). Dopamine receptors and neurodegeneration. *Aging and Disease*, *6*(5), 349–368. https://doi.org/10.14336/AD.2015.0330

Rasband, Matthew N. (2015). Glial Contributions to Neural Function and Disease. *Molecular & Cellular Proteomics : MCP*, *15*(2), 355. https://doi.org/10.1074/MCP.R115.053744

Raz, Amelie A.; Wurtzel, Omri; & Reddien, Peter W. (2021). Planarian stem cells specify fate yet retain potency during the cell cycle. *Cell Stem Cell*, *28*(7), 1307-1322.e5. https://doi.org/10.1016/j.stem.2021.03.021

Reddien, Peter W. (2018). The Cellular and Molecular Basis for Planarian Regeneration. *Cell*, *175*(2), 327–345. https://doi.org/10.1016/j.cell.2018.09.021

Reddien, Peter W.; Bermange, Adam L.; Kicza, Adrienne M.; & Sánchez Alvarado, Alejandro. (2007). BMP signaling regulates the dorsal planarian midline and is needed for asymmetric regeneration. *Development*, *134*(22), 4043–4051. https://doi.org/10.1242/dev.007138

Reddien, Peter W.; Oviedo, Néstor J.; Jennings, Joya R.; Jenkin, James C.; & Sánchez Alvarado, Alejandro. (2005). Developmental biology: SMEDWI-2 is a PIWI-like protein that regulates planarian stem cells. *Science*, *310*(5752), 1327–1330. https://doi.org/10.1126/SCIENCE.1116110

Reddien, Peter W.; & Sánchez Alvarado, Alejandro. (2004). Fundamentals of planarian regeneration. *Annual Review of Cell and Developmental Biology*, *20*, 725–757. https://doi.org/10.1146/annurev.cellbio.20.010403.095114

Richter, Sandra; Hartmann, Beate; & Reichert, Heinrich. (1998). The wingless gene is required for embryonic brain development in Drosophila. *Development Genes and Evolution*, *208*(1), 37–45. https://doi.org/10.1007/S004270050151

Rink, Jochen C.; Vu, Hanh Thi Kim; & Alvarado, Alejandro Sánchez. (2011). The maintenance and regeneration of the planarian excretory system are regulated by EGFR signaling. *Development*, *138*(17), 3769–3780. https://doi.org/10.1242/DEV.066852/-/DC1

Roberts-Galbraith, Rachel H.; & Newmark, Phillip A. (2015). On the organ trail: insights into organ regeneration in the planarian. *Current Opinion in Genetics & Development*, *32*, 37–46. https://doi.org/10.1016/j.gde.2015.01.009

Rosenthal, Arnon. (1997). Specification and Survival of Dopaminergic Neurons in the Mammalian Midbrain. *Advances in Pharmacology*, *42*(C), 908–911. https://doi.org/10.1016/S1054-3589(08)60894-7

Ross, Kelly G.; Currie, Ko W.; Pearson, Bret J.; & Zayas, Ricardo M. (2017). Nervous system development and regeneration in freshwater planarians. *Wiley Interdisciplinary Reviews: Developmental Biology*, *6*(3). https://doi.org/10.1002/wdev.266

Rowlatt, Ursula. (1979). Intrauterine wound healing in a 20 week human fetus. *Virchows Archiv A Pathological Anatomy and Histology*, *381*(3), 353–361. https://doi.org/10.1007/BF00432477

Sagner, Andreas; & Briscoe, James. (2019). Establishing neuronal diversity in the spinal cord: A time and a place. *Development (Cambridge)*, *146*(22). https://doi.org/10.1242/DEV.182154/223189

Sakai, Jill. (2020). How synaptic pruning shapes neural wiring during development and, possibly, in disease. *Proceedings of the National Academy of Sciences*, *117*(28), 16096–16099. https://doi.org/10.1073/PNAS.2010281117

Salat, David; & Tolosa, Eduardo. (2013). Levodopa in the Treatment of Parkinson's Disease: Current Status and New Developments. *Journal of Parkinson's Disease*, *3*(3), 255–269. https://doi.org/10.3233/JPD-130186

Saló, E.; & Baguñà, J. (1984). Regeneration and pattern formation in planarians. I. The pattern of mitosis in anterior and posterior regeneration in Dugesia (G) tigrina, and a new proposal for blastema formation. *Journal of Embryology and Experimental Morphology*, *83*, 63–80.

Sánchez-Pernaute, Rosario; Studer, Lorenz; Bankiewicz, Krys S.; Major, Eugene O.; & McKay, Ronald D. G. (2001). In vitro generation and transplantation of precursor-derived human dopamine neurons. *Journal of Neuroscience Research*, *65*(4), 284–288. https://doi.org/10.1002/JNR.1152

Sasai, Y. (2001). Roles of Sox factors in neural determination: conserved signaling in evolution? *The International Journal of Developmental Biology*, *45*(1), 321–326.

Satapathy, Sandeep; & Wilson, Mark R. (2022). Roles of constitutively secreted extracellular chaperones in neuronal cell repair and regeneration. *Neural Regeneration Research*, *18*(4), 769. https://doi.org/10.4103/1673-5374.353483

Sawamoto, Nobukatsu; Doi, Daisuke; Nakanishi, Etsuro; Sawamura, Masanori; Kikuchi, Takayuki; Yamakado, Hodaka; Taruno, Yosuke; Shima, Atsushi; Fushimi, Yasutaka; Okada, Tomohisa; Kikuchi, Tetsuhiro; Morizane, Asuka; Hiramatsu, Satoe; Anazawa, Takayuki; Shindo, Takero; Ueno, Kentaro; Morita, Satoshi; Arakawa, Yoshiki; Nakamoto, Yuji; ... Takahashi, Jun. (2025). Phase I/II trial of iPS-cell-derived dopaminergic cells for Parkinson's disease. *Nature 2025 641:8064*, *641*(8064), 971–977. https://doi.org/10.1038/s41586-025-08700-0

Schier, Alexander F.; & Talbot, William S. (2005). Molecular genetics of axis formation in zebrafish. *Annual Review of Genetics*, *39*(Volume 39, 2005), 561–613. https://doi.org/10.1146/annurev.genet.37.110801.143752

Scimone, M. Lucila; Srivastava, Mansi; Bell, George W.; & Reddien, Peter W. (2011). A regulatory program for excretory system regeneration in planarians. *Development*, *138*(20), 4387–4398. https://doi.org/10.1242/DEV.068098

Scimone, M. Lucila; Wurtzel, Omri; Malecek, Kathryn; Fincher, Christopher T.; Oderberg, Isaac M.; Kravarik, Kellie M.; & Reddien, Peter W. (2018). foxF-1 Controls Specification of Non-body Wall Muscle and Phagocytic Cells in Planarians. *Current Biology*, *28*(23), 3787-3801.e6. https://doi.org/10.1016/J.CUB.2018.10.030

Sethi, Kapil D. (2010). The impact of levodopa on quality of life in patients with Parkinson disease. *Neurologist*, *16*(2), 76–83. https://doi.org/10.1097/NRL.0B013E3181BE6D15

Sharma, Aditi; Shah, Om Prakash; Sharma, Lalit; Gulati, Monica; Behl, Tapan; Khalid, Asaad; Mohan, Syam; Najmi, Asim; & Zoghebi, Khalid. (2024). Molecular Chaperones as Therapeutic Target: Hallmark of Neurodegenerative Disorders. *Molecular Neurobiology*, *61*(7), 4750–4767. https://doi.org/10.1007/S12035-023-03846-2

Shusharina, Natalia; Yukhnenko, Denis; Botman, Stepan; Sapunov, Viktor; Savinov, Vladimir; Kamyshov, Gleb; Sayapin, Dmitry; & Voznyuk, Igor. (2023). Modern Methods of Diagnostics and Treatment of Neurodegenerative Diseases and Depression. *Diagnostics*, *13*(3), 573. https://doi.org/10.3390/DIAGNOSTICS13030573

Sidransky, E.; Nalls, M. A.; Aasly, J. O.; Aharon-Peretz, J.; Annesi, G.; Barbosa, E. R.; Bar-Shira, A.; Berg, D.; Bras, J.; Brice, A.; Chen, C. M.; Clark, L. N.; Condroyer, C.; De Marco, E. V.; Dürr, A.; Eblan, M. J.; Fahn, S.; Farrer, M. J.; Fung, H. C.; ... Ziegler, S. G. (2009). Multicenter Analysis of Glucocerebrosidase Mutations in Parkinson's Disease. *New England Journal of Medicine*, *361*(17), 1651–1661. https://doi.org/10.1056/NEJMOA0901281

Sidransky, Ellen; & Lopez, Grisel. (2012). The link between the GBA gene and parkinsonism. *The Lancet Neurology*, *11*(11), 986–998. https://doi.org/10.1016/S1474-4422(12)70190-4

Siehr, Meagan S.; Koo, Pamela K.; Sherlekar, Amrita L.; Bian, Xuelin; Bunkers, Meredith R.; Miller, Renee M.; Portman, Douglas S.; & Lints, Robyn. (2011). Multiple doublesex-related genes specify critical cell fates in a C. elegans male neural circuit. *PLoS ONE*, *6*(10). https://doi.org/10.1371/JOURNAL.PONE.0026811

Siletti, Kimberly; Hodge, Rebecca; Mossi Albiach, Alejandro; Lee, Ka Wai; Ding, Song Lin; Hu, Lijuan; Lönnerberg, Peter; Bakken, Trygve; Casper, Tamara; Clark, Michael; Dee, Nick; Gloe, Jessica; Hirschstein, Daniel; Shapovalova, Nadiya V.; Dirk Keene, C.; Nyhus, Julie; Tung, Herman; Yanny, Anna Marie; Arenas, Ernest; … Linnarsson, Sten. (2023). Transcriptomic diversity of cell types across the adult human brain. *Science*, *382*(6667). https://doi.org/10.1126/SCIENCE.ADD7046

Silvin, Aymeric; & Ginhoux, Florent. (2018). Microglia heterogeneity along a spatio–temporal axis: More questions than answers. *Glia*, *66*(10), 2045–2057. https://doi.org/10.1002/GLIA.23458

Sinigaglia, Chiara; Busengdal, Henriette; Leclère, Lucas; Technau, Ulrich; & Rentzsch, Fabian. (2013). The Bilaterian Head Patterning Gene six3/6 Controls Aboral Domain Development in a Cnidarian. *PLOS Biology*, *11*(2), e1001488. https://doi.org/10.1371/JOURNAL.PBIO.1001488

Skeath, James B.; Zhang, Yu; Holmgren, Robert; Carroll, Sean B.; & Doe, Chris Q. (1995). Specification of neuroblast identity in the drosophila embryonic central nervous system by gooseberry-distal. *Nature*, *376*(6539), 427–430. https://doi.org/10.1038/376427a0

Smidt, Marten P.; Asbreuk, Ceriel H. J.; Cox, Joke J.; Chen, Haixu; Johnson, Randy L.; & Burbach, J. Peter H. (2000). A second independent pathway for development of mesencephalic dopaminergic neurons requires Lmx1b. *Nature Neuroscience*, *3*(4), 337–341. https://doi.org/10.1038/73902

Smith, Heather L.; Li, Wenwen; & Cheetham, Michael E. (2015). Molecular chaperones and neuronal proteostasis. *Seminars in Cell & Developmental Biology*, *40*, 142. https://doi.org/10.1016/J.SEMCDB.2015.03.003

Smith, William C.; & Harland, Richard M. (1992). Expression cloning of noggin, a new dorsalizing factor localized to the Spemann organizer in Xenopus embryos. *Cell*, *70*(5), 829–840. https://doi.org/10.1016/0092-8674(92)90316-5

Sonntag, Kai-Christian; Pruszak, Jan; Yoshizaki, Takahito; van Arensbergen, Joris; Sanchez-Pernaute, Rosario; & Isacson, Ole. (2007). Enhanced Yield of Neuroepithelial Precursors and Midbrain-Like Dopaminergic Neurons from Human Embryonic Stem Cells Using the Bone Morphogenic Protein Antagonist Noggin. *Stem Cells*, *25*(2), 411–418. https://doi.org/10.1634/STEMCELLS.2006-0380

Sousa, Sara C.; & Sousa, Mónica M. (2021). The cytoskeleton as a modulator of tension driven axon elongation. *Developmental Neurobiology*, *81*(3), 300–309. https://doi.org/10.1002/DNEU.22747

Sreedharan, Jemeen; Blair, Ian P.; Tripathi, Vineeta B.; Hu, Xun; Vance, Caroline; Rogelj, Boris; Ackerley, Steven; Durnall, Jennifer C.; Williams, Kelly L.; Buratti, Emanuele; Baralle, Francisco; De Belleroche, Jacqueline; Mitchell, J. Douglas; Leigh, P. Nigel; Al-Chalabi, Ammar; Miller, Christopher C.; Nicholson, Garth; & Shaw, Christopher E. (2008). TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science (New York, N.Y.)*, *319*(5870), 1668–1672. https://doi.org/10.1126/SCIENCE.1154584

Srinivasan, E.; Chandrasekhar, G.; Chandrasekar, P.; Anbarasu, K.; Vickram, A. S.; Karunakaran, Rohini; Rajasekaran, R.; & Srikumar, P. S. (2021). Alpha-Synuclein Aggregation in Parkinson's Disease. *Frontiers in Medicine*, *8*, 736978. https://doi.org/10.3389/FMED.2021.736978

Storer, Mekayla A.; & Miller, Freda D. (2020). Cellular and molecular mechanisms that regulate mammalian digit tip regeneration: Mechanisms of Digit Tip Regeneration. *Open Biology*, *10*(9). https://doi.org/10.1098/RSOB.200194/

Stratoulias, Vassilis; Venero, Jose Luis; Tremblay, Marie-Ève; & Joseph, Bertrand. (2019). Microglial subtypes: diversity within the microglial community. *The EMBO Journal*, *38*(17). https://doi.org/10.15252/EMBJ.2019101997

Sugino, Ken; Clark, Erin; Schulmann, Anton; Shima, Yasuyuki; Wang, Lihua; Hunt, David L.; Hooks, Bryan M.; Nkner, Dimitri Tra¨; Chandrashekar, Jayaram; Picard, Serge; Lemire, Andrew L.; Spruston, Nelson; Hantman, Adam W.; & Nelson, Sacha B. (2019). Mapping the transcriptional diversity of genetically and anatomically defined cell populations in the mouse brain. *ELife*, *8*. https://doi.org/10.7554/ELIFE.38619

Suk, Terry R.; & Rousseaux, Maxime W. C. (2020). The role of TDP-43 mislocalization in amyotrophic lateral sclerosis. *Molecular Neurodegeneration*, *15*(1), 1–16. https://doi.org/10.1186/s13024-020-00397-1

Sulston, J.; Dew, M.; & Brenner, S. (1975). Dopaminergic neurons in the nematode Caenorhabditis elegans. *Journal of Comparative Neurology*, *163*(2), 215–226. https://doi.org/10.1002/CNE.901630207

Sulston, J. E. & Horvitz, H. R. (1977). Post-embryonic cell lineages of the nematode, Caenorhabditis elegans. *Developmental Biology*, *56*(1), 110–156. https://doi.org/10.1016/0012-1606(77)90158-0

Sulston, J. E.; Schierenberg, E.; White, J. G.; & Thomson, J. N. (1983). The embryonic cell lineage of the nematode Caenorhabditis elegans. *Developmental Biology*, *100*(1), 64–119. https://doi.org/10.1016/0012-1606(83)90201-4

Sweeney, Patrick; Park, Hyunsun; Baumann, Marc; Dunlop, John; Frydman, Judith; Kopito, Ron; McCampbell, Alexander; Leblanc, Gabrielle; Venkateswaran, Anjli; Nurmi, Antti; & Hodgson, Robert. (2017). Protein misfolding in neurodegenerative diseases: implications and strategies. *Translational Neurodegeneration*, *6*(1), 6. https://doi.org/10.1186/S40035-017-0077-5

Tabar, V.;, Sarva, H.; Lozano, A. M.; Fasano, A.; Kalia, S. K.; Yu, K. K. H.; Brennan, C.; Ma, Y.; Peng, S.; Eidelberg, D.; Tomishima, M.; Irion, S.; Stemple, W.; Abid, N.; Lampron, A.; Studer, L.; & Henchcliffe, C. (2025). Phase I trial of hES cell-derived dopaminergic neurons for Parkinson's disease. *Nature*, *641*(8064), 978–983. https://doi.org/10.1038/s41586-025-08845-y

Takahashi, Kazutoshi; Tanabe, Koji; Ohnuki, Mari; Narita, Megumi; Ichisaka, Tomoko; Tomoda, Kiichiro; & Yamanaka, Shinya. (2007). Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell*, *131*(5), 861–872. https://doi.org/10.1016/j.cell.2007.11.019

Takeda, Hiroyuki; Nishimura, Kaneyasu; & Agata, Kiyokazu. (2009). Planarians maintain a constant ratio of different cell types during changes in body size by using the stem cell system. *Zoological Science*, *26*(12), 805–813. https://doi.org/10.2108/ZSJ.26.805

Takeo, Makoto; Lee, Wendy; & Ito, Mayumi. (2015). Wound Healing and Skin Regeneration. *Cold Spring Harbor Perspectives in Medicine*, *5*(1), a023267. https://doi.org/10.1101/CSHPERSPECT.A023267

Tan, Yun Long; Yuan, Yi; & Tian, Li. (2020). Microglial regional heterogeneity and its role in the brain. *Molecular Psychiatry*, *25*(2), 351–367. https://doi.org/10.1038/s41380-019-0609-8

Tanaka, Elly M.; & Reddien, Peter W. (2011). The cellular basis for animal regeneration. *Developmental Cell*, *21*(1), 172. https://doi.org/10.1016/J.DEVCEL.2011.06.016

Taraviras, Stavros; Marcos-Gutierrez, Camelia V.; Durbec, Pascale; Jani, Harsha; Grigoriou, Maria; Sukumaran, Madhu; Wang, Li Chong; Hynes, Mary; Raisman, Geoffrey; & Pachnis, Vassilis. (1999). Signalling by the RET receptor tyrosine kinase and its role in the development of the mammalian enteric nervous system. *Development*, *126*(12), 2785–2797. https://doi.org/10.1242/DEV.126.12.2785

Taverna, Elena; Götz, Magdalena; & Huttner, Wieland B. (2014). The cell biology of neurogenesis: toward an understanding of the development and evolution of the neocortex. *Annual Review of Cell and Developmental Biology*, *30*(Volume 30, 2014), 465–502. https://doi.org/10.1146/annurev-cellbio-101011-155801

Telley, L.; Agirman, G.; Prados, J.; Amberg, N.; Fièvre, S.; Oberst, P.; Bartolini, G.; Vitali, I.; Cadilhac, C.; Hippenmeyer, S.; Nguyen, L.; Dayer, A.; & Jabaudon, D. (2019). Temporal patterning of apical progenitors and their daughter neurons in the developing neocortex. *Science*, *364*(6440). https://doi.org/10.1126/science.aav2522

Thomson, James A. (1998). Embryonic stem cell lines derived from human blastocysts. *Science*, *282*(5391), 1145–1147. https://doi.org/10.1126/SCIENCE.282.5391.1145,

Tolosa, Eduardo S.; Martin, William E.; Cohen, Harold P.; & Jacobson, Ronald L. (1975). Patterns of clinical response and plasma dopa levels in parkinson's disease. *Neurology*, *25*(2), 177–183. https://doi.org/10.1212/WNL.25.2.177

Trevisan, L.; Gaudio, A.; Monfrini, E.; Avanzino, L.; Di Fonzo, A.; & Mandich, P. (2024). Genetics in Parkinson's disease, state-of-the-art and future perspectives. *British Medical Bulletin*, *149*(1), 60. https://doi.org/10.1093/BMB/LDAD035

Tu, Kimberly C.; Cheng, Li Chun; Vu, Hanh T. K.; Lange, Jeffrey J.; McKinney, Sean A.; Seidel, Chris W.; & Sánchez Alvarado, Alejandro. (2015). Egr-5 is a post-mitotic regulator of planarian epidermal differentiation. *ELife*, *4*(OCTOBER2015), e10501. https://doi.org/10.7554/ELIFE.10501

Ulvklo, Carina; MacDonald, Ryan; Bivik, Caroline; Baumgardt, Magnus; Karlsson, Daniel; & Thor, Stefan. (2012). Control of neuronal cell fate and number by integration of distinct daughter cell proliferation modes with temporal progression. *Development*, *139*(4), 678–689. https://doi.org/10.1242/DEV.074500

Umesono, Yoshihiko; & Agata, Kiyokazu. (2009). Evolution and regeneration of the planarian central nervous system. *Development, Growth & Differentiation*, *51*(3), 185–195. https://doi.org/10.1111/J.1440-169X.2009.01099.X

Ungerstedt, U.; Ljungberg, T.; & Steg, G. (1974). Behavioral, physiological, and neurochemical changes after 6-hydroxydopamine-induced degeneration of the nigro-striatal dopamine neurons. *Advances in Neurology*, *5*, 421–426.

Valadez-Barba, Valeria; Cota-Coronado, A.; Hernández-Pérez, O. R.; Lugo-Fabres, Pavel H.; Padilla-Camberos, Eduardo; Díaz, Néstor Fabián; & Díaz-Martínez, N. Emmanuel. (2020). iPSC for modeling neurodegenerative disorders. *Regenerative Therapy*, *15*, 332–339. https://doi.org/10.1016/J.RETH.2020.11.006

van Wolfswinkel, Josien C.; Wagner, Daniel E.; & Reddien, Peter W. (2014). Single-Cell Analysis Reveals Functionally Distinct Classes within the Planarian Stem Cell Compartment. *Cell Stem Cell*, *15*(3), 326–339. https://doi.org/10.1016/J.STEM.2014.06.007

Varadarajan, Supraja G.; Hunyara, John L.; Hamilton, Natalie R.; Kolodkin, Alex L.; & Huberman, Andrew D. (2022). Central nervous system regeneration. *Cell*, *185*(1), 77–94. https://doi.org/10.1016/J.CELL.2021.10.029

Wagner, Daniel E.; Wang, Irving E.; & Reddien, Peter W. (2011). Clonogenic Neoblasts Are Pluripotent Adult Stem Cells That Underlie Planarian Regeneration. *Science*, *332*(6031), 811–816. https://doi.org/10.1126/science.1203983

Wahbe, F.; Hagege, J.; Loreau, N.; & Ardaillou, R. (1982). Endogenous dopamine synthesis and DOPA-decarboxylase activity in rat renal cortex. *Molecular and Cellular Endocrinology*, *27*(1), 45–54. https://doi.org/10.1016/0303-7207(82)90061-2

Wakabayashi, K.; Takahashi, H.; Takeda, S.; Ohama, E.; & Ikuta, F. (1988). Parkinson's disease: the presence of Lewy bodies in Auerbach's and Meissner's plexuses. *Acta Neuropathologica*, *76*(3), 217–221. https://doi.org/10.1007/BF00687767

Walkers, R. J.; & Holden-Dye, Lindy. (1989). Commentary on the evolution of transmitters, receptors and ion channels in invertebrates. *Comparative Biochemistry and Physiology — Part A: Physiology*, *93*(1), 25–39. https://doi.org/10.1016/0300-9629(89)90188-6

Wang, Irving E.; Lapan, Sylvain W.; Scimone, M. Lucila; Clandinin, Thomas R.; & Reddien, Peter W. (2016). Hedgehog signaling regulates gene expression in planarian glia. *ELife*, *5*(September2016). https://doi.org/10.7554/ELIFE.16996

Watanabe, Hiroshi; Fujisawa, Toshitaka; & Holstein, Thomas W. (2009). Cnidarians and the evolutionary origin of the nervous system. *Development, Growth & Differentiation*, *51*(3), 167–183. https://doi.org/10.1111/J.1440-169X.2009.01103.X

Watanabe, Hiroshi; Hoang, Van Thanh; Mättner, Robert; & Holstein, Thomas W. (2009). Immortality and the base of multicellular life: Lessons from cnidarian stem cells. *Seminars in Cell & Developmental Biology*, *20*(9), 1114–1125. https://doi.org/10.1016/J.SEMCDB.2009.09.008

Watanabe, Yuli; Stanchina, Laure; Lecerf, Laure; Gacem, Nadjet; Conidi, Andrea; Baral, Viviane; Pingault, Veronique; Huylebroeck, Danny; & Bondurand, Nadege. (2017). Differentiation of Mouse Enteric Nervous System Progenitor Cells Is Controlled by Endothelin 3 and Requires Regulation of Ednrb by SOX10 and ZEB2. *Gastroenterology*, *152*(5), 1139-1150.e4. https://doi.org/10.1053/J.GASTRO.2016.12.034

Wei, Yonglong; Wang, Yunguan G.; Jia, Yuemeng; Li, Lin; Yoon, Jung; Zhang, Shuyuan; Wang, Zixi; Zhang, Yu; Zhu, Min; Sharma, Tripti; Lin, Yu Hsuan; Hsieh, Meng Hsiung;, Albrecht, Jeffrey H.; Le, Phuong T.; Rosen, Clifford J.; Wang, Tao; & Zhu, Hao. (2021). Liver homeostasis is maintained by midlobular zone 2 hepatocytes. *Science*, *371*(6532). https://doi.org/10.1126/science.abb1625

Wenemoser, Danielle; & Reddien, Peter W. (2010). Planarian regeneration involves distinct stem cell responses to wounds and tissue absence. *Developmental Biology*, *344*(2), 979–991. https://doi.org/10.1016/j.ydbio.2010.06.017

Westergard, Thomas; & Rothstein, Jeffrey D. (2020). Astrocyte Diversity: Current Insights and Future Directions. *Neurochemical Research*, *45*(6), 1298–1305. https://doi.org/10.1007/s11064-020-02959-7

White, John; Southgate, E.; Thomson, J.; & Brenner, S. (1986). The structure of the nervous system of the nematode Caenorhabditis elegans. *Philosophical Transactions of the Royal Society of London. B, Biological Sciences*, *314*(1165), 1–340. https://doi.org/10.1098/rstb.1986.0056

Wictorin, K.; Brundin, P.; Sauer, H.; Lindvall, O.; & Björklund, A. (1992). Long distance directed axonal growth from human dopaminergic mesencephalic neuroblasts implanted along the nigrostriatal pathway in 6-hydroxydopamine lesioned adult rats. *Journal of Comparative Neurology*, *323*(4), 475–494. https://doi.org/10.1002/CNE.903230403

Widodo, Wahyu; Aprilya, Dina; & Satria, Oryza. (2025). Regenerative Medicine: A New Horizon in Peripheral Nerve Injury and Repair. *Orthopedic Reviews*, *17*, 2025. https://doi.org/10.52965/001C.133572

Wolterhoff, Neele; & Hiesinger, P. Robin. (2024). Synaptic promiscuity in brain development. *Current Biology*, *34*(3), R102–R116. https://doi.org/10.1016/J.CUB.2023.12.037

Xiong, Man; Tao, Yezheng; Gao, Qinqin; Feng, Ban; Yan, Wei; Zhou, Yingying; Kotsonis, Thomas A.; Yuan, Tingli; You, Zhiwen; Wu, Ziyan; Xi, Jiajie; Haberman, Alexander; Graham, Julia; Block, Jasper; Zhou, Wenhao; Chen, Yuejun; & Zhang, Su Chun. (2021). Human Stem Cell-Derived Neurons Repair Circuits and Restore Neural Function. *Cell Stem Cell*, *28*(1), 112-126.e6. https://doi.org/10.1016/j.stem.2020.08.014

Yang, Dali; Zhang, Zhi-Jian; Oldenburg, Michael; Ayala, Melvin; & Zhang, Su-Chun. (2008). Human Embryonic Stem Cell-Derived Dopaminergic Neurons Reverse Functional Deficit in Parkinsonian Rats. *Stem Cells*, *26*(1), 55–63. https://doi.org/10.1634/STEMCELLS.2007-0494

Yntema, Chester L.; & Hammond, Warner S. (1954). The origin of intrinsic ganglia of trunk viscera from vagal neural crest in the chick embryo. *Journal of Comparative Neurology*, *101*(2), 515–541. https://doi.org/10.1002/CNE.901010212

Yntema, Chester L.; & Hammond, Warner S. (1955). Experiments on the origin and development of the sacral autonomic nerves in the chick embryo. *Journal of Experimental Zoology*, *129*(2), 375–413. https://doi.org/10.1002/JEZ.1401290210

Zetterström, Rolf H.; Williams, Reg; Perlmann, Thomas; & Olson, Lars. (1996). Cellular expression of the immediate early transcription factors Nurr1 and NGFI-B suggests a gene regulatory role in several brain regions including the nigrostriatal dopamine system. *Molecular Brain Research*, *41*(1–2), 111–120. https://doi.org/10.1016/0169-328X(96)00074-5

Zhang, Su Chun; Wernig, Marius; Duncan, Ian D.; Brüstle, Oliver; & Thomson, James A. (2001). In vitro differentiation of transplantable neural precursors from human embryonic stem cells. *Nature Biotechnology*, *19*(12), 1129–1133. https://doi.org/10.1038/NBT1201-1129

Zhu, Shu Jun; & Pearson, Bret J. (2016). (Neo)blast from the past: new insights into planarian stem cell lineages. *Current Opinion in Genetics and Development*, *40*, 74–80. https://doi.org/10.1016/j.gde.2016.06.007

Zimprich, Alexander; Biskup, Saskia; Leitner, Petra; Lichtner, Peter; Farrer, Matthew; Lincoln, Sarah; Kachergus, Jennifer; Hulihan, Mary; Uitti, Ryan J.; Calne, Donald B.; Stoessl, A. Jon; Pfeiffer, Ronald F.; Patenge, Nadja; Carbajal, Iria Carballo; Vieregge, Peter; Asmus, Friedrich; Müller-Myhsok, Bertram; Dickson, Dennis W.; Meitinger, Thomas; ... Gasser, Thomas. (2004). Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron*, *44*(4), 601–607. https://doi.org/10.1016/j.neuron.2004.11.005

Barton Journal

A Mathematical Approach to Prion Misfolding

FULL-LENGTH ARTICLE

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CITATION

Cassell, Morgan; Bennett, Ashley L.; & Mazuroski, Nicole L. (2026). A mathematical approach to prion misfolding. *Barton Journal, 1*(1), 47–71. https://bartonjournal.org/vol-1-no-1/2026-cat1-article-no-002

Abstract

Prion diseases are a rare form of infectious neurodegenerative disorders that can infect humans as well as other mammals and can also be transferred from mammals to humans. Currently, these prion diseases remain both fatal and untreatable. These serious prion diseases are ultimately caused by the transformation of the prion protein (PrP^{c}), which is natively expressed in the central nervous system of mammals, into an infectious isoform, PrP^{sc}. High resolution NMR and cryo EM structures of PrP^{c} and PrP^{sc} have revealed vast structural differences between the two isoforms despite having the same amino acid sequence. While much is known about the specific structural differences between the native and infectious PrP isoforms, almost nothing is understood about the initial misfolding events triggering the PrP^{c} to fold into the PrP^{sc} or the specific details of how a misfolded PrP^{sc} infectious isoform and trigger a non-infectious PrP^{c} into the infectious isoform. Here, we provide a mathematical framework for studying prion structures and folding with the goal of building a predictive model. Leveraging experimentally derived constraints we demonstrate a topology-based model that enables a dimensionality reduction of the coordinate space by projection onto the contact space, thus enabling more efficient analysis of the interacting residues and interactions driving the PrP^{c} misfolding to PrP^{sc}. Now that this framework is established, we will integrate with biophysical, structural, and machine learning analyses

to explore the cellular factors that act as predictors for triggering a prion protein misfolding event.

Keywords: prion diseases, protein misfolding, prion protein, neurodegenerative disorders, mathematical modeling, topology, dimensionality reduction, contact space analysis, structural biology

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Introduction

Prion diseases are a class of transmissible neurodegenerative disorders affecting a wide range of mammalian species. Human-specific prion diseases include Creutzfeldt-Jakob Disease (CDJ), Kuru, or Fatal Familial Insomnia (FFI) and remain untreatable and fatal. Prion diseases result when a transmutation of PrP^{c}, which is natively expressed in neurological tissue in mammals, is transformed into the infectious isoform, PrP^{sc}. Aggregation of the prion misfold causes a rapid deterioration of the neuron expressing fibril chains of PrP^{sc} (Miranzadeh Mahabadi & Taghibiglou, 2020).

Much like a viral disease, PrP^{sc} ultimately spreads and infects other nervous tissue in the central nervous system (CNS) of any host mammal. Although both isoforms share identical primary amino acid sequences consisting of approximately 210 residues after post-translational processing, where the difference lies in secondary and tertiary structure, resulting in a distinct fold between the two isoforms. PrP^{c} adopts a globular fold containing three a-helices and two short β-sheets while PrP^{sc} adopts a β-sheet rich fibrillar architecture, typically forming parallel, in-register β-sheets (Kovač & Čurin Šerbec, 2022; Kraus et al., 2021; Wille & Requena, 2018). Structural studies have identified structural variability in the $\beta 2$–$a 2$ loop (residues 165- 175) and the $a 2$–$a 3$ interhelical interface (residues 185-209), regions that are implicated in the transition from PrP^{c} to PrP^{sc} (Kraus et al., 2021). These regions provide plausible candidates for residue pairs (i', j') that contribute to the distance discrepancies between corresponding residue pairs, which can be measured with contact graphs and their threshold proximities. Residue pairs that show the largest differences in the contact maps are potential candidates for driving the misfold and structural separation between PrP^{c} and PrP^{sc}.

Prion proteins can take on many variations with one example being 1FO7, which is a mutant fragment from residues 90-231 containing 60 total conformations calculated, 30 of which have been verified and submitted. The same is true for a mammalian vector such as the Syrian Hamster (*M. auratus*), which examines residues 90-231 and has 100 calculated structures, 25 of which confirm the overall structural conformation of 2 β-sheets and 3 a-helices with sequences binding the 5 main structures of the globular domain.

The precise mechanism of this structural transition remains incompletely understood. This paper integrates topological and distance-geometric analyses to reveal the mechanism(s) of PrP^{c} and its infectious isoform PrP^{sc}. Subsequent stereochemical and structural analysis is used to map mathematical findings to the protein structures and reveal the underlying residue interactions driving prion protein misfolding.

Mathematical Methodology

The primary aim is to demonstrate through proof that a transformation from PrP^{c} to PrP^{sc} is defined and then map the mathematical transformation onto the prion protein isoform structures. While the real-world infectivity of the PrP^{sc} protein misfold is known, much is left unknown about misfolding initiating and propagation mechanisms. Resolving these mechanisms of pathogenesis requires a fresh perspective. We provide a mathematical model of structural transformation for representative prion protein structures 1QLX and 6LNI in $\mathbb{R}^1$, $\mathbb{R}^2$, and $\mathbb{R}^3$ representing sequence, contacts, and coordinate space, respectively. Given that we need a concrete and strong initial base, we can break down the analysis into multiple categories of application.

Proof in $\mathbb{R}^1$

Axiom 1:

Let Σ denotate the 20-letter amino acid alphabet. Post-enzymatic trimming, a mature PrP consists of 210 amino acid sequences. Therefore the sequence space is defined as;

$$S = \Sigma^{210} \text{ where, } \Sigma^{210} = \{a_i \in \Sigma \mid (a_1, a_2, a_3, \dots, a_{210})\}.$$

In addition, there does exist some $s \in S$ which represents an ordered 210-residue sequence.

Axiom 2:

Let $J: S \to Y$ be an invariant and define a relation $\sim_J$ on S by:

$$s \sim_J t \Leftrightarrow J(s) = J(t)$$

Lemma 1: Invariant-Induced Relations is an Equivalence Relation.

Claim: For any function $J: S \to Y$, the relation $\sim_J$ is an equivalence relation on S.

Proof: Define the following terms:

i. Reflexivity: $\exists\, a$ such that, $a = a$
ii. Symmetry: $\exists\, a, b$ such that, $a = b$ & $b = a$
iii. Transitivity: $\exists\, a, b, c$ such that, $a = b$ and $b = c \Longrightarrow a = c$.

Projecting these terms onto the initial claim results in:

i. If $J(s) = J(s)$, then $s \sim_J s$
ii. If $J(s) = J(t)$, then $J(t) = J(s)$
iii. If $J(s) = J(t)$ and $J(t) = J(u)$, then $J(s) = J(u)$.

Which then implies $\sim_J$ is reflexive, symmetric, and transitive. ▌

Axiom 3:

Define the identity invariance as:

$$J_1 : S \to S, J_1(s) = s,$$

Then the relation will satisfy:

$$s \sim_{J_1} t \Leftrightarrow s = t.$$

Because the prion conversion from globular PrP^c to infectious isoform PrP^{sc} is solely a conformational change and not a sequence or residue change, we can establish that the sequence is preserved regardless of conformational change. So, if we take some sequence:

$$s_c, s_{sc} \in S$$

Then the mature sequence residues will exist as:

$$s_c = s_{sc}.$$

Theorem 1: PrP Sequence Indistinguishability

Claim: under the primary invariance J_1, PrP^c and PrP^{sc} lie on the same equivalence class $S/\sim_{J_1}$.

Since: $s_c = s_{sc}$ we can say:

$$J_1(s_c) = s_c = s_{sc} = J_1(s_{sc})$$

$$\Longrightarrow J_1(s_c) = J_1(s_{sc})$$

$$\Longrightarrow s_c \sim_{J_1} s_{sc}$$

$$\Longrightarrow [s_c]_{J_1} = [s_{sc}]_{J_1} \blacksquare$$

Corollary for Theorem 1: Failure of Sequence-Level Detection Must Exist

Claim: no invariant depending solely on primary sequence identity can distinguish PrP^c from PrP^{sc}.

Since: $s_c = s_{sc}$ we can use direct substitution to impose:

$$\Longrightarrow J(s_c) = J(s_{sc}).$$

Therefore, if every invariant is defined solely on a primary sequence PrP which is contained in the enzymatic trimmed chain Σ^{210}, then both PrP^c and PrP^{sc} are indistinguishable. This is further elaborated in the biological perspective in which the PrP parent chain can be expressed either as the infectious fibril misfold or the native globular protein. Thus:

$$(\mathrm{PrP^c} = \mathrm{PrP^{sc}}) \subset \mathbb{R}^1 \blacksquare$$

Because experimentally we know that a misfold occurs somewhere in the protein life cycle, we are going to assume that fact and proceed forward in a fashion that emphasizes mathematical perspective. The goal is to then prove the non-congruence of $\mathrm{PrP^c}$ and $\mathrm{PrP^{sc}}$ in $\mathbb{R}^2$ and $\mathbb{R}^3$. As shown above, the $\mathbb{R}^1$ sequence space is congruent in residue sequence, however the two isoforms are known to be non-congruent in conformation. As the conformational $\mathbb{R}^3$ space is better described experimentally than the $\mathbb{R}^2$ contact space, the proof in $\mathbb{R}^3$ will be written first to easily observe the difference in structural conformation. That difference or conformational change in structure will be more easily presented through contact maps in the $\mathbb{R}^2$ proof.

Proof in $\mathbb{R}^3$

Axiom 4: Index Set

Let I be a finite residue index set on which both coordinate models supply. Concretely, I is taken to be the intersection of the residue indices present in:

- $\mathrm{PrP^c}$, which exists as a globular C-terminal domain and has 3 a-Helices and a short β sheet
- $\mathrm{PrP^{sc}}$, presents parallel in-register intermolecular β-sheets

$$I = (C) \cap (Sc).$$

Defining I as the overlap avoids any non-trivial index matching assumptions beyond the correlation to coordinates and labeled residues.

Axiom 5: Projection Mapping

Fix a representative atom per residue then define the embeddings as:

$$Fc{:}I \to \mathbb{R}^3, Fsc{:}I \to \mathbb{R}^3$$

Where $Fc(i)$ and $Fsc(i)$ be the 3D coordinates of the mmCIF atoms for the common residues in 1QLX and 6LNI, representing $\mathrm{PrP^c}$ and $\mathrm{PrP^{sc}}$, respectively.

Axiom 6: Rigid Motion

A rigid motion in $\mathbb{R}^3$ specifically is a representative mapping in form:

$$g(x) = Rx + v, R \in O(3), v \in \mathbb{R}^3.$$

Where the matrix R belongs to the orthogonal group $O(3)$, defined as:

$$O(3) = \{\mathbb{R} \in \mathbb{R}^{3x3} \mid R^T R = I\}$$

The main advantage of orthogonal matrices is that they preserve Euclidean inner product and thus lengths and

pairwise distances. Consequently, any transformation of the form $g(x) = Rx + v$ where $R \in O(3)$ and $v \in \mathbb{R}^3$ is a Euclidean isometry of $\mathbb{R}^3$. Distance matrices are therefore invariant under such transformations.

Axiom 7: Euclidean Congruence

Define Fc and Fsc as congruent if there exists a rigid motion g such that:

$$Fsc(i) = g(Fc(i)),\ \forall\, i \in I$$

Axiom 8: Distance Matrix on an Embedding

For an embedding in the projection $F{:}I \to \mathbb{R}3$, define its distance matrix D_F such that:

$$D_F{:}I \times I \to \mathbb{R}_{\geq 0},\ D_F(i,j) = \|F(i) - F(j)\|.$$

Given the following axioms, we can begin to establish lemmas 2 and 3 which state claims that rigid motion preserves pairwise distance, which was previously assumed in axiom 7 as well as a contrapositive separation.

