5-1-2024

A Low Dose of Electro-Psychedelic Treatment Increases Neuronal Dendritic Arborization and Filopodic Spine Density

Elaine Aquino Vasquez

A LOW DOSE OF ELECTRO-PSYCHEDELIC TREATMENT INCREASES NEURONAL

DENDRITIC ARBORIZATION AND FILOPODIC SPINE DENSITY

By

Elaine Aquino Vasquez

Bachelor of Science – Biological Sciences
University of Nevada, Las Vegas
2018

A dissertation submitted in partial fulfillment
of the requirements for the

Doctor of Philosophy – Neuroscience

The Graduate College

University of Nevada, Las Vegas
May 2024

Dissertation Approval

The Graduate College
The University of Nevada, Las Vegas

April 15, 2024

This dissertation prepared by

Elaine Aquino Vasquez

entitled

A Low Dose of Electro-Psychedelic Treatment Increases Neuronal Dendritic
Arborization and Filopodic Spine Density

is approved in partial fulfillment of the requirements for the degree of

Doctor of Philosophy – Neuroscience
The Graduate College

Dustin Hines, Ph.D.
Examination Committee Chair

Rochelle Hines, Ph.D.
Examination Committee Member

Daniel Allen, Ph.D.
Examination Committee Member

Frank van Breukelen, Ph.D.
Graduate College Faculty Representative

Alyssa Crittenden, Ph.D.
*Vice Provost for Graduate Education &
Dean of the Graduate College*

Abstract

Neuropsychiatric disorders remain a formidable challenge to the global healthcare system, necessitating innovative treatments to address their complex pathophysiology. Alternative therapeutic approaches, including electroconvulsive treatment (ECT) and psychedelics, have gained attention for their capacity to relieve a broad range of symptoms. ECT is a long-standing effective therapy for patients, especially treatment-resistant ones. Psychedelics, like psilocybin, can induce profound and sustained therapeutic effects. The limited understanding of their mechanisms of action, compounded by the negative stigma surrounding ECT and psilocybin, prevents them from being used as adjunct agents. ECT and psilocybin promote synaptic plasticity and modulate neural remodeling, yet their comparative impact on spine morphology remains largely unexplored. Interactions between microglia and neurons protect against excessive stimulation and promote therapeutic spine pruning, enhancing plasticity. Activation of microglia has been implicated in the symptomology and treatment of many neuropsychiatric disorders, providing a potential clue to understanding the synergistic mechanisms between ECT and psychedelics. The study investigates the differential impact of varying doses of ECT and psilocybin on spine morphology to address their therapeutic potential. Results 35mA of ECS causes an elongation of microglia branches with large end feet, and psilocybin causes an increase in total spine density, specifically filopodia. The co-treatment of ECS and psilocybin shows augmented filopodic spine density in neurons and an increase in endfeet volume. Our findings contribute to the growing body of literature on ECT and psilocybin as potential adjunctive therapies, paving the way for future clinical trials and personalized treatment strategies for individuals with treatment-resistant neuropsychiatric conditions.

Acknowledgments

My mentors, Dustin and Rochelle Hines: Eight years ago, you saw something in me as a young undergraduate. Your guidance and support have been instrumental in shaping me into the scientist and thinker I am today.

April, Haley, and Kendra: You've been by my side through challenges and triumphs since the beginning. Together, we've embarked on numerous adventures and shared countless good times, with many more to come.

Rhiannon, Michelle, Jackson, and Blake: We've shared countless late nights, enjoying much-needed drinks, laughter, and relaxation. You've helped keep me sane.

My labmates: Thank you for the help and support throughout this process.

Dedications

To the coffee shops that kept me fully caffeinated during early mornings and late nights;

To the unforeseen companions who have become lifelong friends;

To my friends Jess and Jan for their love, support, and laughs;

Last but not least,

To my mom and siblings for their love, unwavering support, and patience.

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List of Abbreviations

Acronym / Abbreviation	Meaning
5-HT	serotonin
5-HT2a/b/c	serotonin receptor 2a/b/c
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATP	adenosine triphosphate
BBB	blood brain barrier
BDNF	brain-derived neurotrophic factor
BP	Bipolar Disorder
CNS	central nervous system
CSF	cerebral spinal fluid
DA	dopamine
DRD1/2/3	dopamine receptor D1/2/3
ECS	electroconvulsive shock
ECT	electroconvulsive therapy
EPT	electro-psychedelic therapy
GABA	γ-aminobutyric acid
GAD	Generalized Anxiety Disorder
GLU	glutamate
HTR	head twitch response
Iba1	ionized calcium binding adaptor molecule 1
IGF-1	insulin-like growth factor
IL-1β/4/6/10	interleukin - 1β/4/ 6/ 10
LTD	long_term depression
LTP	long-term potentiation
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitors
MDD	Major Depressive Disorder
NGF	neural growth factor
NMBA	neuromuscular blocking agents
NMDA	N-methyl-D-aspartate
PSTD	post-traumatic stress disorder
SAD	social anxiety disorder
SPARC	secreted protein, acidic, rich in cysteine
SSRI	serotonin norephinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitors
TAO	tricyclic antidepressants
TGF-β	transforming growth factor-beta
TNF-α	tumer necros factor-α
TrkB	tropomyosin receptor kinase B

Chapter I: Proposed Study

The concurrent use of multiple drugs or interventions has emerged as a promising strategy for the treatment of neuropsychiatric disorders. The complexity and heterogeneity of neuropsychiatric disorders often necessitate a multifaceted approach to address diverse symptomatology and underlying pathophysiological mechanisms (Degraff et al., 2023; Pérez-Cano et al., 2023). Combining pharmacological agents with distinct modes of action optimizes the therapeutic outcomes while minimizing adverse effects. Combination therapies are often considered in the context of electroconvulsive therapy (ECT) to mitigate adverse effects associated with ECT and enhance the overall treatment outcome.

ECT has a 75.9% response rate and a 75- 95% remission rate, higher than SSRIs' 57-64% response rate (Husain et al., 2004; Nygren et al., 2023; Petrides et al., 2001; Stahl et al., 2002). The cognitive adverse effects and limited understanding of ECT's therapeutic mechanism of action cause it to be a last-resort treatment despite its long history and unparalleled efficacy (Deng et al., 2024; Sadek et al., 2011). Prominent theories for the therapeutic action of ECT highlight its ability to alter structural plasticity and regulate neuroinflammatory responses (Cano & Camprodon, 2023). ECT rescues spine density and enhances the release of neurotrophins (Maynard et al., 2018a; Ramnauth et al., 2022). Changes in spine density are present 8 hours after ECS administration and can persist for weeks (Maynard et al., 2018a; Meyers et al., 2023; Takeuchi et al., 2020). Microglia, the brain's primary immune cell, regulate the elimination and maintenance of dendritic spines. Microglia's proximity to spines enables them to monitor changes in synaptic activity (Geloso & D'Ambrosi, 2021). Furthermore, ECT induces a rapid, transient increase in immune responses and immunoregulatory markers in microglia following treatment (Baciu et al., 1995; Jansson et al., 2009; Järventausta et al., 2017).

Microglia are dynamic, highly ramified cells that continuously scan their microenvironments for disturbances. Any disturbance or loss of brain homeostasis evokes a process known as microgliosis (Hanisch & Kettenmann, 2007a). Upon activation, microglia change morphology and, in release, migratory and phagocytic behavior is necessary for tissue reconstruction after damage (Hanisch, 2002). Increased microglia activation is prevalent in many neuropsychiatric disorders and affects medication resistance (Beckett & Niklison-Chirou, 2022). Additionally, recent evidence suggests that medication resistance in patients lowers the efficacy of ECT to 48-58% (Nygren et al., 2023; Pluijms et al., 2021; Trifu et al., 2021). It is essential to uncover pharmaceuticals that can diminish adverse effects and increase the effectiveness of ECT for 20-60% of patients with medication-resistant neuropsychiatric disorders (Howes et al., 2022).

Combining classic antidepressants and ECT has gained interest for their ability to modulate spines and neuroinflammation. Research suggests combining classic antidepressants like SSRIs with ECT does not yield greater effectiveness than ECT alone (G.-M. Song et al., 2015). The lack of effectiveness could result from the slow onset of classic antidepressants. Classic antidepressants require daily intake for 4-12 weeks before symptom relief (Hillhouse & Porter, 2015). The diminished efficacy of ECT pushes the need to uncover therapy options that work synergistically with ECT. Potential candidates have a rapid onset and overlapping therapeutic mechanisms to ECT. Serotonergic psychedelics possess a well-established history of therapeutic use, and their capacity to swiftly modify mood and cognitive functions makes them adequate candidates.

Psilocybin is a fungi-derived serotonergic psychedelic with therapeutic effects that appear two to three days after administration and last for months (3-12) after initial administration (F. X. Vollenweider & Preller, 2020; Wulff et al., 2023). Additionally, the acute hallucinogenic effects of psilocybin have restricted its widespread clinical use in Western

societies (Moliner et al., 2023). It is critical to explore the therapeutic mechanism of psilocybin to unlock its full therapeutic potential. Psilocybin induces a change in neuroplasticity in regions associated with neuropsychiatric symptoms (Calder & Hasler, 2023; Vargas et al., 2023; F. X. Vollenweider & Preller, 2020). Psilocybin causes rapid and sustained increases in synaptic plasticity and associated genes (Moliner et al., 2023; Shao et al., 2021).

Current treatments have limited therapeutic efficacy due to their delayed response time and inability to promote dendritic arborization and form spines, which play a pivotal role in the pathophysiology of neuropsychiatric disorders (R. S. Duman et al., 2016; Vargas et al., 2023). Evidence suggests that treatments causing a rapid and sustainable induction of spines result in rapid behavior improvements (C. H. Duman & Duman, 2015). Given the capacity of ECT and psilocybin to rapidly induce changes in spine density and substantial behavioral changes, combining them as electro-psychedelic treatment (EPT) could uncover shared or distinct mechanisms of action. Investigating spine density changes in response to EPT offers a unique perspective into the underlying cellular mechanisms that govern neural plasticity and adaptive circuit reorganization.
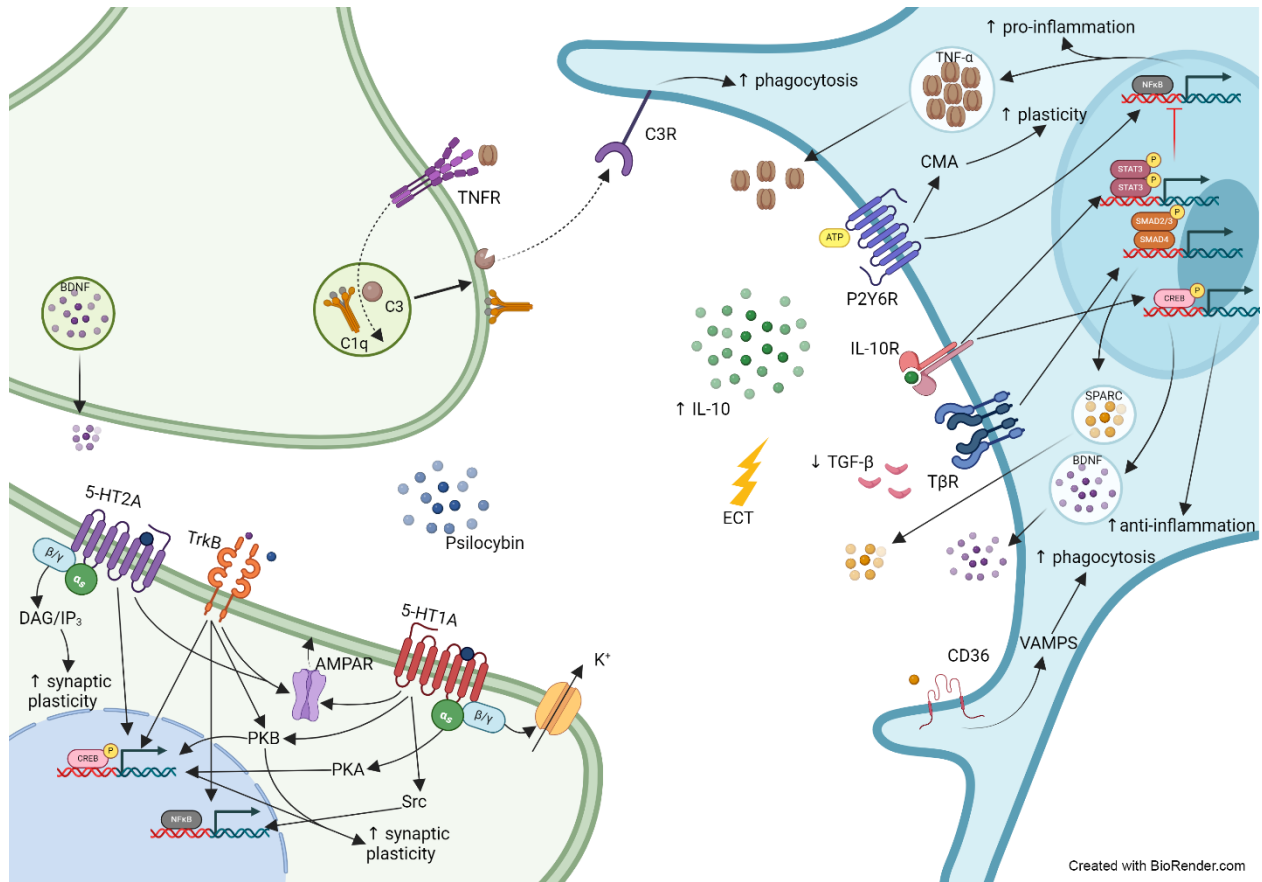
Figure 1: Proposed Mechanism for ECT vs Psilocybin Acronyms: 5-HT1/2A (serotonin 1A/2A receptor); AMPAR (AMPA receptor); ATP (adenosine triphosphate); BDNF(brain-derived neurotrophic factor); C1q (complement component 1q); C3 (complement component 3); C3R (C3 receptor); CD36 (platelet glycoprotein 4); CMA (chaperone-mediated autophagy); CREB (cyclic-AMP response element-binding protein); DAG (diacylglycerol); IP$_3$ (Inositol trisphosphate); IL-10 (interleukin 10); IL-10R (IL-10 receptor); K$^+$ (potassium ion); NFκB (Nuclear factor κ-light-chain-enhancer of activated B cells); P2Y6R (purinergic receptor P2Y6); PKA/B (protein kinase A/B); SMAD2/3/4 (suppressor of mothers against decapentaplegic); SPARC (secreted protein, acidic and rich in cysteine); Src (Proto-Oncogene, Non-Receptor Tyrosine Kinase); STAT3 (signal transducer and activator of transcription); TβR (TGF-β receptor); TGF-β (transforming growth factor-β); TNF-α (tumor necrosis factor α); TNFR (TNF receptor); TrkB (tropomyosin receptor kinase B); VAMPS (vesicle-associated membrane protein)

Chapter II: Introduction

Neuropsychiatric Disorders
Heterogeneity Of Disorders

The heterogeneity of neuropsychiatric disorders is a striking and complex aspect of the field of mental health. Neuropsychiatric disorders encompass an astonishingly vast array of conditions, each characterized by its unique blend of symptoms and underlying mechanisms. From mood disorders to anxiety disorders and from psychotic disorders to neurodevelopmental conditions, the diversity of neuropsychiatric disorders is staggering. Furthermore, even within the same diagnostic category, individuals may exhibit considerable variation in their symptoms, onset, severity, and response to treatment.

Clinical Profile
Mood Disorders

Mood disorders, a category of neuropsychiatric conditions, exhibit a profound heterogeneity that spans a spectrum of symptoms, durations, and intensities (Costello et al., 2002). The diversity underscores the intricate interplay of genetic, environmental, and neurobiological factors influencing the manifestation and course of mood disorders (Nemeroff & Owens, 2002). Comprising conditions such as Major Depressive Disorder (MDD) and Bipolar Disorder (BP), the heterogeneity within mood disorders challenges simplistic categorizations. It demands a nuanced understanding to guide accurate diagnosis and personalized treatment strategies.

MDD is identified when someone consistently experiences a low or depressed mood, loses interest in enjoyable activities (anhedonia), feels guilty or worthless, lacks energy, struggles with concentration, experiences changes in appetite, exhibits psychomotor retardation or agitation, faces sleep disruptions, or harbors suicidal thoughts. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), a diagnosis of MDD requires the presence of at least five symptoms, including either a depressed mood or anhedonia that significantly impacts social or occupational functioning. The heterogeneity within MDD becomes

apparent when considering the myriad ways symptoms present. Some individuals may experience profound lethargy, changes in appetite, and disruptions in sleep patterns, while others might struggle with irritability, restlessness, and psychomotor agitation (Costello et al., 2002; Nemeroff & Owens, 2002). Roughly two-thirds of individuals diagnosed with MDD entertain thoughts of suicide, while approximately 10 to 15 percent tragically follow through with committing suicide (Srivastava & Kumar, 2005). The severity and duration of depressive episodes vary, contributing to the diverse clinical presentations within MDD. MDD typically manifests as a chronic and recurring condition. Following the initial episode, recurrence rates stand at approximately 50%. The recurrence rate escalates to 70% after the second episode and peaks at 90% after the third episode (Lye et al., 2020).

BP introduces another layer of complexity to mood disorders. BP features recurrent episodes of mania or hypomania intertwined with periods of depression, which frequently results in initial misdiagnoses (Hirschfeld et al., 2003). The heterogeneity in BP lies not only in the distinct phases but also in the variations of mood presentation within mood phases. Manic episodes may manifest as elevated mood, increased energy, and impulsivity, while depressive episodes mirror the symptoms of MDD. The cycling between mood poles can vary widely, and some individuals may experience rapid cycling or mixed states, adding further layers of complexity. Additionally, identifying BP can be challenging due to symptom overlap with other psychiatric conditions, frequent comorbidity with both psychiatric and somatic issues, and a potential lack of insight, especially regarding hypomania (Bauer & Pfennig, 2005).

Within the spectrum of mood disorders, atypical presentations contribute to heterogeneity. For instance, seasonal affective disorder (SAD) manifests as recurrent depressive episodes during specific seasons, often in response to reduced sunlight exposure (Magnusson & Boivin, 2003). Postpartum depression is another atypical presentation occurring

in the weeks or months following childbirth (Cooper et al., 2007). Variations within the spectrum of mood disorders highlight the diverse triggers and temporal patterns that characterize them.

Mood disorders often coexist with other psychiatric conditions, contributing to the heterogeneity observed in clinical presentations. Anxiety disorders frequently overlap with mood disorders, leading to a complex interplay of depressive and anxious symptoms (Cosci & Fava, 2021; Hasin et al., 2018). The heterogeneity of mood disorders extends to treatment response and long-term outcomes. Some individuals may respond well to psychotherapy alone, while others may require a combination of psychotherapy and pharmacotherapy. Treatment-resistant depression introduces another dimension, challenging clinicians to explore alternative interventions. The prognosis of mood disorders also varies, with some individuals experiencing episodic symptoms and others facing a chronic or recurrent course.

Anxiety Disorders
Anxiety disorders are among the most prevalent mental health conditions worldwide, affecting millions of individuals across diverse demographics (Baxter et al., 2013; Garakani et al., n.d.). While anxiety is a universal human experience, anxiety disorders manifest in a myriad of forms, each presenting unique clinical profiles and symptomatology. Anxiety disorders represent a complex array of mental health conditions characterized by persistent, excessive worry, fear, or apprehension (Baxter et al., 2013). Anxiety disorders can significantly impair an individual's ability to function daily, affecting their well-being, relationships, work, and overall quality of life. The spectrum of anxiety disorders encompasses a range of conditions, each with its unique symptoms, triggers, and treatment approaches.

Generalized Anxiety Disorder (GAD) stands as a prevalent and persistent mental health condition characterized by excessive and uncontrollable worry about various aspects of life. Unlike the typical concerns that people experience, the anxiety associated with GAD is disproportionate to the situation and often extends beyond a specific event or circumstance

(Wittchen, 2002). Individuals with GAD find themselves trapped in a continuous cycle of worry, fearing the worst outcomes and struggling to manage their anxious thoughts. Pervasive anxiety accompanies physical symptoms, including restlessness, muscle tension, irritability, difficulty concentrating, and sleep disturbances. One distinctive feature of GAD is the chronic nature of the condition, with symptoms persisting for at least six months (M. B. Stein & Sareen, 2015). The constant worry can interfere significantly with daily functioning, impacting work, relationships, and overall well-being.

Panic Disorder is an anxiety disorder characterized by recurrent and unexpected panic attacks, which are intense episodes of overwhelming fear or discomfort that reach a peak within minutes (Roy-Byrne et al., 2006). Panic attacks are often accompanied by physical symptoms such as heart palpitations, sweating, trembling, shortness of breath, chest pain, nausea, and a sense of impending doom. What sets panic disorder apart is the persistent fear of having future panic attacks, leading to behavioral changes and avoidance of situations where attacks might occur (Lambert, 2015; Perrotta, 2019). Panic attacks are common symptoms experienced by individuals with phobias. Specific phobias involve an irrational and overwhelming fear of a particular object, situation, or activity. Individuals with panic disorder or specific phobias may go to great lengths to avoid the object or situation they fear, which can significantly impact their daily functioning and quality of life (Lambert, 2015).

The comorbidity of anxiety disorders refers to the phenomenon where individuals diagnosed with one anxiety disorder are at an increased risk of developing other anxiety disorders or experiencing concurrent mental health conditions. Individuals with one anxiety disorder often have an elevated risk of developing additional anxiety disorders or experiencing symptoms of other mental health conditions (Michael et al., 2007). The interplay between anxiety and depressive disorders is particularly noteworthy, as they often coexist up to 50% of the time (Hirschfeld, n.d.). The comorbidity of anxiety disorders and substance abuse disorder is

common since 35% of individuals with anxiety self-medicate with drugs and alcohol to cope with their heightened anxiety levels (M. B. Stein & Sareen, 2015). The comorbidity of anxiety disorders can complicate diagnosis and treatment. It may increase symptom severity, functional impairment, and poorer treatment outcomes.