Lemma 2: Rigid Motion Preserves Pairwise Distance

Claim: if $Fsc = g(Fc)$ for a rigid motion g then:

$$D_{F_{sc}}(i,j) = D_{F_c}(i,j),\ \forall\, i,j \in I.$$

Proof: $\forall\, i,j \in I$:

$$D_{F_{sc}}(i,j) = \|Fsc(i) - Fsc(j)\| = \|g(Fsc(i)) - g(Fsc(j))\|.$$

Given axiom 7 we can establish $g(x) = Rx + v$ with $R \in O(3)$ such that:

$$\|g(a) - g(b)\| = \|R(a - b)\| = \|a - b\|.$$

Therefore:

$$D_{F_{sc}}(i,j) = \|Fsc(i) - Fsc(j)\| = \|(RFc(i) + v) - (RFc(j) + v)\| = \|R(Fc(i) - Fc(j))\| = \|Fc(i) - Fc(j)\| = D_{F_{sc}}(i,j)\ \blacksquare$$

Lemma 3: Contrapositive Separation

Claim: If there exists a pair $i,j \in I$ such that:

$$D_{F_{sc}}(i,j) \neq D_{F_c}(i,j),$$

then there is no rigid motion g where $Fsc = g(Fc)$.

Proof: If lemma 2 holds true that if rigid motion g exists with $Fsc = g(Fc)$, then all corresponding pairwise distances must agree:

$$D_{F_{sc}}(i,j) = D_{F_c}(i,j),\ \forall\, i,j \in I.$$

Which is the implicit contrapositive of lemma 2 and thus if even 1 pair of residues satisfies:

$$D_{F_{sc}}(i,j) \neq D_{F_c}(i,j)$$

Then the embeddings cannot be related by any rigid motion. Therefore, Fsc and Fc are not Euclidean-congruent. ▮

This, however, is not sufficient evidence alone to establish a loose non-congruence of Euclidean space structures; there must be a witnessed pair that either one structure has, but the other one does not.

Axiom 9: Supremum of Distance Matrixes

Define the discrepancy between the two embeddings by the following:

$$\Delta\infty(Fc, Fsc) = \max_{i,j \in I} |D_{F_c}(i,j) - D_{F_{sc}}(i,j)|.$$

Since I is a finite set, this maximum will exist. This quantity represents the largest pairwise distance disagreement between the two respective embeddings.

Theorem 2: $\mathbb{R}^3$ Non-Congruence Explicit

Claim: From experimental data we assume:

$$\Delta\infty(Fc, Fsc) > 0$$

Therefore, there exists no rigid motion:

$$g(x) = Rx + v, R \in O(3),$$

such that:

$$Fsc = g(Fc).$$

Proof: If the embeddings were Euclidean congruent, then by Lemma 2:

$$D_{F_{sc}}(i,j) = D_{F_c}(i,j), \ \forall\, i,j \in I$$

$$\Rightarrow \Delta\infty(Fc, Fsc) = 0.$$

This contradicts the experimentally derived assumption that $\Delta\infty(Fc, Fsc) > 0$ and thus implies that there exist no rigid motion mapping Fc to Fsc. ▮

We then need to construct a witnessed pair that exists as the set's maximum pair, so we then define:

$$(i', j') \in I \times I$$

Such that:

$$\Delta\infty(Fc, Fsc) = |D_{F_c}(i', j') - D_{F_{sc}}(i', j')|$$

This identifies residues whose specific spatial separation has the largest discrepancy between the two embeddings. Thus:

$$D_{F_c}(i', j') \neq D_{F_{sc}}(i', j'),$$

which confirms an explicit geometric witness of the non-congruence between PrP^c and PrP^{sc}. To further strengthen the above theories and lemmas we will construct a contact graph.

Axiom 10: Contact Graph by an Embedding

Let the function F be defined as the projection of I onto real space:

$$F{:}I \to \mathbb{R}^3$$

Where I is an embedding of a finite index set, as previously stated. This allows for any fixed threshold $\delta > 0$ to define the graph $G(F, \delta)$ with edge set $E(F, \delta)$ such that:

$$G(F, \delta) = (I, E(F, \delta)),$$

Where:

$$(i,j) \in E(F, \delta) \Leftrightarrow \|F(i) - F(j)\| \leq \delta \text{ and } |i - j| > 2.$$

Theorem 3: Separation of Contact Graphs

Claim: If:

$$\Delta\infty(Fc, Fsc) > 0,$$

then $\exists\, \delta > 0$, such that:

$$G(Fc, \delta) \neq G(Fsc, \delta).$$

Proof: Because we know from the experimental assumption:

$$\Delta\infty(Fc, Fsc) > 0,$$

then there exist a witnessed pair such that:

$$D_{F_c}(i', j') \neq D_{F_{sc}}(i', j').$$

So, without loss of generality, we can assume:

$$D_{F_c}(i', j') < D_{F_{sc}}(i', j').$$

We will choose a δ such that:

$$\delta = \frac{D_{Fc}(i\prime,j\prime)+D_{FSc}(i\prime,j\prime)}{2}.$$

This then implies the following transformations:

$$D_{Fc}(i',j') \leq \delta < D_{Fsc}(i',j')$$

$$\Rightarrow (i',j') \in E(Fc, \delta) \text{ and } \nexists (i',j') \in E(Fsc, \delta)$$

$$\therefore E(Fc, \delta) \neq E(Fsc, \delta)$$

$$\Rightarrow G(Fc, \delta) \neq G(Fsc, \delta). \blacksquare$$

This establishes that there exists at least one witnessed pair (i',j') that belongs to one edge set but not the other, which implies that the corresponding contact graphs are non-congruent. To further this idea if we take into account the findings of Miranzadeh Mahabadi & Taghibiglou (2020), then we can observe that conformational misfolds of $PrP^{c} \rightarrow PrP^{sc}$ lies within the β2-*a*2 loop region (residues 165–175), and the *a*2-*a*3 inter-helical interfaces (residues 185–200) of PrP^{c}.

Proof in $\mathbb{R}^2$

Axiom 11: Orthogonal Planar Projections

Retain the same embeddings from the proof in $\mathbb{R}^3$ and with the same embeddings allowing I to be a finite index set of the specific PrP parent chain sequence:

$$Fc, Fsc: I \rightarrow \mathbb{R}^3.$$

If we then define 3 standard orthogonal planar projections, such that for any orthogonal projection denoted O can be represented as:

$$Oxy(x, y, z) = (x, y), Oxz(x, y, z) = (x, z), Oyz(x, y, z) = (y, z).$$

This reduction of geometric space gives 3 possible geometric planes as a result of each $Oa,b: \mathbb{R}^3 \rightarrow \mathbb{R}^2$, which is a linear mapping of $\mathbb{R}^3 \rightarrow \mathbb{R}^2$ created by deleting a single coordinate.

Axiom 12: Distance Structure Under Planar Projection

We can further define this mapping such that for any planar projection $F:I \rightarrow \mathbb{R}^2$ we define the embedding as:

$$D_F(i,j) = \|F(i) - F(j)\|,$$

where the double brackets denote the Euclidean norm on $\mathbb{R}^2$, which is:

$$\|x\| = \sqrt{x_1^2 + x_2^2}, \in \mathbb{R}^2.$$

Additionally, we state that for $P \in \{Oxy, Oxz, Oyz\}$:

$$D^{F_C^P}(i,j) = \|P(Fc(i) - Fc(Fc))\|, D^{F_{Sc}^P}(i,j) = \|P(Fsc(i) - Fsc(j))\|.$$

Axiom 13: Threshold Contact Graph on Planar Projections

To define the threshold graph on this 2-dimensional plane, we need to show that there exists some $\delta > 0$ such that:

$$G(F, \delta) = (I, E(F, \delta)),$$

where some ordered pair $(i,j) \in I$ can be defined as:

$$(i,j) \subset E(F, \delta) \Leftrightarrow \|F(i) - F(j)\| \leq \delta \text{ and } |i - j| > 2.$$

Lemma 4: Projection Identities

Claim: let there exist some vector ω such that $\omega = (x, y, z) \in \mathbb{R}^3$, then we can show:

$$\|Oxy(\omega)\|^2 + \|Oxz(\omega)\|^2 + \|Oyz(\omega)\|^2 = 2\|\omega\|^2.$$

Proof: $\omega = (x, y, z)$, which implies the following cases:

$$Oxy(\omega) = (x, y), Oxz(\omega) = (x, z), Oyz(\omega) = (y, z)$$

$$\Longrightarrow \|Oxy(\omega)\|^2 = x^2 + y^2$$

$$\Longrightarrow \|Oxz(\omega)\|^2 = x^2 + z^2$$

$$\Longrightarrow \|Oyz(\omega)\|^2 = y^2 + z^2.$$

This then give us:

$$(x^2 + y^2) + (x^2 + z^2) + (y^2 + z^2)$$

$$\Longrightarrow 2x^2 + 2y^2 + 2z^2$$

$$\Longrightarrow 2(x^2 + y^2 + z^2)$$

The internal portion of this product can be identified as the Euclidean norm in $\mathbb{R}^3$, which brings us back to our original vector that was proposed so we can conclude that:

$$x^2 + y^2 + z^2 = \|\omega\|^2 \Longrightarrow 2(x^2 + y^2 + z^2) = 2\|\omega\|^2$$

$$\therefore \|Oxy(\omega)\|^2 + \|Oxz(\omega)\|^2 + \|Oyz(\omega)\|^2 = 2\|\omega\|^2 \blacksquare$$

Lemma 5: Imposed Witness to Projection Identities

Claim: using the same pair of witnessed points $(i', j') \in I$ such that the witnessed points must exist in one plane or the other, allowing us to say:

$$\|Fc(i') - Fc(j')\| \neq \|Fsc(i') - Fsc(j')\|$$

$$\Longrightarrow \exists P \in \{Oxy, Oxz, Oyz\} \text{ such that,}$$

$$D^{F_C^P}(i', j') \neq D^{F_{Sc}^P}(i', j').$$

Proof: denote vectors v and u such that:

$$v = Fc(i') - Fc(j'), \text{ and } u = Fsc(i') - Fsc(j').$$

Given the hypothesis, neither v nor u can equal each other so we state that both v and u are unique vectors to the specific witnessed pair (i', j') thus:

$$\|v\| \neq \|u\|.$$

To demonstrate this, we will assume a contradiction that all 3 projections give equal distances on the plane:

$$\|Oxy(v)\| = \|Oxy(u)\|, \|Oxz(v)\| = \|Oxz(u)\|, \|Oyz(v)\| = \|Oyz(u)\|.$$

Given lemma 4 we can then say:

$$\|Oxy(v)\|^2 + \|Oxz(v)\|^2 + \|Oyz(v)\|^2 = \|Oxy(u)\|^2 + \|Oxz(u)\|^2 + \|Oyz(u)\|^2$$

$$\Longrightarrow 2\|v\|^2 = 2\|u\|^2$$

$$\Longrightarrow \|v\| = \|u\|$$

Thus, we reach a contradiction, and this shows that at least one of the coordinate planar projections must satisfy that:

$$\|P(v)\| \neq \|P(u)\|$$

$$\Longrightarrow D^{F_C^P}(i', j') \neq D^{F_{Sc}^P}(i', j')$$

for some unique projection $P \in \{Oxy, Oxz, Oyz\}$.∎

Theorem 4: Separating Planar Groups

If there exist a witnessed pair $(i', j') \in I$ such that:

$$\|Fc(i') - Fc(j')\| \neq \|Fsc(i') - Fsc(j')\|, P \in \{Oxy, Oxz, Oyz\}$$

with a unique threshold $\delta > 0$ such that:

$$G(F_C^P, \partial) \neq G(F_{Sc}^P, \partial).$$

Proof: Induce lemma 5 and then choose one of the 3 unique planar projections P:

$$D^{F_C^P}(i', j') \neq D^{F_{Sc}^P}(i', j').$$

Without a loss of generality, we can assume:

$$D^{F_C^P}(i', j') < D^{F_{Sc}^P}(i', j').$$

We then take a ∂ by the midpoint threshold such that:

$$\partial = \frac{D_{F_C^P}(i\prime, j\prime) + D_{F_{Sc}^P}(i\prime, j\prime)}{2},$$

which gives the statement:

$$D^{F_C^P}(i', j') \leq \partial < D^{F_{Sc}^P}(i', j')$$

$$\Longrightarrow (i', j') \in E(F_C^P, \partial)$$

$$\Longrightarrow (i', j') \notin E(F_{Sc}^P, \partial).$$

This then allows us to establish that the edge sets are not equal:

$$E(F_C^P, \partial) \neq E(F_{Sc}^P, \partial)$$

$$\Longrightarrow G(F_C^P, \partial) \neq G(F_{Sc}^P, \partial) \blacksquare$$

With an established witnessed pair existing, we can say that on the $\mathbb{R}2$ plane, there is at least one pair of coordinate projections that preserves distance inequality, as well as the threshold for that planar distance inequality produces graph separation.

Application

To demonstrate a provable and direct contact graph inequality, we need to interpret the proof through the biological context from which it was derived. The solution NMR structure 1QLX contains the experimentally determined 3D coordinates for globular PrP^c (Bank, 1999) and, alternatively, the coordinates for misfolding amyloid fibril PrP^{sc} are deposited in the high-resolution (2.70 Å) cryogenic electron microscopy (cryo-EM) structure (Data, 2019). This amyloid structure is a parallel in-register intermolecular beta sheet stack or PIRIBS (Data, 2019; Zahn et al., 2000). Several hypotheses propose mechanisms for both the initiating structural change within a neuron and the propagation of the infectious isoform. Here, we apply our mathematical framework with hopes to provide evidence in support of one of the plausible mechanisms of misfolding and

infectivity. To do so we apply the previously derived theorems that explain $\mathbb{R}^2$ & $\mathbb{R}^3$.

Applied proof in $\mathbb{R}^1$

While the PrP^c and PrP^{sc} proteins have the same amino acid sequence, there are some differences in the experimentally determined coordinate structure because of the protein purification process. Specifically, the prion protein purification protocol used to determine the 1QLX structure has a 17 amino acid residue N-terminal tail and a thrombin cleavage site engineered in. This engineered N-terminal sequence in PrP^c structure results in a direct difference in the encoding between PrP^c and PrP^{sc} such that there exist 2 N-terminal residues in the beginning of the 1QLX sequence as well as an N-terminus residue and C-terminal residue on the 6LNI. To accommodate this artifactual sequence change, we limit our analysis to the shared set of residues. This reduces the core residue count from each chain of 210 on each respective protein down to 208. This then allows us to analyze the following sequence code for Major Prion Protein (MPP):

> KKRPKPGGWNTGGSRYPGQGSPGGNRYPPQGGGGWGQPHGGGWGQPHGGGWGQPHG
> GGWGQPHGGGWGQGGGTHSQWNKPSKPKTNMKHMAGAAAAGAVVGGLGGYMLGSA
> MSRPIIHFGSDYEDRYYRENMHRYPNQVYYRPMDEYSNQNNFVHDCVNITIKQHTVTTT
> TKGENFTETDVKMMERVVEQMCITQYERESQAYYQRGS

To simplify the MPP residue chain into a more chewable or easily represented object, we will simply use the sigma notation from the previous Proof in $\mathbb{R}^1$,

$$MPP = \Sigma^{208},$$

where we can then denote 6LNI and 1QLX proteins as a projected reduction of the MPP residues. Specifically, the initial G and S on 1QLX and the beginning M and ending S on 6LNI, which are the respective termini, are truncated, such that we can denote 1QLX as C for a representation of PrP^c and 6LNI as Sc for PrP^{sc}:

$$C: \Sigma^{210} \to \Sigma^{208},\ C = \{a_3, a_4, a_5, \ldots, a_{208}, a_{209}, a_{210}\}$$

$$Sc: \Sigma^{210} \to \Sigma^{208},\ Sc = \{a_2, a_3, a_4, \ldots, a_{207}, a_{208}, a_{209}\}$$

This sequence only representation of MPP, which allows us to take the initial claim of $C = Sc$. Since both sequence representations are now equal to MPP, we can use MP to represent MPP such that the following is true:

$$MP = C = Sc \in \Sigma^{208}$$

We can then impose the identity invariant such that:

$$J_1: \Sigma^{208} \to \Sigma^{208},\ J_1(s) = s$$

$$\Longrightarrow J_1(C) = C = Sc = J_1(Sc)$$

$$\Longrightarrow C \sim_{J_1} Sc$$

$$\Longrightarrow [C]_{J_1} = [Sc]_{J_1},$$

if and only if :

$$MP = C = Sc \in \Sigma^{208}.$$

It should be noted that, based on the raw sequence with no exception to internal residue and considering the termini:

$$C \neq Sc \in \Sigma^{208}. \blacksquare$$

Applied proof in $\mathbb{R}^3$

To demonstrate Euclidean graph invariance, we select the witnessed pair of residues 176 and 190 between the 3D space of 6LNI and 1QLX because these pairs of residues confer not only a local witness of $|i - j| > 2$ but also a non-local witness using some delta as an anchor point.

Axiom 4: Re-applied

Let the index set be defined as the intersection of the structure coordinates of the residue pair, such that:

$$I = (C) \cap (Sc).$$

Limitations in current experimental structural biology lead to missing residue density in experimental PrP structures. Therefore, PDB structure representing *C* and *Sc* are incomplete. The 1QLX structure representing the PrP^c structure is missing residues 21-124 and 229-230 and thus contains coordinates for only the fragment 125-228, which is roughly the 104-count residue of the globular domain. The same exists for 6LNI where the fibril core exists as residues 170-229. This gives the intersecting set of:

$$I = (C) \cap (Sc)$$

$$C = \{125,\dots, 228\}, Sc = \{170,\dots, 229\}$$

$$\Longrightarrow I = (C) \cap (Sc) = \{170,\dots, 228\}$$

$$\Longrightarrow I = |59| \blacksquare$$

We then apply the distance graph of any witnessed pair:

$$i,j \in I, |i - j| > 2,$$

in which the witnessed pair of residues *i*,*j* exist within this 59-residue set. To show that the witnessed pair on both graphs is not equal, we use the residues 176 and 190 as the non-local witness such that $(i',j') = (176, 190)$. This allows us to determine:

$$|176 - 190| = 14 > 2.$$

To show that the pair is a non-local witness, we must project the coordinates of the witnessed pair to the distance graph. As is standard for structural biology analysis, we select the alpha carbon (*a*-carbon) atoms after a structural alignment between 1QLX and 6LNI to represent each residue. For the PrP^{c} structure 1QLX:

- Residue 176 $\in (-10.486, -14.457, -1.843)$
- Residue 190 $\in (-0.774, 1.083, -0.983)$.

And for PrP^{sc} structure 6LNI:

- Residue 176 $\in$ (205.776, 211.731, 243.361)
- Residue 190 $\in$ (179.099, 234.532, 241.349).

To get the residue pair distance for the distance graph we use:

$$Df(i,j) = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2}$$

$$\Longrightarrow D_{F_c}(176, 190) = \frac{\sqrt{10517317}}{125\sqrt{2}}$$

$$\Longrightarrow D_{F_c}(176, 190) = \frac{\sqrt{10517317}}{125\sqrt{2}} \approx 18.34541 \text{ Å}.$$

The standardized data structure for mmCIF atom coordinate files on the PDB enables us to use a Python implementation to automate extraction of distances between the atoms and therefore a more accurate Ångstrom (where Å equals 10^{-10}m or one 10 billionth of a meter and a carbon-to-carbon single bond is ~1.54Å) distance such that for 1QLX the distance projection is:

$$D_{F_c}(176, 190) = 18.347626004 \text{ Å}$$

To show that a graph invariance exists, we perform the same analysis for the PrPSc structure 6LNI:

$$D_{F_{sc}} 176, 190) = \sqrt{(205.776 - 179.099)^2 + (211.731 - 234.532)^2 + (243.361 - 241.349)^2}$$

$$\Longrightarrow D_{F_{sc}}(176, 190) = \frac{\sqrt{617798037}}{500\sqrt{2}} \approx 35.15104.$$

And with the same code implementation, we can observe the encoded distance exists as:

$$D_{F_{sc}}(176, 190) = 35.151046556 \text{ Å}$$

This result demonstrates that not only does the distance graph of the witnessed non-local pair not equal each other but also that the computed residue distances in PrP^{c} and PrP^{sc} do not equal each other. We can now say

that:

$$D_{F_{sc}}(176, 190) \neq D_{F_c}(176,190)$$

This shows that no rigid motion exists in the contact graph. To further prove the two embeddings are not equal we can take the midpoint $\delta > 0$, which was defined in the proof, and compute the midpoint threshold such that:

$$\delta = \frac{18.347626004 + 35.151046556}{2} = 26.749336280 \text{ Å}.$$

And if,

$$D_{F_c}(176, 190) \leq \delta < D_{F_{sc}}(176, 190),$$

then we can determine:

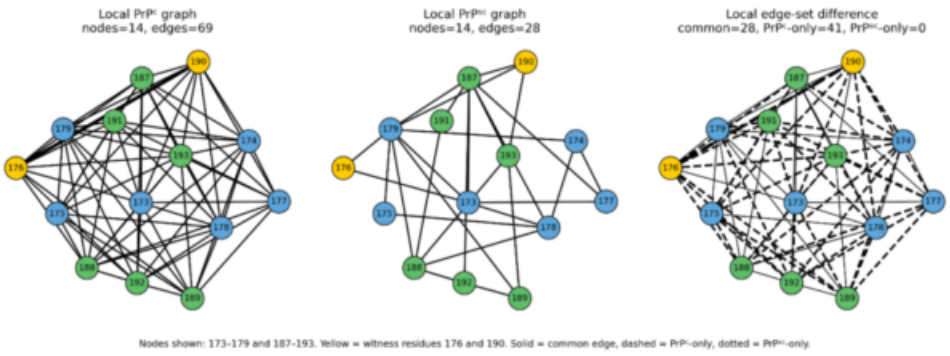
$$(176, 190) \in E(Fc, \delta) \text{ and } (176, 190) \notin E(Fsc, \delta)$$

$$\therefore G(Fc, \delta) \neq G(Fsc, \delta) \blacksquare$$

Using our implementation, we can automate this analysis over all combinations of residue pairs in the 59-residue intersection of the PrP^c and PrP^{sc} structures, building a network graph for all possible witnessed local and non-local residue pairs (Figure 1). This comprehensive network graph demonstrates clearly that the edge set and the connectivity between the edges differ between the PrP^c and PrP^{sc} structures. In the context of structural biology, this means that there are differences in the residues making up the edge sets and how the residues interact with each other in the two isoforms.

Figure 1

Network Graphs of PrP^c and PrP^{sc}



Note. Local network graphs for the intersecting residue set 173–179 and 187–193 in (*left*) PrP^c, (*middle*) PrP^{sc}, and (*right*) the difference between PrP^c and PrP^{sc}. The nodes represent the *a*-carbon atoms of the residues and the edges the interactions between residues in the PrP structures. Yellow (176,190) represents the witnessed

pair selected during the application of the proof. In the panel on the right showing the edge set differences, the solid lines show interactions in common between PrP^{c} and PrP^{sc}, while the dashed and dotted lines represent interactions that are present only in PrP^{c} or PrP^{sc}, respectively.

Applied proof in $\mathbb{R}^2$

To show that there exists a unique orthogonal projection, we impose the same *a*-carbon coordinates such that the difference between the unique witnessed pair (176, 190) would be:

$$F(176) - F(190) = (x_{176} - x_{190}, y_{176} - y_{190}, z_{176} - z_{190})$$

$$\Longrightarrow Fc(176) - Fc(190) = (-9.712, -15.540, -0.906) = C$$

$$\Longrightarrow Fsc(176) - Fsc(190) = (26.677, -22.801, 2.012) = Sc.$$

We can then reduce the dimensionality of the geometric space by constructing a projection from geometric space to relational contact map space, which was previously demonstrated. Given that $\mathbb{R}3$ proof remains true, we can say the previous difference remains true for all values of projection. We define the top value as C and the bottom value to Sc to simplify the projection results. To begin with the proof, all 3 orthogonal planar projections must be observed.

Projection to *xy*

The *xy* projection is shown in Figure 2 and calculated from:

$$Oxy(C) = (-9.712, -15.540), \text{ and } Oxy(Sc) = (26.677, -22.801)$$

$$\Longrightarrow D^{xy}_{F_C}(176, 190) = \|Oxy(C)\| = \sqrt{(-9.712)^2 + (-15.540)^2} = 18.325243354$$

$$\Longrightarrow D^{xy}_{F_{Sc}}(176, 190) = \|Oxy(Sc)\| = \sqrt{(26.677)^2 + (-22.801)^2} = 35.093417188$$

$$\Longrightarrow \partial xy = \frac{18.325243354 + 35.093417188}{2} = 26.709330271 \text{ Å}$$

$$\Longrightarrow D^{xy}_{F_C}(176, 190) \leq \partial xy < D^{xy}_{F_{Sc}}(176, 190)$$

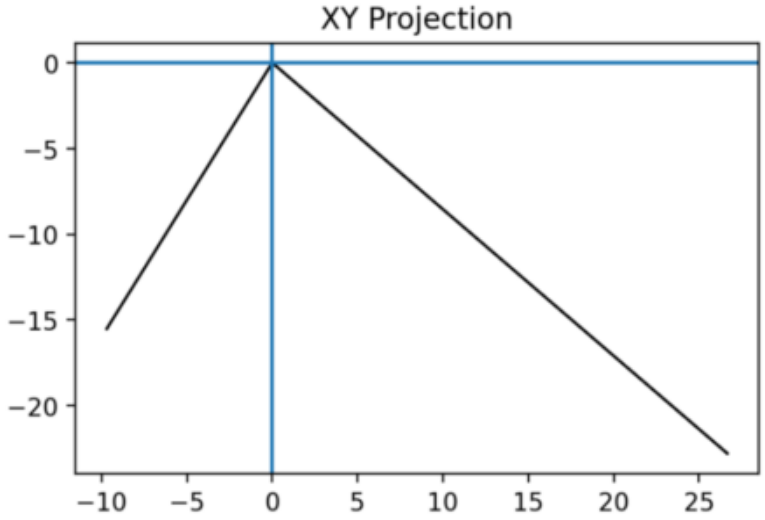
$$\Longrightarrow (176,190) \in E(F_C^{xy}, \partial) \text{ and } (176, 190) \notin E(F_{Sc}^{xy}, \partial)$$

$$\Longrightarrow E(F_C^{xy}, \partial) \neq E(F_{Sc}^{xy}, \partial)$$

$$\therefore G(F_C^{xy}, \partial xy) \neq G(F_{Sc}^{xy}, \partial xy).$$

Figure 2

xy Projection



Note. The *xy* projection of the geometric space onto the relational contact space.

This first orthogonal planar projection already demonstrates that at least one projection exhibits a contact graph difference. However, to be as rigorous as possible, we continue the application with the remaining 2 projections.

Projection to *xz*

$$Oxz(C) = (-9.712, -0.906), \text{ and } Oxz(Sc) = (26.677, 2.012)$$

$$\Rightarrow D_{F_C}^{xz}(176,190) = \|Oxz(C)\| = \sqrt{(-9.712)^2 + (-0.906)^2} = 9.754167314$$

$$\Rightarrow D_{F_{Sc}}^{xz}(176, 190) = \|Oxz(Sc)\| = \sqrt{(26.677)^2 + (2.012)^2} = 26.752765707$$

$$\Rightarrow \partial xz = \frac{9.754167314 + 26.752765707}{2} = 18.25346651 \text{ Å}$$

$$\Rightarrow D_{F_C}^{xz}(176, 190) \leq \partial xz < D_{F_{Sc}}^{xz}(176, 190)$$

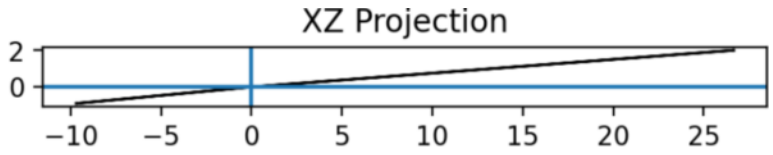
$$\Rightarrow (176,190) \in E(F_C^{xz}, \partial) \text{ and } (176, 190) \notin E(F_{Sc}^{xz}, \partial)$$

$$\Rightarrow E(F_C^{xz}, \partial) \neq E(F_{Sc}^{xz}, \partial)$$

$$\therefore G(F_C^{xz}, \partial xz) \neq G(F_{Sc}^{xz}, \partial xz).$$

Figure 3

xz Projection



Note. The *xz* projection of the geometric space onto the relational contact space.

Thus, there exists now a second planar projection where a graph invariance is observed (Figure 3).

Projection to *yz*

$$Oyz\,(C) = (-15.540,-0.906), \text{ and } Oyz\,(Sc) = (-22.801,2.012)$$

$$\Longrightarrow D_{F_C}^{yz}\,(176, 190) = \|Oyz\,(C)\,\| = \sqrt{(-15.540)^2 + (-0.906)^2} = 15.566388$$

$$\Longrightarrow D_{F_{Sc}}^{yz}\,(176, 190) = \|Oyz\,(Sc)\| = \sqrt{(-22.801)^2 + (2.012)^2} = 22.8895991$$

$$\Longrightarrow \partial yz = \frac{15.566388 + 22.8895991}{2} = 19.22799355 \text{ Å}$$

$$\Longrightarrow D_{F_C}^{yz}\,(176, 190) \leq \partial yz < D_{F_{Sc}}^{yz}\,(176, 190)$$

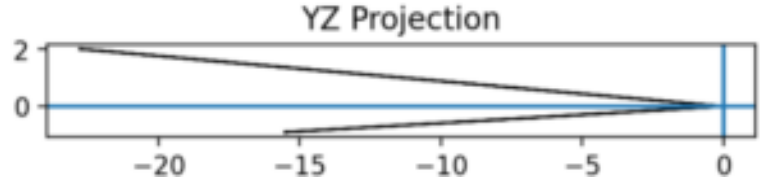
$$\Longrightarrow (176,190) \in E(F_C^{yz}, \partial) \text{ and } (176, 190) \notin E(F_{Sc}^{yz}, \partial)$$

$$\Longrightarrow E(F_C^{yz}, \partial) \neq E(F_{Sc}^{yz}, \partial)$$

$$\therefore\ G(F_C^{yz}, \partial yz) \neq G(F_{Sc}^{yz}, \partial yz).$$

Figure 4

yz Projection



Note. The *yz* projection of the geometric space onto the relational contact space.

The three orthogonal planar projections (Figures 2–4) show that regardless of which chosen planar coordinates

of the witness pair (176, 190) that you will find a discrepancy between their embeddings. This further enforces the original claim of the structural conformation having vastly different structures.

Interpretation

We leverage several key implementations of metric space calculations in the $\mathbb{R}^1$, $\mathbb{R}^2$ and $\mathbb{R}^3$ proofs. Beginning with the initial proof in $\mathbb{R}1$, the concept was introduced of projecting a protein structure into its sequence-based representation. This framework relied on the assumption that both the infectious fibril and the non-infectious version of the major prion protein isoforms are simply expressions of PrP, and that neither protein was assumed to possess terminal edges within their globular domains. Due to the limitations of experimental structural biology methods and their inability to fully resolve atomic positions in flexible protein structures such as PrP, the applied proof in $\mathbb{R}^1$ required stripping the terminal residues of PrP^c and PrP^{sc} and using only purely the backbone of the residues representing the globular domain in the native PrP^c. This truncated sequence space representing the intersection of experimentally resolved residues was then shown to be equivariant using invariances. In other words, there was no way to tell the difference between MPP, *C*, *Sc* given solely their backbone sequence code. Because we cannot differentiate the isoforms in $\mathbb{R}^1$, we use the experimentally observable difference in structure as an assumption to show through proof in $\mathbb{R}^3$ that the structures are indeed different.

The proof in $\mathbb{R}^3$ was designed to show that each contact graph of the proteins had at least one delta which denoted a fixed midpoint for the edge sets to be derived from and allowed for a distance variance to be determined. This was further established in the applied proof where we use the 3D coordinates space from the mmCIF files to calculate the atom distances in PrP^c and PrP^{sc} (Table 1).

Table 1

Coordinates for Witnessed Non-Local Residue Pairs in PrPC and PrPSc

Structure	**Residue**	**X** (Å)	**Y**(Å)	**Z**(Å)
1QLX	176	-10.486	-14.457	-1.843
1QLX	190	-0.774	1.083	-0.937
6LNI	176	205.776	211.731	243.361

6LNI	190	179.09 9	234.53 2	241.3 49

Note. The 1QLX and 6LNI structures provide the coordinates for PrP^{c} and PrP^{sc}, respectively. The X, Y, and Z coordinates expressed in Ångstroms (Å) for the residues 176 and 190 composing the witnessed non-local residue pair in the application of proofs.

The coordinates of the witnessed non-local pair in both $PrP^{c}$and PrP^{sc} structures give the ability to determine through a Euclidean norm that there is a midpoint for the set of intersecting residues representing the native globular domain. We can then use this midpoint as the anchor for distance projection. The distance projection reveals key differences between the two proteins; specifically, when we examine the midpoint delta, only one protein isoform satisfies the projected inequality, such that witnessed pair (176,190) remains within the edge set for the PrP^{c} isoform.

To further demonstrate that there is a difference between the two isoforms, we use the $\mathbb{R}2$ proof to accomplish a projection that successfully reduces the dimensions of witnessed non-local residue pair and thus simplifies computations. We perform a reduction in dimensional space such that, when analyzing any two planar projections of a three-dimensional structure, we can establish that there will be at least one view within that spatial reduction that demonstrates the witnessed pair does not exist in either edge set, and therefore in neither graph projection. This incongruity in graph projections is confirmed for every 3D planar projection in $\mathbb{R}3$regardless of dimensional combination. This further strengthens the claim that there exists a conformational difference between PrP^{c} and PrP^{sc}.

Discussion

As this paper currently stands, there is very little addition to biochemistry, stereochemistry, biophysics, combinatorics, or ionic interaction theory. This will be addressed in the 'Further Research' portion of this paper. Currently, this is an analysis of the basest level that observes sequence variation and applied that onto a 3-dimensional structural space, and that allows for an ability to show a difference in physical properties. The addition of ionic interaction theories as well as proton channels that help regulate cell pH in the CNS is actively being considered as well as further structural analysis of the fibril that PrP^{sc} creates and signaling effects in the host neuron.

Conclusion

A key conclusion from this study is that the edge sets in the contact graphs do represent interacting partners, defined by the chosen distance thresholds between the witnessed residue pairs. However, the presence of an edge does not automatically imply a functional or causative interaction; for example, residues that are distant in the structure may or may not influence protein behavior through allosteric mechanisms, while more local contacts are likely to be more directly relevant. The observed differences in contact graphs reflect how these interactions

act as structural variables and are incrementally modified, rather than providing a direct mapping to ionic interaction theory, biophysical interactions, or conformational dynamics. Importantly, this model aligns with current physical observations that the two forms of the major prion protein, PrP^{c} and PrP^{sc}, are structurally distinct, despite having identical primary sequences.

Further Research

This paper presents findings from ongoing research conducted by Ashley L. Bennett, PhD, and Nicole L. Mazuroski, M.S. Moving forward, this study proposes to incorporate electrostatic and ionic interaction principles to better understand protein conformational dynamics. Specifically, it is hypothesized that metabolic stressors may induce a localized decrease in pH within the central nervous system, leading to an increased concentration of free hydrogen ions promoting protonation of key amino acid residues and inducing backbone conformational changes through altered salt bridge interactions. Additionally, interacting partners of PrP^{c}, may further modulate the local proton environment. For example, zinc may influence neuronal acidity by interfering with proton transport mechanisms, potentially reducing proton efflux, and contributing to intracellular proton accumulation. There is also ongoing discussion about the potential intracellular interactions of calcium, chloride, and copper, although these ideas remain speculative at this stage.

References

Anand, Uttam; Patra, Shubhadeep; Sekar, Rohith Vedhthaanth; Garen, Craig R.; & Woodside, Michael T. (2025). Different folding mechanisms in prion proteins from mammals with different disease susceptibility observed at the single-molecule level. *Proceedings of the National Academy of Sciences, 122*(29). https://doi.org/10.1073/pnas.2416191122

Andre, Ralph & Tabrizi, Sarah J. (2012). Misfolded PrP and a novel mechanism of proteasome inhibition. *Prion, 6*(1), 32–36. https://doi.org/10.4161/pri.6.1.18272

Artikis, Efrosini; Kraus, Allison; Caughey, Byron. (2022). Structural biology of ex vivo mammalian prions. *Journal of Biological Chemistry, 298*(8), 102181.https://doi.org/10.1016/j.jbc.2022.102181

Blumenthal, Leonard M. (1953). *Theory and applications of distance geometry* (1st ed.). Oxford at the Clarendon Press. https://archive.org/details/theoryapplicatio0000leon/page/n7/mode/2up

Boon Seng Wong; Liu, Tong; Li, Ruliang; Pan, Tao; Petersen, Robert B.; Smith, Mark A.; Gambetti, Pierluigi; Perry, George; Manson, Jean C.; Brown, David R.; Sy, Man Sun . (2001). Increased levels of oxidative stress markers detected in the brains of mice devoid of prion protein. *Journal of Neurochemistry, 76*(2), 565–572. https://doi.org/10.1046/j.1471-4159.2001.00028.x

Brown, David R. (2001). Copper and prion disease. *Brain Research Bulletin, 55*(2), 165–173. https://doi.org/10.1016/s0361-9230(01)00453-1

Brown, David R.; Qin, Kefeng; Herms, Jochen; Madlung, Axel; Manson, Jean; Strome, Robert; Fraser, Paul E.; Kruck, Theo; von Bohlen, Alex; Schulz-Schaeffer, Walter; Giese, Armin; Westaway, David; & Kretzschmar, Hans (1997). *The cellular prion protein binds copper in vivo. Nature, 390*(6661), 684–687. https://doi.org/10.1038/37783

Canoyra, Sara; Marín-Moreno, Alba; Espinosa, Juan Carlos; Fernández-Borges, Natalia; Vidal, Enric; Orge, Leonor; Benestad, Sylvie L.; Andréoletti, Olivier; & Torres, Juan María (2025). Classical BSE emergence from Nor98/atypical scrapie: Unraveling the shift vs. selection dichotomy in the prion field. *Proceedings of the National Academy of Sciences, 122*(29). https://doi.org/10.1073/pnas.2501104122

De La Rosa, Victor; Bennett, Ashley L.; & Ramsey, I. Scott. (2018). Coupling between an electrostatic network and the Zn2+ binding site modulates Hv1 activation. *The Journal of General Physiology, 150*(6), 863–881. https://doi.org/10.1085/jgp.201711822

Diestel, Reinhard. (2025). *Graph theory*. Springer.

Edgeworth, Julie Ann; Jackson, Graham S.; Clarke, Anthony R.; Weissmann, Charles; & Collinge, John. (2009). Highly sensitive, quantitative cell-based assay for prions adsorbed to solid surfaces. *Proceedings of the National Academy of Sciences, 106*(9), 3479–3483. https://doi.org/10.1073/pnas.0813342106

Gogte, Kalpshree; Mamashli, Fatemeh; Herrera, Maria Georgina; Kriegler, Simon; Bader, Verian; Kamps, Janine; Grover, Prerna; Winter, Roland; Winklhofer, Konstanze F.; & Tatzelt, Jörg. (2024). Topological confinement by a membrane anchor suppresses phase separation into protein aggregates: Implications for prion diseases. *Proceedings of the National Academy of Sciences, 122*(1). https://doi.org/10.1073/pnas.2415250121

Hirsch, Morris W. (1997). *Differential topology* (Corr. 6. print). Springer.

James, Thomas L.; Liu, He; Ulyanov, Nikolai B.; Farr-Jones, Shauna; Zhang, Hong; Donne, David G.; Kaneko, Kiyotoshi; Groth, Darlene; Mehlhorn, Ingrid; Prusiner, Stanley B.; & Cohen, Fred E. (1997). Solution structure of a 142-residue recombinant prion protein corresponding to the infectious fragment of the scrapie isoform. *Proceedings of the National Academy of Sciences, 94*(19), 10086–10091. https://doi.org/10.1073/pnas.94.19.10086

Matoušek, Jirí. (2002). *Lectures on discrete geometry*. Springer.

Kamali-Jamil, Razieh; Vázquez-Fernández, Ester; Tancowny, Brian; Rathod, Vineet; Amidian, Sara; Wang, Xiongyao; Tang, Xinli; Fang, Andrew; Senatore, Assunta; Hornemann, Simone; Dudas, Sandor; Aguzzi, Adriano; Young, Howard S.; & Wille, Holger. (2021). The ultrastructure of infectious L-type bovine spongiform encephalopathy prions constrains molecular models. *PLOS Pathogens, 17*(6), e1009628. https://doi.org/10.1371/journal.ppat.1009628

Kawauchi, Akio. (2011). Topology of prion proteins: A joint work with Kayo Yoshida. In *Special Session on Knotting in Linear and Ring Polymer Models* [Conference]. AMS Sectional Meeting. https://user.keio.ac.jp/~ishikawa/tms2011/files/tms2011_kawauchi.pdf

Kovač, Valerija; & Čurin Šerbec, Vladka (2022). Prion Protein: The Molecule of Many Forms and Faces. *International Journal of Molecular Sciences, 23*(3), 1232. https://doi.org/10.3390/ijms23031232

Kraus, Allison; Hoyt, Forrest; Schwartz, Cindi L.; Hansen, Bryan; Artikis, Efrosini; Hughson, Andrew; Raymond, Gregory J.; Race, Brent; Baron, Gerald S.; & Caughey, Byron. (2021). *High-resolution structure and strain comparison of infectious mammalian prions. Molecular Cell, 81*(21). https://doi.org/10.1016/j.molcel.2021.08.011

Lee, John M. (2013). *Introduction to smooth manifolds* (2. edition). Springer.