Schizophrenia

Schizophrenia presents a complex and multifaceted clinical profile characterized by a diverse array of symptoms and manifestations, highlighting its inherent heterogeneity. At its core, schizophrenia encompasses a spectrum of cognitive, emotional, and behavioral disturbances that vary widely among individuals (Kremen et al., 2004; Moritz et al., 2020; Tsuang et al., 1990). One of the hallmark features of schizophrenia is the presence of positive symptoms such as hallucinations, delusions, disorganized speech, and grossly disorganized or catatonic behavior. Symptoms often contribute to significant impairments in daily functioning and interpersonal relationships (Bowie et al., 2006; K. R. Patel et al., 2014; Rahman & Lauriello, 2016). However, the clinical presentation of schizophrenia extends beyond positive symptoms to encompass negative symptoms like affective flattening, alogia, avolition, and social withdrawal, which can be equally debilitating and challenging to manage (Andreasen et al., 1994; Andreasen & Carpenter, 1993; Flaum & Schultz, 1996).

Furthermore, the heterogeneity of schizophrenia is evident in the variability of its onset, course, and treatment response. While some individuals experience sudden symptoms during adolescence or early adulthood, others may exhibit a more insidious onset with gradual symptom progression over time (Haas & Sweeney, 1992; Keefe et al., 1991; Ram et al., 1992). Additionally, the course of schizophrenia can be characterized by periods of remission and relapse, with fluctuations in symptom severity and functional impairment (Andreasen et al., 1994; Emsley et al., 2013; Green, 2016).

Symptom Heterogeneity
Cognitive Impairments

        The landscape of cognitive deficits in neuropsychiatric disorders is marked by a profound heterogeneity, reflecting the intricate interplay of diverse biological, genetic, and environmental factors. Unlike uniform patterns of impairment, neuropsychiatric disorders exhibit a spectrum of cognitive manifestations that vary not only across different conditions but also within the same diagnostic category.

Working Memory Deficits

        Working memory, a fundamental cognitive system responsible for temporarily storing and manipulating information, is crucial for various complex mental tasks, including problem-solving, decision-making, and learning (Aben et al., 2012; Baddeley, 1992). Dysfunction in working memory is a common feature across several neuropsychiatric disorders, significantly impacting daily functioning and contributing to the heterogeneous symptomatology observed in neuropsychiatric conditions (Goschke, 2014; Karlsgodt et al., 2011; Mansouri et al., 2015).

        Working memory deficits are a hallmark feature of schizophrenia. Individuals with schizophrenia often exhibit impairments in the encoding, maintenance, and retrieval of information within working memory. Working memory deficits contribute to the disorder's disorganized thinking and difficulties in goal-directed behaviors (Lett et al., 2014). The dorsolateral prefrontal cortex, a critical brain region associated with working memory, shows structural and functional abnormalities in individuals with schizophrenia, further highlighting the link between cognitive deficits and neural dysfunction (Stephan et al., 2006; Zhou et al., 2007).

        Individuals with MDD and BP often experience cognitive impairments, including deficits in working memory. Working memory deficits in MDD contribute to difficulties in concentration, decision-making, and emotional information processing. Negative mood leads to increased negative thoughts and a tendency to focus on negative stimuli, activating mood-matching representations in working memory (Aoki et al., 2011; Gärtner et al., 2018; Siemer, 2005). The

inclination towards negativity makes it difficult to shift attention away from negative cues, hindering task completion and causing deficits in working memory, thus fostering rumination (Gärtner et al., 2018; Gotlib et al., 2004). People with Bipolar Disorder (BP) experience impairments in working memory across mood phases. During manic episodes, individuals may experience difficulties in impulse control and cognitive flexibility related to working memory functions. Patients experiencing depression and hypomania displayed distinct differences in their memory deficits. Specifically, bipolar-depressed patients exhibited a higher degree of retroactive interference, whereas hypomanic patients demonstrated inferior long-term recall (Malhi et al., 2007). Dysregulation in the prefrontal cortex and associated neural circuits plays a role in cognitive abnormalities. Neurobiological factors, such as dysfunction in the prefrontal cortex and hippocampus, are implicated in the working memory deficits observed in MDD.

While anxiety is primarily characterized by excessive worry and fear, individuals with generalized anxiety disorder (GAD) often exhibit working memory deficits. The persistent and uncontrollable nature of worrying in GAD may tax working memory resources, leading to difficulties in cognitive performance (Moon et al., 2016). During a face recognition memory task, emotional distractors significantly reduced performance and caused altered activation in the prefrontal cortex and amygdala, regions associated with working memory and emotional processing, in individuals with GAD compared to healthy controls (Moon et al., 2016).

Executive Function Impairments

Executive functions, a set of higher-order cognitive processes responsible for planning, organizing, initiating, and regulating goal-directed behavior, play a critical role in shaping our abilities to adapt to complex situations. Dysregulation of executive functions is a common thread across various neuropsychiatric disorders, contributing to the diverse array of symptoms observed in neuropsychiatric conditions.

Executive function impairments are prominent in schizophrenia and contribute significantly to the cognitive deficits associated with the disorder (Orellana & Slachevsky, 2013). Individuals with schizophrenia often struggle with planning, cognitive flexibility, and inhibitory control. Executive function deficits impact daily functioning, including maintaining employment, engaging in social interactions, and adhering to treatment plans (Chan et al., 2006; Semkovska et al., 2004). Disruptions in the prefrontal cortex, a critical region for executive functions, are implicated in executive function abnormalities.

Executive dysfunction frequently accompanies mood disorders and anxiety disorders (DeBattista, 2005; Monteiro & Ferreira, 2018; Warren et al., 2021). Individuals often struggle with impaired cognitive functions crucial for daily functioning. Decision-making becomes arduous, with individuals finding it challenging to weigh options and make choices amidst their emotional turmoil. Planning and organization skills are compromised, leading to difficulties in setting and achieving goals (Warren et al., 2021). Cognitive flexibility, essential for adapting to changing situations, becomes limited, resulting in rigid thinking patterns.

Moreover, regulating emotions and impulses becomes problematic, contributing to mood swings and erratic behavior (Warren et al., 2021). The underlying mechanisms of executive dysfunction in mood disorders involve disruptions in brain regions responsible for executive functions, such as the prefrontal cortex, and dysregulation of neurotransmitter systems like serotonin and dopamine. Treatment approaches for mood disorders often include psychotherapy, medication, and lifestyle modifications to address executive dysfunction and improve overall cognitive functioning.

Attentional Abnormalities
Neuropsychiatric disorders often manifest attentional deficits, disrupting an individual's ability to focus, sustain attention, or shift it appropriately. Attention-deficit/hyperactivity disorder (ADHD) is perhaps the most well-known condition characterized by such deficits, with

symptoms including impulsivity, distractibility, and difficulty maintaining concentration. However, attentional impairments are also prevalent in conditions like schizophrenia, depression, and bipolar disorder (Braff & Light, 2004; Clark et al., 2002; X. Wang et al., 2020). In schizophrenia, for example, deficits in sustained attention and selective attention are commonly observed, contributing to cognitive dysfunction and impairments in daily functioning (Gjerde, 1983). Similarly, individuals with depression and bipolar disorder may experience difficulties in concentrating or making decisions, reflecting underlying attentional deficits (Kerr et al., 2005).

Behavioral Aberrations

Neuropsychiatric disorders are characterized not only by cognitive manifestations but also by a spectrum of behavioral aberrations that significantly impact an individual's daily life and interpersonal relationships. The diverse and complex behavioral manifestations provide valuable insights into the underlying neurobiological mechanisms of neuropsychiatric disorders. Understanding the behavioral aberrations is essential for accurate diagnosis, targeted intervention, and fostering a more comprehensive approach to mental health care.

Schizophrenia presents a range of behavioral aberrations that surpass mere cognitive disturbances. Behavioral aberrations in schizophrenia encompass a broad spectrum of disturbances that profoundly impact an individual's daily functioning and interpersonal relationships. Behavioral aberrations may include disorganized speech and thought processes, erratic or unpredictable behaviors, social withdrawal, and impaired emotional expression (Edinoff et al., 2020). Individuals with schizophrenia may exhibit disorganized behaviors that seem incongruent with societal norms or experience difficulty in maintaining coherent conversations due to disjointed thought patterns. Additionally, delusions and hallucinations, characteristic positive symptoms of schizophrenia, can contribute to behaviors that are perplexing or alarming to others (Andreasen & Carpenter, 1993). Negative symptoms such as affective flattening and social withdrawal further exacerbate the complexity of behavioral

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aberrations in schizophrenia, leading to social isolation and functional impairment (Carbon & Correll, 2014). Management of behavioral aberrations often requires a multifaceted approach, including antipsychotic medications, psychosocial interventions, and supportive therapy aimed at enhancing coping skills and improving social functioning.

Mood disorders, such as depression and BP, are accompanied by distinct behavioral manifestations. In depression, individuals may exhibit changes in activity levels, sleep patterns, and appetite. Feelings of worthlessness and diminished interest in previously enjoyable activities contribute to social withdrawal (Teychenne et al., 2010; W. Wang et al., 2021)l. In BP, individuals exhibit behavioral aberrations characterized by cycling between depressive and manic states. During manic episodes, individuals may engage in impulsive behaviors, have elevated energy levels, and experience a decreased need for sleep (Fico et al., 2020; Gonda et al., 2012).

The behavioral aberrations observed in neuropsychiatric disorders often extend beyond specific diagnostic categories, emphasizing the overlap and complexity within the field. Environmental factors, genetic predispositions, and neurobiological dysregulations contribute to the diversity of behavioral manifestations.

Emotional Disturbances
Emotional disturbances represent a multifaceted dimension of neuropsychiatric disorders, showcasing a remarkable heterogeneity that underscores the complexity of the interplay between the nervous system and mental health. Emotional disturbances encompass a broad spectrum of emotions, ranging from pervasive sadness and anxiety to intense mood swings and disturbances in emotional regulation (Reitan & Wolfson, 1997).

Mood disorders exemplify the diverse emotional disturbances within neuropsychiatric conditions. The specific emotional nuances can vary widely among individuals, with some experiencing profound despair and others expressing irritability or agitation. BP introduces

another layer of emotional heterogeneity through its cycling between depressive and manic (or hypomanic) states. Depressive episodes manifest with profound sadness and lethargy, whereas manic episodes often entail elevated mood, heightened energy levels, and impulsivity (Skeppar & Adolfsson, 2006). The emotional spectrum in BP reflects the dynamic nature of mood disturbances, with individuals experiencing a wide range of emotional states.

Anxiety disorders contribute to the emotional heterogeneity within neuropsychiatric disorders. People with GAD experience excessive worry about various topics, which results in chronic feelings of restlessness and irritability (Woody & Rachman, 1994). In contrast, panic disorder involves sudden and intense surges of fear or discomfort, accompanied by physical symptoms such as rapid heartbeat and shortness of breath (Roy-Byrne et al., 2006). Specific phobias introduce unique emotional disturbances, with individuals experiencing overwhelming fear in response to specific objects or situations. Phobias can lead to avoidance behaviors, influencing daily life and activities (Eaton et al., 2018). The emotional experiences within anxiety disorders showcase the diverse ways in which neuropsychiatric conditions can affect the subjective emotional landscape.

PTSD is often accompanied by profound emotional disturbances that can significantly impair daily functioning. Individuals with PTSD commonly experience intense and intrusive memories of the traumatic event, accompanied by recurrent nightmares and flashbacks, which can evoke overwhelming fear, horror, or helplessness (Brady, n.d.). Emotional responses may be triggered by reminders of the trauma, leading to heightened arousal and reactivity. Avoidance of trauma-related stimuli and situations is standard, as individuals may seek to escape or numb themselves from distressing memories and emotions (Magruder et al., 2017). Additionally, PTSD can lead to alterations in mood and cognition, including negative beliefs about oneself or others, feelings of detachment from others, and an inability to experience positive emotions (Hassija & Gray, 2010). Emotional disturbances can have profound effects on

relationships, work, and overall quality of life, underscoring the importance of early intervention and comprehensive treatment approaches for individuals with PTSD. The origins of emotional heterogeneity in neuropsychiatric disorders are multifactorial, involving genetic predispositions, environmental influences, and the intricate neurobiological underpinnings of emotion regulation. Advances in neuroscience and psychopathology continue to shed light on the specific neural circuits and neurotransmitter systems that contribute to the diverse emotional disturbances observed across different disorders.

Pathological Theories
Neurotransmission Abnormalities

The intricate dance of neurotransmitters in the brain forms the foundation of communication between neurons, influencing mood, cognition, and behavior. Dysregulations in neurotransmitter systems are central to the pathophysiology of various neuropsychiatric disorders. Understanding how disruptions in neurotransmission contribute to conditions such as depression, schizophrenia, BP, and anxiety disorders provides crucial insights into the neurobiology of mental health.

Serotonin Dysregulation

Dysregulations in 5-HT signaling have been implicated in various neuropsychiatric disorders, contributing to the complex interplay of biological, psychological, and environmental factors that underlie neuropsychiatric conditions. 5-HT dysregulation is a hallmark feature of MDD. The 5-HT hypothesis of depression suggests that imbalances in 5-HT levels contribute to the pathophysiology of depressive symptoms. Reduced 5-HT availability, particularly in the synaptic cleft, may be associated with the dysregulation of mood, appetite, and sleep observed in individuals with depression (Araragi & Lesch, 2013; Popova et al., 2022; Savitz et al., 2009). selective serotonin reuptake inhibitors (SSRIs), which increase 5-HT levels by blocking reuptake, are commonly prescribed in the treatment of depression (Godlewska et al., 2012; Owens, 2004).

5-HT dysregulation is associated with the pathophysiology of GAD. Abnormalities in 5-HT levels are thought to contribute to heightened arousal and excessive worry observed in individuals with GAD. While the precise mechanisms are complex and multifaceted, medications that modulate 5-HT levels, such as SSRIs, are often utilized to treat GAD (Charney et al., 1990; Guilherme Graeff & Zangrossi Jr., 2010). Panic disorder, characterized by recurrent and unexpected panic attacks, is linked to 5-HT dysregulation. 5-HT is involved in the modulation of the amygdala, a brain region associated with fear responses. Dysfunctions in 5-HT transmission may contribute to the exaggerated fear responses observed in panic attacks. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are some of the medications prescribed to manage panic disorder symptoms (Charney et al., 1990; Guilherme Graeff & Zangrossi Jr., 2010; Maron & Shlik, 2006).

Dopamine Dysregulation

Dysregulation of the DA system is implicated in several neuropsychiatric disorders, contributing to the complex symptomatology observed in neuropsychiatric conditions. DA dysregulation is a cornerstone in the pathophysiology of schizophrenia. The DA hypothesis posits that overactivity of DA transmission in specific brain circuits, particularly the mesolimbic pathway, contributes to positive symptoms like hallucinations and delusions (Meltzer & Stahl, 1976; Seeman, 1987). Conversely, hypoactivity in the mesocortical pathway is associated with adverse symptoms and cognitive deficits. Antipsychotic medications, which block DA receptors, are central to treating schizophrenia symptoms (Meltzer, 1991; Shen, 1999).

DA dysregulation is implicated in the manic and depressive phases of BP (Berk et al., 2007; Cousins et al., 2009). During manic episodes, there is an increase in DA activity, contributing to elevated mood, increased energy, and impulsivity. In depressive episodes, DA dysregulation may manifest as reduced motivation and pleasure (Berk et al., 2007). Mood stabilizers and antipsychotics that modulate DA levels are often part of the treatment regimen

for BP. Schizoaffective disorder shares features with both schizophrenia and mood disorders. DA dysregulation contributes to psychotic symptoms akin to schizophrenia, as well as mood disturbances seen in affective disorders. Antipsychotic medications, which modulate DA transmission, are commonly used to manage symptoms of schizoaffective disorder (Gao et al., 2015; Schloesser et al., 2012; Tohen & Vieta, 2009).

Glutamine Dysregulation

GLU, the primary excitatory neurotransmitter in the brain, is increasingly recognized for its pivotal role in the pathophysiology of schizophrenia (Uno & Coyle, 2019). The NMDA receptor hypofunction hypothesis suggests that dysregulation of glutamate neurotransmission, mainly through NMDA receptors, contributes to the development of schizophrenia symptoms (Goff & Coyle, 2001). Dysfunction in GLU receptors disrupts neural circuitry, affecting cognition, emotion, and perception—core domains affected in schizophrenia (Goff & Coyle, 2001; Uno & Coyle, 2019). Pharmacological studies using NMDA receptor antagonists like phencyclidine and ketamine reproduce symptoms akin to schizophrenia in healthy individuals, reinforcing the GLU hypothesis (Anis et al., 1983; Lahti et al., 1995). Magnetic resonance spectroscopy studies reveal aberrant GLU levels in specific brain regions of individuals with schizophrenia, further supporting GLU dysregulation (De La Fuente-Sandoval et al., 2013; Fuente-Sandoval et al., 2011). Genetic and molecular investigations also highlight variations in genes associated with GLU neurotransmission and alterations in GLU receptor expression and signaling pathways in schizophrenia (Horwitz et al., 2019; Ripke et al., 2014; Y. Yu et al., 2018).

Disruption of glutamatergic neurotransmission not only results in psychosis but can also bring about mood changes. Excessive glutamate release can lead to excitotoxicity, contributing to neuronal damage and impairing synaptic plasticity, crucial for mood regulation (Jun et al., 2014). Chronic stress, a key risk factor for MDD, disrupts glutamate homeostasis, exacerbating excitotoxicity (Musholt et al., 2009). Magnetic resonance spectroscopy studies have revealed

altered glutamate levels in brain regions associated with mood regulation in depressed individuals (Yüksel & Öngür, 2010). Moreover, drugs targeting the glutamatergic system, such as ketamine, have shown rapid antidepressant effects, underscoring the therapeutic potential of modulating glutamate transmission in MDD (Caddy et al., 2015; Maeda et al., 2007).

People with BP experience dynamic shifts in mood states, and research suggests that dysregulation of glutamine function is involved in both manic and depressive episodes (Jun et al., 2014). Findings regarding glutamatergic transmission and levels of NMDARs are inconclusive, suggesting that glutamate might not play a primary role in the pathophysiology of BP. However, it seems that glutamate could be associated with the severity and chronicity of the disorder, potentially resulting in decreased NMDAR density (Weiss et al., 2023). Additionally, gene expression analysis of patients with BP reveals a decrease in the expression of glutamate receptors in both neurons and glial cells (Ginsberg et al., 2012). GLU is implicated in the pathophysiology of PTSD. Dysregulation of glutamatergic neurotransmission is associated with the development and maintenance of PTSD symptoms, including hyperarousal, intrusive memories, and avoidance behaviors (Nair & Ajit, 2008). Alterations in glutamate levels, receptor function, and signaling pathways have been observed in individuals with PTSD (Gruenbaum et al., 2024). The use of anti-glutamatergic drugs such as lamotrigine has shown promise in reducing symptoms such as re-experiencing, avoidance, and hyperarousal associated with PTSD. Its mechanism of action involves inhibition of glutamate release and modulation of glutamate receptor function (Hertzberg et al., 1999).

Gamma-Aminobutyric Acid Dysregulation
GABA is the primary inhibitory neurotransmitter in the central nervous system, crucial for regulating neuronal excitability. Its role extends across various neuropsychiatric disorders. In conditions like anxiety disorders, GABA deficiency or impaired function leads to heightened neuronal excitability, manifesting as excessive worry and fear (Adwas et al., 2019). Similarly, in

epilepsy, where aberrant neuronal firing occurs, GABAergic dysfunction exacerbates seizures (Briggs & Galanopoulou, 2011). Schizophrenia involves dysregulation of multiple neurotransmitter systems, including GABAergic pathways, contributing to cognitive and emotional disturbances (Wassef et al., 2003). Conversely, excessive GABA activity has implications, too, notably in conditions like depression, where it may lead to dampened neuronal activity and emotional blunting (Petty, 1995).

Neuroinflammation

Neuroinflammation, once primarily associated with the immune response to infections or injuries in the CNS, is now recognized as a central player in the pathophysiology of various neuropsychiatric disorders. Neuroinflammation involves activating the brain's immune cells, releasing inflammatory mediators, and subsequent changes in neural functioning (DiSabato et al., 2016). Neuroinflammation in neuropsychiatric disorders is not only a consequence of the underlying pathology but also an active participant, contributing to the progression of the disorders (Lyman et al., 2014). The impact of neuroinflammation is pervasive, influencing the course and symptoms of neuropsychiatric conditions (Benedetti et al., 2020; Monji et al., 2009; Troubat et al., 2021; Won & Kim, 2020).

While the precise etiology of schizophrenia remains elusive, growing evidence supports the involvement of neuroinflammation in the pathophysiology of the disorder. Elevated levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, have been consistently observed in the blood and cerebrospinal fluid of individuals with schizophrenia (Yuan et al., 2022; et al Zhang, 2004). Systemic inflammation reflects a dysregulated immune response that extends to the central nervous system. Post-mortem studies of individuals with schizophrenia have revealed signs of microglial activation, suggesting ongoing immune responses in specific brain regions (Laskaris et al., 2016; Trépanier et al., 2016). The exact triggers for the microglia activation are

complex and involve neurodevelopmental abnormalities, genetic predispositions, or environmental factors.

Prenatal maternal infection has been linked to an increased risk of schizophrenia in offspring, potentially mediated by neuroinflammatory processes. Studies suggest that maternal immune activation during pregnancy can lead to aberrant neurodevelopment and long-term alterations in brain function, contributing to the pathogenesis of schizophrenia (Cheslack-Postava & Brown, 2022; Khandaker et al., 2013). Maternal infection triggers the maternal immune system to produce pro-inflammatory cytokines, which can cross the placenta and affect the developing fetal brain (Brown & Patterson, 2011). Prenatal exposure to inflammatory mediators may disrupt neuronal migration, synaptic pruning, and neurotransmitter pathways critical for normal brain development (Allswede & Cannon, 2018; Gallagher et al., 2013; Ratnayake et al., 2012, 2014). Consequently, individuals exposed to prenatal maternal infection may exhibit structural and functional abnormalities in the brain, increasing their susceptibility to psychiatric disorders like schizophrenia later in life (Brown, 2012; Brown et al., 2009).

Genetic predisposition also plays a significant role in the susceptibility to neuroinflammation in schizophrenia. Studies have identified genetic variations associated with immune dysregulation, particularly within immune-related genes like those in the major histocompatibility complex (MHC) region, which may increase the risk of developing schizophrenia (Herbon et al., 2003; A. L. Jones et al., 2005). Alterations in genes associated with MHC can lead to altered immune responses, including dysregulated cytokine signaling and microglial activation within the central nervous system. Such dysregulation may contribute to neuroinflammation, exacerbating neuronal dysfunction and potentially contributing to the onset and progression of schizophrenia (Herbon et al., 2003).