Masone, Antonio; Zucchelli, Chiara; Caruso, Enrico; Lavigna, Giada; Eraña, Hasier; Giachin, Gabriele; Tapella, Laura; Comerio, Liliana; Restelli, Elena; Raimondi, Ilaria; Elezgarai, Saioa R.; De Leo, Federica; Quilici, Giacomo; Taiarol, Lorenzo; Oldrati, Marvin; Lorenzo, Nuria L.; García-Martínez, Sandra; Cagnotto, Alfredo; Lucchetti, Jacopo; Gobbi, Marco; Vanni, Ilaria; Nonno, Romolo; Di Bari, Michele A.; Tully, Mark D.; Cecatiello, Valentina; Ciossani, Giuseppe; Pasqualato, Sebastiano; Van Anken, Eelco; Salmona, Mario; Castilla, Joaquín; Requena Requena; Banfi, Stefano; Musco, Giovanna; Chiesa, Roberto. (2023). A tetracationic porphyrin with dual anti-prion activity. *iScience, 26*(9), 107480. https://doi.org/10.1016/j.isci.2023.107480

De Berg, Mark; Cheong, Otfried; & Overmars, Mark. (2008). *Computational geometry: Algorithms and applications* (3rd ed). Springer.

Miranzadeh Mahabadi, H., Hajar & Taghibiglou, Changiz.(2020). Cellular Prion Protein (PrPc): Putative Interacting Partners and Consequences of the Interaction. *International Journal of Molecular Sciences, 21*(19), 7058. https://doi.org/10.3390/ijms21197058

Ruffin, Vernon A.; Salameh, Ahlam I.; Boron, Walter F.; & Parker, Mark D. (2014). Intracellular pH regulation by acid-base transporters in mammalian neurons. *Frontiers in Physiology, 5*. https://doi.org/10.3389/fphys.2014.00043

Wang, Li-Qiang; Zhao, Kun; Yuan, Han-Ye;, Wang, Qiang; Guan, Zeyuan; Tao, Jing; Li, Xiang-Ning; Sun, Yunpeng; Yi, Chuan-Wei; Chen, Jie; Li, Dan; Zhang, Delin; Yin, Ping; Liu, Cong; & Liang, Yi (2020). Cryo-EM structure of an amyloid fibril formed by full-length human prion protein. *Nature Structural & Molecular Biology, 27*(6), 598–602. https://doi.org/10.1038/s41594-020-0441-5

Watt, Nicole T.; & Hooper, Nigel M. (2003). The prion protein and neuronal zinc homeostasis. *Trends in Biochemical Sciences, 28*(8), 406–410. https://doi.org/10.1016/s0968-0004(03)00166-x

Westergard, Laura; Christensen, Heather M.; & Harris, David A. (2007). The cellular prion protein (PrPC): Its physiological function and role in disease. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1772*(6), 629–644. https://doi.org/10.1016/j.bbadis.2007.02.011

Wille, Holger & Requena, Jesús. (2018). The Structure of PrPSc Prions. *Pathogens, 7*(1), 20. https://doi.org/10.3390/pathogens7010020

Zahn, Ralph; Liu, A., Lührs, T., Riek, R., Von Schroetter, C., López García, F., Billeter, M., Calzolai, L., Wider, G., & Wüthrich, K. (2000). NMR solution structure of the human prion protein. *Proceedings of the National Academy of Sciences, 97*(1), 145–150. https://doi.org/10.1073/pnas.97.1.145

Zhang, Yongbo; Swietnicki, Wieslaw; Zagorski, Michael G.; Surewicz, Witold K.; & Sönnichsen, Frank D. (2000). Solution Structure of the E200K Variant of Human Prion Protein. *Journal of Biological Chemistry, 275*(43), 33650–33654. https://doi.org/10.1074/jbc.C000483200

Barton Journal

Bioinformatics of the Oral Microbiome

FULL LENGTH ARTICLE

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CITATION

Jensen, Vivianna A.; & Bennett, Ashley L. (2026). Bioinformatics of the oral microbiome. *Barton Journal, 1*(1). 72–89. https://bartonjournal.org/vol-1-no-1/2026-cat1-article-no-003

Abstract

Bioinformatics analysis of the human oral microbiome is facilitating a better understanding of the human oral microbial inhabitants, variation of the oral microbiome across individuals, and links to oral and systemic human health, disease, and function. This research aims to identify patterns in taxonomic composition associated with rheumatoid arthritis and health by integrating bioinformatics with supervised and unsupervised machine learning tools to cluster publicly available human oral microbiome databases for both healthy and rheumatoid arthritis cohorts. Specifically, supervised machine learning was used to train a classifier model to predict the risk of developing rheumatoid arthritis from a given microbial genus cluster. The microbial genus clusters were input into the classifier model for rheumatoid arthritis risk predictions. While the classifier model was not robust for predicting rheumatoid arthritis risk, the classifier was able to make robust predictions about healthy cohorts and identify specific species strongly correlated with health, and identified some species of interest associated with rheumatoid arthritis. Although the classifier could not predict rheumatoid arthritis risk, the discovery of species strongly associated with healthy cohorts highlights the potential for probiotic-based preventive and therapeutic interventions. These findings highlight the importance of taxonomic analysis in facilitating disease risk predictions and advancing personalized dentistry and medicine, and reducing healthcare

costs by implementing more targeted diagnostics and treatments.

Keywords: Bioinformatics, bacteria, taxonomy, periodontal disease, machine learning

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Oral Microbial Diversity and Disease Development

The oral cavity houses about twenty billion bacterial individuals, representing a wide variety of species (Caselli et al., 2020). Alongside bacterial species, microbes such as fungi, viruses, and protozoa cling to the surfaces of the teeth and other oral cavity tissues to survive and reproduce (Baker, 2023). Emerging evidence suggests connections between the oral microbiome and more systemic health effects (Mei et al., 2020). Many oral bacterial microbes in plaque can cause damage to the mouth by eroding the enamel over time with their acidic properties. This metabolic activity is the number one cause of dental caries and tartar buildup (Baker, 2023). Anaerobic bacteria are common in the oral cavity and remain difficult to culture due to the need for a low- or no-oxygen environment. These anaerobic bacteria are the major etiologic agents contributing to chronic periodontitis by directly and indirectly destroying periodontal tissue, causing an intense inflammatory response (How et al., 2016).

The anaerobic bacteria in the oral cavity not only lead to deterioration of periodontal tissues but also increase the risk for adverse systemic health effects, mainly by promoting systemic inflammation and immune dysregulation (How et al., 2016). Furthermore, mounting evidence suggests relationships between the microbial populations and chronic conditions such as rheumatoid arthritis (RA) (Mei et al., 2020). With the link between inflammation and chronic disease well-established, these findings highlight that the oral microbiome is not isolated but interacts dynamically with the rest of the body, making it an important factor in overall health and a potential target for disease prevention and therapeutic intervention.

Age, diet, and dental hygiene are considered key factors in dental health as well. Tissue weakens and stretches over time, leading to gomphosis joint loosening, requiring partial or permanent tooth extractions (Salah et al., 2025). Attentive dental hygiene, like brushing and flossing, significantly slows oral deterioration by removing bacterial colonies that target the enamel, dentin, pulp cavity, and gum tissue (Salah et al., 2025). Flossing further helps by slowly hardening the gum tissue, increasing gum tolerance to penetration and abrasions. Simple dental hygiene procedures reduce the risk of gingivitis and periodontal disease by up to 50% (Salah et al., 2025). Other practices like smoking, vaping, chewing tobacco, and oral nicotine patches have impacts on oral health, frequently leading to significant damage to the mouth, including gum and bone loss (Baker, 2023).

Diet plays a crucial role in the likelihood of microbiome survival. Recent studies have shown that low levels of 2-5% of daily food consumed are used to feed microbiota in the human body (Zaske, 2025). Food's varying levels of pH, temperature, and salinity can impact the body's microbiota by either killing the microbiota or slowing down microbial functions in the body significantly. While the oral microbiome can have negative health impacts, the human microbiome generally provides many benefits, with some species of microbiota required for proper digestion and respiration.

In pursuit of a better understanding of the health impacts of microbes inhabiting the oral cavity, this journal article presents a bioinformatics analysis and machine learning classifier model to predict disease outcomes from the taxonomic genus of species living in the oral microbiome. The initial model serves as a preliminary proof of concept to demonstrate how bioinformatics tools, when integrated with machine learning, can predict health status based on microbial species present in the oral cavity, which could be determined by a simple saliva swab. Future work will expand and generalize this initial model to a wider variety of diseases with the hope of revealing a distinct and predictive microbial pattern between healthy and diseased cohorts.

Literature Review

Bioinformatics is a cocktail of biology, computer science, data science, and mathematics to analyze, store, and interpret large-scale complex biological data, including DNA, protein sequences, and microbiome datasets rapidly since the late 1960's (Baker, 2023). Machine learning is a recent advancement of data science providing several powerful tools that can assist researchers in identifying trends in large-dimensionality data (Zhang et al., 2025).

Background

The oral microbiome is a diverse community of organisms living in the human mouth composed of a diverse abundance of bacterial species, along with fungi and viruses. Three crucial roles of the microbiome are maintaining oral health, preventing pathogen colonization, and supporting digestion (Caselli et al., 2020). When the oral microbiome is disturbed, it can result in mild or severe oral diseases (Salah et al., 2025). The presence of specific microbial species has been shown to promote systemic inflammation and immune dysregulation (How et al., 2016), for which there is a well-established link between systemic inflammation and chronic disease progression (Martel et al., 2022).

Traditional culture-based microbiology has been a great resource for studying microbes, but the inability to culture oral microbes like anaerobic species under standard lab conditions, the failure of culture conditions to replicate natural oral environments, and limited insight into microbial interactions have impeded the identification of causal relationships between oral microbiome populations and disease risk (Uzoukwu et al., 2022; Vartoukian et al., 2017). Bioinformatics and machine learning tools circumvent these shortcomings because the tools organize and identify patterns in high-dimensional datasets, allowing for adequate identification and characterization of uncultured microbes directly from patient samples.

Bioinformatics Approaches

Advances in 16S ribosomal RNA (rRNA) gene amplicon sequencing have enabled the comprehensive characterization of microbial communities within the oral cavity by targeting conserved regions of the bacterial genome to identify and classify microorganisms present in oral samples (Regueira-Iglesias et al., 2023). Shotgun metagenomic sequencing has been employed to provide species- and strain-level resolution and to characterize functional gene content within oral microbial communities (Baker, 2023). Subsequent downstream bioinformatics analyses focus on quantifying microbial diversity and community composition.

To ensure reproducibility and data transparency, modern oral microbiome studies employ standardized workflows, version-controlled code repositories, and public data deposition in repositories such as the NCBI Sequence Read Archive (SRA; Leinonen et al, 2011; Kodama et al, 2012; Katz et al, 2022). Collectively, these bioinformatics tools and techniques provide a robust framework for investigating the structure, diversity, and functional potential of oral microbial communities and for exploring and predicting their roles in oral and systemic health.

Application

Bioinformatics has a wide range of applications across science and healthcare. One example is disease detection. Bioinformatics helps identify microbial biomarkers associated with both oral and systemic disease, allowing for earlier diagnosis before clinical symptoms appear (Yeo et al., 2024). Information yielded from bioinformatics analysis can now inform the development of microbiome-based therapies, making treatments proactive rather than reactive (Salah et al., 2025).

Challenges

Despite the great attributes, bioinformatics has limitations. For instance, managing large datasets requires costly advanced computational resources – mainly vast hard drive space for storing data input and output and massive RAM memory for training models (Baker, 2023). Additionally, the sheer size and complexity of high-dimensional datasets tend to obfuscate identifications of trends. Furthermore, bioinformatic analysis can produce errors if the wrong models are applied, algorithms are misused, and distinguishing correlation from causation in microbiome studies remains an ongoing challenge, which can, in part, be overcome with modern machine learning algorithms (Regueira-Iglesias et al., 2023).

Machine Learning Tools

Machine learning provides powerful tools for analyzing large biomedical datasets and building classifier models to predict disease risk based on molecular, clinical, or microbiome features. In supervised learning, algorithms are trained on labeled datasets (e.g., healthy vs. diseased) to learn relationships between features and outcomes, whereas unsupervised learning methods identify patterns in unlabeled data (Traidl et al., 2025). These methods are applied in various ways to detect natural groupings, reveal disease subtypes, and select informative features for predictive modeling (Naeem et al., 2022).

Principal component analysis PCA is a common analysis to search for variance and identify patterns in large-dimensionality data (Traidl et al., 2025). The first and second components, PC1 and PC2, respectively, indicate the dimensions with the maximum variance and indicate features that may be predictive of different health status classes. Components with high variance are potential candidates as biomarker predictors of disease outcomes. The random forest approach is a particularly well-suited approach for training classifier models by aggregating the results of multiple decision trees into a single output (Traidl et al., 2025), which allows for more robust model predictions for both linear and non-linear data and can automatically select relevant features in the data, which in turn facilitates trend identification in heterogeneous data, such as microbiome and biomedical

data (Traidl et al., 2025).

By enabling rigorous validation, reproducibility across independent datasets, and systematic evaluation of feature importance, machine learning addresses the challenge of distinguishing correlation from causation. When combined with thoughtful study design and experimental validation, these approaches support robust disease prediction and hypothesis generation in complex biological systems.

Findings

Bioinformatics and machine learning tools have revolutionized oral microbiome research, allowing scientists to identify thousands of previously unrecognized species, analyze functional capabilities of microbial communities, and emphasize associations with oral and systemic health. While much has been done to collect oral microbiome data and develop analytical tools, there remains much to be learned about the relationship between the oral microbiome and disease risk.

Methods

The Expanded Human Oral Microbiome Database (eHOMD) documents the human microbiome by providing the identity of >8,000 genomes across > 830 microbial taxa inhabiting the nasal passages, sinuses, throat, esophagus, mouth, and the lower respiratory tract (Baker, 2023; Fernández Escapa et al., 2018). The eHOMD also includes species-level taxonomy based on grouping 16S RNA gene sequences at 98.5% identity, a systematic naming scheme for unnamed and uncultivated microbial taxa, reference genomes to facilitate metagenomic studies, and convenient cross-links to other databases that can facilitate mapping of taxonomic data to known disease status (Baker, 2023; Regueira-Iglesias et al., 2023). The taxonomic data from the eHOMD were chosen for analysis, given the wide diversity of represented species and the standardized formatting to facilitate bioinformatics analysis. mBodyMap also provides the data on >6,000 species isolated from >22 body locations in people of varying health and disease diagnosis, which was used to train the machine learning model to recognize microbial taxonomic genus predictors of disease (Jin et al., 2022). Data was acquired on 24 March 2026.

Implementation

Custom Python analysis scripts implementing Pandas, NumPy, SciPy, Scikit-learn, Biopython, and Matplotlib packages are the primary software packages used to process the data (Buitinck et al., 2013; Harris et al., 2020; Hunter, 2007; pandas development team, 2020; Virtanen et al., 2020). Data input, output, organization, and management were handled by Pandas. Imported taxonomic datasets from the eHOMD database were turned into structured data tables using the Pandas library. The workflow helps to remove incomplete records and format taxonomic labels by sorting, filtering, and grouping microbial species data to make it easier for the machine learning model to analyze. NumPy was used primarily for its ability to perform numerical and mathematical operations on large datasets, allowing for effective handling of large arrays of microbial abundance values with efficient usage of computational memory. The software provides statistical calculation and data transformation tools and improves computational efficiency when processing large microbiome datasets

(Reguieora-Iglesias, 2023). SciPy is exceptionally strong at analyzing relationships between microbial taxa by providing a variety of prebuilt regression models for data fitting, helping support advanced mathematical operations involved with the machine learning algorithms (Baker, 2023).

Scikit-learn and Matplotlib were the final libraries used. Scikit-learn provides functions specializing in building machine learning models and clustering algorithms to identify patterns in microbial communities (Yeo et al., 2024). Matplotlib provides functions for data visualization and helps emphasize trends extracted from taxonomic composition between samples of healthy and RA status.

Machine Learning Workflow

The end-to-end workflow for building the machine learning classifier is depicted in Figure 1 and carried out in a Jupyter Notebook to facilitate thorough documentation of code commands, results, and data visualizations. Taxonomic data were downloaded from eHOMD onto a 2022 MacBook Air M2 with 857.2 GB of available storage, macOS Sonoma 14.4.1 operating system, and the healthy and disease cohort data were downloaded from mBodyMap databases onto the same machine. The downloaded files were renamed to reflect the source of the primary data source and the applications of the data contained within the file.

Once all datasets were downloaded, disease labels were added to the healthy and disease cohorts from the mBodyMap database and combined into a single data file. Subsequently, the combined disease status data were cleaned by removing any entries that had improperly formatted or missing values. The cleaned data were transformed into a feature matrix using the measured abundance as the featurization value. The feature matrix was subsequently normalized to ensure all feature values had comparable scales.

A random forest classifier implemented using scikit-learn with 200 estimators and the 80/20 train/test split was used to train a classifier using the combined, cleaned, and normalized disease status dataset. The 80/20 split of the data works such that 80% of the training data is used for training and 20% is used for model testing, allowing for assessment of model quality based on prediction accuracy for each class (i.e., healthy and RA). The model quality was assessed using the standard internal model quality metrics output by scikit-learn – mainly precision representing class prediction accuracy, recall reflecting the percentage of properly identified classes, f1 score that shows the balance between precision and recall, and support, which demonstrates how many samples in the training data are in each prediction class.

Figure 1

Workflow of Machine Learning Model

Note. A visual depiction of the workflow used to train the machine learning classifier model.

Classifier Model Predictions

After the classifier model was trained, taxonomic genus data from the eHOMD were fed into a k-means clustering algorithm using 5 clusters with the initial centroids chosen from the data at random. The resulting clusters were mapped back to the classifier feature space, normalized, and fed as input to the classifier model to predict the disease status associated with each taxonomic cluster. The species contained within each cluster was determined and compared to reveal potential microbial biomarkers of RA disease vs health and to determine places for improving the classifier model. Matplotlib was used for plotting and visualizing the results.

Results / Findings

The combined training dataset comprises microbial species associated with both healthy and RA class cohorts, with >400 microbial species, including 53 shared between the classes and 19 species specific to the RA class (Table 1). Species showing more than 5-fold change in abundance between healthy and RA classes are *Pseudomonas fluorescens, Treponema succinifaciens, Schaalia meyeri,* and *Schwartzia succinivorans* (Table 2), suggesting that the relative abundance of specific species may be an important predictor.

Table 1

The Total Number of Unique, Common, and Specific Species Observed in the healthy and rheumatoid arthritis (RA) cohorts

Total unique species	41 5
Shared species	52
Healthy only species	34 4
RA only species	19

Table 2

Class Comparison of the Mean Abundance of Shared Species

Species	**Healthy Mean**	**RA Mean**	**Fold Change**
Pseudomonas fluorescens	0.542	24.914	46.005
Treponema succinifaciens	0.082	0.833	10.184
Schaalia meyeri	0.330	2.631	7.967
Schwartzia succinivorans	0.082	0.583	7.130
Streptobacillus hongkongensis	0.122	0.405	3.319
[Eubacterium] saphenum	0.147	0.440	3.000
Prevotella baroniae	0.122	0.365	2.999

Selenomonas sputigena	0.717	1.907	2.661
Selenomonas infelix	1.260	2.563	2.033

Note. Species that were shared between both healthy and rheumatoid arthritis (RA) and demonstrated > 2-fold change in mean abundance between healthy and RA classes.

Classifier Model Performance

The initial classifier model performed strongly on identifying clusters associated with healthy status, accurately predicting 96% of healthy clusters, with 4% of the actually healthy class being mistakenly predicted as the RA class (Table 3). In contrast, the classifier model failed to accurately predict RA disease status, accurately predicting 0% of RA labelled entries (Table 3). Large differences in precision, recall, and F1 scores between the macro average and weighted averages indicate that one of the data classes is either over- or underrepresented (Table 3). The training data contained 54 data points associated with the healthy class and only 2 points with the RA class, demonstrating that the RA data is underrepresented in the training data, consistent with the discrepancy between macro and weighted averages (Table 3). This underrepresentation of the RA data in the training dataset is the most likely reason for the model's failure to predict the RA class accurately.

Table 3

Statistics Reporting Classifier Model Prediction Quality

	precision	**recall**	**f1-score**	**support**
healthy	0.96	1.00	0.98	54
RA	0.00	0.00	0	2
accuracy			0.96	56
macro avg	0.48	0.50	0.49	56
weighted avg	0.93	0.96	0.95	56

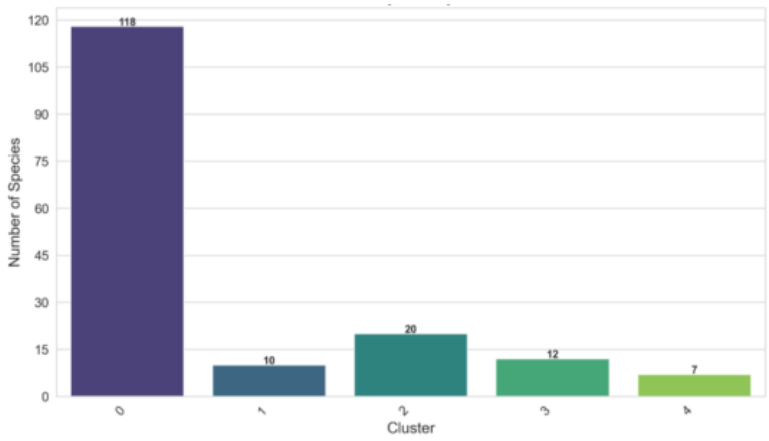
Note. The precision, recall, f1-score, and support metrics determine the model accuracy in predicting healthy and rheumatoid arthritis (RA), given a microbial genus-based clustering.

Microbial Taxonomic Clustering

Cluster 0 was the largest cluster with 118 species (Figure 2). The smaller clusters 1, 2, 3, and 4 contained only a single genus each, with cluster 1 representing *Actinomyces*, cluster 2 representing *Streptococcus*, cluster 3 representing *Neisseria*, and cluster 4 containing *Haemophilus* genera. In contrast, the largest cluster 0 contained a wide diversity of microbial genera, some of which contained multiple species, while others appeared to contain only one species. The mapping of clusters 1-4 to specific genera indicates that a genus-based clustering of microbiome taxonomic genus is effective at separating out the microbial genera that are well represented in the microbiome. However, multiple different genera's presence in cluster 0 suggests that genera with fewer than approximately 5 different species in the dataset are not able to be clustered in a meaningful way based on genus, with only 5 clusters.

Figure 2

Sizes of Microbial Genus Clusters



Note. The size of each microbial genus cluster (x-axis) as measured by the number of species in the cluster (y-axis).

PCA

The PCA of the genus-based clustering of microbes successfully separated the five different clusters, with the identified PC1 and PC2 accounting for about 21% and 20.4% of data variance, respectively (Figure 3A). The PCA of clustered microbial genus data demonstrates that all genus clusters are strongly dominated by the healthy class (Figure 3B). Clusters 0 and 3 have positive correlations with both principal components, cluster 0 positively correlating to PC1 and cluster 3 positively correlating to PC2 (Figure 3B). The remaining three clusters have either neutral or negative correlations with both principal components (Figure 3B). Cluster 3 shows a strong positive correlation with PC2 and contains only healthy class microbial genera, suggesting

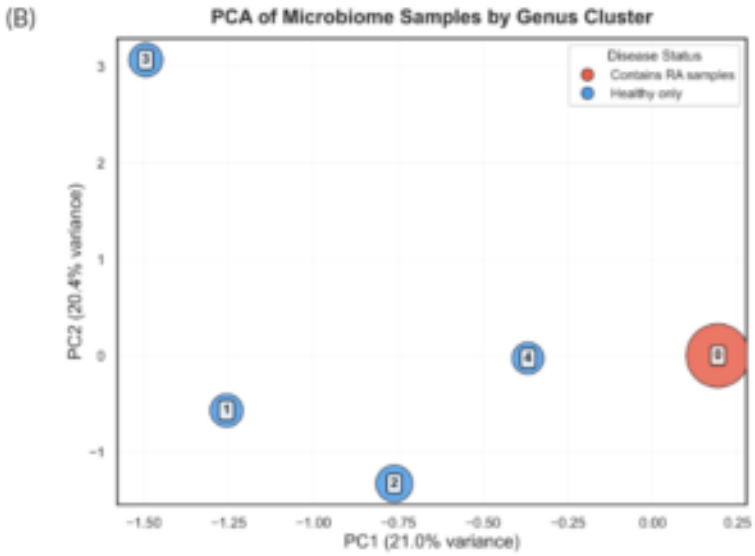
that PC2 is associated with the healthy class. Clusters 1, 2, and 4 all contained only healthy classes and were well-separated along PC1 with a smaller separation along PC2 (Figure 3).

The only cluster with a positive correlation with PC1 is also the only cluster containing any RA class cohorts, which suggests that perhaps PC1 is an indicator of RA class (Figure 3B). However, this cluster is still strongly dominated by healthy class cohorts, which would alternatively suggest that PC1 is also an indicator of healthy class. The correlation between cluster 0 and PC1 is relatively weak and may indicate that the failure of the clustering algorithm to adequately separate out diverse genera is influencing the correlation value and obfuscating pattern detection. Further separation of the species contained in cluster 0 would likely be needed to draw definitive conclusions about the meaning of PC1.

Species examination, most strongly correlated with PC1 and PC2, reveals that *Neisseria bacilliformis* (*N. bacilliformis*) is the species most positively correlated with PC1, while *Streptococcus vestibularis* (*S. vestibularis*) was most negatively correlated with PC2. *N. bacilliformis* was also most positively correlated with PC1, and *S. vestibularis* was also most negatively associated with PC1. Additionally, *N. bacilliformis* and *S. vestibularis* both showed the largest discrepancy between PC1 and PC2 loadings, suggesting that these two species may be better predictors of health status than other species in the dataset. Interestingly, the PCA loadings revealed different species of interest than the fold change in abundances between the classes (Table 2), suggesting that PCA loadings may also be a useful feature to include in training.

Figure 3

Principal Component Analysis of Oral Microbiome Genus Clusters



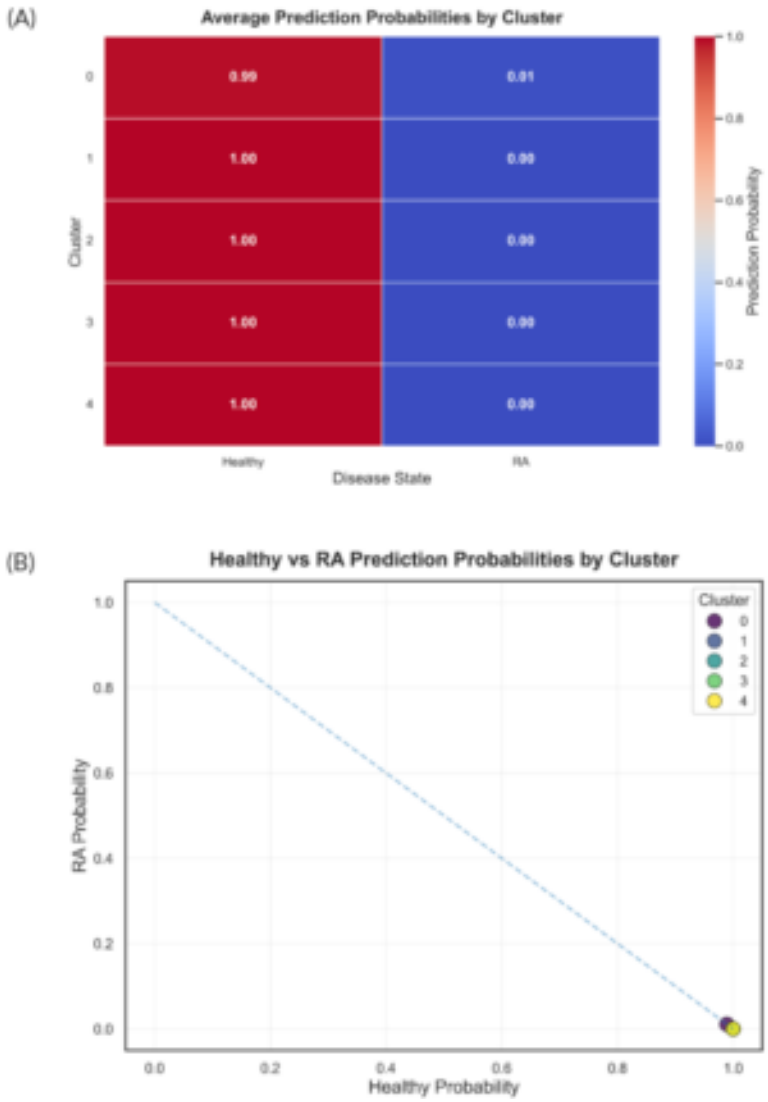
Notes. (A) Principal components 1 (PC1; x-axis) and principal component 2 (PC2; y-axis) explain approximately 21% and 20% of the data variance, respectively. Each point represents a species in the training data, consisting of microbial profiles from both healthy and rheumatoid arthritis cohorts, and is colored according to the cluster they belong to. Blue, orange, green, red, and purple represent cluster 0, cluster 1, cluster 2, cluster 3, and cluster 4, respectively. (B) The same PCA plots the centroids of each cluster, with the node size determined from the number of species contained within that cluster. Cluster nodes are colored according to their disease label: healthy (blue) and rheumatoid arthritis (RA; red), and labeled according to their cluster number.

eHOMD Taxonomic Cluster Model Predictions

Despite the model's failure to accurately predict RA, the eHOMD dataset was input to the classifier model in the hope that the prediction results would inform future efforts to improve and generalize the classifier model. Consistent with previous data observations, only one cluster was associated with a non-zero probability of RA class, with cluster 0 probability of 99% for the healthy class and 1% for the RA class (Figure 4A). Clusters 1-4 had a 100% probability of healthy class prediction (Figure 4B). All the clusters lie on the decision boundary, consistent with the RA class being underrepresented in the training data (Figure 4B). Continued improvements in model accuracy are needed before any further conclusions can be drawn from classifier model predictions.

Figure 4

Class Predictions for Microbial Genera Clusters



Notes. (A) A heatmap of the prediction probabilities for the two model classes (x-axis), healthy and rheumatoid arthritis (RA), in each of the five microbial genus clusters. The color gradient represents model-predicted disease probabilities for each cluster. Values range from 0 (blue), indicating low predicted probability of rheumatoid arthritis, to 1 (red), indicating high predicted probability. Intermediate colors reflect an increasing likelihood of disease classification. (B) A scatter plot representation of the probability of a RA vs. healthy class class predictions. The dashed diagonal line represents the decision boundary where predicted probabilities for Healthy and RA are equal.

Discussion

The presented work leverages publicly available oral microbiome databases to train a machine learning model capable of predicting health outcomes from clustered taxonomic data. Clustering of oral microbiome taxonomic data from the myBodyMap database and comparing the relative abundances of microbial species between healthy and RA cohorts revealed that *Pseudomonas fluorescens, Treponema succinifaciens, Schaalia meyeri,* and *Schwartzia succinivorans* all show more than 5-fold change between the two classes (Table 2). In the context of previous work, the observed clustering patterns suggest that well-represented genera form distinct, stable groupings, some of which are associated with healthy states, as opposed to unbalanced communities that can be potential disease precursors for periodontal and systemic health diseases (Figure 3). These findings are consistent with prior work, which has demonstrated that shifts in microbial composition, particularly increases in specific pathogenic taxa, are associated with disease progression.

The classifier model trained using a random forest algorithm with an 80/20 split in the training data showed robust predictions for the healthy class, but was unable to accurately predict the RA class, limiting the applicability of this model in its current training state. The failure of the classifier model to predict RA class is consistent with an imbalanced dataset used for machine learning training, particularly the underrepresentation of disease states such as RA. This imbalance likely contributed to the model's inability to accurately predict disease outcomes, as it biased predictions towards the dominant healthy class. Additionally, the clustering approach may oversimplify the complexity of microbial ecosystems, particularly for less abundant taxa that could still play important biological roles. Exploring alternative clustering methods with different numbers of clusters would likely result in model improvements, especially for separating out cluster 0 species. Future work to improve this classifier model should incorporate larger datasets for training, especially including a larger diversity of body locations and disease classes to address the small training data size and the underrepresented RA class. Additionally, while the training data remains small, a 90/10 train/test split should be incorporated during model training so that a larger percentage of data can be used for training and a smaller percentage can be used for model testing and validation.

PCA identified PC1 and PC2 components that explain about 21% and 20.4% of the data, respectively. Cluster 3 only contained microbial species associated with the healthy class and was strongly positively correlated with PC2, indicating that PC2 represents the healthy class. While cluster 0 was most positively correlated with PC1 and was the only cluster to contain RA class cohorts, cluster 0 was still dominated by healthy cohorts, and the meaning of PC1 remains unclear.

Clusters 1-4 were dominated by particular genera, including *Actinomyces*, *Streptococcus*, *Neisseria*, and *Haemophilus,* and contained only healthy class cohorts (Figure 3). However, unlike some previous studies that identify clear separations between healthy and disease microbiomes, the present analysis did not find any genus clusters strongly predictive of disease. Cluster 0 contained some cohorts of the RA class, but was still dominated by the healthy class. Taken together, this clustering analysis suggests that taxonomic data alone may not always be sufficient to fully distinguish disease states without additional functional or environmental context.

Future work should focus on expanding the dataset size and diversity, particularly by increasing the representation of disease-associated samples. Incorporating additional data types such as metagenomic, transcriptomic, or metabolomic data and inclusion of more features in the training data may improve model performance and provide deeper insights. Furthermore, the application of more advanced machine learning techniques and strategies to address class imbalance, such as resampling or class weighting, could enhance predictive accuracy. This work contributes to a growing foundation for using microbiome data in predictive modeling and highlights the potential for integrating bioinformatics into clinical and public health applications.

Conclusion

While the classifier model was not successful in predicting RA class, the clustering analysis was able to detect shifts in the microbial populations between the health and RA class cohorts. Identified species of interest include *Pseudomonas fluorescens, Treponema succinifaciens, Schaalia meyeri, Schwartzia succinivorans, Neisseria bacilliformis*, and *Streptococcus vestibularis*. Despite the identification of potentially interesting species to investigate further, much work is needed to improve the clustering and predictive accuracy of disease classes. Improvements to the clustering and classifier can be made through several updates to the modeling workflow, including but not limited to different clustering techniques and the number of clusters, more advanced clustering and training algorithms, and, most importantly, by increasing the training dataset size, body location diversity, and disease classes represented within the training data.

Dentists are now well-positioned to use the results of oral microbioinformatics to prevent and initiate earlier treatment for oral health diseases. Instead of fighting against already present symptoms, dental specialists can use the results of a patient's oral microbiome to reverse, prevent, or slow down periodontitis and gingivitis diseases, allowing older patients a fighting chance at restorative measures instead of major extractions. The prosthodontic, periodontal, and oral surgery possibilities for successful cosmetic and restorative work, including implants, implanted dentures, crowns, bridges, and bone and tissue grafts, will significantly increase the likelihood of positive oral health outcomes due to decreased probability of bone and tissue loss with personalized treatment planning and care.

With the realm of bioinformatics expanding, the application of oral microbiomics does not have to stop at dental medicine. It is likely that these techniques will eventually be incorporated into personalised healthcare and help healthcare practitioners to inform early diagnostics and treatment decisions. As a deeper understanding of the connections between the oral microbiome and systemic disease emerges, dentists will become integral members of the healthcare team and facilitate preventative and personalized oral health care. Dentists can promote early diagnosis by collecting oral swabs from patients and having them sent for taxonomic breakdown in labs, and then studying the results to determine if early disease preventative treatments are necessary for patients' oral health.

Dentists can flag patients whose oral microbiome predicts more systemic health issues and work with primary caregivers to mitigate potential disease development in the future. Additionally, nurses, surgeons, and pharmacists can use bacterial taxonomic information from relevant microbiome studies to better assess

individual patients, as opposed to treating every patient as if they were identical clones. Through this type of predictive screening and personalized medicine, dentists can collaborate with healthcare providers across many disciplines to improve diagnostics, treatments, and prognosis for patients, all while reducing healthcare costs.

References

Baker, Jonathon L. (2023). Illuminating the oral microbiome and its host interactions: Recent advancements in omics and bioinformatics technologies in the context of oral microbiome research. *FEMS Microbiology Reviews, 47*(5), fuad051. https://doi.org/10.1093/femsre/fuad051

Buitinck, Lars; Louppe, Gilles; Blondel, Mathieu; Pedregosa, Fabian; Mueller, Andreas; Grisel, Olivier; Niculae, Vlad; Prettenhofer, Peter; Gramfort, Alexandre; Grobler, Jaques; Layton, Robert; VanderPlas, Jake; Joly, Arnaud; Holt, Brian; & Varoquaux, Gaël. (2013). API design for machine learning software: Experiences from the scikit-learn project. *arXiv preprint arXiv:1309.0238*. https://doi.org/10.48550/arXiv.1309.0238

Caselli, Elisabetta; Fabbri, Chiara; D'Accolti, Maria; Soffritti, Irene; Bassi, Cristian; Mazzacane, Sante; & Franchi, Maurizio. (2020). Defining the oral microbiome by whole-genome sequencing and resistome analysis: The complexity of the healthy picture. *BMC Microbiology, 20*, 120. https://doi.org/10.1186/s12866-020-01801-y

Feng, Mei; Xie, Mengru; Huang, Xiaofei; Long, Yanlin; Lu, Xiaofeng; Wang, Xiaoli; & Chen, Lili. (2020). Porphyromonas gingivalis and its systemic impact: Current status. *Pathogens, 9*(11). https://doi.org/10.3390/pathogens9110944

Fernández Escapa, Isabel; Chen, Tsute; Huang, Yanmei; Gajare, Prasad; Dewhirst, Floyd E.; & Lemon, Katherine P. (2018). New insights into human nostril microbiome from the expanded Human Oral Microbiome Database (eHOMD): A resource for species-level identification of microbiome data from the aerodigestive tract. *mSystems, 3*(6), e00187-18. https://doi.org/10.1128/mSystems.00187-18

Harris, Charles R.; Millman, K. Jarrod; van der Walt, Stéfan J.; Gommers, Ralf; Virtanen, Pauli; Cournapeau, David; Wieser, Eric; Taylor, Julian; Berg, Sebastian; Smith, Nathaniel J.; Kern, Robert; Picus, Matti; Hoyer, Stephan; van Kerkwijk, Marten H.; Brett, Matthew; Haldane, Allan; Del Río, Jaime Fernández; Wiebe, Mark; Peterson, Pearu; Gérard-Marchant, Pierre; Sheppard, Kevin; Reddy, Tyler; Weckesser, Warren; Abbasi, Hameer; Gohlke, Christoph; & Oliphant, Travis E. (2020). Array programming with NumPy. *Nature, 585*, 357–362. https://doi.org/10.1038/s41586-020-2649-2

How, Kah Yan; Song, Keang Peng; & Chan, Kok Gan. (2016). Porphyromonas gingivalis: An overview of the periodontopathic pathogen below the gum line. *Frontiers in Microbiology, 7*, 53. https://doi.org/10.3389/fmicb.2016.00053

Human Oral Microbiome Database (HOMD). (2008). Human Oral Microbiome Database. https://www.homd.org/

Hunter, John D. (2007). Matplotlib: A 2D Graphics Environment. *Computing in Science & Engineering*, *9*(3), 90–95. https://doi.org/10.1109/MCSE.2007.55.