Environmental stressors, such as early-life stress, exposure to toxins, or urban upbringing, can activate immune cells within the CNS and promote the release of pro-

inflammatory cytokines, contributing to neuroinflammation and exacerbating symptoms of schizophrenia (Comer et al., 2020). The implications of neuroinflammation in schizophrenia extend beyond the core symptoms of the disorder. Emerging evidence suggests that inflammation may contribute to treatment resistance and the persistence of symptoms (Shnayder et al., 2022). Additionally, the association between schizophrenia and comorbid conditions with an inflammatory component, such as cardiovascular and metabolic disorders, underscores the systemic nature of immune dysregulations (Braga et al., 2013; Liao et al., 2021).

While neuroinflammation in schizophrenia is now well-established, its exact role in the onset and progression of the disorder remains a topic of active research. One key aspect of neuroinflammation in schizophrenia is its impact on glutamatergic neurotransmission and synaptic plasticity. Neuroinflammation, through its effects on GLU receptors and signaling pathways, contributes to synaptic dysfunction and impaired neural circuitry in schizophrenia (Mei et al., 2018; Müller, 2008).

Major depressive disorder (MDD) is associated with dysregulated neuroinflammatory responses, implicating inflammation as a contributing factor in its pathophysiology. Studies have consistently reported elevated levels of pro-inflammatory cytokines, such as IL-6, tumor, TNF-α, and C-reactive protein, in individuals with MDD compared to healthy controls (Dowlati et al., 2010; Y.-K. Kim et al., 2016; Orsolini et al., 2022). Proinflammatory markers are thought to originate from various sources, including activated microglia in the brain and peripheral immune cells (Becher et al., 2017; Dey & Hankey Giblin, 2018). Elevated levels of pro-inflammatory cytokines disrupt neurotransmitter systems, including DA, 5-HT, and GLU pathways. Neuroinflammation-induced alterations in neurotransmitter synthesis, release, and reuptake mechanisms can lead to imbalances in synaptic transmission and neuronal signaling (Ma & Ou, 2023; Müller & Schwarz, 2007; Tsao et al., 2006). For instance, increased GLU release and

impaired GLU reuptake are associated with neuroinflammation and excitotoxicity, contributing to neuronal damage and cognitive deficits (I.P., 2003; Yilmaz et al., 2002). Similarly, alterations in DA and 5-HT neurotransmission mediated by inflammatory processes may underlie mood disturbances and psychotic symptoms (Merens et al., 2007; Richtand & McNamara, 2008; Tamminga & Carlsson, 2002; Tsao et al., 2006). Moreover, Chronic stress-induced inflammation may further exacerbate depressive symptoms and contribute to the development of treatment resistance (Blackburn-Munro & Blackburn-Munro, 2001; McEwen, 2005; Tafet & Bernardini, 2003).

Emerging evidence suggests a potential link between BP and neuroinflammation, highlighting inflammation's role in the disorder's pathophysiology. Studies have revealed elevated levels of pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, in individuals with BD during mood episodes compared to healthy controls (Bai et al., 2014; Uyanik et al., 2015). Neuroinflammatory processes may dysregulate neurotransmitter systems implicated in BD, including dopamine, serotonin, and glutamate pathways, contributing to mood instability and cognitive dysfunction (Berk et al., 2007; King et al., 2019; Sobczak et al., 2002).

Moreover, genetic and environmental factors associated with BD, such as stress and sleep disturbances, can trigger immune activation and exacerbate neuroinflammation. Chronic neuroinflammation can lead to structural and functional brain changes, further perpetuating the cycle of mood swings and cognitive impairment characteristic of BD (Cyrino et al., 2021; Ferensztajn-Rochowiak et al., 2022; Haarman et al., 2014). The implications of neuroinflammation extend beyond mere association; there is evidence that inflammation may contribute to the severity, chronicity, and treatment resistance observed in mood disorders.

Current Treatments For Neuropsychiatric Disorders

Traditional pharmacological treatments for neuropsychiatric disorders have evolved from a historical understanding of brain function and neurotransmitter systems. The discovery of

medications like chlorpromazine and imipramine in the mid-20th century marked the beginning

of psychopharmacology, revolutionizing the treatment of conditions such as schizophrenia and

depression. Pharmaceutical treatments target neurotransmitter systems to correct imbalances in

dopamine, serotonin, and norepinephrine levels (Leonard, 2003). Subsequent generations of

medications, including selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics,

and mood stabilizers, were developed with improved efficacy and reduced side effects (Dols et

al., 2013; Ferensztajn-Rochowiak & Rybakowski, 2023; Orzelska-Górka et al., 2022; Pigott et

al., 2010). While traditional pharmacotherapy remains a cornerstone of neuropsychiatric

treatment, its limitations, such as variable response rates and adverse effects, underscore the

need for continued research into novel therapeutics.

Monoamine Oxidase Inhibitors
History

The history of monoamine oxidase inhibitors (MAOIs) is intertwined with the evolution of

psychiatric pharmacotherapy, marking a significant breakthrough in the treatment of mood

disorders. In the early 20th century, researchers began exploring neurotransmitters' role in the

central nervous system, particularly monoamines like 5-HT, DA, and NE. As the monoamine

theory of depression gained prominence in the 1950s, scientists sought to develop medications

that could modulate monoamines to alleviate symptoms of mood disorders. The breakthrough

came when researchers accidentally discovered the antidepressant properties of isoniazid, a

hydrazine derivative initially developed as a treatment for tuberculosis (Van Der Walt & Keddy,

2021). Researchers observed that patients taking iproniazide experienced improved mood and

relief from depressive symptoms, sparking interest in developing similar compounds (Cole et al.,

1959; "Discussion," 1959; Wrobel, 2007). Around the same time, two other scientists, Nathan S.

Kline, and Arvid Carlsson, independently identified the enzyme monoamine oxidase (MAO) as a

critical player in the metabolism of neurotransmitters (Wrobel, 2007). The discovery led to the

hypothesis that inhibiting MAO could result in increased levels of monoamines in the brain, offering a potential mechanism for treating depression.

The first generation of MAOIs, including iproniazid and isocarboxazid, entered clinical use in the 1950s. Significant improvement was observed in seventy percent of patients hospitalized for depression, with comparable improvements noted among those receiving outpatient care (Van Der Walt & Keddy, 2021; Wrobel, 2007). Still, the use of MAOIs was limited by side effects and safety concerns, particularly the potential for hypertensive crises when certain foods rich in tyramine were consumed (Thase et al., 1995). Developing exclusive MAOIs, such as tranylcypromine and phenelzine, addressed some of the safety issues associated with the initial compounds (Birkenhäger & Mulder, n.d.; Ramachandraih et al., 2011). Newer MAOIs proved to be effective in treating depression and certain anxiety disorders, expanding the therapeutic options for clinicians. Although they were effective, MAOIs lost popularity in the 1980s with the introduction of newer classes of antidepressants like SSRIs and TCAs, which were thought to have fewer side effects (Ramachandraih et al., 2011).

Therapeutic Efficacy
MAOIs have demonstrated therapeutic efficacy in the treatment of various psychiatric disorders, particularly depression and certain anxiety disorders. In treating depression, MAOIs have shown effectiveness, especially in individuals who do not respond to other classes of antidepressants (Shulman et al., 2013). They exert their therapeutic effects by increasing the concentration of monoamine transmitter in the synaptic cleft by inhibiting the MAO enzyme. Elevating neurotransmitter levels contribute to mood stabilization and improvement of depressive symptoms (Ramachandraih et al., 2011; Shulman et al., 2013). While MAOIs can be highly effective, their use is often reserved for cases where other treatment options have failed due to their side effect profile and potential for dietary and drug interactions.

Side Effects

MAOIs are associated with a distinct set of side effects that have contributed to their limited use and consideration as second-line treatments. One of the most notable side effects is the potential for hypertensive crises, especially when individuals taking MAOIs consume foods rich in tyramine, such as aged cheeses, certain wines, and cured meats (Parker, 2001; Ramachandraih et al., 2011). Tyramine, metabolized by MAO in the gut, can accumulate in the presence of MAOIs, leading to a sudden increase in blood pressure (Andersen et al., 2019; Khwanchuea et al., 2008). The effects of tyramine are generally attributed to its action in promoting the efflux of catecholamines from the sympathetic neurons and the adrenal medulla, indirectly stimulating adrenergic receptors (Andersen et al., 2019). Other common side effects include anticholinergic effects, such as dry mouth, blurred vision, and constipation. MAOIs can also cause orthostatic hypotension, making individuals more prone to dizziness or fainting upon standing up (Yamada & Yasuhara, 2004).

Additionally, MAOIs may interact adversely with certain medications, including sympathomimetic drugs, meperidine, and some antidepressants, potentially leading to 5-HT syndrome or other complications (Foong et al., 2018; Gillman, 2005; Hilton et al., 1997; Meyer & Halfin, 1981). Psychiatric side effects may include insomnia, agitation, or anxiety. Moreover, the discontinuation of MAOIs requires careful management to avoid withdrawal symptoms and prevent a potential rebound of depressive symptoms (Chamberlain & Baldwin, 2021). While the efficacy of MAOIs in treating depression and certain anxiety disorders is acknowledged, the prevalence of side effects has contributed to the development and preference for newer classes of antidepressants, such as SSRIs and TCAs, which are often considered safer and better tolerated.

Tricyclic Antidepressants
History of Tricyclic Antidepressants

TCAs represent a class of psychotropic medications that have been used to treat

depressive disorders since their introduction in 1957. TCAs derive their name from their

distinctive three-ring molecular structure, and they exert their therapeutic effects primarily by

modulating the levels of neurotransmitters in the brain (Koch-Weser & Hollister, 1978; Pereira &

Hiroaki-Sato, 2018). Amitriptyline, imipramine, and nortriptyline are well-known TCAs, each

exhibiting varying affinities for neurotransmitter receptors (Koch-Weser & Hollister, 1978). TCAs'

primary mechanism of action involves the inhibition of the reuptake of neurotransmitters, mainly

NE and 5-HT, at the synaptic cleft. By blocking the reuptake pumps responsible for clearing NE

and 5-H from the synapse, TCAs enhance their availability, increasing the stimulation of

postsynaptic receptors (Feighner, 1999). The enhancement of Ne and 5-HT contributes to the

alleviation of depressive symptoms. While TCAs primarily target NE and 5-HT, their binding

affinities extend to other receptors, including muscarinic acetylcholine and histamine H1

receptors, accounting for the side effects of TCAs (Feighner, 1999; Gillman, 2007).

Therapeutic Efficacy

TCAs constitute a class of medications that have been historically significant in the

pharmacological treatment of various neuropsychiatric disorders. TCAs were initially employed

predominantly for depression management. However, their limited tolerability has led to a shift

in their usage, with TCAs typically reserved for cases where alternative treatments have failed

to yield satisfactory results (Hirschfeld, 1999; T. Kim et al., 2019). While TCAs are most

commonly associated with their use in depressive disorders, their therapeutic effects extend to

other conditions, reflecting the diverse nature of their pharmacological actions. TCAs are first-

line treatments for chronic pain conditions and neuropathic disorders (Deng et al., 2024).

Amitriptyline, in particular, is often prescribed in lower doses for its analgesic effects (Gurba et

al., 2022; Moore et al., 2015). TCAs' modulation of neurotransmitter activity influences pain

perception and processing, making them useful in conditions like diabetic neuropathy,

fibromyalgia, and chronic headaches (Attal, 2019; Gurba et al., 2022; Obata, 2017). In pediatric

psychiatry, TCAs have been utilized as a third-line treatment of enuresis, a condition

characterized by bedwetting (Caldwell et al., 2016; Tsuji & Kaneko, 2023). Imipramine, in

particular, has shown efficacy in reducing the frequency of bedwetting episodes. The exact

mechanism through which TCAs exert their effects on enuresis is not fully understood, but it is

believed to involve alterations in bladder control and sleep architecture (Caldwell et al., 2016).

Despite their effectiveness at treating multiple disorders, TCAs are often considered last resort

treatments today, given the advent of newer psychotropic classes with more favorable side

effect profiles.

Side Effects

TCAs have notable anticholinergic effects, leading to symptoms such as dry mouth,

blurred vision, constipation, urinary retention, and increased heart rate. Side effects can be

bothersome and may impact treatment adherence (Arnold et al., 1981; Schneider et al., 2019).

TCAs often have sedating properties, and individuals taking them may experience drowsiness

or fatigue. The sedative effects can influence daily functioning and may necessitate adjusting

the timing of medication administration to minimize daytime drowsiness (Matheson & Hainer,

2017; Shaha, 2023). TCAs can cause a drop in blood pressure upon standing, known as

orthostatic hypotension, leading to dizziness or lightheadedness and increases the risk of falls,

especially in older adults (Darowski et al., 2009). Monitoring blood pressure regularly,

particularly when initiating treatment or adjusting the dosage, mitigates the risk.

Weight gain is a common side effect of TCAs (Jefferson, 1975; Licht et al., 2009).

Changes in appetite and metabolic effects contribute to weight changes. Individuals on TCAs

should be mindful of potential weight changes and discuss any significant alterations with their

healthcare provider to address concerns and explore strategies for weight management

(Ansseau et al., 1989; M. Fava, 2000; Fernstrom & Kupfer, 1988). TCAs can have effects on the

cardiovascular system, including an increased risk of arrhythmias. Individuals with pre-existing cardiac conditions or those at higher risk for cardiac issues should be closely monitored during TCA therapy (W. K. Jackson et al., 2010).

Similar to other classes of antidepressants, TCAs can contribute to sexual dysfunction, including decreased libido and difficulties with arousal or orgasm (Rothmore, 2020). Addressing concerns openly with healthcare providers is essential to explore potential solutions and ensure overall treatment satisfaction. Furthermore, TCAs have a narrow therapeutic index, meaning the difference between therapeutic and potentially toxic doses is relatively small. Accidental or intentional overdose can lead to severe complications, including life-threatening cardiac effects (Fiaturi & Greenblatt, 2019). The narrow therapeutic index underscores the importance of cautiously prescribing TCAs and educating individuals on proper medication management. While TCAs remain valuable in certain clinical scenarios, newer classes of antidepressants with more favorable side effect profiles have become more commonly prescribed (Schneider et al., 2019).

Selective Serotonin Reuptake Inhibitors
History

The history of SSRIs traces back to the mid-20th century, marked by efforts to develop safer and more effective antidepressant medications. In the 1950s and 1960s, researchers began exploring the role of serotonin in mood regulation and its potential as a target for antidepressant therapy. In the early 1980s, fluoxetine was introduced as the first commercially successful SSRI. Its approval by the U.S. Food and Drug Administration (FDA) in 1987 marked a significant milestone in psychiatric pharmacotherapy (Pereira & Hiroaki-Sato, 2018). The success of fluoxetine spurred the development of other SSRIs, including sertraline, paroxetine, and many more. SSRIs quickly gained popularity due to their improved safety profile and tolerability compared to older antidepressants like TCA and MAOIs (Lopez-Munoz & Alamo, 2009).

SSRIs revolutionized the treatment of depression and other psychiatric disorders, becoming one of the most commonly prescribed classes of medications worldwide. The selective nature of SSRIs, targeting 5-HT specifically, differentiates them from older classes of antidepressants like tricyclic antidepressants and monoamine oxidase inhibitors. The selectivity is believed to contribute to a more favorable side effect profile and improved tolerability, making SSRIs a first-line choice for the treatment of MDD, GAD, and panic disorder (Perez-Caballero et al., 2014). Despite their widespread use, SSRIs are not without side effects, including nausea, sexual dysfunction, and weight gain. Additionally, concerns have been raised about their potential for increasing the risk of suicidal ideation, particularly in young adults (Stahl, 1998). Ongoing research continues to refine our understanding of SSRIs and their optimal use in clinical practice.

Therapeutic Efficacy

SSRIs are considered the first-line treatment for MDD. Depression is often associated with a deficiency in 5-HT signaling, and SSRIs address the imbalance by preventing the reuptake of 5-HT, thereby enhancing its availability in the synaptic cleft. Common SSRIs used in the treatment of depression include fluoxetine, sertraline, and escitalopram (Lochmann & Richardson, 2019; Stahl, 1998). The clinical utility of SSRIs extends beyond their antidepressant effects. They are often prescribed for a range of psychiatric and neurological conditions, including anxiety disorders, PTSD, social phobia, and certain eating disorders (Asnis et al., 2004; DeGeorge et al., 2022; Muratore & Attia, 2022).

SSRIs are commonly prescribed for the treatment of anxiety disorders due to their efficacy and tolerability (Pace et al., 2021; Rappaport et al., 2021; Strawn et al., 2018). They are often considered a first-line treatment due to their favorable side effect profile compared to older antidepressants. Clinical studies have demonstrated that SSRIs can help alleviate symptoms such as excessive worry, fear, panic attacks, and compulsive behaviors associated with anxiety

disorders (Benjamin et al., 2000; Birmaher et al., 2003; Cipriani et al., 2009; Strawn et al., 2015; Walkup John T. et al., 2001).

SSRIs are commonly used as first-line treatment for panic disorder (Quagliato et al., 2018). SSRIs work by increasing the levels of serotonin, a neurotransmitter involved in regulating mood and anxiety, in the brain. Several SSRIs are effective in treating panic disorder, including sertraline, paroxetine, fluoxetine, and escitalopram (Dannon et al., 2004; De Vane et al., 2002; Solyom et al., 1991; Stahl & Li, 2003). They typically start at a low dose and gradually increase to the therapeutic level over several weeks (Buoli et al., 2010). SSRIs have been shown to reduce the frequency and severity of panic attacks, alleviate anticipatory anxiety, and improve overall functioning and quality of life in individuals with panic disorder (Sheehan, 2002).

SSRIs have shown efficacy in the treatment of PTSD. SSRIs are first-line pharmacological interventions for PTSD due to their favorable side effect profile and demonstrated effectiveness in reducing symptoms such as intrusive thoughts, avoidance behaviors, and hyperarousal (Marshall et al., 2007; Tucker et al., 2001, 2003; T. Williams et al., 2022). They modulate fear responses and enhance emotional processing, which is dysregulated in PTSD. Clinical trials and meta-analyses have provided evidence supporting the use of SSRIs in PTSD treatment, particularly in reducing symptoms of re-experiencing, avoidance, and hyperarousal (Lurie & Levine, 2010; Proença et al., n.d.; Schneier et al., 2015; D. J. Stein et al., 2000). Nevertheless, responses to SSRIs can differ among individuals, and certain patients might encounter side effects such as nausea, insomnia, or sexual dysfunction, leading to the cessation of treatment (Lurie & Levine, 2010; Nøhr et al., 2021; Storm & Christensen, 2021).

Side Effects

While SSRIs offer significant benefits in alleviating symptoms and improving overall quality of life, they are not without side effects. Understanding the potential adverse effects of SSRIs is crucial for both healthcare providers and individuals considering or currently using

them. Common side effects are generally mild and often transient, including nausea, gastrointestinal disturbances, headaches, and insomnia (Andrade et al. 2010, 2010; Asnis et al., 1999; Kato et al., 2023). Side effects usually occur early in treatment and diminish over time as the body adjusts to the medication.

One notable side effect associated with SSRIs is sexual dysfunction (Clayton et al., 2014; Jacobsen et al., 2015). Sexual dysfunction can manifest as reduced libido, difficulty reaching orgasm, and erectile dysfunction (Atmaca, 2020; Lorenz et al., 2016; Rothmore, 2020). Sexual dysfunction can significantly impact the quality of life for individuals taking SSRIs, influencing treatment adherence and overall satisfaction with the medication. Additionally, evidence suggests that sexual dysfunction induced by SSRIs can persist for years after treatment ends (Chinchilla Alfaro et al., 2022; Coskuner et al., 2018; Peleg et al., 2022; Reisman, 2020). Weight changes, both weight loss and weight gain, have been reported in individuals taking SSRIs. The impact on weight can vary among medications within the SSRI class and individuals (M. Fava, 2000; Sepúlveda-Lizcano et al., 2023; Shi et al., 2017). Monitoring weight and discussing significant changes with a healthcare provider is essential to address concerns and adjust the treatment plan if necessary.

Serotonin syndrome, a rare but serious condition, can occur when serotonin levels in the brain become too high (R. Z. Wang et al., 2016). Serotonin syndrome can result from the use of SSRIs alone or in combination with other medications that increase serotonin levels. Symptoms include agitation, hallucinations, rapid heartbeat, high blood pressure, fever, sweating, tremors, and, in severe cases, seizures or coma (Foong et al., 2018). Prompt medical attention is crucial if serotonin syndrome is suspected, as it can be life-threatening (Boyer Edward W. & Shannon Michael, 2005). Patients should be cautious when starting or changing SSRI doses and inform their healthcare provider of any other medications or supplements they are taking to minimize the risk of serotonin syndrome.

Discontinuation of SSRIs, especially if done abruptly, can lead to withdrawal symptoms (P. Haddad, 1998; Horowitz & Taylor, 2019). Symptoms may include dizziness, flu-like symptoms, irritability, and sensory disturbances (G. A. Fava et al., 2015). Tapering off the medication under the guidance of a healthcare provider can help minimize withdrawal effects (Horowitz & Taylor, 2019). Specific populations, such as pregnant individuals or those with specific medical conditions, may require careful monitoring and individualized treatment plans (Y. S. Khan et al., 2023; J. Wang & Cosci, 2021). In summary, SSRIs have become integral in the treatment of a variety of mood and anxiety disorders, offering a relatively safer side effect profile compared to older antidepressant classes.

Antipsychotics
History

Antipsychotics, a class of medications originally developed to manage psychotic symptoms, have evolved to play a crucial role in the treatment of various neuropsychiatric disorders beyond schizophrenia. The history of antipsychotic medication dates back to the mid-20th century (Lally & MacCabe, 2015). In 1952, chlorpromazine was introduced, marking the beginning of the era of antipsychotic drugs. Initially used to treat schizophrenia, chlorpromazine revolutionized psychiatric care by effectively alleviating symptoms such as hallucinations and delusions (Seeman, 1987). Following its success, other first-generation antipsychotics like haloperidol were developed (Remington et al., 2021). The primary mechanism of action of first-generation antipsychotics involves antagonism of DA receptors, particularly the D2 subtype (Boyd-Kimball et al., 2019). By blocking excessive DA activity, antipsychotics alleviate positive symptoms of psychosis, such as hallucinations and delusions. However, they often cause severe side effects such as motor disturbances and tardive dyskinesia (Adams et al., 2014).

In the 1980s and 1990s, second-generation antipsychotics, also known as atypical antipsychotics, were introduced. Atypical antipsychotics, in addition to DA receptor blockade, modulate 5-HT receptors, particularly the 5-HT2A subtype (Weiden, 2007). Dual receptor

blockade is believed to contribute to their efficacy in treating a broader range of symptoms and reducing the risk of extrapyramidal side effects compared to typical antipsychotics (Divac et al., 2014). Since then, newer generations of antipsychotics have been developed, focusing on enhancing efficacy, reducing side effects, and targeting specific symptoms.

Therapeutic Efficacy

Antipsychotics are a cornerstone in the management of schizophrenia, a severe mental disorder characterized by disruptions in thought processes and perception. They help reduce the severity and frequency of psychotic symptoms, allowing individuals to regain a level of functioning (Sabe et al., 2022). Atypical antipsychotics, such as clozapine, risperidone, and olanzapine, have become preferred options due to their improved side effect profiles compared to typical antipsychotics (Harrison & Goa, 2004; Hunter et al., 2003; Leucht et al., 2021). Additionally, atypical antipsychotics are commonly prescribed in BP to manage acute manic and mixed episodes (Bowden, 2005; Ghaemi & Goodwin, 1999; López-Muñoz et al., 2018). They help stabilize mood, reduce irritability, and address symptoms of psychosis that may accompany manic states (López-Muñoz et al., 2018). Some atypical antipsychotics, like quetiapine and lurasidone, have received approval for the treatment of bipolar depression (Chiesa et al., 2012; Franklin et al., 2015). Furthermore, medications like aripiprazole and quetiapine, when combined with antidepressants, have demonstrated efficacy in addressing treatment-resistant depression (Nuñez et al., 2022; Reif Andreas et al., 2023; Vas et al., 2023).

Side Effects

First-generation antipsychotics are associated with a range of side effects, often referred to as extrapyramidal symptoms. Side effects include dystonia, manifested as muscle spasms or contractions, particularly in the face, neck, or back (Loonen & Ivanova, 2021; O'Neill & Stephenson, 2022). Parkinsonism symptoms such as tremors, rigidity, and bradykinesia (slowness of movement) are common, resembling those seen in Parkinson's disease (Corekli Kaymakci et al., 2023; Garg et al., 2021; Mamo et al., 1999). Additionally, akathisia,

characterized by restlessness and an urge to move constantly, can be distressing for patients (Wu et al., 2023). Long-term use of first-generation antipsychotics may lead to tardive dyskinesia, a potentially irreversible condition marked by involuntary movements of the face, tongue, and limbs (Hemmati et al., 2010; Modestin et al., 2000).

Neuroleptic malignant syndrome is a rare but severe reaction to anti-psychotics characterized by fever, muscle rigidity, altered mental status, and autonomic dysfunction. It is noteworthy that there were notably more reports linked to atypical antipsychotics, particularly clozapine, compared to traditional antipsychotics (Tse et al., 2015). Immediate medical attention is required if NMS is suspected. Moreover, first-generation antipsychotics can induce sedation, weight gain, and metabolic disturbances, increasing the risk of conditions like diabetes and hyperlipidemia (Saari, 2004; Schwenkreis & Assion, 2004). Metabolic changes are more pronounced with certain atypical antipsychotics. Second-generation antipsychotics are often preferred in part due to their lower propensity for sedation and cognitive side effects.

Abrupt discontinuation of antipsychotic medication can lead to withdrawal symptoms due to neurochemical adaptations in the brain. Withdrawal symptoms may include rebound psychosis, agitation, anxiety, insomnia, nausea, and flu-like symptoms (Dilsaver & Alessi, 1988). Withdrawal effects vary depending on factors like the duration of medication use, dosage, and individual differences in metabolism. Gradual tapering under medical supervision is recommended to minimize withdrawal symptoms and prevent relapse of psychiatric symptoms (Horowitz et al., 2021). Patients should communicate closely with healthcare providers when discontinuing antipsychotics to ensure a safe and manageable transition. In clinical practice, healthcare providers strive to balance the therapeutic benefits of antipsychotic medications with the potential for side effects. The choice of a specific antipsychotic often involves a careful consideration of the individual's psychiatric diagnosis, medical history, and tolerance to side effects.

Mood Stabilizers
History

The history of mood stabilizers dates back to the late 19th century when lithium was first used to treat gout. Lithium carbonate gained recognition as a modern psychiatric medication in the 1950s, marking a significant breakthrough in bipolar disorder treatment (Rybakowski, 2020). In the following decades, other mood stabilizers emerged, including anticonvulsants such as valproate, carbamazepine, and lamotrigine, which were initially developed for epilepsy and showed efficacy in stabilizing mood fluctuations in bipolar disorder (Bowden & Singh, 2012; Grunze et al., 2021; Macritchie et al., 2003). The development of mood stabilizers revolutionized the management of mood disorders, providing more targeted and effective treatments.

Therapeutic Efficacy

Mood stabilizers are the cornerstone of treatment for BP, a condition marked by alternating episodes of mania or hypomania and depression. Lithium, one of the oldest mood stabilizers, remains a first-line treatment for BP (Won & Kim, 2017). It helps stabilize mood, reduce the frequency and intensity of manic episodes, and prevent depressive relapses (Mohamadian et al., 2023; Pacholko & Bekar, 2021). Other mood stabilizers commonly used in BP include anticonvulsants such as valproic acid, lamotrigine, and carbamazepine. Anticonvulsants help regulate mood fluctuations and prevent the extremes of mood associated with BP (C.-K. Chen et al., 2023; Kara et al., 2014; Miranda et al., 2019).

Mood stabilizers are also increasingly recognized for their efficacy in treating depression (Katz et al., 2022; Shelton, 1999). They may be prescribed as standalone treatments for bipolar depression or as adjunctive therapy alongside antidepressants (Caldiroli et al., 2021; Vázquez et al., 2021). Their mechanism of action in treating depression involves the modulation of neurotransmitter systems and neuroprotective effects. Lithium, for instance, modulates neurotransmitter signaling, particularly involving serotonin and norepinephrine, which are implicated in mood regulation (Price et al., 1990; Sastre et al., 2005). It also influences

neuroprotective factors and intracellular signaling pathways (Abu-Hijleh et al., 2021; Gideons et al., 2017; Leyhe et al., 2009; Won & Kim, 2017).

Beyond their mood-stabilizing properties, anticonvulsant mood stabilizers like gabapentin and pregabalin are utilized in the management of neuropathic pain. Gabapentin and pregabalin decrease neuronal excitability and are effective in diabetic neuropathy and postherpetic neuralgia (Mathieson et al., 2020; Senderovich & Jeyapragasan, 2018). Mood stabilizers, commonly used to manage bipolar disorder, have shown promise in treating intermittent explosive disorder. While not officially approved for intermittent explosive disorder, medications like lithium, valproate, and carbamazepine have been utilized off-label due to their ability to stabilize mood and temper impulsive aggression (Olvera, 2002; Turgay, 2004). Mood stabilizers may help regulate neurotransmitter imbalances and temper-dysregulated emotional responses implicated in intermittent explosive disorder.

Side Effects

Mood stabilizers, while effective in managing mood disorders such as bipolar disorder, can entail a range of side effects that warrant consideration. Lithium, a cornerstone in bipolar treatment, may lead to adverse effects such as tremors, weight gain, and thyroid dysfunction, particularly hypothyroidism (Gitlin, 2016; Greil et al., 2023; Rizzo et al., 2017). Additionally, it carries a risk of kidney damage and requires regular monitoring of blood levels to maintain therapeutic efficacy and safety (Gong et al., 2016). Anticonvulsant mood stabilizers like valproate and carbamazepine also pose potential side effects, including weight gain, gastrointestinal disturbances, sedation, and liver function abnormalities (Goldberg, 2024; Kakunje et al., 2018; McKiernan, 2014). Lamotrigine, another anticonvulsant used as a mood stabilizer, may cause skin rashes, including severe conditions like Stevens-Johnson syndrome (Das et al., 2023; X. Wang et al., 2015). Furthermore, mood stabilizers can interact with other medications, leading to adverse reactions or altering their effectiveness (Sarparast et al., 2022).

Healthcare providers must monitor patients closely for side effects, adjust dosages as necessary, and educate individuals about potential risks.

Adjunct Therapies

Adjunct therapies, employed alongside conventional treatments, represent a promising avenue for addressing neuropsychiatric disorders comprehensively. Supplemental approaches encompass various interventions, including psychotherapy, lifestyle modifications, and alternative treatments like mindfulness practices or dietary adjustments (Dunn et al., 2005; Hofmann & Gómez, 2017). By integrating adjunct therapies into treatment plans, clinicians aim to enhance efficacy, minimize side effects, and promote long-term well-being. For instance, in depression management, cognitive-behavioral therapy (CBT) or mindfulness-based interventions may augment the effects of antidepressant medications, fostering symptom relief and preventing relapse (J. L. Jackson et al., 2006; Petersen, 2006). Similarly, in conditions such as schizophrenia or bipolar disorder, psychosocial interventions like social skills training or family therapy can complement pharmacotherapy, facilitating symptom management and improving functional outcomes (Chien et al., 2003; Granholm et al., 2022; Hogarty et al., 1986).

Moreover, emerging modalities like psychedelic-assisted therapy are showing promise as adjuncts in treating various mental health conditions, offering novel pathways to healing. Overall, the integration of adjunct therapies into standard treatment regimens represents a holistic approach to addressing neuropsychiatric disorders, promoting resilience, and optimizing overall mental health outcomes. Integrating adjunct therapies with pharmaceutical interventions signifies a personalized and multidimensional approach to neuropsychiatric care. The holistic strategy acknowledges the complexity of neuropsychiatric disorders and aims to optimize treatment outcomes by addressing various aspects of an individual's mental and emotional well-being.

Psilocybin
History Of Psilocybin

Psilocybin, a naturally occurring psychedelic compound found in certain mushrooms, has a rich medicinal history deeply intertwined with various cultural and spiritual practices. In recent years, renewed scientific interest has focused on its potential therapeutic applications, shedding light on its ability to offer novel approaches to mental health treatment.

Psilocybin has been a sacred conduit to spiritual realms within indigenous and shamanic cultures across the globe. Traditionally, the use of psilocybin is steeped in reverence, intertwined with mystical experiences, and often guided by shamanic practitioners. Indigenous cultures in Mesoamerica, particularly the Aztecs and the Mayans, held psilocybin-containing mushrooms in profound esteem. Revered as the "Teonanácatl" or "flesh of the gods," psychedelic mushrooms were central to religious ceremonies (Spiers et al., 2024). Shamans, acting as intermediaries between the earthly and spiritual realms, consumed psilocybin to induce altered states of consciousness. Subjective experiences were believed to facilitate communication with deities, receive divine guidance, and contribute to communal well-being (K. Williams et al., 2022). Beyond Mesoamerica, various indigenous tribes around the world incorporated psilocybin mushrooms into shamanic practices. Shamans, often considered spiritual guides and healers, utilized the mushrooms to commune with spirits, access hidden knowledge, and diagnose and treat ailments. The ingestion of psilocybin was seen as a means to transcend the boundaries of the physical world and gain insights into the interconnectedness of all existence. In indigenous cultures, psilocybin was not merely a hallucinogenic substance; it was a sacred tool fostering a profound connection with nature and the cosmos. The mushrooms were perceived as allies, gateways to the divine, and personal and communal transformation instruments.

The use of psilocybin in indigenous and shamanic cultures was intricately woven into ceremonial contexts, often accompanied by rituals, chants, and symbolic practices. Sacred

ceremonies aimed to honor the spirits, seek guidance, and foster spiritual growth among participants. The indigenous and shamanic culture surrounding psilocybin reflects a deep understanding of the symbiotic relationship between humans and the natural world. The use of psilocybin was not merely a pharmacological endeavor; it was a sacred journey guided by the wisdom of shamans, fostering a harmonious connection between the spiritual and material realms. Today, as modern research rekindles interest in psilocybin's therapeutic potential, it pays homage to the ancient wisdom embedded in indigenous and shamanic traditions (Spiers et al., 2024; K. Williams et al., 2022).

The mid-20th century marked a pivotal period of rediscovery for psilocybin in Western societies, as the compound found its way from indigenous rituals to the forefront of counterculture movements, sparking a cultural renaissance that challenged societal norms and expanded consciousness (K. Williams et al., 2022). The Western rediscovery of psilocybin can be attributed to ethnomycologists like R. Gordon Wasson, who, in the 1950s, conducted expeditions to Mexico to study indigenous mushroom rituals. Wasson's encounters with psilocybin-containing mushrooms, particularly the sacred Aztec variety known as "Teonanácatl" or "flesh of the gods," sparked a renewed interest in the psychedelic properties of fungi (Nichols, 2004, 2020).

The 20th century saw influential figures like Timothy Leary and Aldous Huxley exploring the mind-altering effects of psilocybin. Leary, a Harvard psychologist, conducted groundbreaking research on psychedelics and advocated for their potential to enhance human consciousness. Huxley, renowned for his literary contributions, mused about the transformative potential of psychedelics in his work, "The Doors of Perception." The 1960s witnessed the cultural renaissance of psilocybin as it became intertwined with the broader psychedelic movement (Spiers et al., 2024). The "psychedelic sixties" saw a wave of experimentation with mind-altering substances, including psilocybin mushrooms. Psychedelics were embraced by

counterculture figures, artists, and musicians, influencing a cultural shift toward questioning

established norms and fostering a deeper connection with spirituality and nature. The cultural

renaissance of psilocybin, however, prompted legal and regulatory responses. Concerns about

the misuse of psychedelics led to restrictive measures and a temporary halt in psychedelic

research, dampening the momentum of the cultural revolution. In recent years, there has been a

resurgence of interest in psilocybin, with a focus on its therapeutic potential. Rigorous scientific

studies have explored its efficacy in treating conditions such as depression, anxiety, and PTSD.

The modern wave of research has sparked a new cultural conversation around psychedelics,

shedding the stigma and paving the way for potential integration into mainstream mental health

care.

Mechanism Of Action

Psilocybin, the psychoactive compound found in certain mushrooms, embarks on a

fascinating journey within the brain, unveiling its effects through intricate interactions with the 5-

HT system. As we delve into the mechanism of action for psilocybin, we discover a nuanced

dance of neurotransmitters, receptors, and neural pathways that collectively orchestrate the

profound alterations in consciousness characteristic of the psychedelic experience.

5-HT Receptor Affinity

Psilocybin, the psychoactive compound found in certain mushrooms, has a profound

affinity for the serotonin 5-HT2A receptor, a subtype of serotonin receptor abundantly distributed

throughout the brain (dos Santos et al., 2021; Schmitz et al., 2022; G. Zhang & Stackman,

2015). Upon ingestion, psilocybin is metabolized into psilocin, which acts as a potent agonist at

5-HT receptors. Activation of 5-HT2A receptors by psilocybin triggers a cascade of

neurochemical events, leading to alterations in neurotransmitter release, particularly dopamine

and GLU, and modulation of neural network activity (dos Santos et al., 2021). Activation of 5-HT

receptors is believed to play a central role in the psychedelic effects of psilocybin, including

alterations in perception, mood, and cognition (G. Zhang & Stackman, 2015). Furthermore,

research suggests that the interaction between psilocybin and 5-HT2A receptors may contribute to therapeutic effects such as promoting neuroplasticity and facilitating emotional processing, offering potential avenues for treating mental health disorders.

Non-Serotonergic Neurotransmitter
As the research into the effects of psilocybin deepens, the intricate interplay between psilocybin and non-serotonergic neurotransmitter systems becomes increasingly fascinating. Beyond its primary interaction with 5-HT receptors, psilocybin exerts its influence on a spectrum of neurotransmitter systems, each contributing to the multidimensional nature of the psychedelic experience.

Dopamine
Studies suggest psilocybin may affect DA release, a neurotransmitter associated with reward, motivation, and pleasure. Research suggests psilocybin may influence DA release in the brain, a neurotransmitter crucial for reward, motivation, and pleasure (Grandjean et al., 2021). The compound's impact on DA pathways contributes to the reported feelings of euphoria, heightened sensory perception, and altered mood during a psilocybin experience (F. Vollenweider et al., 1999). While the exact mechanisms are complex and still under exploration, the modulation of DA release adds a layer of understanding to the psychedelic journey, emphasizing the multidimensional nature of psilocybin's influence on neural circuits associated with emotional and perceptual processing. As our understanding deepens, exploring the interplay between psilocybin and DA opens avenues for unraveling the therapeutic potential of psychedelics in mental health contexts where DA dysregulation plays a role.

Glutamate
Furthermore, psilocybin's impact on the GLUT system, the brain's major excitatory neurotransmitter, has been explored. Research suggests psilocybin may modulate GLU release, impacting neural circuits associated with cognition, learning, and memory (Mahmoudi et al., 2018). GLU is pivotal for synaptic plasticity, the brain's ability to adapt and form new

connections. By influencing GLU levels, psilocybin potentially alters the dynamic interplay between neural networks, contributing to the vivid perceptual and cognitive shifts experienced during a psychedelic journey. Modulation of GLU, coupled with psilocybin's effects on 5-HT receptors, underscores the compound's ability to induce profound alterations in consciousness and highlights its potential therapeutic applications in conditions where glutamatergic dysfunction is implicated, such as depression, anxiety, and addiction (Mahmoudi et al., 2018; Wojtas et al., 2022).

Gamma-Aminobutyric Acid

Psilocybin has been implicated in modulating GABA's activity, the brain's primary inhibitory neurotransmitter. Research suggests that psilocybin may indirectly affect GABAergic signaling by altering the activity of serotonin receptors, particularly the 5-HT2A receptor subtype (Hesselgrave et al., 2021). By binding to 5-HT2A receptors, psilocybin disrupts the balance of neurotransmission, leading to increased GLU release and excitatory activity. Heightened excitability may indirectly influence GABAergic interneurons, potentially leading to alterations in GABAergic transmission (Wojtas et al., 2022). The precise mechanisms through which psilocybin affects GABAergic signaling are still not fully understood and require further investigation. Nonetheless, understanding the impact of psilocybin on GABAergic neurotransmission could provide valuable insights into its therapeutic potential and shed light on its effects on brain function and behavior.

Neural Plasticity And Synaptic Growth

Preclinical studies suggest that psychedelics, including psilocybin, may contribute to neural plasticity—the brain's ability to reorganize and form new connections. Psilocybin is believed to stimulate the growth of new synaptic connections and even promote neurogenesis, challenging the traditional view that the adult brain is static and incapable of generating new neurons.

Synaptic Plasticity

Research suggests that psilocybin interacts with serotonin receptors, influencing neurotransmitter systems pivotal in synaptic plasticity regulation. By modulating the default mode network, psilocybin may facilitate the formation of new synaptic connections or weaken existing ones (Gattuso et al., 2023; Smigielski et al., 2019). Default mode network modulation could potentially induce LTP or LTD fundamental processes underlying learning and memory (Skosnik et al., 2023; J. Song et al., 2023). Alterations in synaptic strength and connectivity may contribute to the therapeutic effects of psilocybin in mental health conditions such as depression and anxiety. While still in its infancy, studying psilocybin's impact on synaptic plasticity offers insights into its mechanisms of action and therapeutic potential, shedding light on novel treatment approaches for various neurological and psychiatric disorders.

Spine Density

Psilocybin profoundly influences dendritic spine density, and the microscopic protrusions on neurons are crucial for synaptic connections. Preclinical studies suggest that psilocybin may increase dendritic spine density, particularly in regions associated with learning and memory (Du et al., 2023; Shao et al., 2021). The effect of psilocybin on dendritic spines implies a potential for enhanced synaptic connectivity and communication between neurons. The intricate dance of psilocybin with 5-HT receptors, particularly the 5-HT2A receptor, is believed to orchestrate dendritic spine changes. While the specific implications for cognitive function and mental health are still being unraveled, the observed impact on dendritic spine density underscores the intricate and transformative nature of psilocybin within the neural landscape, hinting at its potential to facilitate adaptive changes in the brain's architecture.

Integration And Therapeutic Insights

Psilocybin, the psychoactive compound found in certain species of mushrooms, has garnered considerable attention for its ability to induce profound introspective experiences. When ingested, psilocybin interacts with serotonin receptors in the brain, leading to alterations in perception, cognition, and mood. One of the most notable effects of psilocybin is its ability to

facilitate introspection (Carbonaro et al., 2020), allowing individuals to delve deep into their thoughts, emotions, and beliefs. The reflective effect often manifests as heightened self-awareness, introspective insights, and a heightened sense of interconnectedness with one's surroundings and inner self. Many users report experiencing profound revelations about their lives, relationships, and the nature of reality during psilocybin trips. The introspective experiences can have long-lasting positive effects, including increased empathy, openness, and psychological well-being. However, it's essential to note that psilocybin's introspective effects can also be intense and potentially challenging, leading to difficult emotions and psychological confrontations (Carbonaro et al., 2020; Griffiths et al., 2006, 2011). As research into the therapeutic potential of psilocybin continues, understanding its introspective effects may provide valuable insights into how it can be utilized for personal growth and psychological healing. The future of psilocybin therapy holds promise, but challenges persist. Large-scale clinical trials, regulatory approvals, and the development of standardized protocols are essential for establishing psilocybin as a mainstream therapeutic option. The stigma surrounding psychedelics and the need for increased public and professional education represent additional hurdles to be addressed.

Therapeutic Potential Of Psilocybin

Psilocybin has undergone a remarkable renaissance in therapeutic research, challenging preconceived notions and offering new avenues for mental health treatment. The burgeoning field of psychedelic-assisted therapy is revealing the profound therapeutic potential of psilocybin, providing a fresh perspective on how psilocybin can contribute to alleviating various mental health conditions.

Depression

Psilocybin is emerging as a promising avenue in the treatment of depression, offering a paradigm shift in mental health care. Research indicates that psilocybin, when administered in controlled therapeutic settings, may hold the key to alleviating depressive symptoms, especially

in cases resistant to conventional treatments. Studies have demonstrated that a single or limited number of sessions with psilocybin, coupled with psychotherapeutic support, can lead to profound and sustained improvements in mood. The psychedelic experience induced by psilocybin is characterized by introspection, emotional release, and altered perceptions, facilitating a unique therapeutic journey for individuals grappling with depression (Barber & Aaronson, 2022).

The mechanism through which psilocybin exerts its antidepressant effects is thought to involve the modulation of 5-HT receptors in the brain, particularly the 5-HT2A receptor. Interaction with 5-HT2A leads to altered neural pathways associated with mood regulation and emotional processing. The psychedelic experience often includes a sense of interconnectedness, increased self-awareness, and a shift in perspective, allowing individuals to confront and reevaluate deep-seated thought patterns contributing to their depressive states (Sloshower et al., 2023).