Jin, Hanbo; Hu, Guoru; Sun, Chuqing; Duan, Yiqian; Zhang, Zhenmo; Liu, Zhi; Zhao, Xing-Ming; & Chen, Wei-Hua. (2022). mBodyMap: A curated database for microbes across the human body and their associations with health and diseases. *Nucleic Acids Research, 50*(D1), D808–D816. https://doi.org/10.1093/nar/gkab973

Katz, Kenneth; Shutov, Oleg; Lapoint, Richard; Kimelman, Michael; Brister, J. Rodney; & O'Sullivan, Christopher. (2022). The Sequence Read Archive: A decade more of explosive growth. *Nucleic Acids Research*, *50*(D1), D387–D390. https://doi.org/10.1093/nar/gkab1053

Kodama, Yuichi; Shumway, Martin; Leinonen, Rasko; & International Nucleotide Sequence Database Collaboration. (2012). The Sequence Read Archive: Explosive growth of sequencing data. *Nucleic Acids Research*, *40*(Database issue), D54-56. https://doi.org/10.1093/nar/gkr854

Leinonen, Rasko; Sugawara, Hideaki; Shumway, Martin; & International Nucleotide Sequence Database Collaboration. (2011). The sequence read archive. *Nucleic Acids Research*, *39*(Database issue), D19-21. https://doi.org/10.1093/nar/gkq1019

Martel, Jan; Chang, Shih-Hsin; Ko, Yun-Fei; Hwang, Tsong-Long; Young, John D.; & Ojcius, David M. (2022). Gut barrier disruption and chronic disease. *Trends in Endocrinology and Metabolism: TEM, 33(4)*, 247–265. https://doi.org/10.1016/j.tem.2022.01.002

Naeem, Samreen; Ali, Aqib; Anam, Sania; & Ahmed, Muhammad Munawar. (2023). An unsupervised machine learning algorithm: Comprehensive review. *International Journal of Computing and Digital Systems.*

Regueira-Iglesias, Alba; Balsa-Castro, Cristina; Blanco-Pintos, Tamara; & Tomás, Inmaculada. (2023). Critical review of 16S rRNA gene sequencing workflow in microbiome studies: From primer selection to advanced data analysis. *Molecular Oral Microbiology, 38*(5), 347–399. https://doi.org/10.1111/omi.12434

Roy, Somak; Coldren, Christopher; Karunamurthy, Arivarasan; Kip, Nefize S.; Klee, Eric W.; Lincoln, Stephen E.; Leon, Annette; Pullambhatla, Mrudula; Temple-Smolkin, Robyn L.; Voelkerding, Karl V.; Wang, Chen; & Carter, Alexis B. (2018). Standards and guidelines for validating next-generation sequencing bioinformatics pipelines: A joint recommendation of the Association for Molecular Pathology and the College of American Pathologists. *The Journal of Molecular Diagnostics, 20*(1). https://doi.org/10.1016/j.jmoldx.2017.11.003

Salah, Akram N.; Doghish, Youssef A.; Abbass, Shaimaa O.; Mansour, Reda M.; Sayed, Ghadir A.; Elshami, Nourhan H.; Abdel Mageed, Sherif S.; Mohammed, Osama A.; Abulsoud, Ahmed I.; Zaki, Mohamed Bakr.; Mosalam, Esraa M.; Elrebehy, Mahmoud A.; Alfarsi, Kareem; & Doghish, Ahmed S. (2025). Microbiota-based therapies in oral health and disorders. *Folia Microbiologica, 70*, 1217–1240.

https://doi.org/10.1007/s12223-025-01324-x

Shetty, Shruthi H.; Shetty, Sumiksha; Singh, Chandra; & Rao, Ashwath. (2022). Supervised machine learning: Algorithms and applications. In P. Singh (Ed.), *Fundamentals and Methods of Machine and Deep Learning*. https://doi.org/10.1002/9781119821908.ch1

Traidl, S., Mathes, S., & Seurig, S. (2025). AI – one size fits all? *Allergologie Select*, *9*, 75–79. https://doi.org/10.5414/ALX02568E

The pandas development team. (2020). *pandas-dev/pandas: Pandas* (Version latest) [Software]. Zenodo. https://doi.org/10.5281/zenodo.3509134

Uzoukwu, Ekeoma U.; Phandanouvong-Lozano, Vienvilay; Usman, Huda; Sfeir, Charles S.; & Niepa, Tagbo H. R. (2022). Droplet-based microsystems as novel assessment tools for oral microbial dynamics. *Biotechnology Advances, 55.* https://doi.org/10.1016/j.biotechadv.2021.107903

Vartoukian, Samuel R.; Moazzez, Ramin V.; & Wade, William G. (2017). Cultivation strategies for the growth of uncultivated bacteria. *F1000Research, 6*, 578. https://doi.org/10.12688/f1000research.10835.1

Virtanen, Pauli; Gommers, Ralf; Oliphant, Travis E.; Haberland, Matt; Reddy, Tyler; Cournapeau, David; Burovski, Evgeni; Peterson, Pearu; Weckesser, Warren; Bright, Jonathan; van der Walt, Stéfan J.; Brett, Matthew; Wilson, Joshua; Millman, K. Jarrod; Mayorov, Nikolay; Nelson, Andrew R. J.; Jones, Eric; Kern, Robert; Larson, Eric; Carey, CJ; Polat, İlhan; Feng, Yu; Moore, Eric W.; VanderPlas, Jake; Laxalde, Denis; Perktold, Josef; Cimrman, Robert; Henriksen, Ian; Quintero, E. A.; Harris, Charles R.; Archibald, Anne M.; Ribeiro, Antônio H.; Pedregosa, Fabian; van Mulbregt, Paul; & SciPy 1.0 Contributors. (2020). SciPy 1.0: Fundamental algorithms for scientific computing in Python. *Nature Methods, 17*(3), 261–272. https://doi.org/10.1038/s41592-019-0686-2

Yeo, Kenny; Wu, Fei; Li, Rui; et al. (2024). Is short-read 16S rRNA sequencing of oral microbiome sampling a suitable diagnostic tool for head and neck cancer? *Pathogens, 13*(10), 826. https://doi.org/10.3390/pathogens13100826

Zaske, Sara. (2025). Energy supplied by the gut microbiome depends on diet. *Stanford School of Humanities and Sciences.* https://humsci.stanford.edu/feature/energy-supplied-gut-microbiome-depends-diet

Zhang, Yuhan; Luo, Jiahui; Chen, Kuangyu; Li, Na; Luo, Chenyu; Di, Shuang; Qin, Junjie; Zhang, Feng; Chen, Hongda; & Dai, Min. (2025). Cross-cohort analysis identifies shared gut microbial signatures and validates microbial risk scores for colorectal cancer. Journal of Translational Medicine, 23(1), 676. https://doi.org/10.1186/s12967-025-06676-z

Barton Journal

Phototaxis in *Drosophila melanogaster*

FULL-LENGTH ARTICLE

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CITATION

Cyzick, Makenzie; & Dommer, David. (2026). Phototaxis in *Drosophila melanogaster*. *Barton Journal, 1*(1), 90–95. https://bartonjournal.org/vol-1-no-1/2026-cat1-article-no-004

Abstract

The study was conducted to investigate the phototactic response in *Drosophila melanogaster*, also known as fruit flies. *Drosophila melanogaster* were chosen for this study because they have genetic and biological similarities to humans. The study was designed to be completed over a twelve week period looking at Phototaxis, which is how light can affect the movement of organisms. The purpose of this study is to expose *Drosophila melanogaster* to light and observe their behavior. It was intended to observe the positive and negative phototaxis under the controlled environment and see how light plays a vital role in an organism's life and how it can be used for survival. The Drosophila melanogaster would be isolated to a controlled environment, where they will have an artificial light source to see how the organisms react and move to and from the light. Unfortunately, the fruit flies were unable to survive due to unfavorable habitat conditions. The temperatures fluctuated and the fruit flies were unable to flourish in the environmental conditions and prevented the larval from developing. Since the study was unable to be conducted, the research shifted to a literature review focusing on phototaxis and geotaxis on Drosophila melanogaster. Under the guidance of a mentor, students analyzed previous experiments and research to develop a comprehensive understanding of these behavioral responses.

Keywords: *Drosophila melanogaster*, phototaxis, behavior, light, survival

Introduction

Studying phototaxis and geotaxis in animals allows researchers to gain a better understanding how light and magnetic forces can affect their behavioral and sensory functions. Research in phototaxis is beneficial because it can be essential for animals finding food, mates, shelter, migration, and survival. *Drosophila melanogaster* were chosen for this experiment because of the short generation time, high reproductive rate, genetic tools and homology, behavioral assays, and biological similarities fruit flies share with humans. Fruit flies are used in many scientific experiments because of these qualities and how they can relate to behavior, neurobiology, and genetics. The purpose of this experiment was to use *Drosophila melanogaster* as an animal model for phototaxis. This experiment was designed to help future veterinary students learn and understand phototaxis in animals. The experimental phase of this study was focused on the phototactic behavior of fruit flies under a controlled light environment. Although there were minor setbacks in the experiment, the researchers examined literature and did a literature review looking at past experiments. The mentor also provided additional information and resources to help guide and allow a better understanding of phototaxis and geotaxis in animals.

Process

The process of selecting this project was to gain a better understanding of the effects of light and magnetic forces on animals. Learning more about the light sensitives and magnetic forces in animals can allow researchers to understand how genetics and environment can affect animals. Researchers can determine what factors affect mating, behavior, migration, and survival skills of insects, birds, and other species that can help the future of neuroscience, behavior, and genetics. The experiment was unable to be completed since the environment conditions in the Moye Science Hall at Barton College were not suitable for the fruit flies to survive and reproduce. The researchers completed a literature review to gain more knowledge about how phototaxis and geotaxis affect *Drosophila melanogaster*.

Project Selection

This project was selected because learning the light and magnetic factors that affect the behavior and sensory function of animals can help students in the veterinary field gain a better understanding about animal behaviors and functions. Not only is it beneficial for students but also researchers to learn how genetics and environment can impact the behaviors and sensory functions of different species. There are many ways that studying fruit flies can be beneficial in learning more about different species behavior. The sensory processes that are most commonly seen in common between fruit flies and other species are their visual pathways, neurological pathways, and sensory functions. Fruit flies were an ideal subject for this experiment because they have a short generation time, high reproductive rate, similar genetic makeup as other species, and their behavior is easy to observe. It was important to pick a subject that had a short generation time and high reproductive rate, since the experiment was conducted throughout a twelve week period. It typically takes about ten to fourteen days to complete a full generation cycle of fruit flies from egg to adult. The time required to culture fruit flies depends

on various factors such as temperature, food availability, and the specific purpose of the culture. There were multiple researchers conducting this experiment. Each looked at the different behaviors associated with geotaxis and phototaxis and compared whether fruit flies had a positive or negative response to them.

Background and Prior Work

Phototaxis is the behavioral response that affects an animal's movement based on light. The movement that can be seen with phototaxis is either toward or away from the light and it depends on what wavelength of light attracts the species. Positive phototaxis is when an animal is attracted in moves toward the light and negative phototaxis is when the animal moves away from the light. The photoreceptor neurons in the eye are what transmits information to the neural circuits in the brain, causing the animals to either be attracted or unattracted to the light (Humberg & Sprecher, 2017). Phototaxis in fruit flies provides a valuable experimental model for the studying of the genetic, neural, and behavioral mechanisms underlying light perception and response, with relevance to both basic neuroscience research and potential applications in fields such as neurobiology and chronobiology. Studying phototaxis provides insights into the sensory and behavioral mechanisms of organisms. It helps researchers understand how organisms detect and respond to light, which can have implications for fields such as neuroscience, chronobiology, and the development of light-based therapies.

Geotaxis is a behavioral response that affects an organism's movement based on a gravitational force. Positive geotaxis allows the organism to move downward toward the gravitational pull, whereas negative geotaxis is when an organism moves upward against the gravitational pull (Fedele et al., 2014). Negative geotaxis can occur due to two geotactic genes that are found in *Drosophila melanogaster*. The two genes that were found to be important in negative geotaxis were cryptochrome and pigment-dispersing factor (Bae et al., 2016). Another part of negative geotaxis that is important is pyrexia, which senses gravity (Bae et al., 2016). However, there is also an environmental factor that has also been shown that affects geotaxis in organisms. An electromagnetic field can disrupt a fly's negative geotactic ability causing them to be unable to move upward away from the gravitational pull (Fedele et al., 2014). The cryptochrome and pigment-dispersing factor genes are a part of the circadian rhythm machinery (Toma et al., 2002). Cryptochrome is a blue light circadian photoreceptor that is found in *Drosophila* (Fedele et al., 2014). The circadian photoreceptor can be found in the flies brain, which allows the fly to be on a 24-hour clock cycle (Fedele et al., 2014). Cryptochrome can also encode a conserved photo pigmented protein that moderates an element of entrainment (Toma et al., 2002). Pigment-dispersing factor encodes a neuropeptide that moderates circadian locomotor activity (Toma et al., 2002). These genes are important to allow *Drosophila* the capability to be a locomotive and move in the direction that gravity is pulling them, whether it is negative or positive.

Methods

The experimental phase of this study was focused on the phototactic behavior of fruit flies under a controlled light environment. The study was intended to be done across a 12-week period. However, there were challenges faced during this experiment. These challenges were environmental factors that would include the fluctuation of

temperature in the Moye Science Hall. Therefore, the fruit flies were unable to survive and reproduce in the unstable environment and the experiment was not able to be successfully executed. Step one of the experiment included collecting a baseline for the fruit fly behavior. The baseline would be done without light stimuli to establish a control. By finding the control, it would allow there to be a source of comparison when the light exposure trials began. However, since there were inhabitable living conditions for the fruit flies in Moye Science Hall there was not adequate data collected for the experiment. Since the fruit flies were unable to survive, it prevented any collection of data for a variety of light conditions, including changes in intensity, wavelength, and direction of light. Upon the completion of the experiment, the different trials aimed to measure the behaviors of the fruit flies in the different light conditions. Finally, the behavior data would have shown the distance traveled, the time spent in lit and unlit areas, and other applicable metrics. The data collected from this study would have shown the different responses to the variety of light conditions, while also observing the patterns that were found in the fruit flies' phototactic responses. However, since there was a fluctuation of temperatures in the Moye Science Hall, there was no data collected or no observations made. Even though the experimental phase was designed adequately, the environmental factors that were faced in this experiment prevented the experiment from being successful.

In the completion of this experiment, the data was thoroughly processed and analyzed. The data was organized and was thoroughly looked through to ensure that the data was accurate and consistent. When the data is organized, it identifies any irregularities, and then prepared for the evaluation. After the sorting of data, the researchers intended to create a statistical analysis that passed the effects of the variety of light conditions on the fruit flies behavior. This analysis would demonstrate the patterns and correlations found in the phototactic responses of the fruit flies. Lastly, the results of the data would be compared to the experimental hypotheses and existing literature. In this final step, the results would have determined the consistency of the results found within the field of phototaxis.

Outcomes

The results of the project provided an understanding of geotactic (the movement in response to gravity) and phototactic behavior (the movement away from or towards light) of *Drosophila melanogaster* (fruit flies). The key findings of this experiment showed the specific light conditions that the fruit flies have a stronger response—such as different wavelengths, intensities of light, and even magnetic fields. The information found also lines up with other research regarding fruit flies behaviors. There were several challenges that arise when completing this experiment. The Moye Science Hall was where the experiment was supposed to be conducted. However, the building had fluctuating temperatures that created an inhabitable living conditions that prevented the growth and reproduction of the fruit flies. These conditions prevented the completion of the planned phototaxis experiment, therefore, the experiment was unsuccessful. The environmental challenges that were faced in this experiment demonstrated the importance of establishing controlled experimental conditions. The research that was conducted afterwards helped gain a wider understanding of the behavioral adaptations and sensory processes that are found in *Drosophila melanogaster*.

Future Directions and Applications

Studying phototaxis and geotaxis in *Drosophila melanogaster* allows a better understanding of light sensory and behavioral adaptations found in fruit flies and other animals. It can also allow researchers to gain a better understanding in different fields, for example, genetics, neurobiology, etc. *Drosophila melanogaster* is a commonly used model to research the different sensory, motor control, and behavioral adaptations found in animals. Light sensitivity and behavioral responses found in fruit flies can also be used to study other insects or even other species, like birds and humans. The project's findings can also suggest and demonstrate how environmental changes and even light pollution can affect different species behaviors and their ecosystems. However, this project also presented many challenges and also demonstrated the need for experimental challenges to be addressed. In the future, the first step would be to find a solution to the environmental challenges that were faced during the experiment. For example, when conducting the experiment, it should be done in a controlled environment where the temperature can be regulated to help minimize outside variables that result in inconclusive results. Secondly, future researchers can expand on the idea of this project and test a variety of lights with different intensities and wavelengths. When looking at a range of light intensity and wavelengths, we can find more specific phototactic responses found in specific light sources. Researchers that conduct a similar project need to pay close attention to environmental conditions, like temperature, that can influence the behavior and the breeding abilities of the fruit flies.

Conclusion

Although the experiment was unable to be completed, this capstone project was still able to demonstrate the importance of understanding phototaxis and geotaxis found in animals. Phototaxis helps organisms orient themselves in their environment. Examples can be seen when animals use the sun or other celestial bodies as reference points for navigation during migration or daily activities. If animals did not have these senses, they would not be able to fully survive in the world. Studying how gravity and light affect the behavior of animals, allows researchers to understand why animals have particular patterns in their lifestyle. If geotaxis was not found in animals then they would not be able to differentiate between going up and going down. Phototaxis allows animals to either be attracted to or away from light depending on their lifestyle. By studying these important topics, it allows researchers to learn more about how environment and genetics affect the behavior of animals.

References

Bae, Ji-Eun; Bang, Sunhoe; Min, Soohong; Lee, Sang-Hyup; Kwon, Soon-Hwan; Lee, Youngseok; Lee, Yong-Ho; Chung, Jongkyeong; & Chae, Kwon-Seok. (2016). Positive geotactic behaviors induced by geomagnetic field in *drosophila. Molecular Brain, 9*(1), 55. doi:10.1186/s13041-016-0235-1

Fedele, Giorgio; Green, Edward W.; Rosato, Ezio; & Kyriacou, Charalambos P. (2014). An electromagnetic field disrupts negative geotaxis in drosophila via a cry-dependent pathway. *Nature Communications, 5*, 4391. https://www.nature.com/articles/ncomms5391

Humberg, Tim-Henning; & Sprecher, Simon G. (2017). Age- and wavelength-dependency of drosophila larval phototaxis and behavioral responses to natural lighting conditions. *Frontiers in Behavioral Neuroscience*, *11*(66). doi:https://doi.org/10.3389/fnbeh.2017.00066

Toma, Daniel P.; White, Kevin P.; Hirsch, Jerry; & Greenspan, Ralph J. (2002). Identification of genes involved in Drosophila melanogaster geotaxis, a complex behavioral trait. *Nature Genetics, 31*(4), 349–353. https://doi.org/10.1038/ng893

Barton Journal

Unraveling Neuroblastoma: Causes, Treatments, and Future Perspectives

FULL-LENGTH ARTICLE

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CITATION

Hopkins, Sydney; & Mazuroski, Nicole L. (2026). Unraveling neuroblastoma: Causes, treatments, and future perspectives. *Barton Journal, 1*(1), 96–105. https://bartonjournal.org/vol-1-no-1/2026-cat1-article-no-005

Abstract

Pediatric cancers called neuroblastomas are often seen in children five years and younger. This cancer occurs when the neural crest cells in the adrenal glands, located above the kidneys, do not differentiate properly, resulting in abnormal hormone production and tumor growth. Among neuroblastoma cases, the majority arise as a result of genetic mutations in a few specific genes. Namely, these genes include the anaplastic lymphoma kinase (ALK), paired-like homeobox 2B (PHOX2B), and myelocytomatosis-neuroblastoma (MYCN) genes. In all three, the cancer is formed when such genes are amplified. Currently, there are seven main methods of treatment of the disease, with the primary pharmaceutical option being inhibitors of the ALK gene. In this study, a current ALK inhibitor (Crizotinib) was selected and modified through the alkylation of the piperidine ring located in the drug. This alteration shifted the electron density of the molecule, making it more stable when metabolized, and the lipophilicity of the drug was increased. As a result, ALK, ROS, and MET receptors were blocked through competitive inhibition of the active sites, not allowing ALK 1 and 2 ligands to bind. This pharmaceutical decreases tumor growth and increases apoptosis of cancerous cells through a mechanism change by which the tumor forms. Along with this, the side effects of the new drug showed hypothetical decreases in severity and lower dosage amounts.

Keywords: neuroblastoma, ALK inhibitor, Crizotinib, drug metabolism, ALK gene

Unraveling Neuroblastoma: Causes, Treatments, and Future Perspectives

The neuroblastoma is a form of cancer that arises from genetic mutations. It has been seen mostly in children five years and younger. A special type of cell called the neuroblast is the primary cell type responsible for neuroblastoma. As these cells develop, they do not grow, divide, or differentiate properly, causing tumors to form. In most cases, the cancer is found to be sporadic or hereditary, with different genes mutated that were associated with either form or origin. Cases of neuroblastoma have recently been found to have high incidence rates, with a majority coming from first-world countries, suggesting its significance. The three most common mutations were the ALK, N-MYC, and PHOX2B genes. This study focused on the ALK gene and the mechanism of an ALK inhibitor. In the mechanism, the goal of this project was to create a modified version of the ALK inhibitor chosen, Crizotinib, to enhance the anticancer effects and decrease the onset time of the drug. The ALK gene is responsible for cell growth, and hence, tumor growth as well. Crizotinib was the drug selected for modification due to its being the most common ALK inhibitor prescribed for hereditary neuroblastoma. It also has regions in the drug that are highly susceptible to modification.

The drug was modified through the piperidine ring being alkylated on the electronegative nitrogen atom. A piperidine ring is a carbon-nitrogen cyclic structure that acts as a scaffold in most pharmaceuticals. Through the addition of an alkyl isopropyl group—a three-carbon branched chain—to this ring, the drug became more stable in its electronegativity and electron density. As a result, many positive side effects came about, such as an increase in cell membrane permeability, a decrease in solubility, and a decrease in dosage amount needed. Benefits like these suggest possible modifications that could be made to other anticancer agents or even other medications used in modern medicine.

Process

Neuroblastoma was chosen as the condition of interest due to its significance in childhood cancers. A timeline of significant events, discoveries, and pharmaceuticals developed was created in a previously conducted literature review. After completion, a total history of the condition was observed, and areas of possible improvement were identified. Once a history was taken, genes of interest were researched to discover why they create tumors and how they could possibly be reverted to their original state. The way the genes were reverted was through pharmaceutical use.

A drug was selected for modification with the criteria that it is a) prevalent for neuroblastoma treatment, b) is capable of being modified, and c) has dangerous side effects that could be diminished. Crizotinib was the perfect option as such. This drug acts as an inhibitor of one of the major genes mutated in neuroblastoma (ALK) to create an anticancer effect (Crizotinib, n.d.). When the drug was observed, a few areas were noted as being good starting points for modification. Such areas included the piperidine ring, multiple halogens, and a pyrazole ring. The pyrazole ring is another cyclic carbon-nitrogen ring in the compound. Next, a list of possible modifications

was posed, which resulted in the isopropyl alkylation of the piperidine ring being chosen. The mechanism for how this could be done was established, and possible benefits were further analyzed.

Project Selection

Across the globe, neuroblastoma is the leading form of cancer in infants and children (National Cancer Institute, 2024). Such cancer is caused by hereditary or sporadic factors. This idea suggested there were possible ways to prevent hereditary forms from occurring if the genetic mutations could either be reversed or underexpressed. The way this is done is through pharmaceutical drug modification. In such pharmaceuticals, drugs often present negative side effects, but can be altered using chemistry. Drug modification has been a driving force in healthcare, thereby suggesting that theoretical mechanisms have become more prevalent in pharmacy.

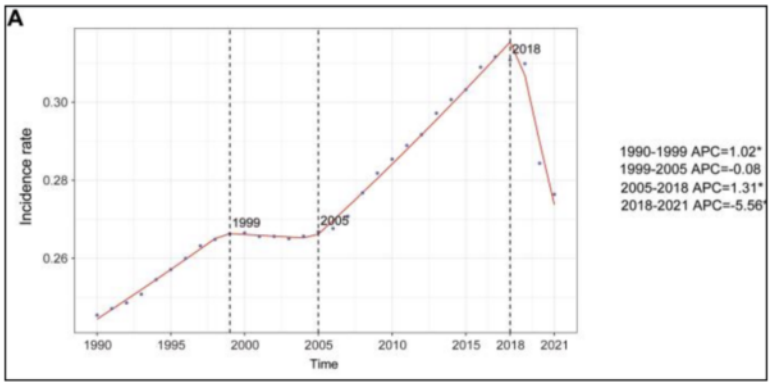
Background and Prior Work

Neuroblastoma, as a form of cancer, was first discovered by a German physician named Rudolf Virchow in 1864 upon discovering abdominal gliomas (Mandal, 2019). Such tumors developed in the adrenal glands and sympathetic nervous system, showing a linkage to neural cells. Specifically, the cells that cause the tumor are identified as neuroblasts, which are a cell type located in the adrenal medulla of the adrenal gland. Such cells are immature in the sense that they are undifferentiated (ACCO, 2022). When cells mature, they transform into cells with a select few responsibilities and are generally located in specific regions of the body. Specifically in neuroblastoma, the cells have not differentiated, meaning they are still stem cells, but have no specific function in the adrenal glands. Due to this, the cancerous cells often secrete higher levels of hormones, like catecholamines, which can be used diagnostically for adrenal tumors (Mandal, 2019).

Since neuroblastoma was first discovered, the incidence rates globally have increased dramatically among children. According to the Cleveland Clinic, this linear increase from 1990 to 1999 and again in 2005-2018 is likely due to hereditary factors (2025). Neuroblastoma has shown no evidence of being carcinogenic, meaning there has not been a specific chemical/substance shown to cause gene mutations resulting in cancer (Cleveland Clinic, 2025). For a cancer to be carcinogenic, it means the cancer is caused by a certain substance or chemical that a person might be exposed to. A common example is nicotine being a carcinogen for lung cancer. The incidence percentage rate from 1990 to 2021 (Figure 1) depicts the trend of cases being diagnosed internationally (Nong et al., 2024). One note of significance was the sharp decline from 2018 onward. A decline like this was likely due to the COVID-19 pandemic and a shift in the focus among healthcare providers to treating patients afflicted with the virus (Nong et al., 2024). It could also have been as a result of more treatments being released around that time period.

Figure 1

Incident Percent Rate Change of Childhood Neuroblastoma 1990-2021

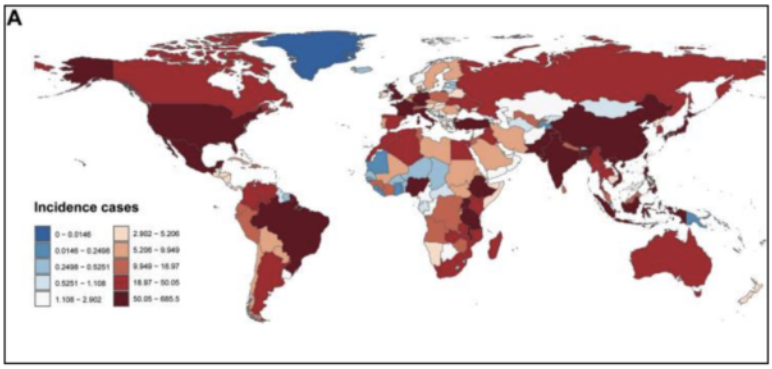


Note. Annual percent change (APC) and trends in global childhood neuroblastoma incidence from 1990 to 2021.

A global image showing the incidence rate of neuroblastoma per country (Figure 2) illustrated the prevalence of neuroblastoma worldwide (Nong et al., 2024). While there are some countries with a low rate of diagnosis, most other countries, especially first-world countries, showed the highest values. This trend likely occurred because of the higher quality of healthcare. A majority of third-world countries do not have the equipment or personnel to diagnose such conditions, potentially contributing to lower rates. There has not been substantial evidence suggesting this, so it was a theory established by the researchers. Even with this in mind, both demographics aided in providing evidence of neuroblastoma having great significance, yet few solutions in the medical field.

Figure 2

Global Demographic of Childhood Neuroblastoma Incidence



Note. Incidence of childhood neuroblastoma across 204 countries and territories. Number of incidents.

In 1896, X-rays were used as an imaging technology to identify internal tumors, specifically, for neuroblastoma (National Cancer Institute, 2024). X-ray machines produce electromagnetic radiation waves that travel through

the patient and hit a wall behind the patient, showing tissue density. Tissues that have a higher density, such as bones, absorb more of the rays, which would produce a lighter color. Lighter tissues, such as skin, do not absorb many rays and would produce a darker color on the scan created.

The N-MYC gene was identified as one of the primary target genes of neuroblastoma in the early 1980s, with the first human antibody treatment for neuroblastoma being discovered (Furman, 2021). This gene region is responsible for cell growth, division, and differentiation through its acting as a transcription factor for DNA and controlling other gene expression. Such a gene as this is labelled as proto-oncogenic, which means the gene could cause cancer (National Cancer Institute, n.d.). When a mutation occurred, the gene was overexpressed, and tumors were produced, causing cells to become oncogenic. With the N-MYC gene, overexpression led to a worse prognosis for the patient after diagnosis. Along with the overexpression, it was commonplace to see a resistance to ALK inhibitors in such cases (Bachetti et al., 2010).

Other genes for neuroblastoma (ALK and PHOX2B) were later discovered in the human genome mapping project in 2008 (Barr & Applebaum, 2018). Much like the N-MYC gene, the ALK gene is responsible for producing the protein ALK receptor tyrosine kinase (ALKRTK), regulating cell growth (Wulf et al., 2021). Most often seen are point mutations of the ALK gene, resulting in overexpression of the gene in sporadic neuroblastomas (Holla et al., 2017). A point mutation is one where one nucleotide is changed, affecting the reading of the amino acid sequence produced. A disruption in this reading causes small ligands called augmentor α and β to over-attach, thus causing overexpression (Shreenivas et al., 2023). When the ALK gene is mutated, tumor growth is the primary effect created (Shreenivas et al., 2023). It is also important to note that ALK mutations often result from hereditary mutations.

The third gene of significance, which is similar to the ALK gene, is the PHOX2B gene. While being attributed to neuroblastoma, the PHOX2B gene focuses on division and differentiation of the neuroblasts (Hereditary Neuroblastoma, n.d.). Neuroblasts are located in the neural crest of the adrenal gland, which is a region that specifically houses these stem cells in fetuses and infants (MFMER, 2025). When mutated, either the amino acid sequence is altered, or several nucleotides are switched, which results in incorrect amino acids being inserted into the gene (U.S. National Library of Medicine, 2019). When this occurs, the neuroblasts improperly differentiate, thus causing tumors to form. It was discovered that each of these three genes is a prevalent cause of the initial tumor formation when mutated.

Once such genes were identified, possible treatments began to be proposed. In 2020, the first monoclonal antibody treatment for neuroblastoma was developed and approved for clinical use. Coined as Danyelza®, the drug targets antigens present on the tumor cells and produces antibodies naturally by the body. The specific antigen is a disialoganglioside antigen, meaning there are acidic residues on the cancer cell affecting its growth and adhesion to other cells.

Methods

Research was conducted to begin as a background of neuroblastoma needed to be established. Once complete, the causes of neuroblastoma were identified. Initially, it was thought there could be a possible carcinogen associated with the condition. However, this was quickly dismissed as all research conducted did not point to a carcinogen causing mutation of the genes responsible for neuroblastoma. After it was determined that neuroblastoma is only caused by genetic mutations, this path was taken.

Drug Modification. Through the identification of the genes associated with neuroblastoma, the treatment options used were then evaluated. It was observed that pharmaceuticals were most often selected as the course of treatment. Using this knowledge, the most common ALK inhibitor prescribed was called Crizotinib and was selected for modification. This drug suggested multiple opportunities for adjustment to reduce harmful side effects and increase effectiveness.

Upon further inspection of the drug, the piperidine ring was suggested as the best area of modification. The reason is due to it having an electronegative nitrogen atom and its structure causing a scaffolding effect in drugs. The orientation of the ring suggests a possible addition of an alkyl group onto the nitrogen. An alkyl group is one that is a hydrocarbon chain, and increases lipophilicity and decreases solubility. Knowing this, a mechanism was created and tested for possible side effects that would occur in the patient. The mechanism was carried out using a base of potassium carbonate (K2CO3). Potassium carbonate acted as a weak base and was able to deprotonate the nitrogen atom. Deprotonation is the act of removing a proton from an atom/molecule. Such results from the mechanism were compared to the original effects of Crizotinib to establish whether the mechanism worked correctly and if the results aligned with the desired effects.

Outcomes

The new mechanism and altered form of Crizotinib were tested for impacts on stability and possible clinical effects within the patient. It was discovered that the mechanism itself is indeed possible with a near one hundred percent yield of the new drug created. These results are likely due to the use of a weak base that does not cleave the ring apart into different components. Additionally, it can be reasoned that the piperidine acting as a scaffold is more reactive than other elements in the drug under the conditions created for alkylation. Due to there being only one hydrogen present on the more electronegative—a chemical property of an element's affinity for lone electrons—nitrogen, this provided the best area for substitution to occur.

There has been no mechanism proposed for this drug to be modified in the manner executed, suggesting alkylation might be more difficult to execute than hypothesized. In other alkylated drugs, results showed that a majority of common chemotherapy drugs were alkylated to increase the anticancer therapy. Alkylation causes DNA (deoxyribonucleic acid) to be disrupted in structure and function, ultimately leading to cell death (Drugs.com, 2025). Since this has been done to other drugs, it was reasonable to theorize that the anticancer effects would be increased as a result of the new mechanism and alkylation. With the goal in mind of enhancing a drug already on the market, the alkylation of this drug fulfilled the goal set.

Regarding other significant characteristics of interest, many of them were altered to give the desired effects. Alkylation of the piperidine ring increased the lipophilicity—a substance's tendency to cross cell membranes that have a phospholipid bilayer—of the drug when ingested. The phospholipid bilayer contains a hydrophobic tail and a hydrophilic head, which allows the membrane of cells to be selectively permeable to certain molecules (Alberts, 1970). The presence of more carbon and hydrogen atoms caused more polar qualities to come about, which include high lipophilicity and low solubility. When compared with previous literature, a higher lipophilicity is likely to cause the drug to pass through the cell membrane more easily, thus decreasing the onset time of the drug.

Additionally, the solubility—how quickly the drug was metabolized—was decreased. When a substance enters the bloodstream, it begins to be broken down until it can no longer be broken down, and at that point, it is ready for elimination. Because the goal was to enhance the drug's already created effects, a decreased solubility indicated the drug was not broken down immediately after entering the bloodstream. Hereby, the anticancer effects were able to be prolonged, which also allowed dosage amounts to be lower. For the patient, this meant that they would not have to receive treatment either as much or in as many doses as the standard.

Interestingly enough, there were not many obstacles that needed to be tackled when creating the drug mechanism. There was only one significant factor, and that was the selection of the drug for modification. The original idea was to use a different drug that inhibited the N-MYC gene instead of the ALK gene, but the common drugs used for that purpose were not modifiable (Whitfield & Soucek, 2021). Such an issue is not severe, though, as this was the first step of analyzing the drug to create the metabolism. More research was conducted until it was found that ALK inhibitors, specifically Crizotinib, were a good match for drug modification.

Pharmaceuticals can be modified in many ways, and these are dependent on the structure and functional groups within the pharmacophore—the active portion of a drug. Crizotinib was a *good* drug to select, as many areas of the drug are subject to change, like electronegative atoms and nitrogenous rings. The use of a weak base and a haloalkane—organic compound with a hydrocarbon chain containing some halogen atom acting as the initiator for the reaction—served to alkylate the nitrogen inside the piperidine ring. Therefore, the new drug enhanced certain anticancer effects already created. Such effects included lipophilicity, solubility, and dosage quantity for patients. It was through the alkylation that the lipophilicity was increased, which allowed the drug to pass more quickly through the cell membrane and begin anticancer effects sooner. The lower solubility caused the drug to not be metabolized by hepatocytes—cells located in the liver—as quickly, prolonging the anticancer effects (Pfizer, n.d.). In doing so, the dosage amount prescribed could be lowered, which could make life slightly easier for the patient. Drug modification is an area of pharmaceuticals still being discovered, and through mechanisms such as the one created, drugs are being improved, and more patients are being saved.

Future Directions and Applications

Future implications include carrying out the new mechanism in a live experiment in the laboratory to see if the yield is correct and whether the product created is the desired hypothesized drug. The product would be tested

using an FT-IR spectrometer (Fourier- Transform infrared spectrometer) instrument that is able to analyze a sample and determine the structure of the analyte very closely. An experiment such as this would need to be completed at an institution or facility with proper equipment to do so. In the field of drug discovery and modification, simulations are barely being used to test for side effects. One of the innovations with AI is to test mechanisms before drugs undergo living trials. It allows for the testing in humans without potentially harming humans or animals. Within the field of pharmacy, anyone who graduates with a PharmD degree is able to become an industrial pharmacist and work on projects exactly like this one, except with the real compounds and machines. During rotations in pharmacy school, a majority of candidates will take rotations in such places, so even having a theoretical project such as this is extremely beneficial.

Conclusion

Neuroblastoma is a form of cancer prevalent in young children. It arises from improperly differentiated neuroblasts and is often caused by genetic mutations. The most common genes altered are the ALK, N-MYC, and PHOX2B genes. All three of these genes are overexpressed in neuroblastoma, causing abnormal cell growth, division, and differentiation. For the ALK gene, drugs identified as ALK inhibitors are used to reduce the overexpression caused by the mutation. The most common ALK inhibitor, known as Crizotinib, can be modified using different reagents to alter the functional groups of the pharmacophore, which changes certain side effects. With the objective in mind of adjusting this pharmaceutical for neuroblastoma to obtain desired results physiologically, a new mechanism was created to slightly alter the drug. The region altered was the piperidine ring, which was alkylated with an isopropyl group. This alkylation resulted in a higher lipophilicity, lower solubility, and lower drug dosage for patients. Drug modification, as witnessed here, is a field of pharmacy being thoroughly explored to enhance drugs already on the market by improving side effects and improving the quality of life for patients undergoing all forms of treatment. The field of medicine would benefit greatly from alterations like this, and many more conditions could become treatable after such alterations.

References

ACCO. (2022, March 10). *Childhood neuroblastoma cancer: Causes, risk factors, and prevention*. American Childhood Cancer Organization. https://www.acco.org/blog/childhood-neuroblastoma-cancer-causes-risk-factors-and-prevention/

Alberts, B. (1970, January 1). *The lipid bilayer*. Molecular Biology of the Cell (4th ed.). https://www.ncbi.nlm.nih.gov/books/NBK26871/

Bachetti, Tiziana; Di Paolo, Daniela; Di Lascio, Simona; Mirisola, Valentina; Brignole, Chiara; Bellotti, Marta; Caffa, Irene; Ferraris, Chiara; Fiore, Michele; Fornasari, Diego; Chiarle, Roberto; Borghini, Silvia; Pfeffer, Ulrich; Ponzoni, Mirco; Ceccherini, Isabella; & Perri, Patrizia. (2010). Phox2b-mediated regulation of ALK expression: In vitro identification of a functional relationship between two genes involved in neuroblastoma. *PLoS ONE*, *5*(10). https://doi.org/10.1371/journal.pone.0013108

Barr, Erin K.; & Applebaum, Mark A. (2018). Genetic predisposition to neuroblastoma. *Children*, *5*(9), 119. https://doi.org/10.3390/children5090119

Cleveland Clinic. (2025, March 19). *What you need to know about carcinogens*. Cleveland Clinic. https://my.clevelandclinic.org/health/articles/25081-carcinogens

DrugBank. (n.d.) Crizotinib*: Uses, interactions, mechanism of action | drugbank online*. DrugBank. Retrieved April 05, 2025, from https://go.drugbank.com/drugs/DB08865

Drugs.com. (2025, April 13). *List of alkylating agents*. Drugs.com. https://www.drugs.com/drug-class/alkylating-agents.html

Furman, Wayne L. (2021). Monoclonal antibody therapies for high-risk neuroblastoma. *Biologics: Targets and Therapy*, *15*, 205–219. https://doi.org/10.2147/btt.s267278

Holla, Vijaykumar R.; Elamin, Yasir Y.; Bailey, Ann Marie; Johnson, Amber M.; Litzenburger, Beate C.; Khotskaya, Yekaterina B.; Sanchez, Nora S.; Zeng, Jia; Shufean, Abu; Shaw, Kenna R.; Mendelsohn, John; Mills, Gordon B.; Meric-Bernstam, Funda; & Simon, George R. (2017). ALK: A tyrosine kinase target for cancer therapy. *Molecular Case Studies*, *3*(1). https://doi.org/10.1101/mcs.a001115

Mandal, Ananya. (2019, February 27). *Neuroblastoma history*. News Medical. https://www.news-medical.net/health/Neuroblastoma-History.aspx

MFMER. (2025, February 25). *Neuroblastoma*. Mayo Foundation for Medical Education and Research. https://www.mayoclinic.org/diseases-conditions/neuroblastoma/ symptoms-causes/syc-2035101

National Cancer Institute. (n.d.). *NCI Dictionary of Cancer Terms*. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/proto-oncogene

National Cancer Institute. (2024, October). *Neuroblastoma treatment*. National Cancer Institute. https://www.cancer.gov/types/neuroblastoma/patient/neuroblastoma-treatment-pdq

Nong, Jusen; Su, Cheng; Li, Changhua; Wang, Congjun; Li, Wei; Li, Yong; Chen, Peng; Li, Yanqiang; Li, Zihao; She, Xinjin; Yuan, Zuxin; Liu, Sentian; Chen, Chao; Liao, Qian; Luo, Yige; & Shi, Bo. (2024). Global, regional, and national epidemiology of childhood neuroblastoma (1990–2021): A statistical analysis of incidence, mortality, and DALYs. *eClinicalMedicine*, *79*, 102964. https://doi.org/10.1016/ j.eclinm.2024.102964

Pfizer. (n.d.). *Xalkori® (crizotinib) Clinical Pharmacology: Pfizer medical information – US*. Pfizer. Retrieved February 27, 2025, from https://www.pfizermedicalinformation.com/ xalkori/clinical-pharmacology

Shreenivas, Aditya; Janku, Filip; Gouda, Mohamed A.; Chen, Hui-Zi; George, Ben; Kato, Shumei; & Kurzrock, Razelle. (2023). ALK fusions in the pan-cancer setting: Another tumor-agnostic target? *Npj Precision Oncology*, *7*(1). https://doi.org/10.1038/s41698-023-00449-x

St. Jude Children's Hospital (n.d.) *Hereditary neuroblastoma*. St. Jude Children's Hospital. Retrieved December 29, 2024, from https://www.stjude.org/care-treatment/treatment/genetic-syndromes/hereditary-neuroblastoma.html

U.S. National Library of Medicine. (2019, September 1). *Phox2b gene: MedlinePlus Genetics*. MedlinePlus. https://medlineplus.gov/genetics/gene/phox2b/

Whitfield, Jonathan R., & Soucek, Laura. (2021). The long journey to bring a MYC inhibitor to the clinic. *Journal of Cell Biology*, *220*(8). https://doi.org/10.1083/jcb.202103090

Wulf, Anna M.; Moreno, Marcela M.; Paka, Chloé; Rampasekova, Alexandra; & Liu, Karen J. (2021). Defining pathological activities of ALK in neuroblastoma, a neural crest-derived cancer. *International Journal of Molecular Sciences*, *22*(21), 11718. https://doi.org/10.3390/ ijms222111718

Barton Journal

FOMO: Understanding How Fear of Missing Out Impacts College Students

SHORT ARTICLE

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CITATION

Wells; Savanna E. ; & Lange, Gerard C. (2026). FOMO: Understanding how fear of missing out impacts college students. *Barton Journal, 1*(1), 106–113. https://bartonjournal.org/vol-1-no-1/2026-cat2-article-no-006

Abstract

Fear of missing out (FOMO) is experienced and determined by four key aspects: belonging, social anxiety, emotion, and acceptance—things experienced by all people, but with a greater impact on some. In the modern digital world, these aspects are deeply tied to social media use and daily online habits. This study examined the emotional experiences of FOMO among students at a small liberal arts college through a survey measuring screen time, social media behaviors, and personal responses to exclusion. Using a cross-sectional design and Likert-scale questionnaire, patterns were analyzed to reveal how students experience and report FOMO. Results suggest that while many students experience FOMO-related feelings, severity varies across individuals and gender groups. Campus culture, including involvement as a student athlete, likely influences how these experiences are reported.