As research on psilocybin and depression continues to advance, the prospect of a transformative and rapid-acting intervention for those suffering from depression becomes increasingly tangible. While legal and regulatory considerations remain, the growing body of evidence suggests that psilocybin could revolutionize the treatment landscape for depression, offering new hope for individuals seeking relief from the burdens of depression (Geyer, 2023).

Anxiety

Psilocybin therapy is emerging as a groundbreaking approach to addressing anxiety disorders, ushering in a novel era of mental health treatment. Research indicates that the psychedelic properties of psilocybin, found in certain mushrooms, can be harnessed to alleviate the grip of anxiety, offering transformative experiences within therapeutic settings.

In controlled clinical settings, psilocybin-assisted therapy has demonstrated remarkable potential in reducing symptoms of various anxiety disorders. The psychedelic journey induced

by psilocybin is characterized by a heightened sense of introspection, emotional release, and altered perceptions, creating a conducive environment for individuals to confront and reevaluate the root causes of their anxiety (Barber & Aaronson, 2022).

The mechanism of action involves the interaction with 5-HT receptors, particularly the 5-HT2A receptor, leading to changes in neural connectivity and emotional processing. The modulation of 5-HT receptors is believed to unlock suppressed emotions, allowing individuals to navigate and transcend anxiety-inducing thought patterns (Nayak et al., 2023).

PTSD

Psilocybin therapy has emerged as a beacon of hope for individuals grappling with PTSD, offering a transformative and innovative approach to healing deep-seated emotional wounds. Research suggests that the psychedelic properties of psilocybin can catalyze profound shifts in consciousness, providing individuals with new perspectives and tools to navigate the aftermath of trauma. In clinical trials, psilocybin-assisted therapy has shown promise in significantly reducing PTSD symptoms (Bird et al., 2021). The therapeutic journey guided by psilocybin is characterized by a heightened emotional release, introspection, and altered perceptions, creating a therapeutic space where individuals can confront and reprocess traumatic memories (S. J. Khan et al., 2016).

The integrative aspect of psilocybin therapy is crucial. Trained therapists guide individuals in making sense of their psychedelic experiences, helping them integrate newfound insights into their daily lives. Studies suggest that a single or a limited number of psilocybin sessions, when integrated with psychotherapy, can lead to enduring improvements in PTSD symptoms, providing relief where traditional treatments may fall short (Fonseka & Woo, 2023; Khanna, 2024).

While regulatory considerations remain, the promising results of psilocybin therapy for PTSD underscore its potential to revolutionize trauma-focused mental health care, offering a

path toward healing and recovery for those whose lives have been profoundly impacted by traumatic events.

Side Effects

Psilocybin can induce various side effects, emphasizing the importance of responsible and supervised use. It's crucial to note that individual responses can vary, and the intensity of side effects depends on factors such as dosage, set, and setting. Profound alterations in perception, mood, and consciousness characterize the subjective experience following psilocybin ingestion. Users often report heightened sensory perception, vivid visual hallucinations, and a deep sense of interconnectedness with their surroundings (Carbonaro et al., 2020). Time distortion and ego dissolution are common, leading to a feeling of expanded consciousness and unity with the universe. Emotions can range from euphoria to introspection, sometimes accompanied by intense spiritual or mystical experiences (Griffiths et al., 2011; Johnson et al., 2019). The overall journey is highly subjective, influenced by factors such as set and setting, dosage, and individual psychology, making each psilocybin experience unique and potentially transformative.

Physiological effects can include nausea, increased heart rate, and changes in blood pressure. They are usually transient and subside as the psychedelic experience progresses (Carbonaro et al., 2020; Goodwin et al., 2022; Griffiths et al., 2006; Johnson et al., 2012; Strassman & Qualls, 1994). In elevated quantities, psilocybin may induce feelings of anxiety, dysphoria, confusion, and occasionally, delusions, termed colloquially as a "bad trip." Clinical research protocols provide safeguards for managing such challenging reactions in unsupervised environments; subjective experiences could result in accidents or risky behaviors (Bienemann et al., 2020; Gashi et al., 2021; Johnson et al., 2019).

Adjunct Treatments

The combination of drugs with psilocybin, the psychoactive compound found in certain mushrooms, represents a nuanced and complex facet of psychedelic exploration. Individuals

engaging in poly-drug use often seek to modulate or enhance their psilocybin experiences, but the effects can be highly variable and context-dependent. From benzodiazepines for anxiety management to cannabis for potential amplification of effects, the choice of substances alongside psilocybin is diverse and subjective. However, poly-drug use comes with inherent risks, as interactions between substances can be unpredictable, leading to intensified experiences or adverse reactions. Poly-drug use underscores the importance of informed decision-making, harm-reduction practices, and consultation with healthcare professionals. Exploring the world of drugs used with psilocybin requires a careful and thoughtful approach, acknowledging the potential impact on the psychedelic journey and prioritizing the well-being and safety of individuals engaging in such combinations.

Cannabis

The concurrent use of cannabis with psilocybin, the psychoactive compound in certain mushrooms, is a practice that intertwines two potent psychoactive substances, each with its effects on perception and consciousness. Cannabis has been purported to amplify the psychedelic experience, often intensifying visual distortions and sensory perceptions induced by psilocybin. However, the combination of cannabis and psilocybin is not without risks and complexities. Cannabis can heighten the overall intensity of the psychedelic journey, potentially leading to a more immersive and reflective experience. Users often report enhanced creativity, altered thought patterns, and an intensified sense of connection to their surroundings. Additionally, some individuals believe that cannabis can alleviate anxiety or nausea associated with psilocybin ingestion.

However, the interaction between cannabis and psilocybin is highly individualized, and its effects can be unpredictable. While some may find the combination enjoyable and synergistic, others may experience heightened anxiety, paranoia, or an overwhelming intensity that leads to a challenging trip. Moreover, the combination of cannabis and psilocybin

substances may impact short-term memory, concentration, and coordination, posing additional

risks, particularly for individuals with a low tolerance for either substance.

Anti-Nausea Medication
    The use of anti-nausea medication with psilocybin, the psychoactive compound found in

certain mushrooms, is a practical consideration aimed at minimizing a common side effect

associated with psychedelic ingestion: nausea (Rossi et al., 2022). Ondansetron, a commonly

prescribed antiemetic, is one medication that alleviates or prevents nausea during a psilocybin

experience. While nausea itself may not pose significant health risks, it can contribute to a less

enjoyable and potentially distressing psychedelic journey (Goodwin et al., 2022). Anti-nausea

medications block 5-HT receptors in the brain and gut, mitigating the signals that trigger nausea

and vomiting (Roila & Del Favero, 1995). The administration of ondansetron before or

concurrent with psilocybin ingestion aims to enhance the overall comfort and well-being of

individuals undergoing a psychedelic experience. By reducing the likelihood of nausea, the

medication contributes to a smoother and more positive journey, allowing individuals to focus on

the psychological and perceptual aspects of the experience rather than grappling with physical

discomfort. Additionally, some argue that nausea is an inherent part of the psychedelic

experience and may be integral to the overall journey, contributing to the therapeutic effects.

Anti-Depressants
    The combination of antidepressants, particularly SSRIs, with psilocybin is a topic that

raises intricate considerations within the psychedelic community. Psilocybin differentially

modulates 5-HT receptor activity than SSRIs, and as a result, individuals on SSRIs experience

diminished effects of psilocybin due to the altered 5-HT dynamics (Barbut Siva et al., 2024).

Some individuals choose to taper off SSRIs, but that causes a potential risk to their mental

health. Research done with individuals with a history of SSRI and psilocybin found that the

diminished effects caused by antidepressant use can last for up to 3 months (Andreasen et al.,

1994). Tapering of SSRIs can prove dangerous with individuals who are already at high risk for

suicidal ideation. Careful consideration and consultation with a healthcare professional are essential for patients wishing to switch to psilocybin as a treatment. In addition to the diminished psychedelic experience, a history of antidepressant use can also lower the anti-depressant effects of psilocybin (Barbut Siva et al., 2024). The diminished effects of psilocybin present difficulties, such as extended periods without treatment before undergoing psychedelic therapy and the potential need to readjust antidepressant dosages if the psychedelic intervention proves ineffective or has limited impact.

Tobacco

The concurrent use of tobacco with psilocybin, the psychoactive compound found in certain mushrooms, is a practice that carries both cultural and individual significance. Historically, some indigenous rituals have incorporated the ceremonial use of tobacco alongside psychedelic substances for spiritual or therapeutic purposes. However, in modern recreational or therapeutic settings, the use of tobacco with psilocybin can have varied effects and considerations. Smoking tobacco, particularly in the form of cigarettes or cigars, is often employed to complement the psychedelic experience. Some individuals report that the ritualistic act of smoking can enhance the sensory and ritualistic aspects of the journey, providing a grounding or meditative element (Riley & Hayward, 2004; Roberts et al., 2020). Nicotine is a powerful psychoactive substance, and its stimulant properties can amplify the physiological effects of psilocybin, potentially leading to increased heart rate, anxiety, or altered perceptions (Parrott, 2015). Contradictory to the enhanced experience attributed to poldy drug use by recreational users, new research indicates that psilocybin could be used to treat tobacco addiction (Higgins & Sellers, 2021; Johnson, 2022; Johnson et al., 2017). Serotonin receptors, particularly 5-HT1A and 5-HT2C, regulate the release of dopamine, a neurotransmitter associated with pleasure and reward. Alterations in serotonin signaling can affect dopamine levels, impacting the brain's reward system and contributing to addictive behaviors (Higgins & Sellers, 2021).

Electroconvulsive Therapy
History Of ECT

The pioneering years of ECT unfolded in the 1930s; driven by the groundbreaking work during electric shock experiments, they hypothesized that inducing controlled seizures might offer therapeutic benefits for psychiatric disorders (Lock, 1994; Prinsloo & Pretorius, 2004). In 1938, they conducted the first electroconvulsive treatment on a patient with acute psychosis, which resulted in a remarkable improvement in symptoms, marking the genesis of ECT as a psychiatric intervention (Prinsloo & Pretorius, 2004). The initial experiments sparked both curiosity and controversy, with subsequent developments including the refinement of techniques, the introduction of anesthesia and muscle relaxants, and the gradual acceptance of ECT as a treatment for severe mental illnesses (Lock, 1994). The pioneering era laid the foundation for the exploration of controlled seizures as a therapeutic tool, setting the stage for the ongoing evolution and utilization of ECT in the field of psychiatry.

The 1940s and 1950s witnessed the rapid expansion of ECT, marking a transformative era in psychiatric treatment. ECT gained widespread popularity and became a cornerstone for addressing various psychiatric disorders, particularly depression and schizophrenia (Metastasio & Dodwell, 2013; Prinsloo & Pretorius, 2004). During the 1940s and 50s, there was a restricted comprehension of mental disorders, and only a limited number of effective therapies were accessible. ECT offered a relatively quick and seemingly effective solution, albeit with significant risks and controversy. The protocol was administered without anesthesia or muscle relaxants, leading to temporary memory loss and sometimes physical side effects (Fink, 2001; Rasmussen et al., 2002). Despite drawbacks, ECT was embraced by many psychiatric institutions due to its efficacy in alleviating symptoms. The rapid expansion was fueled by clinical successes, a greater understanding of anesthesia's role, and the urgency to find effective treatments for debilitating psychiatric conditions (Payne & Prudic, 2009a). However, its indiscriminate application and potential for abuse raised ethical concerns. Moreover, the lack of regulations

surrounding ECT allowed for its widespread use without adequate patient oversight or informed consent (A. Stevens et al., 1996; Yudofsky, 1981). The lack of regulations led to instances of coercion and misuse, contributing to the stigma surrounding the treatment.

In the 1960s and 1970s, ECT underwent widespread use in psychiatric treatment, albeit amidst significant controversy. ECT was often administered without the stringent regulations and informed consent procedures that are standard today. Patients, particularly those in psychiatric institutions, often receive ECT without fully understanding the procedure's potential risks and benefits (Lock, 1994; Taub, 1987). The lack of transparency led to ethical concerns and allegations of abuse within the psychiatric community. Additionally, portraying ECT in popular media, such as films like "One Flew Over the Cuckoo's Nest," further fueled public skepticism and fear surrounding the treatment (Domino, 1983; Payne & Prudic, 2009b). Media portrayals often depicted ECT as a brutal and inhumane practice, contributing to its stigmatization. Despite the controversy, ECT remained a widely used treatment during the 1960s and 1970s, primarily due to a lack of viable alternatives for managing severe psychiatric conditions. The increased scrutiny and advocacy for patient rights led to stricter regulations regarding the use of ECT, including informed consent requirements and limitations on its administration (Livingston et al., 2018; Payne & Prudic, 2009b).

The 1980s and 1990s marked a significant period of reevaluation and modernization for ECT. In response to concerns about its side effects and ethical considerations, researchers and clinicians sought to refine and enhance ECT practices (Abhyankar, 1985). During the 80s and 90s, modifications to electrode placement, waveform, and anesthesia protocols were introduced to improve efficacy and minimize cognitive side effects (Sackeim et al., 1986, 1991). Rigorous studies were conducted to deepen the understanding of the neurobiological mechanisms underlying ECT's therapeutic effects—developing standardized protocols and guidelines to ensure consistent and safe application. The 80s and 90s were an era of scrutiny and refinement

that contributed to the resurgence of interest in ECT, with renewed recognition of its efficacy, particularly in treating severe depression resistant to other interventions (Payne & Prudic, 2009b). The reevaluation and modernization of ECT in the 1980s and 1990s reflected a commitment to optimizing its therapeutic benefits while addressing historical concerns and ethical considerations.

The resurgence of ECT in the 2000s and the present era reflects a renaissance marked by a nuanced understanding, improved techniques, and renewed acceptance. Rigorous research has reaffirmed ECT's efficacy, particularly in cases of severe depression resistant to other interventions (Pagnin et al., 2004; Pearlman, 1991). Standardized protocols and guidelines have been established to ensure patient safety and ethical considerations. Contemporary advancements include the development of modified electrode placement and waveform techniques to enhance therapeutic benefits while minimizing cognitive side effects. Compared to standard sine wave stimulation, the change to an ultra-brief bilateral ECT showed a decrease in remission rates to 35% and significantly minimized cognitive side effects (Sackeim et al., 2008).

Additionally, developments in anesthesia and monitoring allow for precise control and customization of treatment parameters, enhancing patient comfort and safety (Chawla, 2020). The resurgence is accompanied by efforts to destigmatize ECT, emphasizing its evidence-based efficacy and the importance of informed consent. In the current landscape, ECT stands as a specialized and valuable tool in psychiatric treatment, offering hope to individuals facing severe and treatment-resistant neuropsychiatric disorders. Ongoing research and refinement continue to shape the role of ECT in the broader context of mental health care.

Therapeutic Efficacy
Mood Disorders

The primary indication for ECT is severe depression, particularly when other treatments, including medications and psychotherapy, have proven ineffective or are contraindicated. ECT

is considered a viable option for various depressive disorders, including MDD, Bipolar

Depression, and certain types of psychotic depression ("Efficacy and Safety of

Electroconvulsive Therapy in Depressive Disorders," 2003). Several factors contribute to the

effectiveness of ECT in depression. One notable advantage is the rapid onset of action, with

improvement often seen after a few sessions (Subramanian et al., 2022). In a study looking at

253 individuals with MDD, 75% achieved remission after a complete acute course of ECT, with

54% experiencing a reduction in symptoms after three sessions (Husain et al., 2004). Rapid

relief can be crucial for individuals facing severe depressive symptoms that significantly impact

their daily functioning or when immediate intervention is necessary (Lin et al., 2020; M. Patel et

al., 2006; Sienaert et al., 2022). ECT is recommended for individuals with severe symptoms

who exhibit heightened sensitivity to the side effects commonly associated with traditional

pharmacotherapies (Chatham et al., 2022; S. J. Khan et al., 2016; Ward et al., 2018). With

depression affecting 10-20% of pregnant women and limited safe treatment options for both

mother and baby, ECT emerges as a preferred choice, as it poses no additional risk to maternal

health and does not impact the baby's development (Y. M. Hwang et al., 2024; Pearlstein, 2015;

Ward et al., 2018). Not only is ECT a safe alternative for many who can't tolerate the adverse

effects of traditional medicine, but it is the most effective treatment for individuals who have

developed resistance to or intolerance to pharmaceutical drugs. Of the 30% of individuals with

MDD, 48% saw remission after ECT (Heijnen et al., 2010; Zhdanava et al., 2021). Furthermore,

ECT can be a quick and effective treatment for acute manic or mixed episodes in individuals

with BP (Morcos et al., 2021; Yatham et al., 1997). Additionally, individuals with BP are remiss

quicker than those with MDD when treated with ECT (Scheepstra et al., 2022).

Catatonia

       Catatonia is a syndrome linked to various mental health disorders and can also manifest

in conjunction with certain medical conditions. Catatonia is a psychomotor syndrome

characterized by motor and cognitive abnormalities, including stupor, rigidity, and mutism

(Amad, 2023; Edinoff et al., 2020). ECT has been identified as a rapid and highly effective treatment for catatonia, especially when other interventions prove ineffective or when a prompt response is crucial (Amad, 2023; Gandhi et al., 2023). The response rate to ECT is between 80-100% after at least six sessions, even among those without a response to traditional medication. One of the notable advantages of ECT in treating catatonia is its rapid onset of action. While pharmacological interventions may take weeks to show improvement, ECT often significantly reduces catatonic symptoms after just a few sessions (Edinoff et al., 2020; Lloyd et al., 2020; Unal et al., 2017). Rapid relief is particularly crucial in cases where catatonia is associated with severe psychiatric conditions, and the patient's well-being is at risk. The exact mechanisms through which ECT exerts its therapeutic effects in catatonia are not fully understood. Still, the induction of a controlled seizure is believed to produce neuromodulatory changes in the brain that positively influence symptoms.

Adverse Effects

While ECT has evolved significantly to enhance safety and minimize adverse effects, it is essential to acknowledge the potential discomfort associated with the procedure. One of the most common adverse effects experienced by patients is cognitive adverse effects such as short-term memory loss, confusion, and difficulties with attention and concentration. Cognitive effects are often transient and tend to resolve within a few days to weeks after the completion of treatment (Guo et al., 2024; Hammershøj et al., 2022). However, in some cases, individuals may experience more persistent cognitive difficulties, including learning and retaining new information (Guo et al., 2024). The severity of cognitive side effects has significantly reduced with the refinement of stimulation protocol in recent years (Sackeim, 2017).

The seizure triggered by electrical stimulation induces muscle contractions and activates the sympathetic nervous system, potentially leading to adverse musculoskeletal and cardiac effects. Roughly 9% of patients have reported general myalgia that lessens in severity

throughout treatment. Myalgia is usually short-lived and does not result in long-term physical harm (Andrade et al., 2016; Dinwiddie et al., 2010; Haghighi et al., 2016). The addition of muscle relaxers during treatment has significantly diminished the occurrence of myalgia post-ECT. ECT can briefly elevate heart rate and blood pressure during the procedure. Cardiac adverse effects following ECT are relatively rare but can include changes in heart rate, blood pressure, and arrhythmias (Duma et al., 2019). Cardiac effects are typically transient and are closely monitored during ECT sessions to ensure patient safety. However, individuals with pre-existing cardiovascular conditions may be at higher risk for experiencing cardiac complications during or after ECT (Duma et al., 2019; Hermida et al., 2022). Therefore, thorough cardiac evaluation and monitoring are essential before initiating ECT, and adjustments to treatment protocols may be necessary for patients with underlying cardiac issues (Andrade et al., 2016; Hermida et al., 2022).

General adverse effects associated with ECT include dry mouth, nausea, and headaches, which are the results of the anesthetics and anticholinergic drugs used pre-ECT. Adverse effects are self-limiting and dissipate after a few hours (Andrade et al., 2016). Despite the potential for adverse effects, ECT remains a safe and effective treatment option for various psychiatric disorders. The benefits generally outweigh the risks, especially when considering the significant improvement in symptoms and quality of life that many patients experience with ECT.

Comparison Of ECT With Traditional Pharmaceutical Therapies
ECT Vs TCAs

TCAs and ECT are both treatment options for depression, but they differ significantly in their mechanisms of action, efficacy, and side effect profiles. TCAs work by blocking the reuptake of neurotransmitters such as serotonin and norepinephrine, thereby increasing their levels in the brain (Moraczewski et al., 2023). Improvements in mood may occur within the first few weeks of treatment, but it often takes four to six weeks or longer for the full benefits of TCAs

to be realized. They are effective in treating various types of depression. Still, they are often associated with a range of side effects, including sedation, dry mouth, constipation, and cardiac effects such as arrhythmias and orthostatic hypotension (Gillman, 2007; J. Hwang et al., 2008; Moraczewski et al., 2023).

In contrast, ECT is a more invasive treatment that involves the induction of seizures through electrical stimulation of the brain. It is typically reserved for severe, treatment-resistant depression or when rapid symptom relief is needed. Many patients experience significant improvements in symptoms after just a few sessions of ECT, with some reporting relief within days or even hours after treatment (Husain et al., 2004; Scheepstra et al., 2022). ECT is highly effective, with response rates ranging from 70% to 90%, but it can also cause cognitive side effects such as memory loss, confusion, and difficulty concentrating. However, cognitive effects are usually temporary and resolve within a few days to weeks after treatment (Andrade et al., 2016; Haghighi et al., 2016; Hermida et al., 2022).

While both TCAs and ECT can effectively alleviate symptoms of depression, the choice between them depends on various factors, including the severity of symptoms, treatment history, presence of comorbidities, and patient preference. TCAs may be preferred for milder cases of depression or when avoiding invasive treatments. In contrast, ECT may be considered when other interventions have been ineffective or when rapid symptom relief is necessary.

ECT Vs. SSRIs

ECT and SSRIs represent two distinct approaches to treating severe depression, each with its own set of advantages and considerations. ECT is often considered when rapid and robust symptom relief is essential, especially in cases of severe depression that have not responded adequately to other interventions (Sackeim, 2017). ECT induces controlled seizures through the application of electrical currents to the brain, leading to alterations in neuroinflammation and neuroplasticity (Cano & Camprodon, 2023; Glue et al., 1990; Jansson et

al., 2009; Sackeim, 2017). ECT is notable for its rapid onset of action, often producing significant improvements in mood after just a few sessions. The advantages of ECT include its efficacy in cases of treatment-resistant depression and its suitability for individuals who cannot tolerate or do not respond to medications. ECT is particularly effective for severe depressive episodes with features such as psychosis, catatonia, or imminent risk of self-harm (Pearlstein, 2015; Rasmussen et al., 2002; Sackeim, 2017).

SSRIs increase the availability of 5-HT in the brain, which is associated with mood regulation. SSRIs are a first-line treatment for depression due to their ease of use, oral administration, and generally favorable side effect profile. They are often preferred for individuals with less severe depression or those who prefer pharmacological interventions but may take several weeks to exert their full therapeutic effects. ECT is often considered when a rapid response is crucial or other treatments have proven ineffective. SSRIs provide a valuable option for individuals with less acute symptoms or those who prefer a non-invasive approach.

ECT Vs Antipsychotics

ECT and antipsychotic medications represent two distinct yet practical approaches to the treatment of mood disorders, particularly MDD and BP. Both modalities aim to alleviate symptoms and enhance overall functioning, but their mechanisms of action, administration, and potential side effects differ significantly. ECT is a highly effective and rapidly acting treatment for severe mood disorders, especially in cases where individuals are unresponsive to other interventions or experience acute, life-threatening symptoms (Kaliora et al., 2018). Numerous studies have demonstrated the efficacy of ECT in MDD, with response rates ranging from 70-90% in some cases. Additionally, ECT is a first-line treatment for certain subtypes of BP, particularly when rapid stabilization is required during severe manic or mixed episodes. The benefits of ECT include its rapid onset of action, high response rates, and efficacy, even in cases of treatment-resistant depression (Espinoza & Kellner, 2022).

Antipsychotic medications, on the other hand, are commonly used in the treatment of mood disorders, notably BP and psychotic depression. They work by modulating neurotransmitters such as DA and 5-HT, aiming to stabilize mood and reduce symptoms of psychosis. Antipsychotics are often part of maintenance therapy to prevent relapses and maintain stability. In BP, antipsychotics are prescribed to manage manic or mixed episodes. Second-generation antipsychotics, such as olanzapine and quetiapine, have shown efficacy in treating acute episodes and preventing recurrences. In MDD, some atypical antipsychotics are used as adjuncts to traditional antidepressants, especially in cases where individuals do not respond adequately to standard treatments (Keck et al., 2000). The choice between ECT and antipsychotic medications depends on several factors, including the severity of symptoms, the urgency of intervention, individual response to previous treatments, and the presence of specific contraindications or preferences.

ECT Vs. Mood Stabilizers
 Lithium, the classic mood stabilizer, and anticonvulsant medications like valproic acid and lamotrigine are commonly prescribed mood stabilizers to stabilize mood, particularly in BP. Inositol depletion is a proposed mechanism of action for some mood stabilizers, particularly lithium and valproate (Agranoff & Fisher, 2001; Case et al., 2023; Janiri et al., 2021). Mood stabilizers are believed to reduce inositol levels in the brain, thereby influencing intracellular signaling pathways involved in mood regulation. By modulating inositol levels, mood stabilizers may help stabilize mood and prevent manic and depressive episodes in individuals with bipolar disorder (Janiri et al., 2021; Shaltiel et al., 2004; Silverstone & McGrath, 2009). ECT has been linked to the modulation of neuroinflammation and enhancement of neuroplasticity in the brain.

ECT regulates neuroinflammatory pathways and promotes the release of neurotrophic factors that contribute to synaptic remodeling, neuronal survival, and the formation of new neural connections, ultimately leading to improvements in mood and cognitive function (Jinno &

Kosaka, 2008; Limoa et al., 2016; Sepulveda-Rodriguez et al., 2019). Both ECT and mood stabilizers can effectively manage psychiatric symptoms, but they differ in their side effect profiles. ECT may be associated with more acute cognitive and physical side effects related to treatment sessions, whereas mood stabilizers may have more chronic metabolic and endocrine side effects (Andrade et al., 2016; Ferensztajn-Rochowiak & Rybakowski, 2023; Kakunje et al., 2018). ECT offers rapid relief, particularly in severe or treatment-resistant cases of depression or mania, but is typically reserved for acute episodes due to its procedural nature. Mood stabilizers are essential for the long-term management of BP, helping to reduce the frequency and severity of mood swings. They are particularly effective in preventing manic episodes and stabilizing mood over time since their effectiveness often becomes evident over weeks to months of consistent use.

Psychiatric Medications Used In Conjunction With ECT
Mood Stabilizers

The therapeutic efficacy of mood stabilizers as adjunct therapies for ECT is a subject of considerable importance in the management of severe neuropsychiatric disorders, particularly those resistant to conventional treatments. ECT, while highly effective, may be associated with fluctuations in mood and an increased risk of relapse in certain conditions (Johns & Thompson, 1995; Mukherjee, 1993; Sackeim et al., 2001). Mood stabilizers play a crucial role in enhancing the overall effectiveness of ECT and promoting sustained stability, particularly in mood disorders and schizoaffective disorders. Combining ECT with mood stabilizers offers a comprehensive approach, addressing both acute symptoms and long-term management. Mood stabilizers provide continuity of care, reducing the risk of relapse and promoting remission after six months (Brus et al., 2019; Lambrichts et al., 2021; Popiolek et al., 2018; Sackeim et al., 2001). Additionally, they may mitigate some of the cognitive side effects associated with ECT.

Antipsychotics

ECT and antipsychotics serve as complementary strategies in treating severe mental illnesses like schizophrenia and psychotic depression. With its rapid symptom relief, ECT is often used for acute cases or when other treatments fail. Antipsychotics, on the other hand, help manage psychotic symptoms and prevent relapse over the long term. Combining ECT with antipsychotics offers a dual benefit. ECT can quickly alleviate acute negative and positive symptoms, while antipsychotics provide ongoing stabilization and reduce symptom recurrence. The dual benefit of ECT and antipsychotics optimizes treatment outcomes by addressing both immediate crises and long-term management (Haskett & Loo, 2010; Johns & Thompson, 1995; Tharyan & Adams, 2002; W. Wang et al., 2015). Moreover, antipsychotics may help mitigate potential cognitive side effects associated with ECT, enhancing overall tolerability and patient adherence (Haskett & Loo, 2010; Johns & Thompson, 1995). Together, ECT and antipsychotics form a comprehensive treatment approach for severe psychiatric disorders.

Benzodiazepines

Adjunctive use of ECT and benzodiazepines, while feasible in certain situations, requires careful consideration due to potential interactions and effects. Benzodiazepines, like lorazepam or diazepam, are commonly prescribed for anxiety and insomnia and as adjuncts in ECT anesthesia protocols. Benzodiazepines enhance ECT's tolerability by reducing pre-treatment anxiety and promoting sedation during the procedure, improving patient comfort and cooperation. Benzodiazepines can modify seizure thresholds and duration, potentially affecting the efficacy and safety of ECT. Higher doses may be required to induce seizures, leading to adjustments in treatment parameters (Boylan et al., 2000; Chiao et al., 2020). The effect on response rate differs, with some research indicating that benzodiazepines may decrease the efficacy of ECT while others report an increase in efficacy. Contradictory results stem from the drug and stimulation methods used (Delamarre et al., 2019; Jha & Stein, 1996; Nobler & Sackeim, 1993; Shiwaku et al., 2020). Both ECT and benzodiazepines can cause cognitive

side effects, including memory impairment. Concurrent use may exacerbate side effects, although the extent varies among individuals. Benzodiazepines may interact with anesthetic agents used during ECT, influencing their metabolism and effects. Excessive sedation from benzodiazepines may interfere with ECT-induced seizures or lead to over-sedation post-procedure, necessitating cautious dosing (Janjua et al., 2020). Adjunct use of ECT and benzodiazepines can offer benefits in managing anxiety and improving procedural tolerance. However, careful monitoring for adverse effects, adjustments in treatment parameters, and consideration of potential interactions are crucial to ensuring safe and effective treatment outcomes.

Antidepressants

The integration of antidepressants as adjunct therapies with ECT represents a comprehensive approach to the management of severe depression and certain neuropsychiatric disorders. ECT and TCAs serve as adjunct therapies in treating severe depression. With its rapid onset of action, ECT is effective for acute symptom relief, particularly in treatment-resistant cases. When used concurrently during ECT, TCAs can increase therapeutic efficacy, decreasing the number of ECT sessions needed to achieve remission. Long-term effect studies show that when TCAs are used after ECT as a maintenance therapy, TCA's remission rates during a 6-month follow-up decrease from 84% to 60%. Remissions decreased when lithium was added to the cocktail (Kellner et al., 2006, 2016; Sackeim et al., 2001). ECT and TCA combination addresses both acute and chronic aspects of depression, enhancing overall treatment outcomes.

Research on the effects of ECT combined with SSRIs varies depending on the administration time of SSRIs. The use of SSRIs during ECT can increase the duration of the seizure induced by ECT (Baghai et al., 2006). The acute effects of SSRIs used during ECT indicate that SSRIs have no worsening effects on the responsiveness to treatment (Lauritzen et

al., 1996; Mayur et al., 2000). However, when used as a maintenance therapy after ECT, it has

been shown to reduce relapse to 10% after a six-month follow-up (Lauritzen et al., 1996). The

choice, timing, and type of antidepressant medications used in conjunction with ECT should be

carefully considered based on individual patient characteristics, the specific type of depressive

disorder, and potential interactions with anesthetic agents used during ECT.

Mechanism Of Action

The mechanism of action of ECT is complex and not fully elucidated, but it is theorized

to induce therapeutic changes at both neurochemical and neurophysiological levels. The

primary hypothesis is that the induced seizures play a crucial role in the therapeutic effects,

although the exact mechanisms remain subjects of ongoing research.

Neurotransmitter Regulation

Several neurotransmitter systems are believed to be involved in the response to ECT.

The serotonin system plays a crucial role in regulating mood, and its modulation is thought to

contribute significantly to the therapeutic effects of ECT. ECT has been shown to affect

serotonin receptor sensitivity and release, increasing serotonergic activity (Hayakawa et al.,

1993). In addition to its impact on the serotonergic system, ECT has also been found to

influence dopamine levels and receptor function in specific brain regions. Research suggests

that ECT increases dopamine release in the striatum and alters receptor sensitivity, which could

contribute to its therapeutic effects in treating depression (Cumper et al., 2014; Glue et al.,

1990; Landau et al., 2011). ECT may lead to changes in the release of GLU and modulate

receptor activity, contributing to the neuroplastic changes associated with ECT (C. Liu et al.,

2012). Fumagalli and colleagues show that ECS increases phosphorylation of NMDA receptor

subunit NR2B and AMPA subunit GluR-A in rats' hippocampus, enhancing AMPA currents and

reducing NMDA receptor activity. Alterations in neurotransmission collectively contribute to the

observed improvements in mood, cognitive function, and symptom relief, making ECT a

valuable intervention, particularly in cases of severe and treatment-resistant neuropsychiatric disorders.

Neuroendocrine Effects

In addition to the effect on neurotransmission, ECT exerts notable effects on the neuroendocrine system, a complex network of glands and hormones that regulate various physiological processes. The activation of the hypothalamic-pituitary-adrenal (HPA) axis is a key component of the body's stress response and plays a role in the therapeutic effects of ECT (Haskett, 2014). ECT stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH, in turn, triggers the release of cortisol, the primary stress hormone the adrenal gland produces (Kronfol et al., 1991). During ECT, there is a surge in cortisol levels, mimicking the body's response to stress. The surge is transient and typically returns to baseline levels post-treatment. The modulation of cortisol is thought to contribute to the antidepressant effects of ECT, particularly in severe depression, where cortisol dysregulation is often observed (Mickey et al., 2018; Swartz & Chen, 1985). ECT reduces the release of growth hormone (GH) from the pituitary gland. GH is crucial for growth, metabolism, and various physiological functions. The decreased release of GH during ECT suggests a broader impact on neuroendocrine regulation beyond stress response (Pacitti et al., 2011). While the acute stress response induced by ECT is a transient and controlled process, the subsequent hormonal changes contribute to the overall therapeutic effects observed in individuals undergoing ECT. Modulation of neurotransmitters and neuroendocrine activity by ECT can induce alterations in synaptic strength and neural circuitry, consequently influencing neuroplasticity by regulating the brain's formation, maintenance, and pruning of synaptic connections.

Neuroplasticity And Spine Changes

ECT induces significant synaptic changes in the brain, contributing to its therapeutic effects, particularly in treating severe depression. ECT enhances dendritic arborization, dendritic spine density, and spine diversity in regions associated with mood and cognition (Q. Chen et al.,

2018; Hageman et al., 2008; Maynard et al., 2018b; Zhao et al., 2012). Furthermore, ECT has

been found to influence the expression levels of various synaptic proteins. Research indicates

that ECT can upregulate the expression of proteins involved in synaptic transmission and

plasticity, such as synaptophysin, PSD-95, and BDNF (Bolwig & Jørgensen, 1986; Jang et al.,

2017; W. Li et al., 2012; Maynard et al., 2018b). They are essential in facilitating

neurotransmitter release, strengthening synaptic connections, and promoting neuronal survival

and growth. The effects of ECT on spine density and synaptic proteins contribute to restoring

synaptic connectivity and function, which may underlie the therapeutic benefits of ECT.

Neuroinflammatory Effects

ECT has been shown to significantly affect neuroinflammation, a complex process

involving the immune response in the central nervous system. While the precise mechanisms

are not fully understood, ECT appears to modulate inflammatory markers and immune factors,

contributing to its therapeutic effects in certain neuropsychiatric disorders (Guloksuz et al.,

2014).

ECT has been found to exert significant effects on microglia, the immune cells of the

central nervous system. Transient microglia activation in various brain regions, characterized by

morphological changes and increased expression of activation markers in microglia, can be

seen following administration of ECS in rodents (Jansson et al., 2009; Jinno & Kosaka, 2008;

Sepulveda-Rodriguez et al., 2019). Additionally, human studies have shown that ECT increases

macrophage/microglia activation markers in CSF and blood (Yrondi et al., 2018). Activated

microglia release pro- and antiinflammatory cytokines to regulate neuroinflammation. ECT has

been associated with alterations in cytokine levels. (Gay et al., 2021; Mindt et al., 2020). ECT

causes a transient increase in proinflammatory cytokines. Three hours post-treatment, IL-6, and

IL-1β levels increase but return to baseline levels within 24 hours (Lehtimäki et al., 2008). Other

studies have shown that ECT can increase anti-inflammatory cytokines such as IL-10 and TGF-

β (Kartalci et al., 2016). Anti-inflammatory cytokines are crucial in suppressing excessive inflammation, modulating immune responses, and promoting neuroprotection and tissue regeneration. Effects on microglia may contribute to the therapeutic benefits of ECT in treating psychiatric disorders such as depression by promoting neuroplasticity, reducing neuroinflammation, and facilitating neuronal repair and regeneration. However, further research is needed to fully elucidate the mechanisms underlying the interaction between ECT and microglia and their implications for brain function and mental health.

The overall impact of ECT on neuroinflammation leans towards an anti-inflammatory response. ECT has been associated with reduced pro-inflammatory markers and increased anti-inflammatory factors (Desfossés et al., 2021). the shift in the balance of inflammatory processes is thought to contribute to the therapeutic effects of ECT in conditions characterized by neuroinflammatory dysregulation. Conditions such as MDD, BP, and schizophrenia often exhibit aberrant immune responses within the central nervous system. ECT's anti-inflammatory effects may contribute to its efficacy **in neuropsychiatric disorders, where conventional treatments may fall short.**

Microglia
Discovery
Microglia, the resident immune cell of the CNS, were discovered by Pío del Río-Hortega, a Spanish neuroscientist, in the early 20th century. The discovery marked a significant milestone in understanding the CNS's cellular constituents. In the 1910s and 1920s, del Río-Hortega utilized silver staining techniques that allowed for the visualization of cells in the CNS with unprecedented clarity (Boullerne & Feinstein, 2020). He identified a distinct cell type characterized by a unique morphology through meticulous observations—small cells with numerous fine processes radiating from a small cell body. Initially referred to as "third elements," del Rio-Hortega coined the term "microglia" to describe them, highlighting their diminutive size compared to other glial cells (Boullerne & Feinstein, 2020; C. Kaur et al., 2001).

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Del Río-Hortega's studies not only defined the morphological characteristics of microglia but also provided insights into their dynamic behavior. He observed that microglia could transform their morphology in response to various stimuli, transitioning between a ramified, surveillant state and an amoeboid, activated state. Recognizing their immune-like functions, del Río-Hortega postulated that microglia played a role in the defense and maintenance of the CNS (Ginhoux et al., 2013; Rezaie & Male, 2002).

Subsequent advancements in immunohistochemistry and molecular biology techniques have further refined our understanding of microglia, revealing their diverse functions in neuroinflammation, synaptic modulation, and neuroprotection. Del Río-Hortega's seminal discoveries laid the foundation for the exploration of microglial biology, opening avenues for research that continue to uncover the intricate roles of microglia in health and disease.

Development

Microglia are integral to brain health, playing roles in immune response, synaptic pruning, and neural development. The origin of microglia can be traced back to the yolk sac, a crucial site for early hematopoiesis. Around mice embryonic day 8.5 and the third week of human gestation, primitive myeloid cells emerge from the yolk sac and embark on their migratory path toward the developing brain (Ginhoux et al., 2013; Takahashi & Naito, 1993). Precursor cells traverse the developing circulatory system, reaching the brain through intricate routes. Once at the brain, microglial precursors penetrate the neural tissue, marking the initiation of colonization (Takahashi & Naito, 1993).

Guided by chemotactic signals and molecular cues, microglia actively navigate the developing brain's intricate architecture. They respond to gradients of signaling molecules, ensuring precise localization within distinct brain regions (Kierdorf et al., 2013; Mizutani et al., 2012). Microglia undergo further maturation as they populate the neural tissue, transitioning from an amoeboid to a ramified morphology equipped with highly branched processes. The

migration and subsequent maturation are essential for microglia to fulfill their roles in immune

surveillance, synaptic pruning, and overall maintenance of neural homeostasis throughout an

individual's life (Ginhoux et al., 2013; Takahashi & Naito, 1993). The embryonic journey lays the

foundation for microglia's multifaceted roles in maintaining brain homeostasis, responding to

insults, and actively participating in sculpting neural circuits critical for proper brain function.

Morphology And Function
Morphological Diversity
Microglia are pivotal in maintaining homeostasis and responding to various pathological

conditions. The morphological diversity of microglia is a crucial aspect that reflects their

functional versatility. Microglia exhibit a spectrum of phenotypes, ranging from a ramified resting

state to an activated amoeboid form, each associated with distinct functions. In their resting

state, microglia display a ramified morphology characterized by small cell bodies and numerous

thin processes extending in multiple directions (Hanisch & Kettenmann, 2007b; Kettenmann et

al., 2011). The surveillance phenotype allows them to monitor their microenvironment

continuously for signs of injury or infection. Microglia undergo rapid morphological changes

upon encountering a pathological stimulus, transitioning into an activated state. Activated

microglia retract their processes and adopt an amoeboid morphology, with enlarged cell bodies

and fewer, thicker processes (Hanisch & Kettenmann, 2007b; Jansson et al., 2009). The

transformation facilitates migration to the site of injury or inflammation and enables them to

phagocytose pathogens, cellular debris, and damaged neurons.

Additionally, activated microglia release various pro-inflammatory and anti-inflammatory

cytokines, contributing to the immune response and tissue repair (Hanisch, 2002; Hanisch &

Kettenmann, 2007b; Kettenmann et al., 2011; Wolf et al., 2017). Microglia morphology is tightly

linked to their dynamic functions in immune surveillance, inflammation, and neuroprotection.

Furthermore, recent studies have identified a continuum of intermediate morphologies,

highlighting the complexity of microglial activation states. Factors such as the type and

magnitude of the stimulus, as well as the microenvironment, contribute to the heterogeneity in microglial morphology (Paolicelli et al., 2022; B. Stevens, 2003).

Surveillance and Immune Response

The primary role of microglial surveillance is to promptly detect any signs of disturbance, injury, or potential threats within the CNS. Microglia possess an array of receptors, including toll-like and purinergic receptors, enabling them to recognize various molecular patterns associated with pathogens, damaged cells, or other abnormalities (Hanisch & Kettenmann, 2007b). The molecular sensing capability positions microglia as first responders to any perturbations in the CNS. The surveillance function of microglia extends beyond pathogen detection to include the identification of synaptic activity and neural network dynamics (Paolicelli et al., 2022; Wolf et al., 2017). Microglia actively interact with neurons and synaptic elements, participating in synaptic pruning during development and refining neural circuits throughout life (B. Stevens, 2003; Tzioras et al., 2021). The bidirectional communication between microglia and neurons highlights the integral role of microglia in sculpting and modulating neural connectivity.

Neurotransmitter Regulation

The role of microglia as simple immune cells has expanded to encompass a dynamic involvement in the regulation of neurotransmitters, a critical aspect of neuronal communication. Microglia actively participate in the modulation of GLU, the primary excitatory neurotransmitter. Activated microglia maintain synaptic balance under normal conditions by clearing excess GLU (Iovino et al., 2020; Y.-K. Kim & Na, 2016). Under pathological conditions or upon activation, microglia activation releases pro-inflammatory cytokines and reactive oxygen species, disrupting GLU homeostasis. GLU dysregulation is implicated in neurodegenerative disorders and neuropsychiatric conditions, including schizophrenia.

Consequently, individuals with some neurodegenerative disorders have decreased expression of GLU receptors, causing the excess release of cytokines by microglia, ultimately causing more cell death (Noda, n.d.). Also, microglia express metabotropic GLU receptors and

can release GLU, contributing to excitotoxic damage to neurons. In Parkinson's Disease, chronic inflammation is accompanied by excess GLU signaling, leading to the dysfunction of DA signaling via DA neurons (Iovino et al., 2020).

DA, a neurotransmitter associated with reward and motivation, is also influenced by microglial activity. Microglia express dopamine receptors and enzymes involved in dopamine metabolism, allowing them to respond to and influence dopamine levels in the brain. High dopamine levels induce neuroinflammation by activating the dopamine receptor on microglia D3. Low dopamine levels induce the anti-inflammatory processes in microglia by activating microglial DA receptors D1 and D2 (Pike et al., 2022; Vidal & Pacheco, 2020). Moreover, in response to inflammatory stimuli, activated microglia can produce reactive oxygen species and pro-inflammatory cytokines that impair dopamine neuron function and promote neurodegeneration in conditions such as Parkinson's disease (Iovino et al., 2020; Pajares et al., 2020). Drug use activates microglia, leading to dopamine-mediated neuroinflammation and toxicity (Kohno et al., 2019; Shaerzadeh et al., 2018). Furthermore, studies have shown that the use of anti-inflammatory medications can attenuate substance abuse (Kohno et al., 2019).