Keywords: Fear of Missing Out (FOMO), social media use, college students, social comparison, digital behavior

Introduction

Whether online, in person, or across daily life, interactions between one person and another are shaped by an individual's sense of belonging, social anxiety, emotions, and desire for acceptance by others. These four key aspects are also what influence a person's fear of missing out from interactions, commonly referred to as FOMO. Researchers such as Liebowitz (1987), Pryzybylski (2013), and Elhai (2017) have examined these aspects of personal interaction, showing how unmet needs, anxious thoughts, and constant access to social media contribute to repeated cycles of FOMO. While FOMO may encourage social engagement, FOMO is often associated with negative outcomes such as anxiety, stress, and feelings of inadequacy. Understanding how these ideas work independently and collectively is necessary to reveal how FOMO is not simply about missing a concert or social event, but about deeper psychological needs that influence behavior.

On college campuses, FOMO is especially relevant because peer relationships, social comparison, and inclusion are central to student life. Students often feel pressure to check social media frequently, stay aware of social events, and remain updated on group activities out of fear that they might miss out on something important. Emotional discomfort resulting from FOMO can involve behavioral patterns such as constantly refreshing apps, feeling the urge to respond quickly to messages, or adjusting daily routines to avoid exclusion.

This study measured FOMO and related behaviors among students enrolled at a small, liberal arts college in order to better understand how digital connection, emotional experience, and campus culture intersect in shaping student experiences.

Literature Review

This study is grounded in four psychological components of FOMO: belonging, social anxiety, emotion, and acceptance. Together, these components illustrate how FOMO is not a single feeling, but an interaction of internal needs and external pressures that shape both behavior and self-perception. Although some of these sources are older, they are foundational to understanding the development of FOMO and social anxiety, and continue to be widely referenced in current research.

Belonging

Belonging shows how important it is for people to feel accepted and connected to others. It makes one feel as if one's worth is measured by one's ability to fit in with a certain group or status. According to Liebowitz (1987), individuals with social anxiety often avoid group interactions, which determines their sense of belonging. Although the term FOMO was originally coined by Patrick J. McGinnis (2004), Pryzybylski (2013) expanded this perspective by suggesting that FOMO emerges when basic needs are not met, specifically relatedness, or the need to feel socially connected and valued by others. Elhai (2017) added that unmet social needs drive compulsive phone and social media checking. Collectively, these researchers revealed that the desire to stay connected reflects an underlying fear of being excluded from meaningful opportunities or relationships.

Social Anxiety

Social anxiety places individuals in a difficult position: they want to belong, but are afraid of being judged. The Liebowitz Social Anxiety Scale (LSAS) captures this fear and avoidance (Liebowitz, 1987). The scale measures levels of social fear and avoidance across a range of everyday social situations, providing insight into how individuals experience and respond to social anxiety. Building on this understanding of social anxiety, Pryzybylski (2013) demonstrated that FOMO is tied to negative emotions and heightened self-monitoring. Similarly, Elhai (2017) found that FOMO often serves as the pathway between anxiety and smartphone use. Relying on screens may not lessen anxiety, but instead reinforces avoidance behaviors.

Emotion

Emotion is at the root of FOMO because fear, worry, and unhappiness shape how people experience missing out. Liebowitz (1987) emphasized fear and avoidance as central emotional responses in social anxiety. Expanding on this idea, Przybylski (2013) found that FOMO correlates with negative emotions such as worry and discontent when individuals are excluded from valued events. Emotion makes FOMO self-reinforcing, as these negative feelings increase online engagement, which can intensify comparison and stress.

Acceptance

Acceptance is a core part of human relationships because individuals naturally seek approval from others. Liebowitz (1987) showed that fear of rejection often leads to avoidance of social interactions, threatening one's sense of acceptance. Supporting this concept, Przybylski (2013) explained that FOMO arises when needs such as belonging and acceptance are unmet. Additionally, Elhai (2017) connects unmet acceptance needs with unhealthy phone use. In the context of seeking acceptance from others, recognition through likes and comments, as visible forms of social approval, can strengthen dependence on online validation.

Study Design

The design of this study aimed to measure FOMO and related behaviors among college students in a structured and reliable way. A survey-based approach was used because FOMO involves internal experiences and personal habits, best represented through self-reporting. Grounded in established FOMO research and key psychological components, the study design guided the selection of variables related to social media behaviors and emotional responses. The study specifically examined emotional experiences of FOMO through social media habits, screen time, triggers, and platform usage. Data were collected using a Google Forms survey distributed to participating students, faculty, and staff at a small liberal arts college. Participation was voluntary and anonymous. The survey included demographic questions, daily screen time, social media usage, a FOMO scale, and open-ended responses. Likert-style questions strengthened reliability and aligned with previous FOMO research.

Survey questions measured anxiety about friends' activities, social media checking habits, discomfort when offline, comfort taking breaks, and questioning one's social life after viewing posts. Responses varied across participants, with many clustering around neutral or disagreeing options, though some indicated moderate

agreement with FOMO-related behaviors. Questions included: a) *on average, how much time do you spend on your phone each day* (Hours); b) *I get anxious when I don't know what my friends are doing* (Q1); c) *I often check social media to see what others are doing* (Q2); d) *I feel uncomfortable when I am offline for too long* (Q3); e) *I feel fine taking breaks from social media for a few days* (Q4); f) *seeing others' posts makes me question my own social life* (Q5); g) *which platform triggers your FOMO the most* (Q6); and h) *on a scale of 1–10, how often do you experience FOMO in your daily life* (Q7).

Population

The population for this study consisted of individuals who voluntarily responded to a survey about Fear of Missing Out (FOMO) and social media behaviors. The survey was distributed to all members of the college community, including students, faculty, and staff, to increase the sample size and capture a broader range of perspectives. A total of 45 participants completed the survey. Participants ranged in age from 18 to 76 years old, although the majority of respondents were traditional college-age students between the ages of 18 and 25. Although the campus itself is in a rural setting, the college is a small, private, liberal arts institution with a close-knit student community and strong emphasis on undergraduate education. The student population includes individuals from both rural and urban backgrounds, reflecting a diverse mix of social experiences and levels of engagement, which provides a variety of perspectives on social media use and social comparison.

Data

The design of the survey questions was inspired by the LSAS scale, with wording adapted to fit the content of social media use and FOMO. The questions were organized into categories that focused on behavioral habits and emotional responses. Habit-based questions asked about frequency of social media use, screen time, and engagement patterns. Emotion-based questions explored feelings such as anxiety, exclusion, and the urge to stay connected. This structure allowed for a clearer understanding of how behaviors and emotions contribute to the experience of FOMO. Respondents were organized by gender and age group. Of the respondents, 12 identified as male, 26 as female, and 1 as nonbinary. The majority of the participants (38) were between the ages of 18 and 25, and no respondents fell within the 36-45 age range. Ultimately, participants over age 25 were excluded in order to have a meaningful analysis focused on traditional college-age students (Table 1).

Table 1

Responses from Participants Aged 18–25

No. (f/m)	Hours	Q1	Q2	Q3	Q4	Q5	Q6	Q7

1 (f)	6–8	–	–	–	–	–	Instagram	9
3 (m)	4–6	–	–	–	–	–	Instagram	9
4 (m)	4–6	–	–	–	–	–	Other	2
7 (f)	4–6	d	–	–	–	–	Instagram	5
8 (f)	6–8	sd	–	–	–	–	Instagram	5
9 (f)	4–6	d	–	–	–	–	Instagram	7
10 (f)	6–8	n	–	–	–	–	TikTok	7
12 (m)	4–6	sa	–	–	–	–	Facebook	4
14 (f)	6–8	–	–	–	–	–	Snapchat	10
15 (m)	4–6	sd	–	–	–	–	TikTok	3
16 (f)	4–6	d	d	d	a	n	Instagram	4
17 (f)	2–4	sd	n	sd	sd	d	Snapchat	3
21 (m)	4–6	sd	sd	sd	a	sd	–	1
22 (m)	2–4	a	d	sd	a	n	Instagram	2
23 (f)	> 8	sd	a	a	d	a	Snapchat	6
24 (f)	4–6	d	sd	sd	sd	sd	Instagram	3
25 (f)	4–6	d	d	d	a	sa	Instagram	6
27 (f)	> 8	n	a	n	d	d	Snapchat	2
28 (f)	4–6	d	sa	d	a	sa	Snapchat	3
29 (m)	< 2	n	sd	d	a	d	Snapchat	2
30 (f)	4–6	d	a	n	n	n	Instagram	4
31 (f)	6–8	d	d	sd	d	sd	Instagram	3
32 (f)	4–6	sd	d	d	a	d	Instagram	6
33 (f)	4–6	sd	d	d	a	d	Snapchat	6

34 (f)	4–6	sa	n	sd	n	sd	Snapchat	2
35 (f)	4–6	a	a	n	d	n	Snapchat	8
36 (m)	2–4	a	n	d	n	a	Instagram	7
37 (f)	2–4	a	n	d	a	n	Instagram	6
38 (f)	2–4	sd	a	n	d	a	Instagram	8
39 (m)	4–6	d	n	d	n	d, n	TikTok	2
40 (m)	2–4	–	d	sd	n	sd	–	2
41 (m)	4–6	d	sd	d	sd	d	Snapchat	5
42 (f)	6–8	d	n	sd	d	n	Instagram	2
43 (f)	2–4	sd	n	d	d	n	TikTok	4
44 (m)	4–6	–	sd	sd	sd	sd	TikTok	2

Note. Respondents arranged by age (youngest to oldest). Abbreviations used include: agree (a), strongly agree (SA), neutral (n), disagree (d), strongly disagree (SD), and no response (–).

Findings

Overall, the results suggest that many students experience feelings related to FOMO, though severity differs. Some participants reported stronger concerns about social comparison and exclusion, while others reported lower levels of these feelings. More male participants reported that seeing posts from others made them question their own social lives more than female participants did. These differences may be influenced by factors such as maturity, social involvement, or campus culture. Some research has found that males report higher levels of FOMO among college-aged individuals (Brailovskaia et al., 2023; Qutishat et al., 2020). However, other studies have found little to no gender difference in FOMO experiences, suggesting that social comparison and online behavior patterns may play a larger role than gender alone (Servidio et al., 2024; Li et al., 2024). These mixed findings suggest that while gender may influence how some students experience social comparison online, other factors such as peer groups, campus involvement, and social media habits may also shape their experiences. The results of this study reflect a similar pattern, as male participants showed slightly stronger social comparison responses when viewing others' social media posts.

The college's large student-athlete population may have influenced the results. Student-athletes make up approximately 54% of the student body (T. Little, personal communication, Dec. 11, 2025). Student-athletes often have demanding schedules due to practices, games, and team commitments, which may reduce free time. Their social lives may center around teammates, potentially reducing reliance on social media for connection.

However, seeing events they cannot attend may also influence how they experience FOMO. Athletic involvement was not measured and may have acted as a confounding variable.

Limitations

Limitations of this study include sample size, incomplete responses, and lack of athletic participation data. Future studies should account for athletic involvement and expand participant numbers for stronger conclusions. A small sample size limits how well the findings can be generalized to a larger population. Incomplete responses might reduce the reliability of the data, as missing information can weaken overall patterns and interpretations. Additionally, not accounting for the athletic population overlooks an influential variable, as involvement in sports may affect time availability, social engagement, and social media use, all of which are connected to experiences of FOMO.

Conclusion

Among college students, digital platforms amplify feelings of belonging, acceptance, emotion, and social anxiety. These influences ultimately shape how exclusion is experienced. Findings suggest that while many students report moderate FOMO-related feelings, severity varies depending on individual and contextual factors. Campus culture, particularly athletic involvement, might influence how students experience social comparison and digital connection. Future research should repeat the study while accounting for athletic participation and expanding the sample size. Aside from these potential areas for broadening the research, information obtained in this study confirms the use of established measures related to belonging and social anxiety as means of measuring FOMO. Furthermore, it should be noted that understanding FOMO in college populations remains important for addressing student well-being and the impact of social media on mental health.

References

Brailovskaia, Julia; Ozimek, Philipp; & Bierhoff, Hans-Werner. (2023). Vulnerable narcissism, fear of missing out (FoMO), and addictive social media use. *Computers in Human Behavior*. https://doi.org/10.1016/j.chb.2023.107725

Elhai, Jon D.; Levine, Jason C.; Dvorak, Robert D.; & Hall, Brian J. (2017). Fear of missing out, need for touch, anxiety, and depression are related to problematic smartphone use. *Computers in Human Behavior, 63*, 509–516. https://doi.org/10.1016/j.chb.2016.05.079

Li, Yiyu; Koning, Inge M.; Finkenauer, Catrin; Boer, Mareike; & Van Den Eijnden, Rutger J. J. M. (2024). The bidirectional relationships between fear of missing out, problematic social media use and adolescents' well-being: A random intercept cross-lagged panel model. *Computers in Human Behavior, 154*, 108160. https://doi.org/10.1016/j.chb.2024.108160

Liebowitz, Michael R. (1987). Social phobia. *Modern Problems of Pharmacopsychiatry, 22*, 141–173. https://doi.org/10.1159/000414022

McGinnis, Patrick J. (2004). *Social theory at HBS: McGinnis' two FOs.* The Harbus. https://www.harbus.org/post/social-theory-at-hbs-mcginnis-two-fos-2

Przybylski, Andrew K.; Murayama, Kou; DeHaan, Cody R.; & Gladwell, Valerie. (2013). Motivational, emotional, and behavioral correlates of fear of missing out. *Computers in Human Behavior, 29*(4), 1841–1848. https://doi.org/10.1016/j.chb.2013.02.014

Qutishat, Mohammad et al. (2020). *Gender differences in fear of missing out experiences among undergraduate students.* Journal of American College Health. https://doi.org/10.2174/0250688202002022003

Servidio, Rocco; Soraci, Paolo; Griffiths, Mark D.; Boca, Stefano; & Demetrovics, Zsolt. (2024). Fear of missing out and problematic social media use: A serial mediation model of social comparison and self-esteem. *Addictive Behaviors Reports, 19*, 100536. https://doi.org/10.1016/j.abrep.2024.100536

Barton Journal

Digital Transformation in Professional Sport: A Case Study of Artificial Intelligence Integration in a German Second-Division Ice Hockey Club

CASE STUDY

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CITATION

Stockfisch, Jannik; & Cuthrell, Andrea. (2026). Digital transformation in professional sport: A case study of artificial intelligence integration in a German Second-Division ice hockey club. *Barton Journal, 1*(1), 113–118. https://bartonjournal.org/vol-1-no-1/2026-cat2-article-no-007

Abstract

Artificial Intelligence (AI) is no longer a futuristic concept only used in elite-tier global sports franchises; it has become a fundamental operational tool for professional sports organizations at all levels (TFL, n.d.). This case study examines the digital transformation of a second-division German ice hockey club through the lens of a marketing and operations internship. The organization uses a diverse AI strategy, including engagement analysis through automated marketing systems (Forbes Technology Council, 2025), performance optimization with tracking data (Panchal & Singh, 2025), and strategic scouting through data-driven recruitment (Vuorenmaa, 2025). Through the use of design tools, automated newsletters for sponsor analysis, and tactical video software, the club shows how mid-sized enterprises can attain efficient operations (LBS, 2026). Important insights suggest that the success of AI depends on striking a balance between human insight and fast processing capabilities (TFL, n.d.). Nevertheless, such a shift calls for organizational preparedness and strong data protection policies (Vuorenmaa, 2025; Asiabar et al., 2025). The enterprise represents how AI operates as an online assistant,

allowing human workers to focus on creativity and strategy in a highly competitive sporting setting (TFL, n.d.; Vuorenmaa, 2025).

Introduction

The international sports industry is currently witnessing a significant transformation, with the AI sports market expected to grow to roughly $30 billion by 2032 (TFL, n.d.). AI will eventually become an essential component of sports, and its implementation will be crucial for organizations to stay ahead of their competition. While most of the academic literature and articles focus on the top-tier level, such as the NFL or English Premier League, the real importance of AI is presented in mid-tier professional leagues where resources are tight, and efficiency is essential, because it shows what a difference AI can make (Vuorenmaa, 2025). At this level, the implementation of new systems must be well-calculated and bring benefits to the organizations in the near future (PwC, 2024, as cited in Vuorenmaa, 2025). This case study focuses on a German second-division ice hockey club to show how AI integration changes sports management from the front office to the locker room.

Artificial Intelligence in this context is defined as technology that simulates human learning, problem-solving, and decision-making (TFL, n.d.). In the organization, AI is applied across five key areas: strategy and tactics, talent recruitment, fan engagement, health and performance, and design (TFL, n.d.). In these areas, AI is used in different ways and for different purposes, but in the end, it is to make work more efficient. For a club that is fighting for promotion back to the top level, these technologies provide a major advantage over competitors relying on traditional, slower methods, since not all teams across the league are at the same stage of this restructuring process (TFL, n.d.; Vuorenmaa, 2025). This research shows the organization's change, highlighting how AI leads to deeper fan connections, streamlines sponsorship management, and enhances athletic performance and health through predictive analytics (Forbes Technology Council, 2025; Panchal & Singh, 2025). High performance in all these areas is essential to bring the best results on the ice and lead the club back to success.

Context and Background

The organization is a founding member of the German Hockey League (DEL) and has a significant history with both championships and financial restructuring. After the last restructuring, the club is currently competing in the second German Hockey League (DEL2), where they are in the playoffs fighting for promotion, which shows the organization's high ambitions. The club operates as a for-profit professional sports organization, focusing on high-level ice hockey and entertainment. Under its new owner, who took over the club as well as the team's multi-purpose arena, in 2021, a major responsibility of the organization is not just to market the hockey team but also the arena for other events, like concerts. Since the new owner took over the organization, there has been a visible change from a traditional club towards a more modern approach to set the foundation for future success (TFL, n.d.; Vuorenmaa, 2025). Focusing on the hockey team, the organization has a business model centered around three major revenue streams: ticket sales, regional sponsorship partnerships, and merchandise

sales, with ticket sales and sponsorship deals being the major portion of it (Vuorenmaa, 2025).

The stakeholder landscape of the organization is complex and directly related to the performance on and off the ice. Primary stakeholders include the owner, loyal and supportive fans, and a network of regional sponsors who use the club as a platform to showcase their products. The fans and sponsors have a major impact on the organization's success, which is why their satisfaction is a major priority for the club to drive engagement and boost loyalty (Forbes Technology Council, 2025; Vuorenmaa, 2025). The organization employs a mix of full-time administrative staff, including marketing, management, and finance, as well as professional athletes and a specialized and diverse coaching team.

All these stakeholders must work hand in hand to succeed in an environment of high emotional visibility and performance pressure (Vuorenmaa, 2025). In professional sports, one wrong decision can cost success and millions of dollars, making data-driven decision-making essential (Vuorenmaa, 2025). In past years, the organization implemented major changes, including the renovation of the arena to make room for more fans and the expansion of the marketing and management staff to work more efficiently.

The club also prioritized a digital transformation, utilizing AI as a "strategic tool" to redefine how the sport is coached and managed (LBS, 2026). This allows the club to bridge the gap between its second-division resources and its first-division ambitions through the intelligent use of data (Vuorenmaa, 2025). These changes are not just made to reach short-term success but to ensure the organization remains long-term sustainable on the highest level while safeguarding athlete well-being (Asiabar et al., 2025; Panchal & Singh, 2025).

Case Description

During a five-week internship in the marketing department during the winter of 2025-2026, I directly experienced how Artificial Intelligence (AI) is influencing the organization's work (TFL, n.d.). The workload was mostly divided into three major sectors: sponsorship management, event planning, and digital content creation. It also became evident that AI was also used by the coaching staff for tactical analysis, performance monitoring, and scouting issues (TFL, n.d.; Vuorenmaa, 2025).

The marketing department utilized AI-powered design tools, specifically Canva's AI assistants, ChatGPT, and Google Gemini, to handle repetitive tasks such as background removal and merchandise layouts. While the creative ideas still originated from humans, AI acted as a "virtual assistant" that helped handle the "heavy lifting" of design to create final products for social media (TFL, n.d.). This significantly reduced the time needed and improved the quality of social media content and website materials (TFL, n.d.). To manage the sponsoring network, the organization also implemented an automated engagement system for a newsletter. This system helped create content in advance and send it at specific times using a scheduled send-out option. The manager of the marketing department noted that professionals should develop an understanding of how to use AI tools effectively and in a balanced manner for specific use cases (L. Thier, personal interview, 2026).

More important than the scheduling option is the AI tracking that created statistics on who and how many sponsors opened and engaged with the newsletter (Forbes Technology Council, 2025). For the marketing

department, it is extremely important to see which sponsors are invested in the product to secure sponsorship renewals (Forbes Technology Council, 2025). As noted by another employee, analytics tools for reach measurement and trend analysis are already essential and will be even more critical in the future (T. Kurtz, personal interview, 2026).

Beyond marketing, the coaching staff implemented AI into game preparation. Computer-vision-based video analysis is used to get data-driven insights on other teams, such as attacker shot locations or goalie save percentages, which allows for a more objective evaluation of the game (LBS, 2026). This technology reads the game pixel by pixel, providing objective tactical patterns while eliminating human subjectivity (LBS, 2026). This allows players to work on specific save routines and helps coaches develop game-day strategies based on win probabilities and historical performance data (TFL, n.d.; LBS, 2026).

The medical and athletic staff used wearable trackers to monitor biometrics like heart rate, distance skated, and time on ice (TFL, n.d.). These tools are part of a broader trend toward precision healthcare in sports (TFL, n.d.). Through analysis of these datasets, it is possible for medical personnel and athletic trainers to foresee future injury risk and performance degradation, and make better decisions concerning player rotation and rest periods (Panchal & Singh, 2025; Asiabar et al., 2025). It should be noted that in fast-paced environments, this is a crucial element toward extending an athlete's career (Panchal & Singh, 2025). Research findings suggest that the AI models used can predict performance with 85-90% accuracy and minimize overuse injuries by 20-30% (Panchal & Singh, 2025).

Another area where artificial intelligence has had an important impact is rostering, where organizations have used a data-driven method to scout for players (Vuorenmaa, 2025). This is achieved through scouting platforms using analyzed data via AI, thus making it possible to access statistical information for thousands of athletes to find those that match the criteria of a team (TFL, n.d.). While the scouting process eliminates bias, finding the right mix of both AI models and human judgment is key to making good recruiting decisions (Vuorenmaa, 2025; TFL, n.d.).

Analysis

In the organization, there is the usage of artificial intelligence in various departments as for varying purposes. A critical area in this case is that AI is a benefit and assistant, and not a replacement for human judgment (TFL, n.d.; Vuorenmaa, 2025). As the sources indicate and based on the experience during the internship, modern sports professionals must act as a bridge between AI insights and human intuition to use these tools to the organization's benefit (TFL, n.d.; Vuorenmaa, 2025). For the organization, this was applicable in the marketing department, where AI handled the "heavy lifting" of data processing and design interaction, while the staff was able to focus on high-level creativity, community engagement, and relationship building with sponsors (TFL, n.d.; Vuorenmaa, 2025). However, an understanding of how AI works and the risks associated with it, such as algorithmic bias, is essential to ensure it does not influence operations negatively (Vuorenmaa, 2025; Asiabar et al., 2025). This is one of the reasons that the manager of the marketing department emphasized that basic technology knowledge is already a professional requirement (L. Thier, personal interview, 2026).

It can be concluded that the successful implementation of AI at the DEL2 level is possible through a combination of three elements: commitment from the leadership, strong strategy, and knowledge of technology (Vuorenmaa, 2025). The organization demonstrated the commitment under the new ownership as it has shown a desire to shift its processes and methods from traditional to more modern and digital ones (TFL, n.d.; Vuorenmaa, 2025). Such commitment is crucial, considering that while tradition plays a significant role in sports, there is a need for organizational change in order to maintain competitiveness and viability (Vuorenmaa, 2025). Using a phased process makes it possible to introduce more advanced technologies to the work process without interfering with ongoing operations (Vuorenmaa, 2025). Thus, introducing advanced technological progress to the organization prevents it from falling behind because of the unwillingness to adopt innovations (Vuorenmaa, 2025).

The use of wearables to collect biometric and personal data raises the ethical issue of data privacy (Asiabar et al., 2025; Vuorenmaa, 2025). Considering the fact that the information being collected through the system can be classified as sensitive, the organization should have strong legal regulations, such as GDPR, to protect the data of both the organization and the athletes (Asiabar et al., 2025; Vuorenmaa, 2025). Therefore, it is crucial to use such data exclusively for the purposes of helping the athletes and protecting it from unauthorized access (Panchal & Singh, 2025; Asiabar et al., 2025). Since safety through law takes the highest priority, the organization needs to consult specialists who would evaluate such AI-based solutions and create a proper framework (Asiabar et al., 2025).

Implications and Conclusion

The case study of this second-division ice hockey club proves that the transition to AI-supported operations is not exclusive to world-elite organizations (Vuorenmaa, 2025). For clubs at the DEL2 level, AI provides a critical competitive advantage in a fast-paced market and a crowded entertainment landscape (Vuorenmaa, 2025). These findings offer broader lessons for future sports professionals, highlighting that small to mid-sized organizations can benefit from AI to minimize administrative burdens and close the gap with the top tier in terms of efficiency (Vuorenmaa, 2025). AI also assists these clubs in scouting global talent and analyzing opponents without the need for massive budgets (LBS, 2026; Vuorenmaa, 2025). Another major benefit is the ability to create a personalized fan experience through automated newsletters and interactive social media, which deepens the connection with fans—the primary economic driver for sustainability (Forbes Technology Council, 2025; TFL, n.d.).

In conclusion, this organization's journey shows that data-driven decision-making has become the new standard for professional sports organizations at all levels (TFL, n.d.; Vuorenmaa, 2025). While the human narrative and the unpredictability of play remain the heart of hockey, AI provides the analytical skeleton that supports the club's athletic and economic goals (TFL, n.d.). As technology evolves, organizations must adapt, and individuals entering the sports market should be prepared to bring specific skills in AI and new technology to the table to help their organizations succeed (Vuorenmaa, 2025; TFL, n.d.).

References

Dig Watch. (2026, February 6). AI *drives bold change with five technologies at Milano Cortina 2026*. Digital Watch Observatory. https://dig.watch/updates/ai-drives-bold-change-with-five-technologies-at-milano-cortina-2026

Ghorbani Asiabar, Mojtaba; Ghorbani Asiabar, Morteza; & Ghorbani Asiabar, Alireza. (n.d.). *Ethical implications of artificial intelligence in predicting sports injuries and protecting athlete privacy*. Preprints.org – The Multidisciplinary Preprint Platform. https://doi.org/10.20944/preprints202511.1681.v1

Kunert, Jessica. (2020, July 10). Automation in sports reporting: Strategies of Data Providers, software providers, and media outlets: Article. *Media and Communication, 8*(3). https://www.cogitatiopress.com/mediaandcommunication/article/view/2996

LBS. (n.d.). *Artificial vision in sport: Beyond var and hawk-eye.* Laliga Business School: Mbas, Masters and Sports Courses, Liga de Fútbol Profesional. Retrieved 2026, from https://business-school.laliga.com/en

Panchal, Maynak; & Singh, Manish. (2025). Artificial intelligence in sports analytics for performance enhancement and injury prevention*. International Journal of Innovative Research and Creative Technology*, 1–15. https://www.ijirct.org/viewPaper.php?paperId=2503052

TFL. (n.d.). G42: The future of sport and AI. The Future Laboratory. https://www.tiffin.edu/wp-content/uploads/ Report-Future-of-AI-and-Sport.pdf

Vuorenmaa, Henrietta. (2025, May). Artificial Intelligence supporting scouts [Masters thesis]. Jamk University of Applied Science. https://www.theseus.fi/bitstream/handle/10024/893642/Vuorenmaa_Henrietta.pdf;jsessionid=ABD49A7FCA30E8E1DEFBDBE905BEE744?sequence=2

Wang, Xuelong (2019, June 1). Application of grey relation analysis theory to choose high reliability of the network node. *Journal of Physics: Conference Series, 1237*(3). doi:10.1088/1742-6596/1237/3/032056

Barton Journal

Mindful Horizons: A Mental Health Wellness Center Proposal for Nashville, NC

CASE STUDY

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CITATION

Kaestner, Katelynn E.; Larkins, Sarah M.; Rodgers, Savannah G.; & Hamm, Randy. (2026). Mindful horizons: A mental health wellness center proposal for Nashville, NC. *Barton Journal, 1*(1), 120–126. https://bartonjournal.org/vol-1-no-1/2026-cat2-article-no-008

Abstract

Mental health remains a significant yet often overlooked issue in the United States. In rural towns such as Nashville, North Carolina, limited resources and few clinics intensify the problem. Nashville's primary clinic, Primary Care and Urgent Care of Nashville, cannot prescribe psychiatric medications, resulting in patients having to seek help at emergency departments and causing treatment delays. To examine these issues, this study utilizes descriptive research methods and case study analysis, as well as scholarly articles, a windshield survey, and descriptive observations to identify gaps in mental health services. The windshield survey gathered firsthand information from local community members, drawing on all five senses: taste, sight, smell, sound,, and touch. Cross-referencing resources and community findings showed that a business proposal foundation for Nashville, NC, would be beneficial. This proposal consists of building a mental health wellness center to address the mental health crisis in the small town of Nashville, NC, and providing individuals with proper treatment and medication administration.

Keywords: mental health, health care, nursing

Introduction

Untreated mental health is a very serious topic in many communities; however, the solution lacks available resources. Mental health can be affected by many things, such as an individual's socioeconomic status, physical health, and substance abuse. In the 2021-2022 Nash County Community Health Needs Assessment, behavioral health was named as one of the top three areas of priority. It was stated that the issue should be addressed by community engagement to understand the issue, resources provided to improve it, and progress progress tracked (Hill et al., 2022)

While conducting the research in the community of Nashville, NC, the findings suggested a significant need for mental health services in the community, and that an intervention could be made by providing the community with a mental health clinic. This clinic would be placed in a vacant building in the downtown area of the community and would consist of mental health nurses, office managers, therapists, and a psychiatrist. It would also provide a variety of mental health services, such as cognitive behavioral therapy, group and individual therapy sessions, and classes to teach participants how to heal and maintain a healthy mental status.

It was evident that mental health was a very important topic and that there are currently no resources available directly in the Nashville community for mental health treatment. There is also no access to public transportation in the community, meaning that personal transportation to surrounding communities is the only access the community has to mental health care services.

The purpose of this research project was to address as many mental health needs in the community as possible to improve the overall mental health status of the community. The local facility will provide the community with easier access to treatment. If constructed correctly, the facility should cause a decrease in mental health crises within the community over a period of time.

Context and Background

The research took place in the rural area of Nashville, North Carolina. This area consists of an urgent care facility for medical treatment and a pharmacy for pharmacological needs. However, the urgent care is not able to provide treatment or medication for mental health conditions. They also have to provide a referral to a different cities' facilities in the event of a mental health crisis. Because of the lack of mental health services, members of the community must travel to the surrounding communities of Wilson, North Carolina, or Rocky Mount, North Carolina, for mental health treatment. This serves as an issue for community members with no means of transportation because Nashville lacks access to public transportation systems.

The lack of mental health services serves as an issue for a large variety of stakeholders. First, there are a large number of community members affected by mental health diagnoses. No local mental health treatment means

that community members do not have direct access to the resources necessary to sustain a healthy mental status. There is also a financial barrier due to the cost of traveling to surrounding communities to receive care, and a burden to families or caregivers of mental health patients in the area. Because there are no local services, caregivers have to take on a larger role in the maintenance of mental health diagnoses, especially in the case of mental health crises. Because the caregiver is also required to ensure that these patients have transportation to receive care, this increases the chances of caregiver strain.

Not only does the lack of mental health care cause strain on patients and families, but it also causes an increased strain on medical services in the community and surrounding areas. First, it serves as a strain on the urgent care and primary care providers within the community. With the lack of mental health services, community members go to their primary care or urgent care to seek treatment for mental health. This causes an unnecessary increase in patient visits and increases the strain on providers to make the proper referrals. The mental health of the community also affects the health care services in surrounding communities. One example of this is the increase in mental health crises seen in surrounding emergency departments. If mental health services were available in Nashville, emergency departments at UNC Nash and Wilson Medical would likely see a decrease in mental health patients.

Case Description

When discussing mental health in rural areas such as Nashville, NC, there were some common mental health medications found from using the Windshield Survey. Some common medications were prescribed in Nashville, according to workers at CVS Pharmacy in Nashville, NC. These common medications consisted of antipsychotic medications for schizophrenia and "hormonal" medications. When in rural care, many individuals with a mental health illness often go unnoticed or do not get the proper treatment, as there are not enough resources available for them. Within Nash County, 20% of individuals indicated that they were unable to receive mental health care due to the high cost and insurance, 19% indicated that they lacked the knowledge of where to go, and 10% did not have the time to go (HECSC, 2024). When looking into substance abuse, alcohol was the highest-ranked health issue in the survey, which led to concerns about alcohol usage, prescription drug misuse, and individuals coping with substance use (HECSC, 2024). Concluding the review of commonly prescribed medications in Nashville, NC, and the county's overall approach to mental health, it is evident that these factors significantly impact individuals' well-being.

At Nashville's "Primary Care and Urgent Care of Nashville," the Nurse Practitioners indicated that when patients come in for psychiatric help that includes medication, they should be referred to the nearest hospital, Nash General Hospital in Rocky Mount, NC. The clinic in Nashville is roughly 10 minutes away from the hospital. However, mentally ill patients who are not at risk of harming themselves or others tend to wait hours to be seen, Emergency Departments identify in triage which patients need to receive care first (Kurhayati et al., 2025). This can cause individuals to push away from wanting to obtain help because the waiting hours can be unbearable for some, such as those with schizophrenia, who can experience their symptoms escalating and cause poorer thinking and processing skills (Mayo Clinic, 2024), leading to one leaving the emergency room before

being seen. This is due to their symptoms, such as their psychosis, causing them to lose sight of reality (Mayo Clinic, 2024). With the delay of treatment, individuals' symptoms can worsen, which makes it difficult for them to perform daily activities or hold a job, and can eventually lead to death by suicide (Mayo Clinic, 2024). Mental illness is a chronic condition and needs constant treatment and medications prescribed to help the individual maintain their daily activities and be able to function independently. However, as mentioned previously, individuals struggle to afford or lack the resources to get the help they need.

Alternatively, with further research, establishing a for-profit mental health wellness center can specifically help these individuals get the care they need. These outpatient services can help individuals receive proper treatment and medications when the right team is assembled. The right team will include a psychiatrist, as they are allowed to prescribe psychiatric medications that are beneficial for mental health illnesses. There is evidence that factors in the physical environment reported as beneficial include sensory design elements, such as colors around the individual, sounds, and textures (Sui et al., 2023). These sensory designs, such as the plant colors "green, light green, white-green, green-yellow, and green-red" (Sui et al., 2023), have been shown to reduce stress levels in an individual's everyday life (Kexiu et al., 2021). Not only that, but these plant colors have shown a correlation with positive feelings, including "calmness, comfort, and naturalness" (Kexiu et al., 2021), which suggests that these colors can have a positive impact on relaxation and emotional status (Kexiu et al., 2021). Next, engagement qualities that serve as a distraction, such as crafting (Sui et al., 2023) and art therapy, have been shown to help mental health as it is a way for individuals to express themselves, which will then help improve not only their mental health but also their interpersonal relationships (Shukla et al., 2022). The third benefit is the social relationship aspects, including privacy and connection (Sui et al., 2023). An environment that helps individuals feel they have their own personal space and are not in a crowded area can help decrease negative emotions such as anxiety or feelings of exposure (Sui et al., 2023). Lastly, affective experiences are the space itself, as this environment needs to have the individual feel "safe, calm, in control, self-aware, or creative was beneficial" (Sui, et al., 2023).

Overall, a positive environment that is patient-centered for individuals with mental health illnesses can improve their well-being. Implementing different types of therapy, such as Art Therapy, can also help individuals' mental health, by improving their depression through self-expression or helping with schizophrenia with what they are seeing through their hallucinations or delusions. Along with providing a sense of calm and a place of security, it also offers opportunities for emotional regulation and finding better ways to cope.

Analysis

The case of limited mental health access in Nashville, North Carolina, can be effectively interpreted through several public health and nursing frameworks, including the Social Determinants of Health (SDOH) and the Health Belief Model (HBM). These frameworks provide a comprehensive way to understand the barriers identified in the community. They also help support the rationale for establishing a local mental health wellness center. The Social Determinants of Health framework highlights how environmental and socioeconomic factors influence health outcomes (WHO, 2023). In this case, key determinants such as limited transportation, financial

constraints, and lack of local healthcare infrastructure impact access to mental health services. The absence of public transportation creates a geographic barrier, while financial limitations and lack of insurance further restrict people's ability to seek care. The SDOH principles emphasize that health inequities are often rooted in systemic issues rather than individual choices. This directly reflects the findings discovered during this case study. The proposed wellness center directly addresses these disparities by improving geographic accessibility and potentially reducing financial strain associated with travel.

The Health Belief Model helps explain why individuals in the community may delay or avoid seeking mental health care (Alyafei & Easton-Carr, 2024). According to the HBM, health behaviors are influenced by perceived susceptibility, severity, and barriers, along with cues to action. In Nashville, individuals may recognize the severity of their mental health conditions, but are discouraged by long wait times in emergency departments, cost, or the lack of knowledge about available resources. There is also stigma surrounding mental illness that may further reduce perceived benefits of seeking care. Establishing a local wellness center can act as a "cue to action" by increasing awareness, reducing stigma through community engagement, and making services more approachable and accessible. Additionally, the concept of patient-centered care is evident in the proposed design of the clinic (Edgman-Levitan & Schoenbaum, 2021). Research supports that therapeutic environments, including calming sensory elements and opportunities for creative expression, can improve mental health outcomes. By integrating these features, the wellness center aligns with holistic nursing principles that address not only psychological needs but also environmental and emotional well-being.

Systems theory can be applied to understand the broader impact of the intervention (Komashie et al., 2021). The lack of mental health services affects multiple interconnected systems, including families, primary care providers, and regional hospitals. By introducing a local wellness center, this "intervention" has the potential to reduce strain on emergency departments and enhance overall community health outcomes. Applying these frameworks demonstrates that the mental health challenges in Nashville are complex and require a comprehensive intervention. The wellness center is supported by established public health and nursing theories, making it a practical and evidence-based solution to address the identified gaps in care.

Implications

The findings from this case study have significant implications for public health practice, healthcare delivery, and community-level interventions in rural settings. Addressing the identified gaps in mental health services in Nashville, North Carolina, highlights the critical need for increased accessibility, affordability, and awareness of care. The implementation of a local mental health wellness center could reduce healthcare disparities by minimizing transportation barriers and alleviating the burden on emergency departments and primary care providers. Furthermore, integrating patient-centered and evidence-based approaches, such as cognitive behavioral therapy and therapeutic environmental design, may improve treatment adherence and overall outcomes. These implications also extend to policy development, emphasizing the importance of funding and resource allocation for rural mental health infrastructure. Strengthening community partnerships and increasing mental health education can reduce stigma and encourage early intervention. This case underscores the necessity

for interdisciplinary collaboration among healthcare providers to ensure comprehensive and continuous care for individuals with chronic mental health conditions. Future research should evaluate the long-term effectiveness of such interventions in similar rural communities to inform sustainable healthcare models and improve population health outcomes.

Conclusion

The findings from this case study illustrate the impact that limited access to mental health services can have on individuals and communities, particularly in rural areas such as Nashville, North Carolina. The lack of local resources, transportation barriers, financial constraints, and limited awareness creates a system in which many individuals are unable to receive timely and appropriate care. As a result, mental health conditions often go untreated or worsen over time. This can lead to increased reliance on emergency departments and added strain on families and healthcare systems.

This case highlights broader lessons about the importance of accessibility and early intervention in improving mental health outcomes. Communities with limited infrastructure require targeted, locally driven solutions that address both systemic barriers and individual needs. The proposed mental health wellness center demonstrates how integrating patient-centered care, community engagement, and evidence-based practices can create a more effective and sustainable model of care. Additionally, the case emphasizes the need to view mental health through a holistic lens, recognizing the influence of social, economic, and environmental factors on overall well-being. Ultimately, this case reinforces the importance of investing in rural healthcare systems and prioritizing mental health as a critical component of public health. By applying established frameworks and tailoring interventions to community-specific needs, similar rural areas can work toward reducing disparities, improving access to care, and fostering healthier populations.

References

Alyafei, Alyafei; & Easton-Carr, Raul. (2024, May 19). The health belief model of behavior change. *StatPearls* https://www.ncbi.nlm.nih.gov/books/NBK606120/

Edgman-Levitan, Susan; & Schoenbaum, Stephen. (2021, March 5). Patient-centered care: Achieving higher quality by designing care through the patient's eyes. *Israel Journal of Health Policy Research, 10*(21). doi:10.1186/s13584-021-00459-9

Hill, William; Garner, Jerome; Barnes-Staton, Latesha; Isley, L. Lee; & Slade, Kirby. (2022). 2021-2022 community health needs assessment. *Nash Community Health Department*. https://schs.dph.ncdhhs.gov/units/ldas/cha2021/Nash2021-CHA.pdf

Kexiu, Liu; Elsadek, Mohamed; Liu, Binyi; & Fujii, Eijiro. (2021). Foliage colors improve relaxation and emotional status of university students from different countries. *Heliyon*, *7*(1), e06131. https://doi.org/10.1016/j.heliyon.2021.e06131

Komashie, Alexander; Ward, James; Bashford, Tom; Dickerson, Terry; Kaya, Gulsum K.; Liu, Yuanyuan; Kuhn, Isla; Gunay, Aslı; Kohler, Katharina; Boddy, Nicholas; O'Kelly, Eugenia; Masters, Joseph; Dean, John; Meads, Catherine; & Clarkson, P. John. (2021, January 19). *Systems approach to health service design, delivery, and improvement: a systematic review and meta-analysis.* BMJ Careers. https://bmjopen.bmj.com/content/11/1/e037667

Kurhayati, Kurhayati; Etika, Emaliyawati; & Yanny, Trisyani. (2025). An updated scoping review of factors associated with length of stay in emergency department. *Journal of Multidisciplinary Healthcare*, *Volume 18*, 3191–3203. https://doi.org/10.2147/jmdh.s525451

Mayo Clinic. (2024, October 16). *Schizophrenia*. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/schizophrenia/symptoms-causes/syc-20354443

Shukla, Apoorva; Choudhari, Sonali G.; Gaidhane, Abhay M.; & Quazi Syed, Zahiruddin. (2022). Role of art therapy in the promotion of mental health: A critical review. *Cureus*, *14*(8). https://doi.org/10.7759/cureus.28026

Sui, Tiffany; McDermott, Shannon; Harris, Brooke; & Hsin, Honor. (2023). The impact of physical environments on outpatient mental health recovery: A design-oriented qualitative study of patient perspectives. *PLOS ONE*, *18*(4), e0283962. https://doi.org/10.1371/journal.pone.0283962

HECSC. (2024). *Nash County 2024 community health needs assessment*. The Health ENC CHNA Steering Committee. https://stmlnashncus001.blob.core.windows.net/public/Health%20ENC%202024%20CHNA%20Report_Nash_FinalRev_5.14.25.pdf

WHO. (2023). *Social determinants of health*. World Health Organization. https://www.who.int/health-topics/social-determinants-of-health

Barton Journal

Rivalytics: The Role of Marketing Perception in Shaping Consumer Loyalty in Nike and Adidas—Evidence from Primary Survey Data

CRITICAL ESSAY

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CITATION

Pascual Biosca, Eulalia; & Lanier, Charles. (2026). Rivalytics: The role of marketing perception in shaping consumer loyalty in Nike and Adidas—Evidence from primary survey data. *Barton Journal, 1*(1), 127–134. https://bartonjournal.org/vol-1-no-1/2026-cat2-article-no-009

Abstract

Since 1964, Nike and Adidas have dominated the sports industry, developing a rivalry that extends beyond products and is now focused on building emotional branding to develop their desired consumer perception and achieve customer loyalty. This study addressed the role of marketing perception in influencing consumer loyalty. Using a quantitative research design, primary data was collected through an online survey designed to compare consumer perceptions. The survey was completed by 134 respondents, and sent exclusively to members of the college community with an official institutional email address. The survey was organized into five sections—demographics, financial performance, sponsorships, marketing strategy, and consumer perception—allowing for both quantitative and qualitative insights. Responses were analyzed and compared with real-world data, revealing the significant role that marketing plays when maintaining consumer loyalty. Findings within this sample reveal consumer perceptions of Nike and Adidas do not fully align with prevailing industry trends or global data. Many differences were identified regarding brand perception and consumer preferences. This

suggests that within a specific consumer group, expected brand association may change. While the study includes a limited and demographic sample size, it demonstrates valuable outcomes for companies, reinforcing the necessity to continuously evaluate their message across different audience segments.

Key words: consumer loyalty, marketing, emotional branding, Adidas, Nike

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Introduction

The rivalry between Nike and Adidas has always been influential within the modern sports wear industry. Each brand's customer loyalty is a key to continuing as a leader in many worldwide sports markets. For instance, Adidas is the biggest sportswear manufacturer in Europe and second largest globally, following Nike (Han, 2025). Nevertheless, both brands go beyond athletic performance and play a significant role in streetwear fashion and cultural identity.

In today's digital era, brand loyalty has adapted into a new form, known as emotional branding, a term introduced by Marc Gobé, focused on targeting customers' emotions (Wong, 2024). It is a strategy where consumers engage with brands that transmit their values within their content, creating real relationships rather than just transmitting functional business benefits (Akgün et al., 2013). Therefore, digital platforms have also transformed marketing, focusing on creating relationships based on emotional storytelling and personalized engagement in order to create and shape loyalty. Within this context, the significance of the Nike and Adidas rivalry lies in its cultural and economic influence, as each brand deploys distinct strategies that shape modern marketing strategies and consumer engagement.

The purpose of this study was to analyze and compare how Nike and Adidas use digital ecosystems, emotional branding, and cultural positioning to construct consumer loyalty. This research incorporates primary data collected through a real survey conducted within a defined audience, with all collected data presented in a website specifically developed for the study. The central argument is that brand loyalty is no longer driven mainly by product superiority but by emotions, engagement and identity construction. Rivalytics research combines theoretical information with original survey data to analyze how Nike and Adidas compete for consumer loyalty and which areas dominate in today's sport industry. The term Rivalytics, created for this study by merging rivalry and analytics, refers to a data-driven approach to understanding competitive brand relationships.

Contextual Framework and Scholarly Positioning

The rapid evolution of digital technology has changed the relationship between consumers and brands. Consumers are not only looking for products and services that solely meet their respective needs, but also to connect emotionally with brands and their mission. Within this context, the concept known as *emotional branding* becomes highly relevant. Emotional branding is a marketing strategy that seeks to create connections through storytelling, customer experience, and transmission of brand values. In other words, emotional

branding strategies are a key factor to increase customer loyalty (Hasibuan et al., 2025). Without customer loyalty, all efforts to create deeper emotional connections with customers are useless, since the final objective would not have been achieved: to make purchases be constant and create an emotional commitment to the brand (Hasibuan et al., 2025).

Nike and Adidas are the two most popular sporting equipment companies in the world. In fiscal year 2024, Nike reported total revenues of approximately $51.4 billion (Nike, Inc., 2024), while Adidas generated about $23.6 billion in revenue (Adidas AG, 2025). Each brand's image and perception are exceptional, and both companies have similar strategies and suppliers, making their rivalry more noticeable. Nike Inc, is an American multinational corporation mainly focused on the sports industry, selling footwear, apparel, equipment, accessories and services (Mahdi et al., 2015). Headquartered in Beaverton, Oregon (USA), and founded in 1964 as Blue Ribbon Sports, the company was officially renamed Nike, Inc. in 1971. Nike is the world's leading sportswear company (Ozanian, 2013). According to Forbes, Nike accounts for over one-third of the athletic gear maker's market value, dominating the international market through a powerful combination of performance-driven design, emotional storytelling, and digital marketing (Ozanian, 2013).

Nike follows many strategies in order to become a world leader in sports. One of these strategies is a continuous focus on innovation and research in order to produce and offer the best equipment to contribute to athletic performance, motivation and comfort (Mahdi et al., 2015). Moreover, Nike is a pioneer within this industry by using the Market Segmentation Strategy, an approach that advertises its products throughout strategic sponsorships with celebrity athletes, such as Michael Jordan, professional teams, and other college athletic teams (Mahdi et al., 2015). Beyond performance, the company emphasizes sustainability and social responsibility through many initiatives. According to its sustainability data, Nike has achieved a 96% renewable electricity coverage for its operations, as well as a 69% reduction of absolute emissions from operations (Sustainability, n.d.). Today, Nike stands as the most valuable sportswear brand globally, leading in both revenue and brand equity. Nike's unique combination of innovation and inspiration continues to shape global sports culture, giving Nike a higher competitive advantage in the industry.

By comparison, Adidas, founded in 1949 in Germany, is also one of the most influential sportswear and lifestyle brands in the world. Adidas's iconic three-stripes logo has become widely recognized across global markets. The company focuses more on differentiation and multi-brand strategies, with the aim of having a diverse brand portfolio, colliding the worlds of sports and fashion culture. This allows them to target all segments of the market, from professional athletes to everyday consumers (Mahdi et al., 2015). The brand maintains a strong presence in European markets, while also being represented internationally. This influence is especially visible in football (soccer) , where Adidas sponsors elite teams such as Real Madrid and FC Bayern Munich (Adidas, 2025). Beyond performance, Adidas has developed impactful marketing initiatives related to environmental responsibility, such as Parley for the Oceans, a shoe creation made from reclaimed marine plastic waste and recycled from ocean waste (Parley, 2023).

Adidas defines itself as a brand focused on generating innovative concepts that unite performance and culture,

creating campaigns that positively influence social wellbeing in all possible ways. The insights previously obtained from the conceptual framework are used in Rivalytics to interpret and compare them with the primary data acquired in the research. Stated differently, the general market data have been considered to be a baseline of expected patterns regarding consumers' perception and brand positioning about Nike and Adidas. These measures are compared with the data collected through the survey component of the study. This comparative analysis enables the detection of any deviations from the general expectations, allowing the study to highlight those shifts and demonstrate how individuals relate differently to the two brands within a specific context.

Argument Development

This section develops the core argument of the Rivalytics study by examining the research methodology, consumer loyalty patterns, emotional branding strategies, and marketing insights related to Nike and Adidas.

Research Design and Methodology

This survey-based research was conducted through an online survey designed to compare consumer perceptions of Nike and Adidas in relation to marketing strategies, brand image, and purchasing behavior. The survey was distributed through institutional email, exclusively to members of a small, liberal arts college with a high percentage of student-athletes. A total of 134 respondents completed the survey, with questions divided into five sections: *demographics*, *financial performance*, *sponsorships*, *marketing strategy*, and *consumer perception*. This design allowed for both quantitative and qualitative insights. Responses were analyzed to identify patterns in brand preference and perception between Nike and Adidas, and later compared with real-world data obtained from official brand reports, market analyses, and academic sources.

Consumer Loyalty Patterns — Survey Results

Survey data from 134 participants demonstrated a strong preference toward Nike. When forced to choose one brand, 70.9% selected Nike, while a smaller proportion preferred Adidas. Similarly, 60.4% reported purchasing Nike more frequently, reinforcing the brand dominance within the sample. Moreover, Nike obtained higher recommendation scores, between 4–5 range scale, and frequent purchasing behavior among its users, demonstrating stronger behavioral loyalty. Nevertheless, Adidas loyalty perception was tied to symbolic associations, as its consumers showed more attachment in the lifestyle and comfort-oriented areas. When focusing on the research pattern-based observations, loyalty appears to be controlled by perception rather than external promotions. Product quality and performance still dominates over any collaboration with celebrities and athletes, as data showed that sponsorship influence is minimal (<30%).

Open-ended responses allowed the research to develop a more critical interpretation of the perceptions of each brand. The data connected Nike with an athletic self-identity, linking athletic excellence, iconic athletes, and performance with the brand. One respondent described Nike as "more consistent and friendlier to larger individuals," reinforcing the perception of Nike as a brand that not only focuses on performance, but also resonates with a broader range of consumers. However, Adidas data was more associated with comfort and fashion, indicating a lifestyle brand image. As one participant explained, Adidas is "more about everyday style

rather than intense performance."

Emotional Branding and Identity Construction — Evidence from Data

Nike dominates the international market by staying true to its mission: bring continuous inspiration and motivation (Nike Inc., n.d). This message is constantly reinforced in most of the content to create a whole brand voice around performance and empowerment. In fact, Nike has a specific focus on motivational storytelling; for instance, using campaigns such as Just Do It and Winning Isn't for Everyone to inspire personal improvement and athletic achievement (Samadji, 2024). Although most of Rivalytics participants (85.8%) stated that marketing campaigns do not influence their purchases much, 44.8% viewed Nike campaigns as more motivating. Taking this into consideration, survey patterns closely reflected Nike's association with inspiration and athletic performance, as respondents view the brand as a symbol of personal achievement and self-improvement in the sports field.

When evaluating Adidas's emotional associations, it is important to focus on the areas the audience connects this brand with: soccer, comfort, and fashion. Adidas is internationally recognized for blending sport with fashion, lifestyle, and cultural expression, often driven by collaborations with designers, musicians, and influencers (Vizologi, 2025). The research findings reinforced earlier observations, as a large majority of respondents (76.9%) viewed Adidas's advertising as more creative and aligned with fashion, lifestyle and cultural identity.

Rivalytics insights revealed a surprising contradiction to the general research trends. An important part of Adidas's reputation relies on its sustainability initiatives, such as its Parley recycled polyester products, attracting trend-conscious and environmentally aware consumers (Parley, 2023). Nonetheless, the research sustainability perception was weaker than expected. As shown in Figure 3, 71.6% of respondents did not strongly associate Adidas with environmental leadership. The emotional drivers that correlate most with loyalty were performance perception linked to Nike, and lifestyle identity strongly associated with Adidas. In other words, this demonstrates that most of the consumer loyalty patterns in the survey aligned closely with global data. In view of the previously examined data, brands focus beyond product value. Brands seek emotional meaning to create their desired perception to customers, thus indirectly building brand loyalty and preference.

Data-Driven Marketing and Consumer Behavior Insights

Research data shows that Nike and Adidas have distinct marketing strategies, each designed to target specific audience connections. It was possible to observe behavioral differences in loyalty within consumers of each brand. On one hand, Nike-loyal consumers are performance-oriented, with a higher repeat purchase frequency and are less influenced by sponsorship and more by product performance. On the other hand, Adidas-loyal consumers are more lifestyle and comfort-driven, with a lower purchase frequency but with a strong positioning in the lifestyle and cultural industry.

Considering the data from the Rivalytics research, three consumer segments can be identified: performance-driven buyers, fashion-oriented buyers, and a mix of both, the quality-driven buyers. According to the

demographic data of the study, many of the respondents identified as people who consider the two main categories equally. Nevertheless, particular attention should be given to the results about marketing campaigns in the research. Most participants (85.8%) stated that marketing campaigns do not influence their purchases more than product quality. Even though respondents make this claim, they are still aware of the brand's mission, its innovations, and recent actions, demonstrating a long-term influence on their consumer behavior.

Comparative Strategic Interpretation & Outcomes

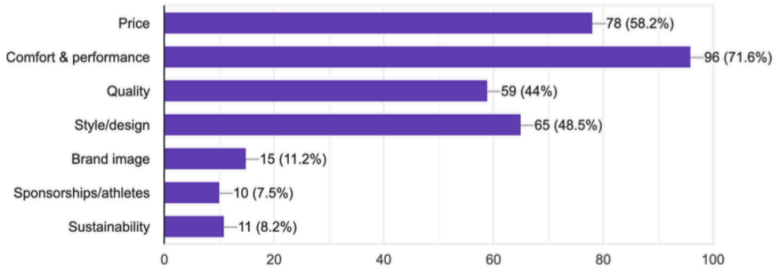
The outcomes highlight Nike as the brand with the strongest emotional loyalty, supported by the primary data, in having a higher preference (70.9%), recommendation scores and identity alignment with the audience. However, Adidas demonstrated being the strongest in cultural and lifestyle identification. The brand has the highest perception of creativity and fashion alignment (76.9%), strongly associated with lifestyle within its target consumers and a present community involvement.

Counterarguments, Limitations, and Complications

A counterargument throughout the research can be seen in the main drivers of loyalty. A combined 71.6% and 58.2% of respondents prioritized comfort, performance and price, respectively (Figure 1). Therefore, despite the rise of emotional branding, product performance and price are still the main factors in customer decision-making.

Figure 1

Main Factors Influencing Consumer Purchase Decisions In The Sports Industry



Note: Data collected through original survey conducted for the Rivalytics study (N = 134).

This study presents several limitations that should be considered. First, the primary data reflects responses from 134 participants drawn from a small, private, liberal arts college, representing the perspectives of a defined population within a particular academic setting. Second, the research focuses exclusively on Nike and Adidas, therefore, the findings are difficult to generalize into the sportswear industry as a whole. Additionally, the survey was only conducted within the U.S, although a few participants were from other countries, meaning that cultural and geographical differences among consumers were not perfectly captured within the study's sample. Finally, it needs to be noted that the rapid evolution of today's digital environment will affect marketing strategies, thus, the future applicability of *Rivalytics*. Rivalytics' findings offer insights into how to shape

broader implications and its future directions. The study provides strategic primary data on customer perception of the two main brands, therefore, deepening the role of data analytics in this study may be a long-term direction to use those results to strengthen customer engagement and behavior. Future research should explore the growing role of AI, especially in consumer personalization, with the aim of focusing on how machine learning, predictive analytics, and real-time behavioral data enable brands to deliver highly customized experiences.

Conclusion

This project argues that the rivalry between Nike and Adidas reveals how today's brand competition is driven not only by marketing strategy and performance, but by emotional branding, identity brand construction, and data-driven consumer insight, which support the development of loyalty in the long run. Key findings indicate that consumers are influenced by how effective brands are in positioning themselves, transmitting their brand message and narrative. Furthermore, in order to build the strong community of loyal consumers that every company seeks, the study demonstrates that product quality, effective emotional branding, and identity-based perception are key drivers of brand preference over competitors in the market.

Rivalytics results reveal that brand perception within a small, focused audience does not always align and may diverge from global market expectations. Therefore, these findings not only highlight the importance of collecting specialized and segmented consumer data rather than relying solely on macro-level brand positioning, but also illustrates the need for companies to continually evaluate how their message and mission resonate with specific audience segments. Nike and Adidas have always been dominant brands in the global sports industry. They compete not just through their product and service offerings, but also through the messages they create around their brands. Their rivalry surpasses product performance, focusing on building emotional connections and influencing how consumers view themselves through the brand. Understanding the Rivalytics framework requires recognizing that today's brand loyalty reflects community belonging that goes beyond functional or economic value.

References

Adidas. (n.d.). *Annual report 2024.* Adidas. https://report.adidas-group.com/2024/en/group-management-report-our-company/description-of-business-model/product-and-mar keting.html

Adidas AG. (2025, March 5). *Adidas reports strong results for 2024 and expects top- and bottom-line momentum to continue in 2025.* Adidas. https://www.adidas-group.com/en/media/press-releases/adidas-reports-strong-results-for-2024-and-expects-top-and-bottom line-momentum-to-continue-in-2025

Akgün, Ali Ekber, Koçoğlu, İpek, & İmamoğlu, Salih Zeki. (2013). An emerging consumer experience: Emotional branding. *Procedia – Social and Behavioral Sciences, 99*, 503–508. https://doi.org/10.1016/j.sbspro.2013.10.519

Han, Xingyu. (2025). Comparison of marketing strategies between Nike and Adidas. *Highlights in Business, Economics and Management*, *60*, 215–221. https://doi.org/10.54097/2rxvyw17

Hasibuan, Ahmad Nurdin, Laksono, Rudi., Limakrisna, Nandan., & Moeins, Anoesyirwan. (2025). Influence Of Emotional Branding On Customer Loyalty In The Digital Era. *Procedia Environmental Science, Engineering and Management*, *12*(1). https://www.procedia-esem.eu/pdf/issues/2025/no1/5_Hasibuan_25.pdf

Mahdi, Hussain. A. Ali., Abbas, Mohammed., Mazar, Taher. Ilyas., & George, Shaju. (2015). A comparative analysis of strategies and business models of Nike, Inc. and Adidas Group with special reference to competitive advantage in the context of a dynamic and competitive environment. *International Journal of Business Management and Economic Research, 6*(3), 167-177. https://www.semanticscholar.org/paper/A-Comparative-Analysis-of-Strategies-and-Busin ess-%2C-Mahdi-Abbas/b0a72e2fb2b7d23121895f1582289a221229c91c

Nike, Inc. (n.d.). *About Nike*. Nike, Inc. https://about.nike.com/en/mission/ Nike, Inc.

Nike, Inc. (2024, June 27). *NIKE, Inc. reports fiscal 2024 fourth quarter and full year results.* Nike, Inc. https://investors.nike.com/investors/news-events-and-reports/investor-news/investor-news-details/2024/NIKE-Inc.-Reports-Fiscal-2024-Fourth-Quarter-and-Full-Year-Results/default.aspx

Nike, Inc. (n.d.). *Sustainability*. https://about.nike.com/en/mission/focus-areas/sustainability

Ozanian, Mike. (2013, March 26). The Forbes Fab 40: The world's most valuable sports brands. *Forbes.* https://www.forbes.com/sites/mikeozanian/2012/10/17/the-forbes-fab-40-the-worlds-most-valuable-sports-brands-4/?ctpv=searchpage

Parley. (2023, June 15). *Adidas X Parley* Parley. https://parley.tv/initiatives/adidasxparley

Vizologi. (2025, July 23). *What is the target market of Nike and Adidas?*. Vizologi. https://vizologi.com/what-is-target-market-of-nike-and-adidas/

Wong, Jessica. (2024, December 5). Emotional Branding—Connecting With Consumers On A Deeper Level. Forbes. https://www.forbes.com/councils/forbescommunicationscouncil/2024/12/05/emotional-branding-connecting-with-consumers-on-a-deeper-level/

Barton Journal

Understanding Radiographic Chemistry

SHORT ARTICLE

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CITATION

Olson, Savannah, & Mazuroski, Nicole L. (2026). Understanding radiographic chemistry. *Barton Journal, 1* (1), 135–141. https://bartonjournal.org/vol-1-no-1/2026-cat2-article-no-010

Abstract

This study researched radiographic compounds with the intention of gaining a better understanding of the chemical structure and mechanism of action of radiographic contrast agents. Through a series of experiments and research methods, conclusions have been drawn about the properties of contrast agents and their effects on the body and medical images. Before working with chemical agents, ample research was done on the composition and chemistry of radiographic contrast agents. Laboratory experiments were then produced and executed using smartphone colorimetry as a tool to receive RGB values for various solutions. These labs were created with the intention of using compounds that make up radiographic contrast agents to observe reactions in a controlled, less invasive environment. Experimental results align with the research conducted, indicating the solubility, redox behavior, and chemical properties of contrast agents. The findings can be used to deepen knowledge of contrast agents and, in turn, have an impact on medical technology; the eyes of medicine.

Introduction

This study will analyze the role of contrast agents in radiographic chemistry by examining the mechanisms of action and chemical stability. Conducted as a semester-long project, it involved testing and analyzing contrast agents in the lab. The work consisted of a combination of research methods and a physical lab component over the course of twelve weeks. Iodinated contrast media contain iodine and are used in X-ray techniques, including CT (Murphy et al., 2026). The primary administration of iodine-based contrast agents is through an IV, though they can also be administered differently depending on the test type or patient needs. Due to their high atomic number, iodinated contrast agents produce adequate contrast of tissues in the body, increasing image quality. Iohexol is one contrast agent that is used in computerized tomography. Another major type of contrast agent used in medical imaging is barium-based contrast agents. Typically, these agents are used for images of the lining of the gastrointestinal tract but can be dangerous if there are perforations in the bowel. Barium-based agents are administered rectally or orally, as opposed to intravenously like iodine-based contrast agents (Noah Chemicals, 2024).

Additionally, this study primarily focuses on the mechanism of action and chemical stability of iodine-based contrast agents. Each type of contrast agent has its own chemical composition that makes it more efficient for different medical imaging types. Knowing the chemical stability of different agents helps determine which agents to use for each test and explains why they are used for images in different body regions. Iodinated contrast media are either high or low osmolality, which refers to the rate at which water diffuses. High osmolality contrasts are specifically dangerous near the respiratory system due to a high risk of pulmonary edema (Zeligman, 2010). Side effects like this are crucial for healthcare providers to be aware of to prevent patients from being harmed or dying. These contrasts are safe for medical imaging that does not require administration by swallowing or through a tube (Zeligman, 2010).

Iodinated contrast media are also commonly used in the field of radiology due to the excellent medical images that can be produced by iodine's ability to absorb X-rays and make internal bodily structures visible (Yang et al., 2018). Iodine's high atomic number allows photons to be absorbed, and structures like blood vessels appear bright white on the images. Researchers are constantly working to find ways to adapt contrast agents to create the highest visibility in medical images to better diagnose diseased areas of the body. Many Magnetic Resonance Images (MRIs) use contrast agents to aid in this process. MRIs are used as a diagnostic tool to reveal inflammation, tumors, and tissue abnormalities (Lv et al., 2023). It is important for contrast agents used for MRIs to have the ability to polarize water molecules and yield a high-contrast, high-quality image that can be used to diagnose diseases. Due to the composition of the human brain, different contrast agents may be needed, as contrast is lower in the brain than in other areas of the body (Lv et al., 2023). Body parts and mechanisms of action should be considered when determining which contrast agents to use for different diagnostic radiographic procedures.

Methods & Materials

The first procedure completed was a smartphone colorimetry experiment. The Redox of Iodine Using Apple

Juice and Smartphone Colorimetry lab was created and produced to showcase the change iodinated compounds encounter over time when a Vitamin C source is added. The purpose of this study is to gain a better understanding of the core chemistry behind contrast agents. Materials needed included 0.05M iodine, starch solution, apple juice, water, small beakers, pipettes, white paper, and an iPhone camera. To prepare the starch indicator, 1 teaspoon of cornstarch was mixed with 20 mL of warm water in a small beaker and stirred until cloudy. The iodine-starch complex was then created by adding 5 mL of iodine and 3 mL of starch solution. This mixture was stirred until it became a deep blue hue. Next, 3 mL of apple juice was added as the reducing agent. The solution was swirled and observed. The cup was placed onto a white sheet of paper as the background, and smartphone colorimetry measurements were taken every two minutes using a color-analyzer app. Each time a new picture was taken, the RGB values were recorded. Iodine is a stable element, but it can exist in various forms. When Vitamin C is added, iodine is reduced to iodide. Fortunately, Vitamin C levels in the body are not high enough to reduce iodine in iodine-based contrast agents on their own, so there is not an effect on imaging quality based on normal values. Vitamin C has been tested and is believed to be a radioprotector. Studies conducted on mice introduced ascorbic acid to the organism, where it acted as a radioprotector (Narra et al., 1993). While there is still ample research to be done, this could be a monumental finding in medicine if Vitamin C can be used to protect humans from radiation in the future.

A second experiment completed during this study was Partitioning Water vs. Oil to determine how hydrophilic iodine is. Iodine-based contrast agents are designed to be hydrophilic to allow for safe dissolution into the bloodstream and removal via the kidneys. Iodinated contrast agents are commonly composed of tri-iodinated benzene rings (Murphy et al., 2026). This structure allows the contrast agents to be highly water-soluble and safe for administration in diagnostic radiographic imaging. The protocol demonstrates solubility and lipophilicity, explaining why many contrast agents are formulated as water-soluble. Materials used included iodine solution, corn oil, test tubes, pipettes, starch solution, and smartphone colorimetry. One vial was labeled *Before* and one was labeled *After*. In the Before vial, distilled water and iodine solution were combined, and a baseline photograph was taken. In the After vial, distilled water, iodine solution, and vegetable oil were combined, then shaken to allow partitioning. After sitting for 10 minutes, the layers separated. A sample from the aqueous layer was removed and analyzed using the same colorimetry method. This procedure demonstrated lipophilicity, hydrophilic properties, and osmolality of iodinated contrast agents. Some common contrast agents used for CT scans, categorized as low osmolality and highly water-soluble, include iohexol, iopamidol, iopromide, ioversol, and ioxilan (Murphy et al., 2026).

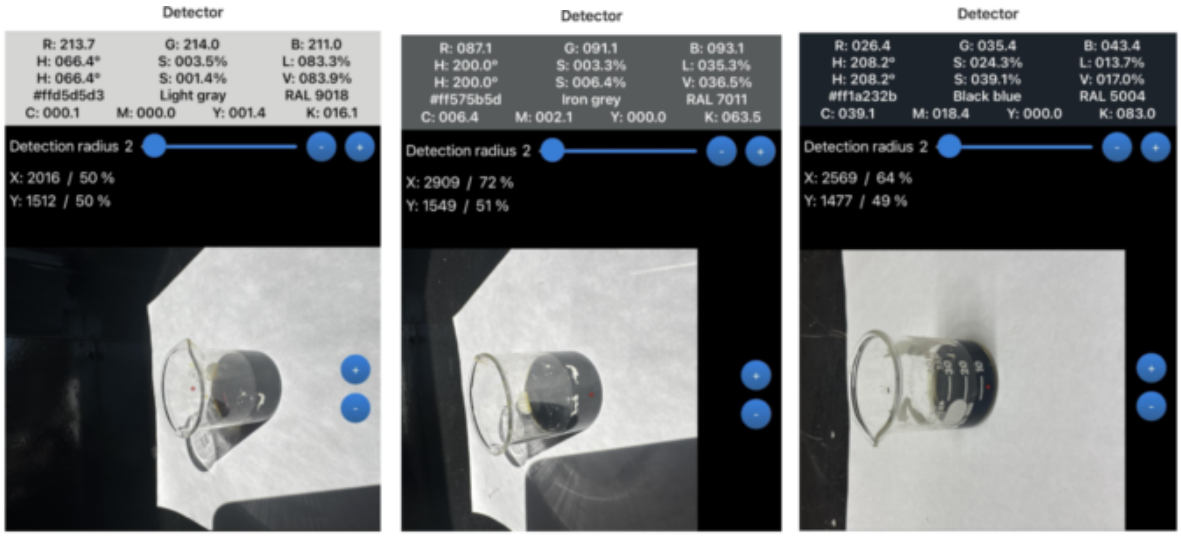
Results & Discussion

In the first experiment, the solution was observed over several minutes, and the RGB values provided by the smartphone colorimetry app were recorded. Values of importance in this lab were the Blue values. Iodine was converted to iodide in this reaction, which does not bind to starch and led to the color fading. As minutes passed, the blue concentration became lower, which was expected with Vitamin C added into the iodine-starch solution (Figure 1). The blue value fell from 211.0 to 182.9 to 102.0 to 98.3, 93.1, 86.8, 80.8, 54.9, 43.4 to 43.4. Over 18 minutes, the blue value fell by 167.6. This color change is not visible to the human eye, which is why the

smartphone colorimetry app is needed to detect numerical values. Vitamin C reduces iodine to iodide and dilutes it, which reduces the blue hue of the solution. As time passed, the iodine became more diluted and less concentrated. Although the addition of Vitamin C to iodine does not directly affect radiographic image quality, it does change the chemical stability of iodine. If anything alters the state of iodinated contrast agents, it could affect how they react in the body and how well they contrast bodily structures in medical images. The blue RGB value is measured since the yellowish/brown color of iodine absorbs light in the blue wavelength. Vitamin C can also lessen the negative effects of iodinated radiation. While iodinated contrast agents themselves do not expose people to radiation, imaging techniques such as X-rays do (Mustafa, 2024). Understanding iodine chemistry is important, as it can be reduced with Vitamin C to help prevent radiation damage. Healthcare professionals can use this knowledge to help patients and potentially reverse radiation exposure if needed.

Figure 1

Blue Value Changes Over Time



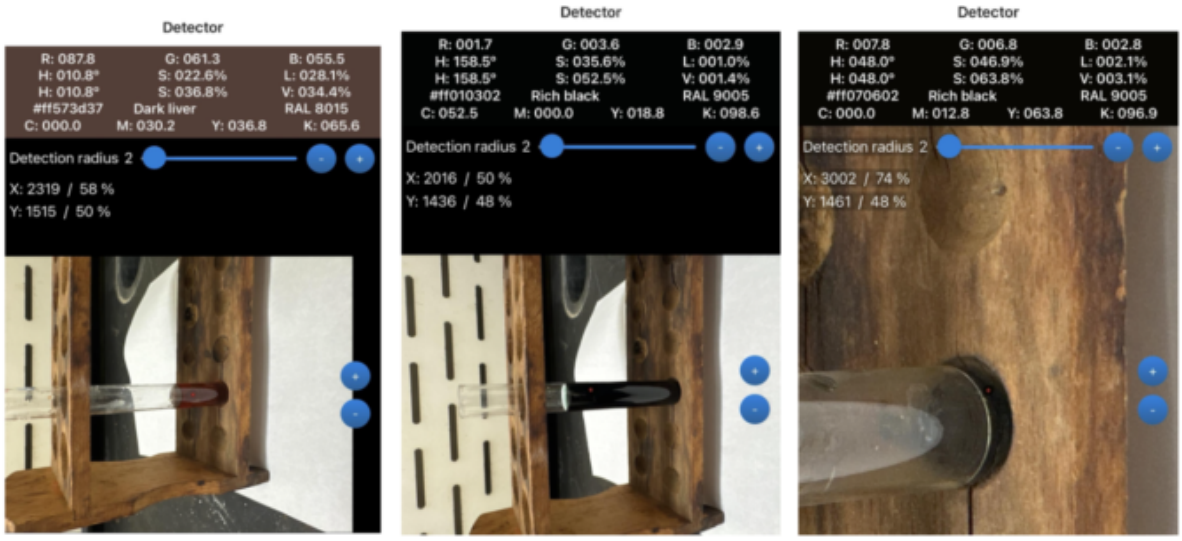
Note. Shown at initial stage, 8 minutes, and 16 minutes.

Results of the second portion of the physical lab component are shown below. These results demonstrate that most iodine remained in the aqueous phase, relating to radiographic contrast agents that are designed to be hydrophilic and remain in the blood. Iodine is water-soluble and dissolves into the bloodstream, moving through it before being excreted by the kidneys. This property is a key component of iodinated contrast agents. Oil-based contrast agents, however, are used in radiology for high visibility and specialized imaging. Their chemical makeup differs from iodine-based agents. Being hydrophobic, they do not dissolve in water, which is the opposite behavior of iodinated contrast media. This lab demonstrates how oil-based contrast agents form layers when distributed among substances. Such layering accurately mimics how these agents behave in the body. Oil-based agents are commonly used to capture images of the fallopian tubes and uterus, as partitioning produces high visibility and allows them to remain in the system longer than other types of contrast agents

(Morita et al., 2025). They may also be injected into ducts to detect tumors and are often preferred because of their extended retention time. Additionally, their chemical structure contributes to high contrast and viscosity, leading to clearer images and aiding diagnosis. Some concerns exist with the use of oil-based contrast agents. In one study involving a pregnant patient who underwent an abdominal radiograph, complications were observed. Because these agents remain in the body longer, they may be identified as foreign objects (Morita et al., 2025). Although the complications in that case were not harmful, the response raises concern about how the body may react.

Figure 2

Results Showing Iodine Remained in the Aqueous Phase



Note. Shown are the Before vial, After vial, and label removed.

Conclusion

In the Vitamin C colorimetry experiment, iodine and starch created the blue complex, and apple juice contained ascorbic acid, the reducing agent in the reaction. Iodine converts to iodide, which does not bind to starch, causing the color to fade. The solution began dark blue and progressively faded. Similar to observations in this lab, radiographic contrast agents contain iodine and change chemically in predictable time courses. Using iodine in a controlled environment allowed for the mimicking of processes of radiographic contrast agents. The corn-oil diffusion lab models how radiographic contrast agents behave in the body. It demonstrated how a hydrophobic, fat-soluble substance navigates an aqueous environment. Corn oil is hydrophobic and separates rather than dissolving in water. A similar reaction occurs in oil-based contrast agents. Immiscible liquids divide into layers, which is also what happens to contrast agents that remain in different tissues.

The Vitamin C smartphone colorimetry lab measured the concentration of Vitamin C and yielded a redox reaction. A smartphone colorimetry iPhone application was used to gain qualitative and numerical data for

analysis. This tool was very useful in determining if color had faded, as chemical changes are not always apparent to the naked eye. RGB values provide ample information and allow observation of the rate of fading. The reaction was completed to mimic measuring contrast dosage and absorption. The corn oil diffusion lab measured solubility and physical distribution, showing the difference between hydrophilic and hydrophobic reactions. Results can be observed visually through the separation of oil from the aqueous solution. Layering observed in this lab is comparable to layering that occurs in radiographic contrast agents within human tissues.

Research on radiographic contrast agents, along with laboratory procedures, was carried out throughout the semester with the goal of understanding chemical structure and how components influence function. It is important to note margins of error when conducting laboratory work and drawing conclusions. During earlier stages of the semester, the same experiments were performed, but results were not as expected. Encountering obstacles and making mistakes is common while learning, and documenting factors that may influence results is essential. In the first trials, user error occurred while working with the smartphone colorimetry app. Data presented in this report reflects results from the final experiments.

References

Lv, Jie; Roy, Shubham; Xie, Miao; Yang, Xiulan; & Guo, Bing. (2023). Contrast Agents of Magnetic Resonance Imaging and Future Perspective. *Nanomaterials (Basel, Switzerland)*, *13*(13), 2003. https://doi.org/10.3390/nano13132003

Morita, Akari; Kakinuma, Toshiyuki; Segawa, Arimi; Harada, Satoshi; Takae, Seido; Tamura, Midori; & Suzuki, Nao. (2025). Prolonged retention of oil-based iodinated contrast medium observed on plain abdominal radiograph after cesarean section: A case report. *World Journal of Clinical Cases*, *13*(29), 110454. https://doi.org/10.12998/wjcc.v13.i29.110454

Murphy, Andrew; Wilczek, Mateusz; Campos, Arlene; Sharma, Rohit; Bell, Daniel J.; Scappatura, Giuseppe; Hutson, Russell, Bickle, Ian; Jones, Jeremy; Johnston, Aimee; Knipe, Henry; Deng, Francis; Hacking, Craig; and Weerakkody, Yuranga. (2026). Iodinated contrast media. Reference article, *Radiopaedia*. https://doi.org/10.53347/rID-48582

Mustafa, Dunya Ali; Abdul Jabbar, Hind Moafak; Joudha, Luma Naji; & Radhi, Muhammed Mizher. (2024). Evaluation study: the effect of using ascorbic acid with and without contrast agent on patient blood samples exposed to different x-ray by cyclic voltammetry. *Al-Nisour Journal for Medical Sciences*, *6*(2), Article 2. https://doi.org/10.70492/2664-0554.1001

Narra, V. R.; Howell, R. W.; Sastry, K. S.; & Rao, D. V. (1993). Vitamin C as a radioprotector against iodine-131 in vivo. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*, *34*(4), 637–640. https://pubmed.ncbi.nlm.nih.gov/8455081/

Noah Chemicals. (2024, August 14). *The essential role of barium sulfate in medical imaging*. Noah Chemicals. https://www.noahchemicals.com/the-essential-role-of-barium-sulfate-in-medical-imaging/

Yang, Jai-Sing; Peng, Yan-Ru; Tsai, Shih-Chang; Tyan, Yeu-Sheng; Lu, Chi-Cheng; Chiu, Hong-Yi; Chiu, Yu-Jen; Kuo, Sheng-Chu; Tsai, Yuh-Feng; Lin, Ping-Chin; & Tsai, Fuu-Jen. (2018). The molecular mechanism of contrast-induced nephropathy (CIN) and its link to in vitro studies on iodinated contrast media (CM). *BioMedicine*, *8*(1), 1. https://doi.org/10.1051/bmdcn/2018080101

Zeligman, E. Bernard. (2010). Chapter 67 – Radiography and radiographic-flouroscopic contrast examinations. *GI/Liver Secrets, 23*(1), 477–488. https://doi.org/10.1016/B978-0-323-06397-5.00067-8

Barton Journal

Selling Beauty, Selling Identity: The Business and Psychology Behind the Beauty Industry

COMMENTARY

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CITATION

Sáez Lozano, Alexandra; & Elizalde, Miguel. (2026). Selling beauty, selling identity: The business and psychology behind the beauty industry. *Barton Journal, 1*(1), 142–147. https://bartonjournal.org/vol-1-no-1/2026-cat3-article-no-011

Abstract

This commentary explores how the modern beauty industry works at the intersection of psychology and business strategy. While beauty products are marketed based on their functional benefits, this article argues that emotional branding, and identity-based communication play a greater role in influencing consumer behavior. Exposing qualitative insights from interviews with a psychology expert, and a business professional, this article highlights how beauty marketing connects products with consumers' self-perception, aspirations, and social identities. From a psychological point of view, beauty standards are directly linked to self-esteem, cultural expectations, and all the ways individuals evaluate their own worth. From a business perspective, companies strategically segment their audiences by age and lifestyle, using storytelling and branding to create loyalty among consumers. This article examines as well the role of social media in amplifying beauty ideals while also creating a space for movements such as body positivity. Ultimately, this commentary article argues that the success of beauty brands depends not merely on the product's performance but also on their ability to build meaningful

narratives that resonate with consumers.

Introduction

In today's saturated beauty industry, success is not merely determined by product efficacy. While formulas, pigments, and textures are important factors, the real differentiator for modern beauty brands lies in their ability to connect emotionally with their consumers. Beauty products have become more than tools for aesthetics because they now serve as vehicles for self-expression and social belonging (Amalia et al., 2023). The relationship between beauty and identity has been discussed in previous studies that highlight how beauty ideals influence society and consumer behavior (Smith, 2022a). This relationship became even clearer through the interviews conducted for this research, where both a business professional and a psychologist expressed that beauty is rarely only about appearance. Instead, it reflects deeper motivations that are directly related to confidence, identity formation, and the firm desire to belong to a particular social group.

From anti-aging creams that target mature consumers to TikTok advertisements about makeup trends for Gen Z, beauty marketing has evolved into an extremely complex interplay of emotional storytelling (Darmatama & Erdiansyah, 2021). Social media platforms have drastically changed the way beauty brands communicate with their consumers (Nugraha et al., 2024). More and more, advertising strategies rely heavily on celebrity or influencer representations (Herman et al., 2023). Interviews conducted with Susan Mathewson, Business Internship Coordinator at Barton College, and Ashley B. Gardner, Assistant Professor of Psychology at Barton College, also highlighted that the digital platforms have drastically increased the visibility of beauty standards at much younger ages (A. Gardner, S. Matthewson, personal communication, March 2026). This means that individuals are constantly exposed to altered images of appearance, and this constant exposure contributes enormously to shaping how consumers evaluate themselves as a person and the products they choose to purchase and use.

This social shift brings in a new trend: consumers are increasingly looking for products that promise them not only functional benefits, but also emotional resonance (Jie et al., 2025). Studies show that beauty advertising shapes how individuals perceive attractiveness and identity (Muñoz-Muñoz & Martínez-Oña, 2024). Interviews with industry and psychology experts illustrate the dual forces that are shaping this phenomenon. Mathewson emphasized that beauty branding has to strategically align products with consumers' self-image, aspirations, and life stages (S. Mathewson, personal communication, March 2026). She explained that beauty marketing is unique because it is extremely age-specific, meaning that companies have to design completely different strategies depending on whether they are targeting teenagers, young adults, or older consumers. Gardner highlighted that on the other hand, the profound psychological influence that beauty has on self-esteem, identity, and overall decision-making on people. She also explained that from an evolutionary perspective, humans may associate beauty with health, while from a more sociocultural perspective, beauty standards are shaped by gender expectations, culture, and the specific social context is targeted. By combining both of these perspectives, there is a deeper understanding that selling beauty is as much about emotional connections as it is about promoting

physical products (Smith, 2022a).