5-HT, a neurotransmitter crucial for mood regulation, is another target of microglial influence. While microglia do not directly synthesize serotonin, they express serotonin receptors, particularly 5-HT2A and 5-HT2B subtypes (Glebov et al., 2015). Activation of 5-HT receptors on microglia influences their morphology, motility, and release of inflammatory mediators (Albertini et al., 2023; Kolodziejczak et al., 2015). Additionally, serotonin can regulate microglial activation states, with evidence suggesting that serotonin can either enhance or suppress microglial inflammatory responses depending on the context (Albertini et al., 2023; Glebov et al., 2015; Lu et al., 2021). Dysregulation of microglial serotonin signaling has been implicated in various neuropsychiatric disorders, including depression, schizophrenia, and autism spectrum disorders.

The cross-talk between microglia and neurotransmitter systems microglia modulate neurotransmitter functions is essential for unraveling the neurobiological underpinnings of various neurological and psychiatric disorders, offering potential targets for therapeutic interventions to restore balance and mitigate the impact of dysregulated neurotransmission.

Neurotrophic Support

Microglia are increasingly acknowledged for their ability to provide neurotrophic support to neurons, influencing neuronal survival, growth, and synaptic plasticity. Microglia are a source of various neurotrophic factors, including NGF, IGF-1, and BDNF. Neurotrophic factors exert trophic effects on neurons, promoting their survival, neurite outgrowth, and synaptic connectivity (Bhalla et al., 2022; Bracci-Laudiero & De Stefano, 2016; Colucci-D'Amato et al., 2020). Microglial-derived BDNF has been implicated in enhancing synaptic plasticity and cognition, highlighting the neurotrophic influence of microglia on neural networks (Colucci-D'Amato et al., 2020; Ding et al., 2020; Parkhurst et al., 2013). Furthermore, microglia actively participate in neurodevelopmental processes, influencing neuronal differentiation and migration. During embryonic and early postnatal stages, microglia interact with developing neurons, providing trophic support critical for proper circuit formation (Bracci-Laudiero & De Stefano, 2016; Ferraguti et al., 2023; Rodríguez-Carrillo et al., 2023). The intricate crosstalk between microglia and neurons involves releasing neurotrophic factors and modulating cellular signaling pathways, contributing to establishing functional neural networks. In the context of injury or neurodegenerative conditions, activated microglia can release neurotrophic factors as part of a reparative response, aiming to support neuronal survival and regeneration (Y. Wang et al., 2022; Yan et al., 2022; J. Zhang et al., 2021).

Neuroinflammation Processes

Pro-inflammation and anti-inflammation represent two opposing states of microglial activation, crucial in regulating immune responses within the CNS. Pro-inflammation involves the activation of microglia in response to various stimuli such as infection, injury, or

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neurodegeneration (Graeber & Streit, 2010). Activated microglia release pro-inflammatory

cytokines, chemokines, and reactive oxygen species to initiate the immune response, clear

pathogens, and remove cellular debris (Graeber & Streit, 2010). The pro-inflammatory state is

essential for defending against threats to CNS homeostasis and promoting tissue repair.

However, sustained or excessive pro-inflammatory responses can damage neurons and

exacerbate neurodegenerative diseases (Rodríguez-Gómez et al., 2020).

On the other hand, anti-inflammatory processes involve the resolution of inflammation

and the promotion of tissue repair within the CNS. Microglia can adopt an anti-inflammatory

phenotype characterized by the release of anti-inflammatory cytokines and growth factors and

the expression of neuroprotective molecules (Aloisi, 2001). Anti-inflammatory microglia are

crucial in limiting tissue damage, promoting neurogenesis, and restoring CNS function. The

balance between pro- and anti-inflammatory microglial activation is essential for maintaining

CNS homeostasis and preserving neurological function. Dysregulation of microglial activation

can contribute to the pathogenesis of various neurological disorders (Tremblay et al., 2011),

Pro-Inflammatory Functions
Activated microglia release a repertoire of proinflammatory mediators, including IL-6, IL-

1β, and TNF-α cytokines. Proinflammatory cytokines serve as potent signaling molecules,

orchestrating a cascade of immune responses within the CNS. Additionally, microglia produce

nitric oxide and ROS as part of their proinflammatory arsenal, eliminating pathogens and

damaged cells (Werneburg et al., 2017). The pro-inflammatory functions of microglia are

instrumental in the clearance of invading microorganisms and cellular debris. They actively

participate in the phagocytosis of pathogens and dead or dying cells, playing a crucial role in

resolving acute insults to the CNS.

Furthermore, proinflammatory microglia contribute to the activation of astrocytes and

recruitment of peripheral immune cells, fostering a comprehensive immune response to combat

threats within the neural microenvironment (L.-R. Liu et al., 2020; Orihuela et al., 2016; Paolicelli et al., 2022; Werneburg et al., 2017). While proinflammatory microglial responses are pivotal for the defense against acute insults, dysregulation of proinflammatory functions can lead to chronic neuroinflammation, a hallmark of neurodegenerative diseases. The sustained release of proinflammatory cytokines and neurotoxic molecules may exacerbate tissue damage, impair synaptic function, and contribute to neuronal dysfunction (Fakhoury, 2020; G. Kaur & Singh, 2021; Sun et al., 2023; Zelic et al., 2021).

Anti-Inflammatory Functions
Microglia secrete anti-inflammatory cytokines, such as IL-10, and the expression of molecules associated with tissue repair and resolution of inflammation. Anti-inflammatory microglia attenuate immune responses and limit collateral damage to surrounding neural tissue (Werneburg et al., 2017). One of the primary anti-inflammatory functions of microglia is the clearance of debris and apoptotic cells. Microglia efficiently phagocytose cellular remnants and damaged neurons, preventing further release of pro-inflammatory signals and facilitating the resolution of inflammation. Microglial phagocytic activity has been observed in both preclinical models and post-mortem human brain studies. Aberrant phagocytosis may lead to the accumulation of cellular debris and compromised clearance of apoptotic cells, contributing to chronic inflammation and potential disruptions in neural connectivity (Westman et al., 2020).

Additionally, anti-inflammatory microglia can release neurotrophic factors, promoting neuronal survival and regeneration (Z. Chen & Trapp, 2016; Fu et al., 2014; He et al., 2020; Tang & Le, 2016). Also, microglia can release anti-inflammatory mediators, including transforming growth factor-beta (TGF-β) and IL-10, which exert immunomodulatory effects and facilitate the transition to an anti-inflammatory state. Microglial involvement in regulating the BBB further underscores their anti-inflammatory functions. Microglia participate in the maintenance of BBB integrity, preventing the infiltration of peripheral immune cells and limiting

the escalation of neuroinflammation (Haruwaka et al., 2019; Ronaldson & Davis, 2020; Z. Yu et al., 2022). The balance between pro-inflammatory and anti-inflammatory microglial phenotypes is crucial for maintaining immune homeostasis within the CNS. In neuropsychiatric disorders, alterations in microglial anti-inflammatory functions may contribute to chronic neuroinflammation and impact neurotransmitter systems implicated in mood regulation and cognition.

Synaptic Modulation and Synaptic Pruning

Microglia play a crucial role in synaptic pruning—a dynamic process essential for sculpting neural circuits during development and maintaining synaptic homeostasis throughout life (Paolicelli et al., 2011; Schafer et al., 2012a). Synaptic pruning refers to the selective elimination of excess or less active synapses, optimizing the efficiency and precision of neural circuits. Microglia actively survey the synaptic landscape during early brain development, interacting with neurons and their synapses. The process involves recognizing and engulfing weak or redundant synapses by microglial phagocytosis (Hanisch & Kettenmann, 2007b; Lehrman et al., 2018; Paolicelli et al., 2011). The targeted removal of synapses contributes to the refinement of neural circuits, allowing for the establishment of appropriate synaptic connections and the elimination of excessive or aberrant synapses.

The molecular mechanisms underlying microglia-mediated synaptic pruning involve a complex interplay of signaling molecules, including complement proteins and various receptors expressed on the surface of microglia (Hong & Stevens, 2016; Lehrman et al., 2018; Schafer et al., 2012a). Complement-mediated tagging of synapses facilitates the identification of targets for elimination, marking them for subsequent phagocytosis by microglia (Hong & Stevens, 2016; Schafer et al., 2012a; B. Stevens, 2003). Phagocytosis ensures a fine-tuned balance between synapse formation and elimination, which is critical for developing functional neural networks. Aberrant microglial activity may lead to either excessive or insufficient synaptic pruning, contributing to synaptic abnormalities observed in many neuropsychiatric disorders. Post-

mortem studies of the brains of individuals with neuropsychiatric disorders have revealed altered patterns of synaptic density and aberrant microglial activation (Germann et al., 2021). In schizophrenia, for example, disruptions in synaptic connectivity and alterations in the expression of genes related to synaptic pruning have been observed (Tzioras et al., 2021). Excessive pruning in neuropsychiatric disorders leads to dysregulation of behavior, memory loss, etc (Andoh et al., 2019; Deng et al., 2024; Sellgren et al., 2019; Y.-L. Wang et al., 2018).

The dysregulation of microglial-mediated synaptic pruning can contribute to synaptic imbalances, disrupted neural circuitry, and aberrant connectivity observed in neuropsychiatric disorders (Cardozo et al., 2019). Synaptic modulation by microglia involves a sophisticated interplay between microglia and the synapses they surveil. Microglia express an array of receptors that enable them to detect changes in synaptic activity, including neurotransmitter release and alterations in synaptic strength (Schafer et al., 2012a, 2013). Upon sensing shifts in the neural microenvironment, microglia respond by releasing signaling molecules, such as cytokines and chemokines, influencing the activity and plasticity of neighboring synapses (Paolicelli et al., 2011; B. Stevens, 2003; Wolf et al., 2017). LTP and LTD facilitate swift modifications in the efficacy of individual synapses triggered by particular temporal sequences of synaptic activity. Microglia can enhance LTD by inducing the internalization of GLU AMPA receptors following activation of glial NMDA receptors (Collingridge & Peineau, 2014). Signals like adenosine triphosphate (ATP) are released by neurons during synapse activation. ATP is then degraded to adenosine by microglia, which activates the adenosine receptor to prevent hyperactivity (Badimon et al., 2020). Dysregulated microglia activation leads to synapse abnormalities and is associated with many neuropsychiatric disorders, including autism, OCD, and schizophrenia (Derecki et al., 2012; Hashimoto, 2008; Monji et al., 2009; Morgan et al., 2010). Elucidating the intricacies of microglial-mediated synaptic pruning holds promise for

understanding both normal brain function and the pathophysiology of neurodevelopmental and

neurodegenerative disorders.

Table 1: Summary Of Neuropsychiatric Treatments

Summary of Neuropsychiatric Treatments				
Treatment	Year	Primary Mechanism of Action	Therapeutic Use	Side Effects
Anti-Psychotics	1954	Block D2 receptor Block 5HT2A receptor (2nd gen)	Schizophrenia Treatment-resistant Depression BPD Aggression in children with ASD	Extrapyramidal symptoms Acute Dystonia Tardive Dyskinesia Weight gain Increased Appetite Alterations in lipid and glucose metabolism Sedation Coginitive impairments Hyperprolactinemia QT interval prolongation Orthostatic Hypotension Neuroleptic Malignant Syndrome Oculogyric Crisis
Electroconvuslive Therapy (ECT)	1938	Exact mechanism unknown	Depression OCD Schizophrenia Catatonia	Temporary memory loss Brief elavated heart rate Muscle tiffness and soreness Headache Brief elevated blood pressure Short-term confusion and disorientation Nausea Jaw pain

Monoamine Oxidase Inhibitors (MAOIs)	1951	Block monoamine oxidase enyzme increasing monoamine concentration	MDD anxiety disorders	Hypertension dry mouth blurred vision constipation orthostatic hypotension insomina agitation anxiety
Mood Stabilizers	1949	Downregulation of the inositol transporter	Mania BPD MDD Neuropathic Pain Diabetic Neuropathy Postherpetic Neuralgia Impulse control disorders Anxiety Disorders	Weight Gain Changes in libido Hypothyroidism Tremors Ataxia Cognitive difficulties Dyslipidemia Insulin Resistance Sexual Dysfunction Alterations in reproductive hormones Renal impariments (nephrogenic diabetes; chronic kidney disese
Psilocybin	Natural: 9000-7000 BC Synthetic: 1958	5HT2A receptor agonist Trkβ receptor agonist	Depression Anxiety PTSD Addition	Nausea Increased heart rate Change in blood pressure Anxiety Confusion Paranoia Feeling of fear and discomfort

Tricyclic Antidepressants (TCAs)	1959	Block reuptake pump of neurotransmitters (norepinephrine, 5-HT, muscarinic acetylcholine, Histamine (H1))	MDD GAD chronic pain neuropathic pain diabetic neuropathy fibromyalgia chronic headaches OCD enuresis (pediatric)	Dry mouth blurred vision constipation urinary retention tachycardia drowsiness fatigue orthostatic hypotension weight gain increased risk of arrhythmias and other cardiac issues cognitive impairments sexual dysfunction
Selective 5-HT Reuptake Inhibitors (SSRIs)	1987	Block 5-HT transporter (SERT)	MDD Anxiety disorders OCD PTSD chronic pain premenstrual dysphoric disorder certain eating disorders	Nausea gastroinstentinal distrubance headaches, insomnia sexual dysfunction weight changes drowsiness fatigue 5-HT syndrome

Chapter III: Methods And Materials

Animals

C57BL/6J mice from the Jackson Laboratory were used in the present study. Animals were group-housed in the University of Nevada, Las Vegas AAALAC-approved animal facility, with a 12-hour light/dark cycle. They were allowed unlimited access to food and water. Animal care and procedures were completed following The Institutional Animal Care and Use Committee (IACUC) guidelines at the University of Nevada, Las Vegas.

Electroconvulsive Shock

The electroconvulsive shock was administered using standard auricular electrodes and a Ugo Basile pulse generator (number 74100; Ugo Basile) with adjustable settings for frequency, pulse width, duration, and current. The shock parameters were set at 100 pulse/s frequency, 3 ms pulse width, 1 s shock duration, and the current was set at 0 mA, 25 mA, 35 mA, or 50 mA, accordingly. Shock parameters were chosen based on their ability to produce tonic-clonic seizures, with 50 mA always producing a seizure, 35 mA producing a weaker seizure, and 25 mA producing no seizure. Before treatment, mice were anesthetized by inhalation of isoflurane and remained anesthetized throughout the procedure.
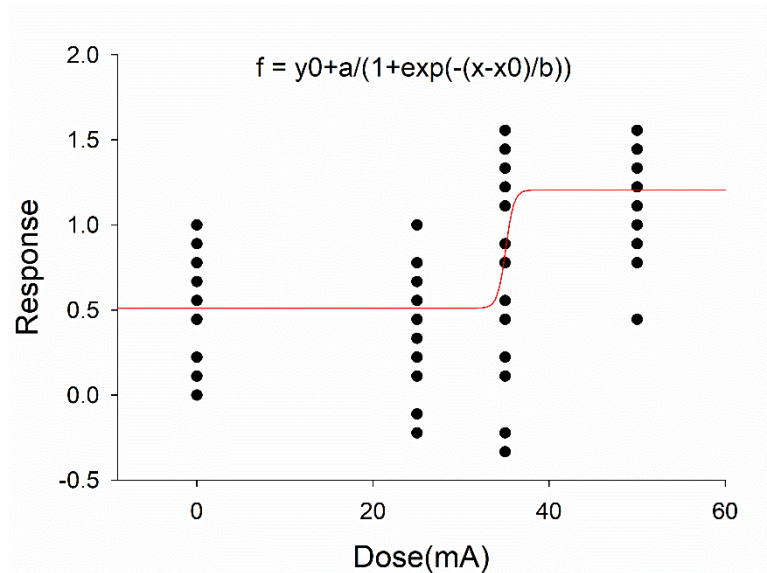
Figure 2: Dose Respone Curve Electroconvulsive Shock

Pharmacology

Psilocybin (Cayman) was prepared in saline and administered intraperitoneally according to the animal's weight to achieve doses at 1.5 and 2.0 × 10−5 mg kg−1 dose. Psilocybin was administered 24 hrs after ECS.

Immunohistochemistry

Animals were individually anesthetized via isoflurane and transcardially perfused with periodate-lysine-paraformaldehyde (PLP) fixative following a wash with phosphate buffer. After fixation and removal, brains were cryo-protected in a 30% sucrose solution. Coronal sections were cut at 40μm on a microtome and stored in a polyvinylpyrrolidone

and ethylene glycol-based cryoprotectant at -20 degrees Celsius before staining. Sections were washed three times in PBS solution at ten-minute intervals, placed in 5% lysine and 5% sodium meta-periodate for fifteen minutes, and again washed three times in PBS solution at ten-minute intervals before being placed in 1% bovine serum albumin (BSA) and 10% normal goat serum (NGS) blocking solution for 2 hours. After blocking, sections were placed in a modified blocking solution (1% BSA and 2% NGS) containing the primary antibody combinations and incubated in a humidity chamber overnight.

At least twelve hours later, sections were washed three times in PBS solution at ten-minute intervals and then placed in the secondary solution for 2 hours. The secondary solution consisted of a modified blocking solution (1% BSA and 2% NGS) containing the Alexa-tagged secondary antibody combinations. Sections were washed in PBS three times and were mounted onto slides with a Fluoromount-G with DAPI mounting medium.

Golgi-Cox

Mice were anesthetized using isofluorane. Brains were removed and placed in 20 ml Golgi–Cox solution (Gibb & Kolb, 1998). The brains were stored in the dark for ten days and then moved into 30% sucrose. The brains sat in the dark until fully saturated (2–5 days) before sectioning. The brains were mounted on a sectioning stage and covered with 6% agarose. The vibratome reservoir was filled with 8% sucrose to a level that covered the sectioning blade. The vibratome speed and amplitude were set at 3.2, the midpoint on both scales. Sections (200 μm) were saved and placed on 2% gelatinized microscope slides. The sections were kept wet during sectioning. Once all sections of interest were collected and placed on the slides, the sections were pressed onto the slides by applying pressure to the slides with bibulous paper. Blotted slides

were kept in a humidity chamber until they were stained. Slides were placed in a staining tray and processed in the following manner: distilled water for 1 min, ammonium hydroxide for 30 min, distilled water for 1 min, Kodak Fix for Film for 15 min, distilled water for 1 min, 50% ethanol, 70% ethanol, and 95% ethanol for 1 min each, 100% ethanol for 5 min thrice, a solution of 1/3 chloroform, 1/3 HemoDe and 1/3 100% ethanol for 10 min and HemoDe for 15 min twice. Stained slides were covered in Permount and then coverslipped.

Chapter IV: Results

Dose-Dependent Effects On Microglia Morphology And Neuron Dendritic Arborization And Spine Density

To determine if ECS applied at different amperages could differentially affect microglia morphology, tissue from animals treated with ECS was stained for IBA1, a biomarker for microglia (Fig3A), and the morphology of IBA1+ cells was analyzed. Analysis of microglia branching morphology indicates that ECS alters microglia branching specifically ($p<0.001$). A pairwise comparison shows that 50 mA significantly reduced the number of microglia branches (Fig.3B, N = 20+ cells, control: $p<0.001$; 25 mA: $p<0.001$; 35 mA: $p=0.001$). Sholl analysis of microglia branches shows significant differences between treatment and branch order. Low amperage of ECS does not change microglia branch morphology, high amperage significantly decreases branch length, and 35 mA decreases the number of short branches but maintains the longer branches (Fig.3C, dose: $p<0.001$; amperage: $p<0.001$; dose x amperage: $p<0.001$). With changes to their branching, we investigated whether those changes were coupled with changes in cell volume. Results from a one-way ANOVA show that there is a significant difference between groups (Fig.4A, $p = 0.021$), but analysis of endfeet volume indicates there could be a slight increase in endfeet volume (Fig.4)

To determine if there are any dose-dependent changes in neural plasticity following administration of ECS, tissue from animals were treated with a low (25 mA), medium (35 mA), or high (50 mA) amperage were Golgi-Cox stained (Fig.5). Two way ANOVA of sholl analysis show that there is a dose-dependent change to neuronal dendritic arborization. 25 mA and 50 mA had no significant change in the number of dendrites near the soma but significantly increased dendrites 150 um from the soma. 35 mA caused a significant increase in the number of dendrites regardless of distance (Fig.5B, N = 20+, dose: $p<0.001$; distance: $p<0.001$; dose x distance: $p<0.001$). Alterations in dendrites indicate that ECS increases connectivity in the PFC.