Argument-Perspective

The importance of emotional branding in the beauty industry can be explained by both business practices and psychological dynamics. From a commercial point of view, beauty products are designed to resonate with specific demographics based on age targeted marketing (Jie et al., 2025). Mathewson explained that brands such as Laura Geller and Jones Road are targeting mature consumers by presenting relatable spokespersons, who represent the product's promise. She stated "enhancing natural beauty at one's current stage of life." She emphasized that one of the reasons branding becomes so important is because consumers often look for people who resemble their own age when deciding which product to trust (S. Mathewson, personal communication, March 2026). Older consumers may trust more founders or public figures that are around their life stage. Conversely, younger audiences are more likely to purchase a beauty product if they are influenced by aspirational figures, such as celebrities or social media influencers (Somadi et al., 2022). The goal of beauty brands is to stay consistent across demographics because the consumer is invited to buy into a narrative, not just a moisturizer or a lip liner (Smith, 2022b). Mathewson also said that the beauty industry differs from many others because of the wide variety of points of sale, ranging from drugstores and department stores to online platforms and home shopping networks. She stated that each environment requires different communication strategies and branding approaches.

The psychological point of view reinforces the business perspective. Gardner highlighted that societal emphasis on appearance, particularly for women, links beauty to self-worth (Amalia et al., 2023). Products, therefore, are not simple commodities anymore, they are instruments through which consumers negotiate their own personal identity (Lazar, 2011). During the interview, Gardner explained that from a very early age many women are socialized to associate their value to their appearance, while men are often encouraged to connect their value with financial success. This difference is a clear example that demonstrates how deeply beauty expectations are associated with social and cultural norms. Emotional marketing evokes desire, fear, or aspiration. For example, anti-aging campaigns exploit the universal fear of growing up, while promising restored confidence among women. Gardner noted that fear-based emotions, such as the fear of aging, can be powerful motivators in purchasing decisions because emotional reactions often influence choices more strongly than rational thinking. Social media amplifies this effect by providing a constant visual that matches attractiveness with success (Tarba et al., 2025). However, she also said that social media has allowed for movements such as *body positivity*, creating a contradictory environment to societal beauty standards.

Emotional branding relies heavily on narrative coherence. Consumers are more likely to buy products that align with their personal story or desired self-image (Solomon et al., 1992). Mathewson's recounting of Cindy Crawford's *Meaningful Beauty* campaign illustrates that despite a product failing to deliver on its miraculous promises, the narrative and whoever is representing the image are the ones who create enduring brand loyalty (Somadi et al., 2022). During the course of the interview, Mathewson shared a personal experience of purchasing a product after being convinced by the story behind it, demonstrating that persuasive branding

narratives can be extremely powerful (S. Mathewson, personal communication, March 2026). In a similar way, campaigns that promote inclusivity and body positivity can generate trust by simply demonstrating that their emotional branding does not need to exploit insecurities in order to be effective (de Lenne et al., 2021).

However, ethical implications of beauty marketing should not be overlooked. Gardner stated that companies should avoid strategies that manipulate consumers' fears or promote unrealistic promises that will not happen. Gardner also stated businesses have the responsibility to communicate honestly and ethically, especially when their products directly affect women's self-image and confidence. The psychological factors that make emotional branding persuasive can also be misused by shaping negative self-image or encouraging impossible beauty ideals. For this reason, brands need to start communicating responsibly by combining messaging with honest representations to preserve consumer trust and support in their overall well-being (Prabhakar, 2025).

Conclusion

The modern beauty industry shows how psychology and business work together. Emotional branding helps companies connect with their consumers, and influence how people see themselves (Amalia et al., 2023). Beauty products are no longer just about how they make a consumer look, but about symbols connected to identity, confidence, and personal expression. Companies design their strategies to match consumers' goals, age groups, and social influences, while psychology helps explain why these strategies are so important and effective. Interviews conducted with Mathewson and Gardner highlighted an important idea: selling beauty is about selling a feeling of confidence, identity, and belonging. Both experts demonstrated that understanding consumer emotions and social influences can lead to an understanding of why beauty marketing is so powerful in modern society.

Emotional branding also highlights the ethical responsibilities brands face. Companies should protect consumers from being manipulated through their vulnerable points (Hidayat et al., 2023). Branding exists to inspire people through dreams, yet it must also be trustworthy. As highlighted in both interviews, companies can still promote their products effectively without the need of exaggerating unrealistic outcomes, or transforming insecurities into weapons. Future research needs to combine effective storytelling methods together with honest communication techniques (Herman et al., 2023). Beauty brands can establish better consumer relationships through understanding business and psychology, which can help maintain customer loyalty across extended periods. Beauty industry success requires both exceptional products, and the creation of positive emotional customer experiences (Tarba et al., 2025).

References

Amalia, Fatya; Andani, Adiva A.; & Guteres, Alexandre. (2023). The perception of young women towards beauty value in beauty advertisements. *Journal of Marketing Innovation (JMI)*, *3*(1). https://doi.org/10.35313/jmi.v3i1.63

Darmatama, Metta; & Erdiansyah, Rezi. (2021). *The influence of advertising in Tiktok social media and beauty product image on consumer purchase decisions*. 888–892. https://doi.org/10.2991/assehr.k.210805.140

de Lenne, Olivier; Vandenbosch, Laura; Smits, Tim; & Eggermont, Steven. (2021). Framing real beauty: A framing approach to the effects of beauty advertisements on body image and advertising effectiveness. *Body Image*, *37*, 255–268. https://doi.org/10.1016/j.bodyim.2021.03.003

Herman, H.; Derin, T.; Purba, R.; Warman, J. S.; & Setiono, A. (2023). When actors take over the products: Showcasing Hallyu-influenced Indonesian beauty product advertising through multimodal analysis. *Lingua Cultura*, *17*(2), 161–166. https://doi.org/10.21512/lc.v17i2.9878

Hidayat, Ziaggara; Budiman, Amanda L.; Pratama, Yudi; Annisa, Shinta M.; Tambunan, Desri F. N.; & Puspita, Virienia. (2023). The respect for race and culture in a modern feminist society: An analysis of beauty product advertising messages on instagram. *Journal of Intercultural Communication*, 82–94. https://doi.org/10.36923/jicc.v23i2.114

Jie, Fang; Ramachandaran, Sharmila; Sagadavan, Revathi; & Doraisingam, Puspanthan. (2025). The influence of advertising strategies on corporate performance: A study in the beauty industry. *International Journal of Management and Sustainability*, *14*, 654–668. https://doi.org/10.18488/11.v14i2.4279

Lazar, Michelle M. (2011). The right to be beautiful: Postfeminist identity and consumer beauty advertising. In R. Gill & C. Scharff (Eds.), *New Femininities: Postfeminism, Neoliberalism and Subjectivity* (pp. 37–51). Palgrave Macmillan UK. https://doi.org/10.1057/9780230294523_3

Muñoz-Muñoz, Ana M.; & Martínez-Oña, Mar M. (2024). Análisis del canon de belleza femenina y su manipulación digital en la publicidad de perfumes. *Kamchatka. Revista de Análisis Cultural* (23), 527–549. https://doi.org/10.7203/KAM.23.26989

Nugraha, Asep E.; Sari, Rianita P.; Santoso, Deri T.; & Rachmat, Muhamad T. (2024). Postural ergonomic risk assessment of augmented reality user interface on smartphones in cosmetic industry advertising. *SHS Web of Conferences*, *189*. https://doi.org/10.1051/shsconf/202418901051

Prabhakar, Vaishali. (2025). Dove's Real Beauty Campaign in India: Localizing a global purpose brand. *Journal of Business and Management Studies*, *7*(6), 15–23. https://doi.org/10.32996/jbms.2025.7.6.3

Smith, Matthew. (2022a). *Consuming female beauty: British literature and periodicals, 1840-1914*. Edinburgh University Press. https://doi.org/10.1515/9781474470117

Smith, Matthew. (2022b). The celebrity as beauty icon. In M. Smith, *Consuming female beauty* (pp. 135–158). Edinburgh University Press. https://doi.org/10.3366/edinburgh/9781474470094.003.0006

Solomon, Michael R.; Ashmore, Richard D.; & Longo, Laura. C. (1992). The beauty match-up hypothesis: Congruence between types of beauty and product images in advertising. *Journal of Advertising*, *21*(4), 23–34. https://doi.org/10.1080/00913367.1992.10673383

Somadi, Maknun T.; Said, Ikhwan; & Hasjim, Munira. (2022). Representation and object (RO) marking iconicity relationship in Wardah Cosmetics commercial TV advertising. *Theory and Practice in Language Studies*, *12*(1), 193–203. https://doi.org/10.17507/tpls.1201.24

Tarba, C. I.; Bătrânu-Pinţea, V.; & Coman, C. (2025). The shift from traditional to online advertising. Influencers' role in advertising. *Bulletin of the Transilvania University of Brasov. Series VII, Social Sciences and Law.*, *18*(1), 185–192. https://doi.org/10.31926/but.ssl.2025.18.67.1.20

Barton Journal

13th Annual Day of Scholarship and Engagement

NOTE ON CONFERENCE PROCEEDINGS

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CITATION

Davis, Emma; & Lange, Gerard C. (2026). 13th Annual Day of Scholarship and Engagement [Conference proceedings]. *Barton Journal, 1*(1), 148–149. https://bartonjournal.org/2026-conf-proceedings-no-012

Note

Since 2012, Day of Scholarship and Engagement (DOSE), formerly known as Barton College Scholars Symposium, was established as a celebration of students and faculty research conducted at the college. From its inception, students and faculty have been given the option to present academic conference-style lectures or posters about their research. In 2012, it was not required to submit abstracts pertaining to research projects, but all potential presenters submitted an application for review. The application process was then used primarily for students competing for grant funding to support their research project. These grants were themselves provided by a grant awarded to college to establish DOSE as an annual event. Later, when the external funding was exhausted, the college shifted away from the application model, opting to require students to submit abstracts that summarized their research projects. In 2025, for the first time, abstracts about the student and faculty research projects were published in the DOSE program. This action paved the way for the college to found and launch the *Barton Journal*.

In fall 2025, the Barton College administration, under the leadership of President Dr. Douglas N. Searcy decided to create an academic journal to publish student-led research, thereby creating an outward facing representation of research at Barton College. Development of the journal included meticulous research on undergraduate journals from across the United States (and some other countries), in order to evaluate best practices—research that was conducted by two students, Emma Davis and Berkley Ann Hicks, under the direction of Dr. Gerard C. Lange, director of the Center for Undergraduate Research and Scholarship. In total, 30 journals were examined to model, shape, and learn from the production process in order to form the basis of

Barton Journal. This research culminated in a white paper and proof of concept issue presented to the college at the end of the term. Ms. Davis and Ms. Hicks were then selected as junior editors to work under Michael K. Brantley, Barton College associate professor and Elizabeth H. Jordan Chair of Southern Literature, who was chosen to be the senior editor. Through the development of the *Barton Journal*, the solicitation of submissions, along with editing, publication, and stylistic guidelines have been established. At present, a Digital Object Identifier (DOI) and a Library of Congress number (LCN) are all in the process of being completed for this journal, and an International Standard Serial Number (ISSN) has been assigned.

In volume 1, no. 1, of the *Barton Journal*, there are 11 core articles including the lead article by Dr. Taylor Medlock-Lanier, Barton College class of 2020, and keynote speaker for the 2026 DOSE, four full-length articles, three short articles, one case study, one critical essay, and one commentary. Following this note about the journal, there are 40 abstracts, each included in the 2026 DOSE as lecture or poster presentations. In total, there are 51 presentations of various types included in the 2026 DOSE, that include the aforementioned article types.

Barton Journal

The Acute Cardiovascular Response to Exercise

CONFERENCE ABSTRACT

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CITATION

Parker, Carleigh; Biscardi, Lauren; & Ottinger, Charlie. (2026). The acute cardiovascular response to exercise [Conference abstract]. *Barton Journal, 1*(1), 150–151. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-013

Abstract

Caffeine is one of the most widely consumed psychoactive substances, and is commonly used for its stimulating effects on the central nervous system. By blocking adenosine receptors, caffeine increases alertness, reduces perceived effort, and may enhance exercise performance. While its effects on aerobic exercise are well-established, less is known about caffeine's impact on resistance training in the cardiovascular response. The purpose of this study was to examine the effects of caffeine on heart rate, blood pressure, and rating of perceived exertion during full-body circuit-style resistance training. College students ages 18 to 25 participated in two exercise conditions (caffeine and placebo) in a single-blind, randomized crossover design. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and rating of perceived exertion (RPE) were measured at baseline, mid-exercise, and post-exercise. Data were analyzed using repeated measures ANOVA, and alpha was set at 0.05. Heart rate increased significantly over time ($p < .001$), rising from baseline to mid-exercise and remaining elevated post-exercise, with no significant effect of condition ($p = .09$). Systolic blood pressure showed significant effects of both condition ($p = .034$) and time ($p < .001$), increasing from baseline to mid-exercise and remaining elevated post-exercise. Rating of perceived exertion also showed effects of both condition and time ($p < .05$), increasing throughout exercise and differing between caffeine and placebo conditions. No significant

differences were observed for diastolic blood pressure ($p > .05$). Overall, caffeine increased systolic blood pressure and reduced perceived exertion during exercise, but did not significantly affect heart rate or diastolic blood pressure. These findings suggest caffeine alters both cardiovascular and perceptual responses to full-body circuit-style resistance training.

Keywords: caffeine, college students, blood pressure

Barton Journal

Advantages and Disadvantages of Taking a Gap Year before Undergrad and Graduate School

CONFERENCE ABSTRACT

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CITATION

Graham, Takyla; & Avant, Tamara. (2026). Advantages and disadvantages of taking a gap year before undergrad and graduate school [Conference abstract]. *Barton Journal, 1*(1), 152–153. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-014

Abstract

Taking a gap year can improve students' academic performance, likely because those students adopt a growth mindset (Blackburn et al, 2005). I hypothesized that participants who took a gap year (before entering either undergraduate or graduate school) are more prepared and have better academic performance than students who did not take a gap year. Participants (N = 46) were current and former college students who answered a questionnaire on their gap year status, self-assessments (i.e., how they feel), and an evaluation (i.e., their behavior/actions) of their academic preparedness and performance. Independent t-tests showed that results did not match my hypothesis, as there was no significant difference in perceived performance for those taking a gap year (M = 3.41, SD = 1.08) or not (M = 3.88, SD = 0.64), $t(44) = 1.29$, $p = 0.20$. There were also no significant differences in their perceived preparedness for college, $t(44) = 1.38$, $p = 0.17$. However, students who felt more prepared for college had a higher average performance evaluation (M = 4.01, SD = 0.77) than students who felt less prepared for college (M = 3.13, SD = 0.63), $t(44) = 2.88$, $p < 0.01$. Additionally, there was a significant positive correlation between the preparedness and performance evaluations for all participants ($r(44) = 0.86$, $p <$

.0001), but this relationship was stronger for participants who took a gap year ($r(3) = 0.95$, $p = 0.05$) than those who did not ($r(41) = 0.83$, $p < .0001$).

Keywords: gap year, academic performance

References

Blackburn, George Alan; Clark, Gordon; & Pilgrim, David. (2005). The gap year for geographers: Effects and paradoxes. *Geography*, *90*(1), 32–41. https://doi.org/10.1080/00167487.2005.12094115

Barton Journal

An Investigation into the Relationship between Reactive Strength and the Game Realistic High-Speed Movement among Male NCAA DII Lacrosse Players

CONFERENCE ABSTRACT

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CITATION

Woollard, Luke; & Biscardi, Lauren. (2026). An investigation into the relationship between reactive strength and the game realistic high-speed movement among male NCAA DII lacrosse players [Conference abstract]. *Barton Journal, 1*(1), 154–155. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-015

Abstract

High-speed movement is a critical physical component of field sports because these sports require dynamic movements performed at high velocity. Among lacrosse players, these high-speed movements are distinguishing factors between starters and non-starters. The reactive strength index (RSI & RSImod) can be used to quantify the stretch-shortening cycle, which is a mechanism that allows for the rapid muscular contractions required to sprint and change direction at a high velocity. This research aimed to recruit 30 NCAA lacrosse players from the Barton Men's Lacrosse team to participate in two data collection sessions. High-speed movement will be measured using the Change of Direction and Acceleration test (CODAT). Brower timing gates will be used to record the time taken to complete each run. Athletes will be given two acclimatization trials, and following three maximal efforts, their fastest time will be used in data analysis. RSI and RSImod will be measured using PASCO force platform data from both bilateral and unilateral drop jumps and countermovement jumps. RSI and RSImod will be calculated by dividing the values of jump height by contact time or movement time. The best RSI and RSImod scores will be used in a two-tailed Pearson bivariate correlation to assess the strength of their

relationship with CODAT times. Unilateral RSI/RSImod values from dominant and non-dominant limbs will be used to calculate the symmetry index (SI) of each athlete. The SI will then be compared to the athletes CODAT time to evaluate the relationship. Existing literature would suggest this research will find a moderate to strong negative correlation between high-speed movements and both measures for reactive strength. It is also expected that the athletes with lower SI values will perform better during high-speed movement trials.

Keywords: lacrosse, reactive strength index, change of direction and acceleration test

Barton Journal

Bayesian Integrative Approach Identifies Hidden Intermediates in DH270-Induced Structural Transitions of HIV-1 Envelope

CONFERENCE ABSTRACT

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CITATION

Vrable, Alaina; & Bennett, Ashley L. (2026). Bayesian integrative approach identifies hidden intermediates in DH270-induced structural transitions of HIV-1 envelope [Conference abstract]. *Barton Journal, 1*(1), 156–157. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-016

Abstract

HIV-1 Envelope glycoprotein (Env) undergoes a sequence of structural transitions, from a closed conformation to an open structure, initiates host-cell infection, and alters exposure of antibody epitopes. Closed-to-open transition proceeds through both short-lived disordered and more stable open-occluded intermediates, exposing distinct antibody binding surfaces. Designing effective HIV-1 vaccines requires a deeper understanding of how Env opening changes antibody engagement. DH270 is a broadly neutralizing antibody with neutralization capacity against a range of HIV-1 strains, and stabilizes closed Env structure. Env structural changes on microsecond timescales, induced by DH270 binding, were first captured at high temporal resolution using time-resolved, temperature-jump small-angle X-ray scattering (TR, T-Jump SAXS). Interpretation of these low-resolution data are challenging due to substantial conformational heterogeneity involved in binding processes. To enable high-confidence structural interpretation of TR, T-Jump SAXS signals, a novel integrative approach combining Markov state models, homology modeling, and a Bayesian inference framework to fit theoretical structures to experimental data was developed. Structural models for each known Env conformation,

closed, disordered, open-occluded, and open, each in one of several possible DH270-bound states were generated. This yielded 9,600 unique DH270-bound Env models. Comparison of theoretical SAXS profiles from these models, along with experimental data indicates open-occluded intermediate and partially DH270-bound closed Env states contribute substantially to DH270-induced Env motions. Inclusion of these partially bound encounter complexes significantly improves model fits. Disordered intermediate and fully open Env conformations appear to play no role in DH270-induced structural response, consistent with prior evidence that DH270 stabilizes closed Env conformation. Improvements to the fit remain needed and suggests additional, as-yet-unidentified Env conformational states may be required to fully capture experimental TR, T-Jump SAXS signals. These results can be leveraged to engineer antibody affinity and neutralization potency in potential vaccine immunogen candidates. Newly characterized structural transitions provide a foundation for future structure-guided HIV-1 vaccine design.

Keywords: HIV-1, SAXS, time-resolved, structural biology, modeling, protein dynamics, immunogen design, vaccine, broadly neutralizing antibodies

Barton Journal

Brain Bites: Exploring the Connection Between Food Choice and Emotional Wellness

CONFERENCE ABSTRACT

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CITATION

Miller, Joshuah; Stallings, Seth; Younker, Cali; & Gardner, Ashley. (2026). Brain bites: Exploring the connection between food choice and emotional wellness [Conference abstract]. *Barton Journal, 1*(1), 158. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-017

Abstract

Brain Bites is designed for student athletes at Barton College to help improve dining options, operating hours, and overall dining experience. Access to nutrition is crucial for students' physical wellness and academic success. However, the limited variety and restricted operating hours create a barrier for some students. The purpose of this agency is to bring awareness to the issue by gathering information on how students feel about the current dining options, their dietary habits, and areas they feel need improvement. Through a campus-wide survey, Brain Bites will collect data to identify the best solution for on-campus dining. The findings will be presented to students and staff on the Day of Scholarship and at the Wellness Fair. Funding is requested to help support the research and presentation of our proposal. Brain Bites aims to promote students' physical wellness and support students reaching their full potential.

Keywords: college campus, dining, student life

Barton Journal

Bulldog Backup: Increasing Perception of Campus Safety at Barton College

CONFERENCE ABSTRACT

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CITATION

Ryan, Grace; Granstam, Irma; Williams, Ammon; & Gardner, Ashley. (2026). Bulldog backup: Increasing perception of campus safety at Barton College [Conference abstract]. *Barton Journal, 1*(1), 159. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-018

Abstract

Campus safety is the most important issue on college campuses for students who live on campus and those who work at the college. Since Barton College is located in the middle of a neighborhood, concerns about unauthorized people entering the campus have grown. Previously, buildings like the Hackney Library always had their doors accessible, but that has changed. Team Safety, a student-developed organization, has applied the Eight Dimensions of Wellness Framework to help with student and worker safety concerns on this college campus. Team Safety is composed of three students who have lived on campus or currently do, and there are plans to make safety kits available for staff and students. These kits will be at the college's Health and Wellness Fair held annually during the Spring semester. The objective of the safety kits is to increase the overall safety on campus, thus improving the physical and emotional wellness of the community. The total funding requested for creating these safety kits is estimated to be $461.

Keywords: campus safety, eight dimensions of wellness

Barton Journal

Catching Seniors Before They Fall: The Wellness Kit Initiative, Senior S.A.F.E. Net

CONFERENCE ABSTRACT

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CITATION

Graham, Takyla; Carlton, Ariyana; Morris, Brenson; & Gardner, Ashley. (2026). Catching seniors before they fall: The wellness kit initiative, senior S.A.F.E. net [Conference abstract]. *Barton Journal, 1*(1), 160–161. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-019

Abstract

Senior SAFE Net is a student-created organization, composed of three seniors from Barton College. Many colleges tend to have a lack of resources or funding specifically for senior students transitioning out of the college community, and more resources and workshops for freshmen transitioning from high school into college. The goal of Senior SAFE Net's proposed project is to bring awareness to the lack of resources for seniors, and be a gateway into inspiring more future- specialized classes or resources to help seniors transition into the professional world. Our team will provide mid-semester care kits that consist of various tools such as. resource cards with information about business offices, a link to Pathway U assessments, and a link to BetterHelp or other free online therapy sites. Affirmation/motivational cards will be provided to show care and understanding, and to motivate students to keep being resilient throughout the semester or year. Stress balls will be a tool that will provide temporary, recreational relief from active stressors. Stickers and candy will also be provided as not only a small reward for students getting through the semester, but as an incentive for the

students to use the kit. The total funding has been calculated to be at least $200 for 50–60 kits. Assessments will occur to evaluate the success of the initiative.

Keywords: education, students, affirmation

Barton Journal

Cold Water Immersion vs. Passive Rest: Effects on Athletic Recovery

CONFERENCE ABSTRACT

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CITATION

Schrubb, Aubree; & Biscardi, Lauren. (2026). Cold water immersion vs. passive rest: Effects on athletic recovery [Conference abstract]. *Barton Journal, 1*(1), 162–163. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-020

Abstract

Cold water immersion (CWI) is used by athletes to improve recovery following intensive exercise. CWI is believed to reduce fatigue and help maintain performance, but its effectiveness compared to passive rest is still not fully understood. Performance measures such as jump height, strength, and muscular endurance are often used to assess recovery in athletes. The purpose of this study is to compare the effects of CWI and passive rest on performance following a fatiguing exercise protocol. In this study, 12 collegiate athletes were recruited to participate. Participants completed a lower body exercise protocol designed to induce fatigue. Following the exercises, jump height, strength, muscular endurance, and perceived recovery were measured. Participants were then placed into one of two conditions: CWI or passive rest. The CWI condition involved sitting in water up to their hips at 10-12 degrees Celsius, while the passive rest condition involves seated rest with no recovery intervention. Performance metrics were measured again after 6 hours of recovery and results were analyzed to compare differences between the two conditions. Based on previous research, participants in the CWI condition were expected to show a smaller decrease in performance compared to those in the passive rest condition. Jump height, strength, and muscular endurance were expected to decline less following CWI, indicating improved

recovery. It was expected that CWI will be found as a more effective recovery strategy than passive resting.

Keywords: cold water immersion, student-athlete, injury, recovery

Barton Journal

Collegiate Sports Marketing

CONFERENCE ABSTRACT

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CITATION

Welch, Jack; & Pooni, Navpreet S. (2026). Collegiate sports marketing [Conference abstract]. *Barton Journal, 1*(1), 164. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-021

Abstract

Name, Image, and Likeness (NIL) policies have significantly altered the landscape of collegiate athletics, especially at the Division II level, yet they are under-researched. This study aims to investigate the impact of NIL opportunities and marketing at Division II football programs, with a particular focus on a supposed correlation between increased spending on marketing and NIL. Data was collected with a structured survey distributed to Division II programs across multiple institutions, including Barton and peer colleges. The survey was designed to gather statistics on the NIL and marketing funding and the amount of staff and resources provided, and then compared that to the success of the football program at that institution. It was hypothesized that with an increase in spending and resources in these areas, there would be an increase in the success and prestige of the institution's football team. The anticipated findings of this study are expected to contribute to a deeper understanding of how NIL and marketing affect Division II football programs, and how they should be managed and used by Barton College to improve its own program.

Keywords: name image and likeness (NIL), NCAA Division II, football

Barton Journal

Correlation Between Linear Sprint Speed and Force Production

CONFERENCE ABSTRACT

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CITATION

Waldridge, Nathan; & Biscardi, Lauren. (2026). Correlation between linear sprint speed and force production [Conference abstract]. *Barton Journal, 1*(1), 165–166. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-022

Abstract

Linear sprinting is essential for athletic performance, especially in sports that require rapid acceleration and top-end speed. Force production is a known contributor to sprinting ability; however, the specific roles of horizontal and vertical force across sprint phases are not fully understood. This study aimed to examine the relationship between linear sprint speed and force production in college baseball players, hypothesized that horizontal force would better predict acceleration, and vertical force would better predict maximal velocity. Thirty male collegiate baseball players (ages 18–24) participated in this correlational study. Acceleration was measured using a 10-yard dash, while maximal velocity was assessed with a 10-yard fly sprint, following a 20-yard build-in. Horizontal force production was evaluated using countermovement and pause broad jumps. Vertical force production was measured using countermovement and pause vertical jumps. The stretch-shortening cycle (SSC) was assessed by comparing countermovement and pause conditions. Sprint times were recorded with Brower timing gates, and jump performance was measured using jump mats. Pearson correlations were used to examine relationships between sprint and jump variables, and paired t-tests compared jump conditions. Statistical significance was set at $\alpha = .05$. Strong, significant negative correlations were found between 10-yard sprint times and all jump measures, indicating that greater force production corresponded with faster acceleration. Correlations ranged from $r = -0.66$ to $r = -0.72$ ($p < .001$). The 10-yard fly sprint also showed

moderate-to-strong negative correlations with all jump variables ($r = -0.55$ to -0.61, $p \leq .002$), suggesting that both horizontal and vertical force production contribute to maximal velocity. A moderate positive relationship was observed between eccentric utilization ratio (EUR) in the broad jump and maximal velocity ($r = 0.48$, $p = .007$). Additionally, countermovement jumps produced significantly greater distances and heights than pause jumps in both horizontal and vertical conditions ($p < .001$), demonstrating the benefit of SSC utilization. Force production was found to be strongly associated with both acceleration and maximal sprint speed. While horizontal force plays a key role in acceleration, vertical force also contributes meaningfully across sprint phases. The SSC enhances force output and should be incorporated into training. Overall, a combination of horizontal, vertical, and SSC-focused training methods is recommended to optimize sprint performance.

Keywords: athletic performance, force production, vertical force

Barton Journal

Customer Experience and Leadership Development in the Modern Luxury Car Industry

CONFERENCE ABSTRACT

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CITATION

Foss, Fredrik; & Pooni, Navpreet S. (2026). Customer experience and leadership development in the modern luxury car industry [Conference abstract]. *Barton Journal, 1*(1), 167–168. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-023

Abstract

This project observes how customer experience has become one of the most important factors in the modern car industry, especially in luxury dealerships. Today, selling a car is not just about the product itself– it is also about how the customer feels throughout the entire process. To better understand this, I used my internship at Bilia Insignia as a hands-on case study, combined with an interview with a manager and feedback from customer reviews. During my internship, I observed and participated in a variety of tasks, including preparing cars for delivery, assisting customers in the showroom, answering calls, and helping with internal logistics. These experiences gave me insight into how service quality, the dealership environment, leadership, and the use of digital tools work together to foster a positive experience for customers. The study shows that even small details, like how welcoming the staff are or how organized the showroom is, can make a big difference in customer satisfaction and loyalty. By combining personal experience with research and customer feedback, this project highlights the importance of creating a memorable, high-quality customer experience in a luxury setting. It also shows how practical skills and good communication are essential for professional growth in the automotive

industry. Overall, this project emphasizes that in today's competitive market, a strong focus on customer experience can be just as important as the product itself in building trust, loyalty, and long-term success.

Keywords: leadership, automotive dealerships

Barton Journal

Design and Evaluation of an Ambien–Kava Hybrid Molecule and its Pharmacological Effects

CONFERENCE ABSTRACT

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CITATION

Daniels, Clayton; & Mazuroski, Nicole L. (2026). Design and evaluation of an Ambien–Kava hybrid molecule and its pharmacological effects [Conference abstract]. *Barton Journal, 1*(1), 169–170. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-024

Abstract

Ambien is a medication used to treat insomnia. This drug is considered a sedative hypnotic which affects the brain's neurotransmitters, creating sleep-inducing effects, and some side effects can include memory issues, sleepwalking, dizziness, and even addiction. Insomnia is a condition that affects sleep, causing people to stay up at night or have difficulty falling asleep. Kava is a natural substance, obtained from the Piper methysticum plant roots, specifically found in parts of the Pacific Islands. Unlike Ambien, Kava is a common supplement used every day for some common side effects like relaxation, reduced anxiety, and sedation effects. This study will explore the pharmacological effect and interactions with Ambien (Zolpidem) and Kava (Dihydrokavain) by combining elements of each to make a single molecule. Both molecules target the gamma-aminobutyric acid type A (GABA-A) receptors, which create sedation effects and help regulate regular sleep. This research aims to explore how the combination of Ambien and Kava can affect pharmacological activity, binding affinity, and even lipophilicity. By using a molecular modeling program, feasibility of this new hybrid compound can be examined.

Expected outcomes include increased sedation effects, increased potency, and even increased duration. This study will help to gain a deeper understanding of drug design, associated with combining two already useful drugs.

Keywords: Ambien, Zolpidem, Kava, Dihydrokavain, insomnia

Barton Journal

Dictatorship or Democracy: The Power of Grand Strategy & Civil Resistance

CONFERENCE ABSTRACT

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CITATION

Costelo, Airene; & Van Horn, Olivia. (2026). Dictatorship or democracy: The power of grand strategy & civil resistance [Conference abstract]. *Barton Journal, 1*(1), 171–172. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-025

Abstract

This research presentation explores the persistent struggle between dictatorship and democracy through grand strategy and civil resistance, focusing on the parallel histories and current events of the Philippines and the United States. At the heart of this investigation is Gene Sharp's uncompromising argument in *From Dictatorship to Democracy*, when fundamental rights are denied, resistance, rather than negotiation, is the only viable path to transformation. Sharp's framework, applied across international conflicts, demonstrates that nonviolent action can dismantle authoritarian regimes where dialogue would only deepen them. Maria Ressa's *How to Stand Up to A Dictator* brings these ideas into the present, sharing her fight for press freedom and democratic accountability under authoritarian pressure in the Philippines. Her story illustrates the personal risks and necessity of civil resistance in the digital age. Spoma Jovanovic's *Democracy, Dialogue, and Community* highlights the power of dialogue and grassroots activism in sustaining democracy, particularly through the story of the Greensboro Massacre in North Carolina. Placing these perspectives in conversation, the research presentation will reveal both the unyielding necessity of resistance in the face of dictatorship and the ongoing work required to maintain democracy, even in societies where it is presumed secure. The continued existence of democracy, whether in the Philippines or the United States, depends on a willingness to stand firm when

compromise is no longer possible, and on careful, consistent efforts to uphold democratic principles. Ultimately, it is ordinary people and communities who are courageous, persistent, and hopeful who determine whether democracy endures.

Keywords: dictatorship, democracy, community, Philippines, United States

Barton Journal

Digital Branding and Athlete Revenue Models

CONFERENCE ABSTRACT

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CITATION

Washington, Justin; & Pooni, Navpreet S. (2026). Digital branding and athlete revenue models [Conference abstract]. *Barton Journal, 1*(1), 173. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-026

Abstract

The financial structure of professional and collegiate athletics has undergone a significant transformation during the digital era. Historically dependent on league contracts and traditional endorsement agreements, athletes now operate within a decentralized digital marketplace shaped by social media engagement and Name, Image, and Likeness (NIL) policy reform. This paper argues that digital branding and NIL regulations have fundamentally redefined athlete revenue models by enabling diversified income streams independent of team-controlled exposure. Using financial trend analysis and case-based examples of high-profile NIL athletes, this study evaluates how direct platform monetization, sponsored content, and brand partnerships contribute to both financial expansion and revenue diversification. The findings contribute to sports finance scholarship by demonstrating that digital visibility now functions as an independent economic asset within modern athlete compensation structures. As the digital sports economy continues to evolve, understanding how online engagement translates into financial opportunity becomes increasingly important for both athletes and sports organizations.

Keywords: name image and likeness (NIL), collegiate athletics, student-athletes

Barton Journal

The Effect of Personality Traits and Political Affiliation on the Misinformation Effect in Fake News Headlines

CONFERENCE ABSTRACT

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CITATION

Hellum-Lilleengen, Leonie; & Avant, Tamara. (2026). The effect of personality traits and political affiliation on the misinformation effect in fake news headlines [Conference abstract]. *Barton Journal, 1*(1), 174–175. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-027

Abstract

The misinformation effect is a cognitive bias where, after being exposed to misleading information, individuals recall an event inaccurately (Ayers & Reder, 1998). Despite the rise of *fake news*, it remains unclear what makes an individual more susceptible to misinformation. This study examined how personality traits and political affiliation influenced susceptibility to the misinformation effect in fake news. Using a between-subjects quasi-experimental design, participants were a) asked about their political affiliations; b) completed the Big 5 Personality Assessment (Lang et al., 2011); and c) chose whether they believed 20 news article headlines were real or fake. Accuracy scores were calculated as the percentage of correct responses (i.e., higher scores indicated better ability to distinguish between real/fake headlines). Contrary to hypotheses, political affiliation was unrelated to susceptibility to misinformation, but personality traits were significant predictors of accuracy. Overall, accuracy was significantly positively correlated with conscientiousness [$r(57) = 0.109$, $p < 0.0001$], openness [$r(57) = 0.314$, $p < 0.0001$], and agreeableness [$r(57) = 0.171$, $p < 0.0001$], suggesting that participants

with higher levels of these traits were more accurate/less susceptible. However, accuracy was significantly negatively correlated with both neuroticism [$r(57) = -0.295$, $p < 0.0001$] and extraversion [$r(57) = -0.103$, $p < 0.0001$], suggesting that participants with higher levels of these traits were less accurate/more susceptible. Although the negative correlation between accuracy and neuroticism was significant for all political affiliations, the relationship was strongest for Republicans, [$r(20) = -0.401$, $p < 0.0001$].

Keywords: misinformation effect, susceptibility, conscientiousness

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References

Ayers, Michael S.; & Reder, Lynne M. (1998). A theoretical review of the misinformation effect: Predictions from an activation-based memory model. *Psychonomic Bulletin & Review, 5*(1), 1–21

Lang, Frieder R.; John, Dennis; Ludtke, Oliver; Schupp, Jürgen; & Wagner, Gert. (2011). Short assessment of the Big Five: robust across survey methods except telephone interviewing. *Behavior Research Methods, 43*, 548–567.

Barton Journal

The Effects of Sleep Quantity and Quality on Athletic Performance and Recovery

CONFERENCE ABSTRACT

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CITATION

Williams, Christopher Walt; & Biscardi, Lauren. (2026). The effects of sleep quantity and quality on athletic performance and recovery [Conference abstract]. *Barton Journal, 1*(1), 176–177. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-028

Abstract

The importance of optimizing sleep has increased significantly in recent years regarding athletic performance and recovery. However, many athletes struggle to achieve sufficient sleep quantity or quality. This narrative review examines the links among sleep duration, sleep quality, and targeted sleep interventions designed to enhance athletic performance and recovery. This review also investigates the effects of inadequate sleep on physiological and psychological performance, and analyzes how targeted sleep strategies may improve athletic outcomes. This narrative review relied on a range of peer-reviewed journal articles in sports medicine and exercise science. Selected sources addressed sleep-related interventions, effective sleep hygiene, or the influence of training and competition on athletes' sleep. By incorporating systematic reviews, meta-analyses, and observational studies, this review thoroughly explores the effects of sleep habits on athletic performance, recovery, and athletes' health. Findings from the research indicate that suboptimal sleep will negatively affect an athlete's reaction time, cognitive abilities, mood, and performance, as well as an athlete's ability to recover from

injury or training. Conversely, interventions including extending sleep, practicing better sleep hygiene, and using strategic napping techniques have demonstrated improvement in both athletic performance and recovery. In addition to the above-mentioned interventions, other variables (training load, travel schedule, competition schedule) might have an impact on disrupting an athlete's ability to get adequate amounts of sleep. Ultimately, this review supports the concept of sleep being an easily modified variable that can be utilized by coaches and athletes to maximize athletic performance and maintain a healthy lifestyle.

Keywords: sleep, athletes, human performance, recovery

Barton Journal

Enhancing SSRI Treatment Outcomes: Curcumin as an Adjunct to Fluoxetine for Major Depressive Disorder

CONFERENCE ABSTRACT

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CITATION

Hinton, Destini; & Mazuroski, Nicole L. (2026). Enhancing SSRI treatment outcomes: Curcumin as an adjunct to fluoxetine for major depressive disorder [Conference abstract]. *Barton Journal, 1*(1), 178–179. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-029

Abstract

Major Depressive Disorder (MDD) is a multifaceted psychiatric condition linked to neurochemical discrepancies and biological elements such as persistent inflammation and diminished neuroplasticity (Miller & Raison, 2016). MDD is often managed with selective serotonin reuptake inhibitors (SSRIs) like fluoxetine; nonetheless, delayed effects and incomplete responses continue to be notable challenges for patients, and a considerable number of MDD patients do not attain complete remission (Rush et al., 2006). This research investigated curcumin, a natural substance derived from turmeric, as a supplementary treatment to enhance fluoxetine treatment results by utilizing complementary mechanisms. Curcumin shows anti-inflammatory and neuroprotective properties that could improve the effectiveness of antidepressants like SSRIs. The suggested approach entails merging curcumin with fluoxetine to enhance the effectiveness of antidepressants. Merging curcumin with fluoxetine might enhance treatment results by addressing both serotonin signaling and inflammation. Fluoxetine boosts serotonin levels by blocking the serotonin transporter, whereas curcumin

decreases inflammation and promotes neuroplasticity by elevating BDNF expression. This combination affects several biological pathways related to depression, and could enhance MDD treatment response when compared to SSRI therapy alone.

Keywords: Major Depressive Disorder, selective serotonin reuptake inhibitors, neuroplasticity

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References

Miller, Andrew H.; & Raison, Charles L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology, 16*(1), 22–34. https://doi.org/10.1038/nri.2015.5

Rush, A. John; Trivedi, Madhukar H.; Wisniewski, Stephen R.; Nierenberg, Andrew A.; Stewart, Jonathan W.; Warden, Diane; Niederehe, George; Thase, Michael E.; Lavori, Philip W.; Lebowitz, Barry D.; McGrath, Patrick J.; Rosenbaum, Jerrold F.; Sackeim, Harold A.; Kupfer, David J.; Luther, James & Fava, Maurizio. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps. *American Journal of Psychiatry, 163*(11), 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Barton Journal

Examination of Neuroticism and Acute vs. Chronic Stress in College Athletes

CONFERENCE ABSTRACT

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CITATION

Granstam, Irma; & Avant, Tamara. (2026). Examination of neuroticism and acute vs. chronic stress in college athletes [Conference abstract]. *Barton Journal, 1*(1), 180–181. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-030

Abstract

Student-athletes' acute and chronic stress affects their well-being and confidence before competition (Malone, 2022). College athletes face various challenges, including managing school, athletics, and personal life, under internal and external pressure. However, it is unclear how specific demographics (e.g., academic year, gender, individual/team sport) play a part in the perception of acute/chronic stress and neuroticism. Participants (N = 69) completed three different scales of chronic and acute stress (PSS, STAI, respectively) and personality traits (BIG5). It was hypothesized that higher neuroticism scores would positively correlate with higher acute and chronic stress scores, and that females/younger student-athletes would perceive both more acute and long-term stress, and have higher neurotic scores. It was also hypothesized that people participating in individual sports would express higher stress levels. There was a significant positive correlation with all three scales, rs(67) = 0.40-0.67, $p < .001$. There was a significant gender difference, showing that women experience greater chronic stress, $t(66) = -2.45$, $p < 0.05$, acute stress, $t(66) = -3.18$, $p < 0.01$, and higher levels of neuroticism, $t(66) = -3.50$, $p < 0.001$. Freshmen experienced significantly more neuroticism than upperclassmen, $F(2, 63) = 5.43$, $p < 0.05$, $R2 = 0.17$. When controlling for gender and year, student-athletes participating in individual (versus team) sports have higher levels of acute stress, $F(12,55) = 1.82$, $p < 0.05$. $R2 = 0.28$. To conclude, freshman, female,

individual sport athletes experienced greater chronic/acute stress and have neurotic personality types.

Keywords: stress, student-athletes, neuroticism

References

Malone, Tyler L.; Kern, Adam; Klueh, Emily; & Eisenberg, Daniel. (2022). Psychological distress and its association with subjective athletic performance. *Journal of Sport Behavior, 45*(2), 173–184. https://www.proquest.com/scholarly-journals/psychological-distress-association-with/docview/2756705167/se-2

Barton Journal

Exercise Intensity Prescription in Cardiac Rehabilitation: A Narrative Review Comparing High-Intensity Interval Training Versus Moderate Continuous Training

CONFERENCE ABSTRACT

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CITATION

Parker, Carleigh; & Biscardi, Lauren. (2026). Exercise intensity prescription in cardiac rehabilitation: A narrative review comparing high-intensity interval training versus moderate continuous training [Conference abstract]. *Barton Journal, 1*(1), 182–183. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-031

Abstract

Cardiac rehabilitation is a critical component of secondary prevention for cardiovascular disease, with exercise prescription playing the central role in improving patient outcomes. Moderate continuous training (MCT) is the standard approach; however, high-intensity interval training (HIIT) has emerged as a potential alternative to MCT. This narrative review aims to compare HIIT and MCT in cardiac rehabilitation, focusing on physiological effectiveness, clinical outcomes, safety considerations, adherence, and clinical decision-making. This narrative review synthesizes current literature examining HIIT and MCT within cardiac rehabilitation settings. Peer-reviewed studies were identified, with emphasis on adult cardiac populations; specifically individuals post-myocardial infarction, coronary artery bypass grafts, stents, and heart failure. Articles were selected based on relevance to key subtopics, including cardiovascular adaptations, functional outcomes, adverse events, and patient adherence. The findings were analyzed to identify consistent themes and differences between training modalities. Current evidence suggests that, while maintaining a safe environment when appropriately

prescribed and supervised, HIIT may obtain greater improvements in aerobic capacity and cardiovascular function compared to MCT Additionally, HIIT may enhance patient adherence due to its time efficiency and variability. However, considerations regarding patient risk stratification and program design remain crucial. Understanding the benefits and limitations of HIIT and MCT can help improve individualized exercise prescription and optimize outcomes in cardiac rehabilitation, particularly for younger or previously active patients.

Keywords: HIIT, high-intensity interval training, MCT, moderate continuous training, rehabilitation

Barton Journal

Exploring Differences in Compassionate Traits Within Adult Virtual-Pet Hobbyists

CONFERENCE ABSTRACT

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CITATION

Stallings, Seth; Avant, Tamara. (2026). Exploring differences in compassionate traits within adult virtual-pet hobbyists [Conference abstract]. *Barton Journal, 1*(1), 184–185. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-032

Abstract

Tsai and Kaufman (2010) demonstrated that caring for virtual pets (i.e., consistent interactions between children and a virtual pet dog) led to greater empathetic/humane behavior. This study examined compassionate behavior in adult fans of virtual pets (V-Pets) by examining how differences in playing behavior may be connected to participants' levels of compassion. A survey was sent out to online spaces dedicated to V-Pet hobbyists (e.g., websites and discussion forums), asking participants (N = 303) about their favorite parts of interacting with V-pets, followed by the 5-point Compassion Scale (2019). Findings show overall high total compassion scores (M = 4.09, SD = 0.47). Those who reported caretaking as a preferred way of play scored significantly lower on the common humanity subscale (M = 4.27, SD = 0.58) than those who did not (M = 4.41, SD = 0.54), $F(1, 301) = 4.48$, $p < .05$. Common humanity scores were also influenced by how they reported playing with V-Pets; those who used both sites and devices showed the lowest mean common humanity scores (M = 4.06, SD = 0.64), followed by just devices (M = 4.29, SD = 0.59), with V-Pet site players having the highest common humanity scores (M = 4.40, SD = 0.53), $F(2, 300) = 4.76$, $p < .01$. These findings suggest that higher

common humanity scores may impact how adults choose to interact with V-pets, and the preference of V-pet sites, which have more inherent human interaction, over devices, which can be operated individually and without additional social interaction.

Keywords: virtual pets, compassion, social interaction

References

Tsai, Lily & Kaufman, David. (2014). Interacting with a computer-simulated pet: Factors influencing children's humane attitudes and empathy. *Journal of Educational Computing Research. 51*, 145–161. doi:10.2190/EC.51.2.a

Pommier, E., Neff, K. D., & Tóth-Király, I. (2020). The development and validation of the compassion scale. *Assessment, 27*(1), 21–39. doi:10.1177/1073191119874108

Barton Journal

Familial Impact on Student Success

CONFERENCE ABSTRACT

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Davis, Emma; & High, Jennifer. (2026). Familial impact on student success [Conference abstract]. *Barton Journal, 1*(1), 186–187. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-033

Abstract

There are never two students who come from the same family background, so students who arrive at university or college have different preconceived ways to approach social and academic success. This study examined the impact of familial circumstances, upbringing, and home life on students' overall success on a college campus. After a literature review of contemporary researchers' findings, *academic success*, *social success*, and *familial impact* were defined as key terms to understand how these factors fit together. To study familial impact on student success, a survey was conducted among students at a small, liberal arts school with a student population of about one thousand. The survey included questions about their home life, academic success, and social success on campus; using long-form answers, pertaining to qualitative results, and short-form answers, pertaining to quantitative results. Four groups of student data show that certain populations display a stronger or weaker effect on a student's academic and social success due to familial impact. Qualitatively, data also show how students feel about their academic and social success, as well as how they feel about their home life. Data

collected from this project will help higher education faculty and administrators better understand how best to help students succeed on a college campus.

Keywords: familial impact, social success, academic success

Barton Journal

How Leadership Styles of College Coaches Affect Student-Athlete Satisfaction

CONFERENCE ABSTRACT

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CITATION

Miller, Joshuah; & Avant, Tamara. (2026). How leadership styles of college coaches affect student-athlete satisfaction [Conference abstract]. *Barton Journal, 1*(1), 188–189. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-034

Abstract

This research focused on the foundation of organizational management and leadership and correlated it with college athletics. Throughout this research, the main question that was posed is how do leadership styles affect student-athlete well-being? Participants were 42 student athletes, both male and female, on various athletic teams. A modified version of Mefi and Asoba's (2021) Leadership Styles and Employee Job Satisfaction Scale was used to assess coaches' leadership style and how coaches made them feel personally, using a 5-point Likert scale. In general, the positive correlation of player satisfaction between head coaches and assistant coaches was significant, $r(30) = 0.534$, $p < .002$. Overall, participants were satisfied with their head coaches ($M = 3.565$, $SD = 0.478$) and their assistant coaches ($M = 3.53$, $SD = 0.326$). The relationship of player satisfaction and leadership styles followed the same pattern for head and assistant coaches. Athletes were least satisfied with autocratic leadership styles, [$r(30) = 0.05$, $p = 0.791$ for assistant coaches, $r(41) = -0.21$, $p = 0.183$ for head coaches]. Athletes were most satisfied with transactional leadership styles, [$r(30) = 0.82$, $p < 0.0001$ for assistant coaches, $r(41) = 0.822$, $p = 0.0001$ for head coaches]. This data will be presented pertaining to each individual athletic team and their satisfaction, and implications will be discussed.

Keywords: coaching, leadership, student-athlete, satisfaction

References

Mefi, Nteboheng P.; & Asoba, Samson N. (2021). Leadership styles and employee job satisfaction: A case of head of departments in Walter Sisulu University. *Academy of Entrepreneurship Journal, 27*(4s), 1–497. https://www.abacademies.org/articles/leadership-styles-and-employee-job-satisfaction-a-case-of-head-of-departments-in-walter-sisulu-university-10942.html

Barton Journal

The Lumbo-Pelvic-Hip Complex and How It Relates to Strength and Performance

CONFERENCE ABSTRACT

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CITATION

Williams, Christopher W.; & Biscardi, Lauren. (2026). The lumbo-pelvic-hip complex and how it relates to strength and performance [Conference abstract]. *Barton Journal, 1*(1), 190–191. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-035

Abstract

The lumbo-pelvic-hip complex is crucial for generating forces, as well as enhancing movement efficacy. Anatomical variations within the lumbo-pelvic-hip complex could potentially affect both an athlete's ability to produce strength and perform movements efficiently. The purpose of this study was to examine the relationships between lumbo-pelvic-hip complex anthropometrics (leg length, femur length, and trunk length) and measures of strength and functional movement. It was hypothesized that these structural variables would significantly relate to both force production and movement quality. Thirteen athletes from various collegiate sports completed the assessments. Lower extremity anthropometry and athletic performance was assessed through two separate strength tests: the isometric mid-thigh pull (IMTP) and the isometric mid-shin pull (IMSP). Additionally, all participants completed the Functional Movement Screen (FMS). Leg length demonstrated significant positive correlations with IMTP max (r = .655, p = .015) and IMSP max (r = .683, p =

.010), and a significant negative correlation with FMS scores (r = −.727, p = .005). Femur length was significantly negatively correlated with FMS scores (r = −.589, p = .034), but showed no significant relationships with strength measures. Trunk length had a significant positive correlation with IMSP max (r = .589, p = .034) and a significant negative correlation with FMS scores (r = −.676, p = .011). A very strong positive correlation was found between IMTP max and IMSP max (r = .982, p < .001). Both IMTP max (r = −.701, p = .008) and IMSP max (r = −.776, p = .002) were significantly negatively correlated with FMS scores. In conclusion, this study provides evidence that anthropometric variations of the lumbopelvic-hip complex can affect both an athlete's strength performance and their movement quality. While longer limbs are likely to result in greater force production due to increased mechanical advantage, they may compromise movement quality and increase susceptibility to injury.

Keywords: lumbo-pelvic-hip complex, athletes, human performance

Barton Journal

Mental Health and Athletic Performance Post-Major Surgical Operations on the Knee

CONFERENCE ABSTRACT

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CITATION

Jenkins, Bryson; & Basinger, Mark. (2026). Mental health and athletic performance post-major surgical operations on the knee [Conference abstract]. *Barton Journal, 1*(1), 192–193. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-036

Abstract

Athletes face struggles on and off the field when faced with injuries; they lose their self-identity, struggle with mental battles, and feel like they are missing out while being unable to participate. Despite athletes struggling post-surgery and throughout the rehabilitation process, there has yet to be research combining tests that mix both physical measurements and mental questionnaire measurements. Approximately 150,000 to 400,000 ACL injuries occur in the United States per year, with 70% of those cases being athletes; there are roughly 74,000 MCL injuries, and about 1 million individuals have meniscal tears. Athletes are known to be ready to return to sports as early as possible, but typically question their athletic ability due to a mental block. My research goal was to analyze whether there is a difference in athletic performance between the athletes' non-surgical knee and surgical knee, as well as whether they are trusting and displaying confidence in their knee to make sport-specific movements. In addition, I was asked whether there was any correlation between higher athletic performance in the participant's surgical leg versus non-surgical leg due to differences in rehabilitation training. My study was composed of two parts: a physical portion where the tests provide a quantitative measure, and a questionnaire

that provides more quantitative data on how much pain, inflammation, and trust the athlete has to complete the specified movements. I gathered my participants by asking teams at lifts if anybody had knee surgery and would be willing to participate in the study, and had close to a 1:1 ratio of female to male participants. The majority of the athletes who participated in the study ended up performing better on their surgical knee in the agility testing, due to the majority of their sports requiring more quick cutting movements rather than explosive upward movements. For example, an athlete who requires more of an upwards jump within their sport performed better at the single-leg explosive jump upwards on the jump mat. Expecting athletes to come back weaker and slower post major surgical operations was proven wrong throughout the results gathered, but the significant difference was the questionnaire portion, where athletes had very little trust and experienced more pain in their surgical knee daily. As I watched the athletes complete the physical testing, it was evident that the majority of the athletes were being cautious in their movements with their surgical leg, which can be a variable that impacts the data as a whole. Conclusively, I believe that healthcare as a whole has advanced significantly and assisted these athletes in returning to sports to their previous athletic capability. However, athletes and their mental state can advance an athlete past their physical ability because their mental block is not allowing them to completely go after their goal because of the constant fear of pain, injury, or the rehabilitation process all over again.

Keywords: Injuries, rehabilitation, performance

Barton Journal

Mind & Care Kits Initiative

CONFERENCE ABSTRACT

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CITATION

Harold, Morgan; Rodriguez, Josephine; Watkins, Skylar, & Gardner, Ashley. (2026). Mind & care kits initiative [Conference abstract]. *Barton Journal, 1*(1), 194–195. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-037

Abstract

Applying the Eight Dimensions of Wellness Framework, *Mojo's* is a student-led initiative focused on improving mental well-being and reducing hygiene insecurity among students at Barton College. Many college students face financial stress and housing instability, which can limit their access to essential hygiene products and negatively impact their mental health, confidence, and academic performance (Nasr et al., 2024; Roy & Biswas, 2025). *Mojo's* proposes the Mind and Care Kits Initiative, which aims to assemble and distribute up to 100 hygiene kits containing toothbrushes, toothpaste, travel-size hygiene products, and handwritten encouragement notes to students experiencing financial hardship. These kits were distributed through accessible campus locations and partner offices in order to reduce stigma and increase reach. The goal of this project was to reduce hygiene insecurity, promote emotional well-being, and support students' academic and personal success. Methods included bulk purchasing hygiene supplies, assembling kits, advertising via flyers and email, and hosting a campus distribution event. The total funding requested for this initiative was approximately $500. With support from campus partners and a clear evaluation plan, *Mojo's* was committed to ensuring the kits were distributed effectively and positively impacted student well-being.

Keywords: mental health, hygiene, confidence, performance

References

Nasr, Ramona; Rahman, Abir Abdel; Haddad, Chadia; Nasr, Nada; Karam, Joanne; Hayek, Jessy; Ismael, Ibrahim; Swaidan, Eman; Salameh, Pascale; & Alami, Nael. (2024). The impact of financial stress on student wellbeing in Lebanese higher education. *BMC Public Health, 24*(1809), 1–13. https://doi.org/10.1186/s12889-024-19312-0

Roy, Sharmistha; Biswas, Ashis Kumar & Sharma, Manoj. (2025). Stress, anxiety, and depression as psychological distress among college and undergraduate students: A scoping review of reviews guided by the socio-ecological model. *Healthcare, 13*(16), 1–20. https://doi.org/10.3390/healthcare13161948

Barton Journal

Modifying and Enhancing Lamotrigine with Allicin

CONFERENCE ABSTRACT

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CITATION

Cool, Hannah; & Mazuroski, Nicole L. (2026). Modifying and enhancing lamotrigine with allicin [Conference abstract]. *Barton Journal, 1*(1), 196–197. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-038

Abstract

Lamotrigine is an anticonvulsant and mood stabilizer drug that was first put on the market in 1994 in the United States. Lamotrigine is primarily used to treat partial seizures, tonic-clonic seizures, bipolar I disorder, and Lennox-Gastaut syndrome. Other off-label uses include treating acute bipolar depression, fibromyalgia, schizophrenia, and unipolar depression as well. Lamotrigine's mechanism of action is not fully defined, but likely targets and inhibits voltage-gated sodium channels found in neurons, suppressing the release of the excitatory amino acid glutamate. Toxicity in lamotrigine is associated with severe central nervous system depression, seizures, cardiac conduction delays, and wide complex tachycardia. This study will examine combining lamotrigine (lamictal) with allicin (diallythiosulfinate) and how it enhances its pharmacological effects. Allicin is a well known medicinal compound used for thousands of years, known for its antimicrobial, antioxidant, anti-inflammatory, and cardiovascular protective properties. Under ammonia (NH3) and heat, a substitution for organic reaction to produce our modified drug can be created. A double bond in allicin will break down and substitute one of the chlorine atoms on Lamotrigine, resulting in the modified drug and HCl as a byproduct of this reaction. It is expected to see increased flexibility and polarity, and decreased insaturation. The new drug should have better potency, stability, and solubility when metabolized and absorbed through

permeable membranes. Allicin will be sourced from freshly crushed up garlic, and with alterations it may help with treating partial seizures and bipolar disorder maintenance.

Keywords: lamotrigine, lamictal, allicin, diallythiosulfinate, bipolar I, Lennox-Gastaut syndrome

Barton Journal

More Than Athletes: The Dependable Athlete Wellness Guide System (D.A.W.G.S.)

CONFERENCE ABSTRACT

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CITATION

Howard, Gracie; Walsh, Kendall; & Gardner, Ashley. (2026). More than athletes: The dependable athlete wellness guide system (D.A.W.G.S.) [Conference abstract]. *Barton Journal, 1*(1), 198. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-039

Abstract

More Than Athletes, a mental health-focused organization, was created by two psychology students who experienced the struggles of being student-athletes with multiple roles on campus. The purpose of the proposed program is to provide more mental health and wellness resources to Barton College students, specifically for those in the "athlete-plus" category. There is a growing issue regarding mental health in student-athletes that must be addressed. Applying the Eight Dimensions of Wellness Framework, More Than Athletes plans to address the mental health struggles experienced by student-athletes through the establishment of D.A.W.G.S., a peer mentoring program tailored specifically for athletes who serve in multiple capacities on campus. Additionally, each student reached will receive a pamphlet with information about D.A.W.G.S., mental health resources, and self-care tips. To accomplish this initiative, More Than Athletes is requesting a total of $500.00 to bring this proposal to fruition.

Keywords: student-athlete, eight dimensions of wellness

Barton Journal

The Most Effective Way to Communicate While Coaching Athletes

CONFERENCE ABSTRACT

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CITATION

Grehan, Kale; & Biscardi, Lauren. (2026). The most effective way to communicate while coaching athletes [Conference abstract]. *Barton Journal 1*(1), 199–200. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-040

Abstract

Lacrosse is one of the fastest growing sports in the world. Field Lacrosse and Box Lacrosse have seen exponential growth over the past decade, although both versions are extremely different. Field Lacrosse is played on a football field with 10 players per team on the field, making it a much more technical game. The 80-second shot clock allows for longer possessions and more time to set up on both offense and defense. Box Lacrosse is played in a hockey rink with 30-second shot clocks and five players per team. Box Lacrosse is all about quick decision-making and creating plays in a small area within a short amount of time. Based on accessibility to hockey rinks and equipment, Box Lacrosse is more popular in Canada, while Field Lacrosse is more popular in the United States. In North Carolina, there is barely any exposure to Box Lacrosse. In this study, 12 Field Lacrosse players were coached in Box Lacrosse over four sessions. Typically, it is easier for a Box Lacrosse player to be good at Field Lacrosse, but hard for a Field player to be good at Box Lacrosse. Field players have the skills, but some lack the quick decision-making that makes a successful Box player. To find out how to help an athlete be a successful Box player, the group of 12 was divided into two teams. Team 1 would only be communicated to while they are in live play. Team 2 would only be communicated to during rest periods on the bench. After three practices, the teams played against each other to see which communication style showed more improvement over

the four sessions. Using prior coaching knowledge, it was predicted that the coaching styles would not affect the improvement of the team, but would help the individual athletes. This prediction was correct. Some athletes responded well to the different communication style, while others on the same team did not. This made the point that coaches need to get to know their athletes to find out what coaching and communication style works best for the individual athlete. Ultimately, it was found that a combination of the two styles is typically the best for the individual athlete, because talking to an athlete during live play is better for decision-making, while talking during a rest period helps teach.

Keywords: lacrosse, field lacrosse, box lacrosse, coaching

Barton Journal

Online Transparency: How Social Work Can Function Better in the Spotlight

CONFERENCE ABSTRACT

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CITATION

Koekemoer, Ethan; Richardson, Yvette. (2026). Online transparency: How social work can function better in the spotlight [Conference abstract]. *Barton Journal, 1*(1), 201–202. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-041

Abstract

Social work originated with a primary focus on addressing immediate physical needs for individuals experiencing challenging life circumstances, including access to housing and basic care. Over time, the profession has expanded to encompass broader social conditions that perpetuate inequality, including systemic injustice, stereotyping, and structural barriers. Contemporary practice reflects this dual focus, integrating direct service provision with efforts to challenge and transform the social structures that sustain these unmet needs. Central to this approach are relationship building, community engagement, and meeting individuals and families within their lived contexts. The increasing use of social media by social work organizations has introduced debate regarding the role of digital transparency. Questions persist about whether online representation reflects authentic organizational values or serves as performative engagement. While some perspectives emphasize the potential of social media to enhance visibility, build trust, and broaden outreach, others highlight concerns related to misrepresentation, ethical boundaries, and the potential diversion of attention from direct service

delivery. Examination of these contrasting perspectives suggests the possibility of a balanced approach in which social media transparency is applied both ethically and strategically. Consideration of this issue through a business-oriented lens further indicates that intentional transparency may support organizational sustainability while maintaining a commitment to community-centered practice. Strengthening the impact of social work within communities requires critical engagement with these competing viewpoints. Recognizing and navigating the tension between visibility and authenticity may provide a more effective framework for leveraging social media to address immediate needs and contribute to long-term social change.

Keywords: social work, relationship building, community engagement

Barton Journal

The Psychological Factors Contributing to the Yips in Sports Performance

CONFERENCE ABSTRACT

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CITATION

Harold, Morgan; & Avant, Tamara. (2026). The psychological factors contributing to the yips in sports performance [Conference abstract]. *Barton Journal, 1*(1), 203–204. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-042

Abstract

The present study examined how psychological pressure contributes to the yips, a performance breakdown characterized by involuntary disruptions in fine motor control during athletic tasks (e.g., McDaniel et al., 1989; Saleh, 2023). It was hypothesized that athletes experiencing greater psychological pressure and anxiety would report yips. These yips include disruptions and poorer performance under high-pressure conditions. Participating student-athletes (N = 43) averaged 8-10 years of sport experience, with nearly half reporting experiencing yips. Participants completed a survey measuring competition anxiety, overthinking, and fear of mistakes, followed by a sport-specific skill task performed under low- and high-pressure conditions. They reported moderate competition anxiety (M = 5.86, SD = 2.04), higher anxiety during high-pressure moments (M = 6.83, SD = 2.32), as well as moderate levels of overthinking (M = 3.02, SD = 1.20) and fears of mistakes (M = 3.50, SD = 1.21). Contrary to hypotheses, there was no effect of experience on factors contributing to poorer performance; however, participants with a history of choking under pressure were significantly more concerned about impact of pressure (M = 6.23, SD = 1.59) than those without this experience (M = 4.56, SD = 2.24), $F(2, 38) = 4.99$, $p < .05$, $R2$ = 0.21. A subset of participants completed a sport-specific skill task and performed marginally better in the low-pressure condition (M = 83.5%, SD = 19.6), t(3) = 2.45, p = 0.09. These

findings contribute to understanding psychological mechanisms underlying the yips and may inform targeted interventions to reduce anxiety and improve performance.

Keywords: yips, disruptions, anxiety, pressure

References

McDaniel, K. D.; Cummings, J. L.; Shain, S. (1989). The "yips": A focal dystonia of golfers. *Neurology, 39*(2 Pt 1), 192–195. doi:10.1212/wnl.39.2.192.

Saleh, Naveed. (2023, July). *When athletes get "the yips."* Psychology Today. https://www.psychologytoday.com/us/blog/the-red-light-district/202307/when-athletes-get-the-yips

Barton Journal

The Quality of Athletic Playing Surface and its Influence on Performance

CONFERENCE ABSTRACT

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Robinson, Kathryn; & Biscardi, Lauren. (2026). The quality of athletic playing surface and its influence on performance [Conference abstract]. *Barton Journal, 1*(1), 205–206. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-043

Abstract

This narrative review examines how the quality of outdoor athletic playing surfaces influences injury risk and overall human performance. It focuses on how surface type, consistency, and maintenance practices affect athlete stability, movement efficiency, and exposure to injury. The central question explores how variability in field conditions contributes to injury prevention and what standards are necessary to ensure safe and optimal performance environments. This study uses a narrative review methodology, synthesizing existing literature on outdoor athletic surfaces, including natural grass and artificial turf. Sources include peer-reviewed journal articles, sports governing body guidelines, and field maintenance reports. The review qualitatively analyzes findings related to surface hardness, traction, and upkeep practices to identify patterns linking surface quality with injury rates and performance outcomes. Understanding the relationship between playing surface quality and injury prevention is critical for athletes, coaches, and facility managers. Poorly maintained or inconsistent fields can increase the likelihood of acute and overuse injuries, while high-quality surfaces may enhance performance and safety. This review contributes to the field by highlighting key risk factors and emphasizing the importance of standardized maintenance and surface evaluation. The findings can inform best practices,

improve athlete safety, and support the development of guidelines for safer athletic environments.

Keywords: athletics, playing surface, human performance, injury

Barton Journal

The Role of Outdoor Playing Surface Quality on Injury Prevention and Performance: A Narrative Review

CONFERENCE ABSTRACT

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CITATION

Robinson, Kathryn; Biscardi, Lauren; & Ottinger, Charlie. (2026). The role of outdoor playing surface quality on injury prevention and performance: A narrative review [Conference abstract]. *Barton Journal, 1*(1), 207–208. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-044

Abstract

Anterior cruciate ligament (ACL) injuries commonly occur during noncontact movements like landing and jumping, making biomechanics a key factor in injury risk. The Landing Error Scoring System (LESS), along with research on playing surfaces and athlete perceptions, highlights how environmental and movement factors influence injury likelihood. The purpose of this study was to examine differences in athletes' Landing Error Scoring System (LESS) scores and perceived risk of lower-extremity injury when performing on natural grass versus artificial turf surfaces, as well as to determine how the playing surface may influence injury risk among athletes. Twelve female collegiate soccer athletes (21 ± 3 yrs) completed a modified questionnaire (Mears et al., 2018) on perceived injury risk. Participants then performed three jump-landing trials from a 12-inch box on both surfaces. Trials were recorded and scored using the 19-point Landing Error Scoring System analysis tool, validated to reliably measure potential injury risk (Padua et al., 2015). The data were analyzed using a Wilcoxon signed-rank test to assess differences in LESS scores between the artificial turf and the natural grass surfaces.

Statistical significance was defined as $p < .05$. All participants believed field conditions increased injury risk, and 75% reported a surface-related injury, with 50% citing grass as the increased risk, and 50% citing turf. Bumpy, hard, and inconsistent conditions were most frequently cited as conditions that may increase injury risk. The Shapiro-Wilk test showed the data were not normally distributed, $W = 0.78$, $p = .006$. A Wilcoxon signed-rank test indicated there was a significant difference in LESS scores between turf and grass playing surfaces, $z = -3.06$, $p = .002$, $r = -1.00$. LESS scores on the turf (Mdn = 4.0) were lower than LESS Scores on the grass (Mdn = 5.5). According to LESS criteria, 83% scored in a worse category on natural grass, while 17% remained in the same category. Both perceived and measured injury risk were influenced by surface type. Natural grass, particularly when poorly maintained, was associated with worse landing mechanics and higher perceived risk. These findings suggest alignment between subjective and objective measures and highlight the need for improved field maintenance and further research on surface properties.

Keywords: ACL, Anterior cruciate ligament, athletes

References

Mears, Aimee C.; Osei-Owusu, Paul; Harland, Andy R.; Owen, Alun; & Roberts, Jonathan R. (2018). Perceived links between playing surfaces and injury: A worldwide study of elite association football players. *Sports Medicine – Open, 4*(1). https://doi.org/10.1186/s40798-018-0155-y

Padua, Darin A.; DiStefano, Lindsay J.; Beutler, Anthony I.; De La Motte, Sarah J.; DiStefano, Michael J.; & Marshall, Steven W. (2015). The landing error scoring system as a screening tool for an anterior cruciate ligament injury-prevention program in elite-youth soccer athletes. *Journal of Athletic Training, 50*(6), 589–595. https://doi.org/10.4085/1062-6050-50.1.10

Barton Journal

Second Season Success: Helping Seniors Transition From Sport to Career

CONFERENCE ABSTRACT

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Watson, Danni; Murray, Christopher; Walker, Charlotte; & Gardner, Ashley. (2026). Second season success: Helping seniors transition from sport to career [Conference abstract]. *Barton Journal, 1*(1), 209–210. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-045

Abstract

The *Final Whistle Foundation* is a student-centered organization focusing on senior student-athletes transitioning to life outside their sport after graduation. Student-athletes often face challenges when dealing with a structured schedule their whole competitive career, then transitioning to post graduate employment or further education (Wood, 2014). The problems are trying to tackle translating athletic skills into career skills, having limited engagement to different career paths, and having loss of a daily structure (Stout, 2018). Using the Eight Dimensions of Wellness Framework, the *Final Whistle Foundation* proposed a senior student athlete-oriented seminar that aimed to increase career readiness, improve transferable skills, and enhance self-confidence. To accomplish the given objectives, the seminar will be held for two to three hours, by a student-athlete alumnus. This seminar will include structured reflection, a skill translation workshop, action planning, and building new professional schedules supported by a collaboration with athletics. A total of $500 was requested to support materials, facilitator compensation, and participant engagement resources.

Keywords: grant proposal, competitive career, student-athletes

References

Stout, M. Lisa. (2018). Does participation in college athletics prepare student-athletes for careers and life after college sports? A review of the literature. *Kinesiology, Sport Studies, and Physical Education Synthesis Projects, 42*.

Wood, M. (2014). The end game: How the NCAA has failed to prepare student-athletes for careers after sports. *Arizona State University Sports and Entertainment Law Journal, 4*(2), 466–538.

Barton Journal

Social Media Detoxing and its Effect on Self Esteem

CONFERENCE ABSTRACT

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Younker, Cali; & Avant, Tamara. (2026). Social media detoxing and its effect on self esteem [Conference abstract]. *Barton Journal, 1*(1), 211–212. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-046

Abstract

A person's well being can easily be affected by social media. Lui et al. (2025) explains how social media leads to information overload, social comparison, and digital fatigue. It was predicted that most people are highly affected by social media and allow other people's content to affect how they feel about themselves, subconsciously changing their everyday habits because they were influenced to do so. Participants in this study were mostly freshmen. After conducting a t-test, correlation, and ANOVA, results showed that women (M = 16, SD = 4.02) and men (M = 15, SD = 4.84) had no significant differences in Social Media Addiction (*SMA*). When measuring the correlation between gender and social media with the Rosenberg Self-esteem Scale (*RSS*), results indicated a significance for female participants. For women, there was a moderate negative correlation between *RSS* total and *SMA* total, $r\,(21) = -.42$, $p < .05$. For men, the correlation between *RSS* total and *SMA* total was not statistically significant, $r\,(11) = -.30$, $p = .325$. These results indicated that women's self esteem was more negatively related to social media than men's. Because of this, a social media detox for both genders would improve self esteem and well being overall.

Keywords: well-being, social media, social comparison, digital fatigue.

Reference

Liu, Yuyang; Mohamad, Emma M. W.; Azlan, Arina A.; & Tan, Yunpeng. (2025). Am I happier without you? Social media detox and well-being: A meta-analysis of randomized controlled trials. *Behavioral Sciences, 15*(3).doi.org/ 10.3390/bs15030290

Barton Journal

Specificity of Squat Variations: A Theoretical Framework for Adaptations and Performance Outcomes

CONFERENCE ABSTRACT

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Woollard, Luke; Biscardi, Lauren; & Ottinger, Charlie. (2026). Specificity of squat variations: A theoretical framework for adaptations and performance outcomes [Conference abstract]. *Barton Journal, 1*(1), 213–214. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-047

Abstract

The barbell back squat is a bilateral, multi-joint, closed-kinetic-chain movement that has become a staple in exercise programming for strength training, athletic conditioning, and rehabilitation. The modern back squat originated in the early 20th century and has become one of the most popular exercises for developing lower-body strength, power, and hypertrophy. In the strength and conditioning field, training specificity is critical if athletes wish to optimise the transfer of physiological and biomechanical adaptations in the weight room to athletic performance in competition. Therefore, the purpose of this narrative review is to evaluate how different variations of the modern barbell back squat can facilitate different biomechanical and physiological adaptations. This review will collect relevant literature that explores joint angles, muscle activation, and physiological adaptations, and compare the findings to sporting examples across a variety of athletic disciplines. This article will contribute to the field of strength and conditioning by educating and informing strength coaches on how different squat variations can be programmed with specificity in mind. Moreover, this review

hopes to identify which variations of the barbell back squat should be implemented for specific sporting examples.

Keywords: squat, exercise, programming, human performance

Barton Journal

Stress Management in High Pressure Scenarios in Aviation

CONFERENCE ABSTRACT

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Alexandre, Natan; & Gardner, Ashley. (2026). Stress management in high pressure scenarios in aviation [Conference abstract]. *Barton Journal, 1*(1), 215–216. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-048

Abstract

Aviation safety is primarily focused on technology-based systems, standard operating procedures, and rigorous training programs. Despite this, there is growing recognition of the importance of human performance, especially in how pilots manage stress under extreme pressure and time constraints. Research has investigated decision-making, workload, and CRM; however, there has been limited focus on the personal experience of pilots who experience stress during operational events (Casner et al., 2013). The purpose of this study was to fill this gap by examining the experiences of three commercial airline pilots from American Airlines, Gol Linhas Aereas, and Air France who all fly narrow-body aircraft. The three pilots reported having approximately 18,000 total flight hours. Semi-structured interviews using a qualitative, phenomenological design method were used to investigate how pilots experienced and regulated stress during abnormal and emergency flight situations. Three primary themes emerged from the data analysis process. These were: training/procedure discipline, time pressures/decision making, and communication via CRM. The three pilots consistently stated that their job required them to be constantly working under pressure. To mitigate the effects of stress, the pilots relied heavily

on the structured nature of routine work, checklists, and team-based decision making to maintain control over flights. The pilots also reported that instead of completely removing stress from their jobs, they learned to effectively manage their stress levels through preparation, prioritizing tasks, and coordinating efforts among crew members in the cockpit. These results emphasize the need for understanding both technical proficiency and psychological performance in the field of aviation. Additionally, these findings provide insights into developing training programs that can better prepare pilots to deal with stressful operational events, thereby promoting greater safety and more efficient flight operations.

Keywords: aviation, pilots, training,

References

Casner, Stephen M.;, Geven, Richard W.; & Williams, Kent T. (2013, June). The effectiveness of airline pilot training for abnormal events. *Human Factors, 55*(3):477–485. doi:10.1177/0018720812466893

Barton Journal

Taking Leadership Development Through Sport into High-Pressure Environments

CONFERENCE ABSTRACT

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Summerfield, Hayden; & Goines, Melissa. (2026). Taking leadership development through sport into high-pressure environments [Conference abstract]. *Barton Journal, 1*(1), 217–218. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-049

Abstract

The purpose of this study is to explore how participation in collegiate sport contributes to the development of leadership and disciplinary skills, and how these skills transfer into high-pressure professional careers. The research targets former collegiate student-athletes who have a leadership role in a high-pressure environment, such as the military, coaching, or management. The study aims to understand how experiences in sport, such as teamwork, communication, discipline, and performing under pressure, prepare individuals for leadership responsibilities beyond athletics. This study uses a qualitative research design and implements purposive sampling of former college student-athletes who are currently working in leadership roles in high-pressure professional environments. The interviews were held by phone and lasted approximately 20- 40 minutes. The responses were audio-recorded, transcribed, and then categorized by utilizing thematic analysis to identify common patterns. This was done to connect responses to leadership development, discipline, communication, and the ability to manage pressure. Overall, this study will contribute to a more developed understanding of the

relationship between sport participation, leadership development, and having a professional role in a high-pressure environment. This research stems from current leadership and sport psychology scholarship, whilst providing new qualitative data and may provide valuable insight for coaches, educators, and organizations who wish to develop leadership qualities in athletes that extend beyond the sporting world.

Keywords: collegiate sport, leadership, high-pressure environment

Barton Journal

Towards Suppression of Polycyclic Aromatic Hydrocarbons Leaching from Creosote-Treated Wood

CONFERENCE ABSTRACT

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Paydar, Amirhomayoon; Kabani, Salena; Salinas, Briana; Taylor, Alex J.; Hlavinka, Bryan; & Russell, Kenneth E. (2026). Towards suppression of polycyclic aromatic hydrocarbons leaching from creosote-treated wood [Conference abstract]. *Barton Journal, 1*(1), 219–220. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-050

Abstract

Creosote produced from coal-tar distillate is an archaic, highly toxic wood preservative commonly used today, predominantly in utilitarian applications (e.g., utility poles, railroad crossties, and marine pilings). Creosote consists of a mixture of carbon-based compounds, most of which are known human carcinogens, with high persistence to leaching and threatening groundwater and soil. As the total phase-out of creosote-treated wood is a long-term goal, the development of retroactive coatings to mitigate leaching is a high-priority environmental strategy. This study reports on the PAH leaching suppression efficacy of a poly(organosiloxane)-based nanocoating, designated Sol-186-3, that can be retroactively applied via spraying directly to creosote-treated wood substrates. The coating, composed of tetra-ethoxysilane, propyl-functional, and epoxide-functional alkoxysilanes, forms a matrix through sol-gel condensation. This coating provides a hydrophobic structure

capable of interacting with wood lignocellulosic sites and creating a siloxane network. The coating is proposed to reduce PAH leaching through physical encapsulation within a hydrophobic matrix and non-covalent interactions. Aqueous leaching tests, followed by UV-absorbance spectroscopy were conducted to evaluate immobilization efficiency. The results showed suppression of peaks characteristic of PAHs, and after 3 hours of leaching, Sol-186-3-treated samples had a 66% reduction in overall leachate compared to untreated creosote wood. Water-repellent efficiency, after extended immersion in water, was confirmed by conducting the test in accordance with ASTM D103. These findings confirm that poly(organosiloxane) nanocoatings can be used as a viable and environmentally friendly means of reducing toxic leaching from existing creosote-treated wood. Beyond utilization as a mitigator, the same chemical framework proves itself as a promising wood preservative alternative for creosote without entailing the harmful consequences.

Keywords: creosote, polyorganosiloxane, nanocoatings

Barton Journal

Understanding the Effects of Hawthorn Berry on Antihypertensive Pharmacology

CONFERENCE ABSTRACT

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Dupree, Layton; & Mazuroski, Nicole L. (2026). Understanding the effects of hawthorn berry on antihypertensive pharmacology [Conference abstract]. *Barton Journal, 1*(1), 221–222. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-051

Abstract

Hypertension is one of the most prevalent and dangerous cardiovascular risk factors, and is often mitigated through long-term pharmacological management. This disease is often treated through pharmacological methods, due to the fact that there is no true cure for hypertension currently available. One of the drugs used for hypertension is called Amlodipine, an antihypertensive drug that is a calcium channel blocker (CCB). Amlodipine increases vasodilation which reduces blood pressure. Hawthorn berry is a naturally occurring plant that also increases vasodilation through its active ingredient, oligomeric procyanidins. Using these together could benefit the patient in multiple ways. With both of these affecting vasodilation, a possible lower dose of amlodipine could be used in conjunction with the hawthorn berry. The aim of this experiment was to find a dosing system that combines normal antihypertensive drugs and Hawthorn berry to lessen the effects of hypertension on the body; specifically, finding a safe threshold for hawthorn berry to be used in conjunction with amlodipine. It is believed that with proper dosing and drug management, hawthorn berry can be taken

alongside other drugs. This research will be beneficial to polypharmacy patients, as it the lower a antihypertensive drug dose.

Keywords: hypertension, hawthorn berry, oligomeric procyanidins

Barton Journal

Video Games and their Effects on Heart Rate and Heart Rate Variability

CONFERENCE ABSTRACT

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CITATION

Goldschmidt, Colby; Biscardi, Lauren; & Ottinger, Charlie. (2026). Video games and their effects on heart rate and heart rate variability [Conference abstract]. *Barton Journal, 1*(1), 223–224. https://bartonjournal.org/vol-1-no-1/2026-cat4-article-no-052

Abstract

Heart rate variability (HRV) measures the fluctuation of time intervals between heartbeats and is used to indicate how the body manages stress, recovery, and general cardiovascular health. High HRV can indicate good fitness or physical recovery, while low HRV can indicate high stress, fatigue, or illness. This study evaluates whether a competitive Fortnite Reload game impacts players' heart rates and heart rate variability. Fifteen participants on the Barton College Esports team were split up into three groups of five (beginner, intermediate, or expert) based on experience level. Each person was assessed wearing a Zephyr monitor that allowed their respiration rate, heart rate, and HRV to be monitored during Fortnite Reloaded gameplay. Heart rate was measured at rest, then the active heart rate was measured after they performed 20 pushups. During gameplay, their RR, HR, and HRV were recorded during kills, deaths, and at the outcome (win/loss). One-way ANOVA was used to compare outcomes between skill levels. Alpha was set at .05. Expert and intermediate players had more total kills than beginners ($p = .003$). No significant differences were observed in HR, RR, or HRV between skill levels during kills, deaths, or outcome ($p > .05$). Active HR was higher than gameplay HR ($p < .001$). According to the data, a game of Fortnite Reloaded caused a physiological stress reaction less than what

occurs during moderate exercise. Experience level had no impact on the RR, HR, or HRV of players during gameplay. It also showed that experience levels affect gameplay skills. This shows that while not as physically taxing as exercise, video games, specifically Fortnite Reload, do have physiological effects on the body.

Keywords: heart rate variability, cardiovascular health, Fortnite Reload, stress