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Dendritic spines are the functional communication unit in neurons, so to further validate the alteration in connectivity, 10 um sections of dendrites were analyzed to determine spine density and diversity (Fig.6A). Results indicate that there was no overall change in the number of spines following administration of ECS (Fig.6B, N = 75, p = 0.023). Spines are categorized into different types based on morphologies that indicate the stability of their synaptic connections. A two-way ANOVA results indicate a dose-dependent change in spine type density (p<0.001). Results show that application of ECS significantly reduces the number of mushroom spines compared to controls (Fig.6C, 25 mA: p<0.001; 35 mA: p<0.001; 50 mA: p<0.001). Medium and high doses of ECS significantly decrease mushroom compared to low doses of ECS (35 mA: p,0.001; 50 mA: p<0.001). Analysis of filopodia shows that 35 mA increases the number of filopodia spines compared to control and other ECS groups (Fig.6D, control: p>0.001; 25 mA: p>0.001; 50 mA: p>0.001). Results found that 50 mA increases thin spine density compared to control (Fig.6E, p>0.001). Additionally, all doses of ECS also increased the number of stubby compared to control (Fig.2F, 25 mA: p<0.001; 35 mA: p<0.001; 50 mA: p<0.001). There was no change to the number of branched spines following ECS (Fig.6G)
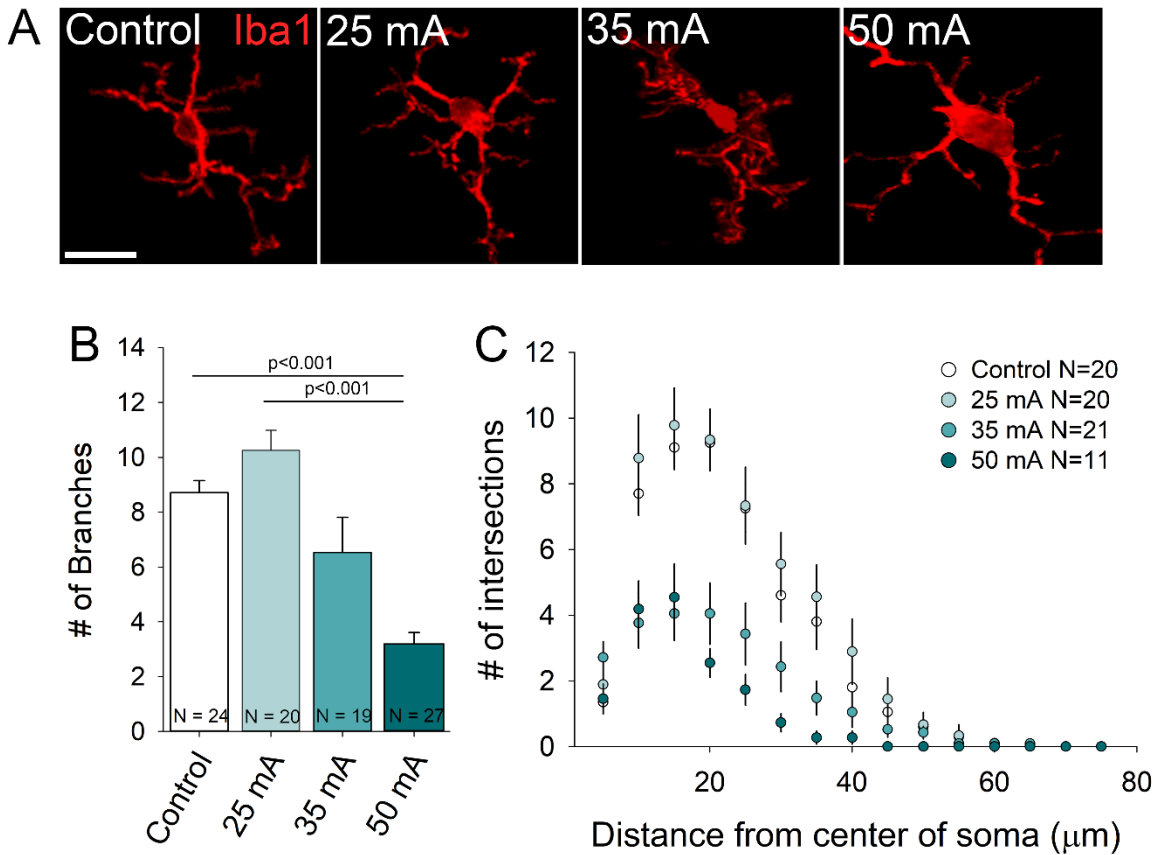
Figure 3: Changes In Microglia Morphology Following ECS Administration At Different Amperages. A) Representative confocal images of immunohistochemically stained Iba1+ cells. Scale bar = 20 um B) Quantification of the average number of branches each IBA1+ cell has indicates that as the dose of ECS increases, the fewer branches Iba1+ cells have. C) Quantification of sholl analysis of Iba1+ cells indicates that 35mA retains the longer branches. D) Quantification of the total cell volume following treatment indicating that 50 mA of ECS significantly decreases the total volume of Iba1+ cells. E) Quantification of Iba1+ cell endfeet volume shows that only 35mA increases the endfeet volume of cells. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant
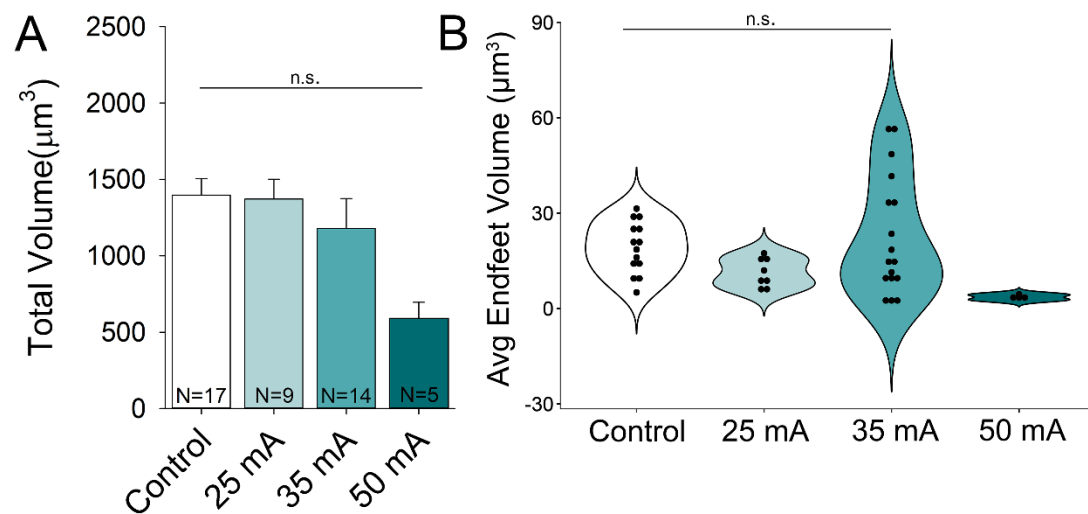
Figure 4: Microglia Volume Changes Following Administration Of ECS At Different Amperages.
A) Quantificaiton of total cell volume showing ECS does not change the total cell volume of microglia.
B) Quantification of the average endfeet volume showing endfeet volume does not change following
administration of ECS at different doses. All graphs plot mean and standard error. P values from
ANOVA or subsequent t-test. n.s. = not significant
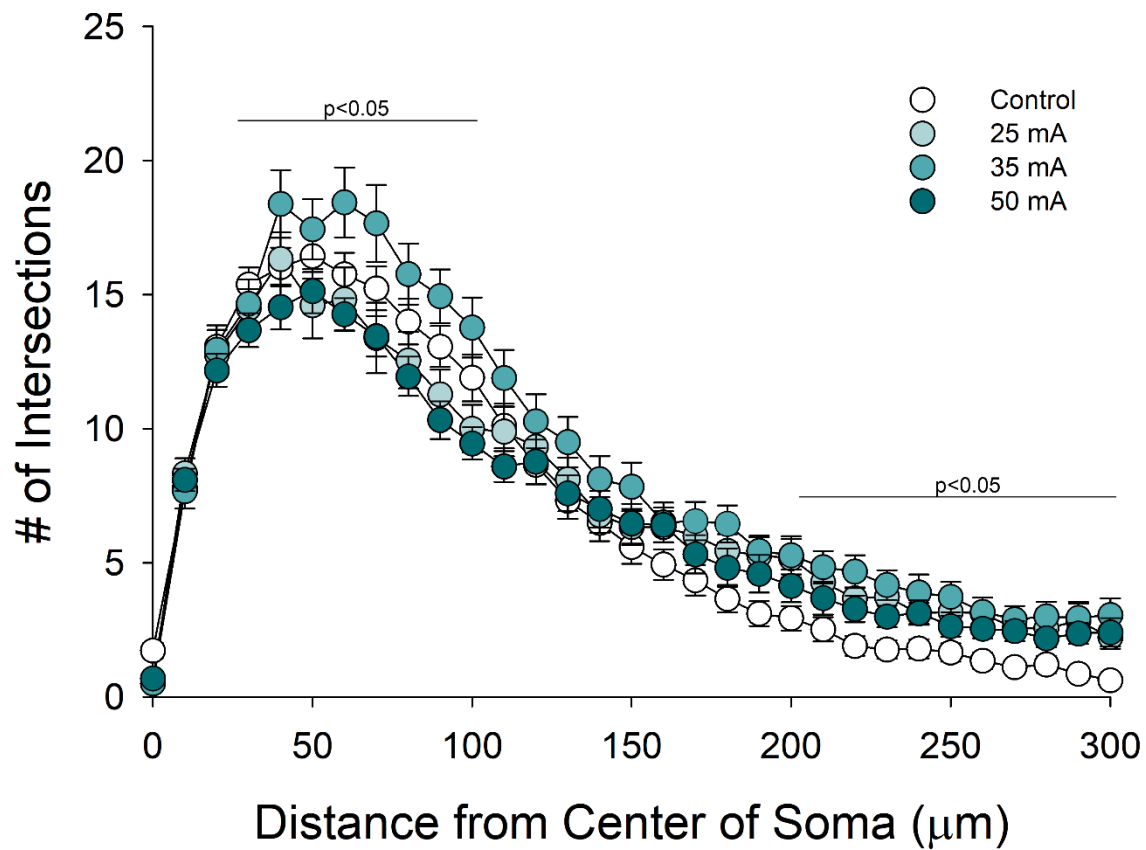
Figure 5: Changes In Dendritic Arborization Following ECS At Different Amperages. A) Sholl analysis of neurons indicating that all doses of ECS increases dendritic length and 35mA also increases the number of short dendrities. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant
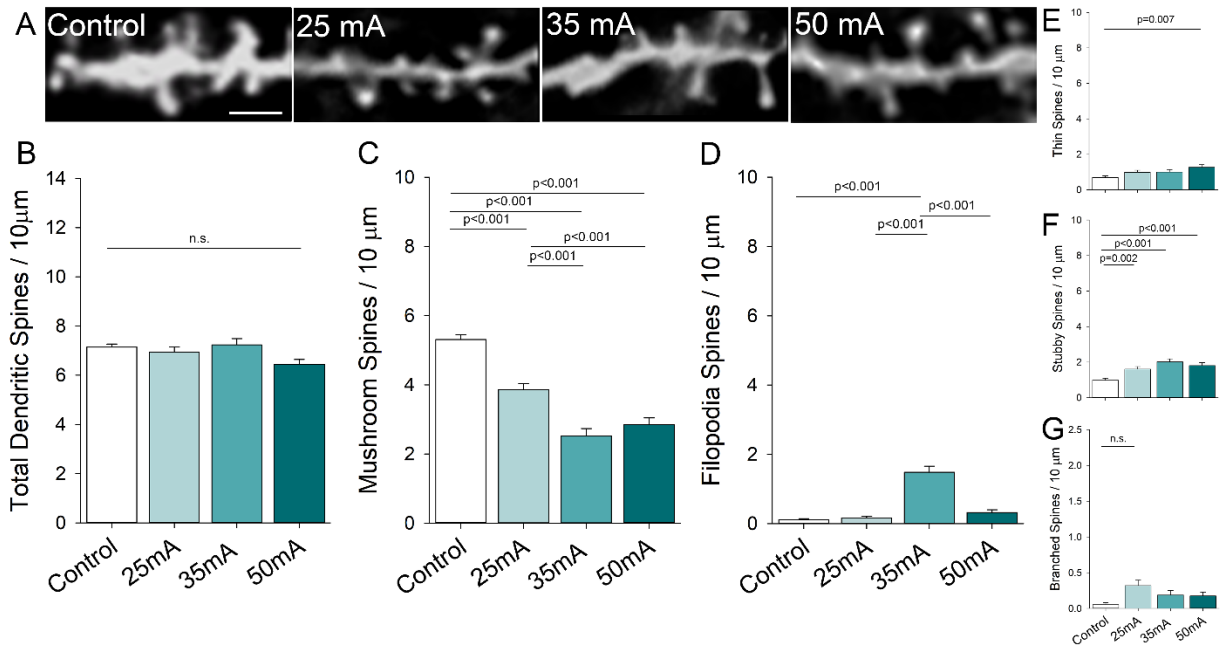
Figure 6: Changes In Dendritic Spine Density And Diversity Following ECS At Different Amperages. A) Representative images of 10 um sections of neuronal dendrites from control mice and those treated with ECS at 25, 35 and 50 mA. Scale bar = 2 um B) Quantification of total spine density within 10 um dendritic segment showing that ECS does not alter total spine density regardless of dose. C) Quantification of mushroom spine density showing all treatments decreased mature spine density. D) Quantification of filopodia spine density showing ECS increases increases filopodia spine density at 35mA. E) Quantification of thin spine density indicating that all treated groups, regardless of dose, increased thin spine density. F) Quantification of stubby spine density showing that low and medium doses of psilocybin increase stubby spine density. G) Quantification of branching spines showing no group alters branched spine density. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant

**Dose-Dependent Changes To Neuron Dendritic Arborization And Spine Density**

        To determine if Psilocybin causes dose-dependent changes in neural plasticity, tissue from animals treated with 1.5 mg/kg (low) or 2.0 mg/kg (high) of Psilocybin were stained with Golgi-Cox (Fig.7A). Two-way ANOVA of sholl analysis indicates there is a dose-dependent change in dendritic arborization following psilocybin administration. The low dose of psilocybin increases the dendrites within 150 um from soma. A high dose of psilocybin increases the number of dendrites over 150 um from soma. (Fig.7B, N = 20+, dose: $p<0.001$; distance: $p<0.001$; dose x distance: $p<0.001$). Arborization changes suggest circuitry alterations; hence, assessing spine density becomes crucial as spines serve as the functional components of neurons (Fig.8). One-way ANOVA results indicate that there is a significant difference between groups ($p<0.001$) and both doses of psilocybin significantly increase total spine density (Fig.8B, N = 75, 1.5 mg/kg: $p<0.001$; 2.0 mg/kg: $p=0.019$). When we analyzed the effects on individual spine types, results from a two-way ANOVA indicated dose-dependent changes in spine type density ($p<0.001$). Regardless of dose, all treated groups decreased mushroom spines compared to control (Fig.8C, 1.5 mg/kg: $p<0.001$; 2.0 mg/kg: $p<0.001$). Further analysis shows that both doses increase filopodia and stubby spines. Still, only low doses of psilocybin increase thin spines (Fig.8D-F, filopodia: 1.5 mg/kg: $p<0.001$, 2.0 mg/kg: $p<0.001$; filopodia: 1.5 mg/kg: $p<0.001$; stubby: 1.5 mg/kg: $p<0.001$, 2.0 mg/kg: $p<0.001$). None of the treatment groups increase branched spines (Fig.8G).
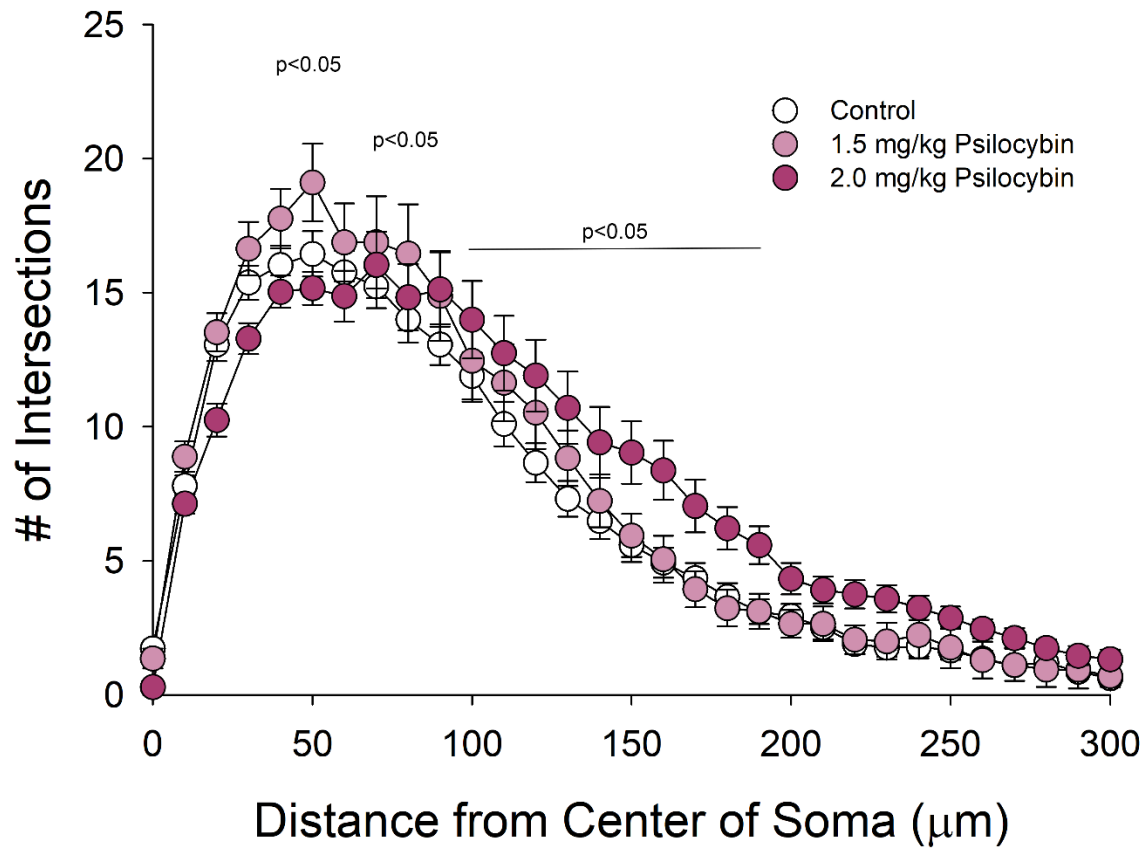
Figure 7: Changes In Dendritic Arborization Following Psilocybin Administration At Different Doses A) Sholl analysis of neurons indicating that 1.5 mg/kg of Psilocybin increases the number of dendrites under 100 um and 2.0 mg/kg of Psilocybin increased the number of dendrites between 100 and 200 um. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant
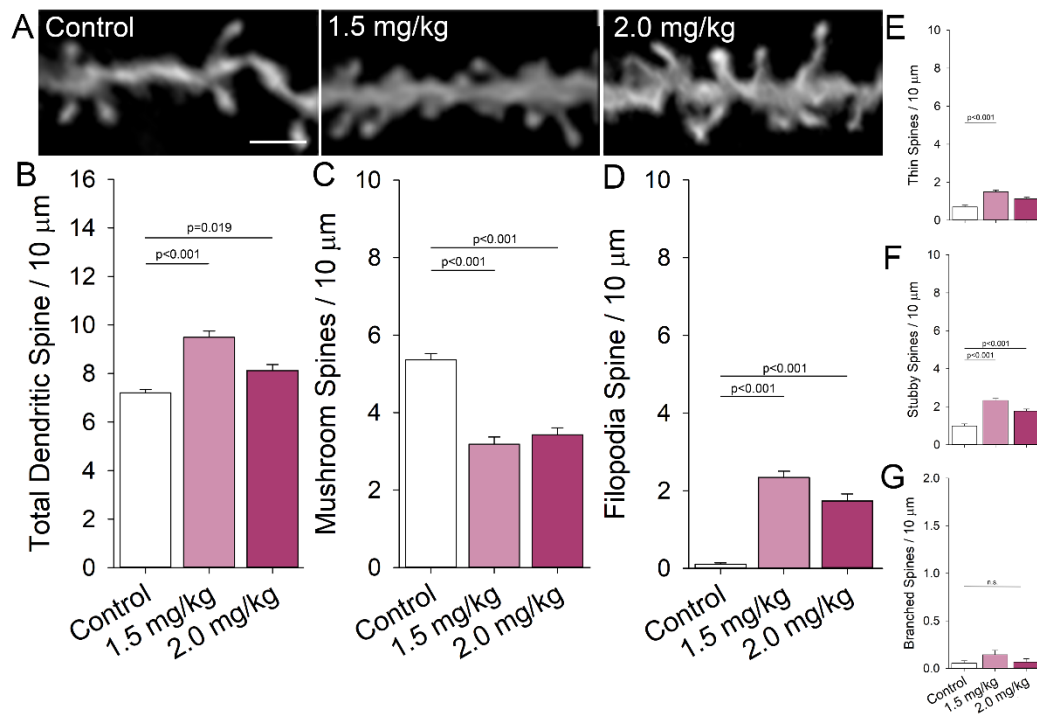
Figure 8: Changes In Dendritic Spine Density And Diversity Following Psilocybin Administration At Different Doses. A) Representative images of 10 um sections of neuronal dendrites from control mice and those treated with low, medium, and high doses of Psilocybin. Scale bar = 2 um B) Quantification of total spine density within 10 um dendritic segment showing low and medium doses of psilocybin significantly increase in total spine density. C) Quantification of mushroom spine density showing that regardless of dose, psilocybin decreases mature spine density. D) Quantification of filopodia spine density showing low and medium doses of psilocybin increases filopodia spine density. E) Quantification of thin spine density indicating that all treated groups, regardless of dose, increased thin spine density. F) Quantification of stubby spine density showing that low and medium doses of psilocybin increase stubby spine density. G) Quantification of branching spines showing no group alters branched spine density. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant

Effects Of EPT On Neural Circuitry And Microglia Morphology

Based on the results we got from assessing changes in arborization and microglia

morphology, we decided to combine a suspected sub-therapeutic dose of ECS and a low dose

of Psilocybin. To determine if combining treatments could improve therapeutic efficacy, we

investigated the dendritic arborization to assess changes in circuitry (Fig.9). Results from the

two-way analysis show a significant group difference between treatment distance and significant

interaction between the two. EPT enhanced dendritic arborization by increasing the number of

dendrites regardless of distance (Fig.9B, N= 20+ cells, treatment: $p>0.001$; distance: $p>0.001$;

treatment x distance: $p>0.001$). The change in dendritic arborization after the EPT is a

combination of the effects caused by ECS and Psilocybin independently. To assess if the

combined effect carried onto spine density, we compared the effects of the EPT to control, ECS,

and psilocybin-treated groups (Fig.10). To our surprise, administering a low dose of psilocybin

following ECS does not induce significant changes to spine density except for filopodia, which is

similar to ECS. A pairwise comparison of total spine density indicates that psilocybin

significantly increases total spine density (Fig.10B, N=75, control: $p>0.001$; ECS: $p>0.001$; EPT:

$p>0.001$). Even though there was no change to the total density, we analyzed spine type density

to determine if there were functional changes to the spines that existed. All treatment groups

diminish the number of mature mushroom spines (Fig.10C, ECS: $p>0.001$; psilocybin: $p>0.001$;

EPT: $p>0.001$). Psilocybin-treated and combined-treated groups significantly increase the

number of filopodia spines (Fig.10D, psilocybin: $p>0.001$; EPT: $p>0.001$). Additionally, the

psilocybin-treated group shows significant increases in thin-type spines (Fig.8E, $p> 0.001$ while

all groups increased stubby spine (Fig.10F, ECS: $p=0.001$; psilocybin: $p>0.001$; EPT: $p=0.001$).

There was no significant difference in branched spines (Fig.10G).

Figure 9: The Effects Following EPT On Neuronal Dendritic Arborization. A) Sholl analysis of neurons indicating that EPTincreases the number dendrites between 30 - 50 um and 130-180 um from the soma. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant

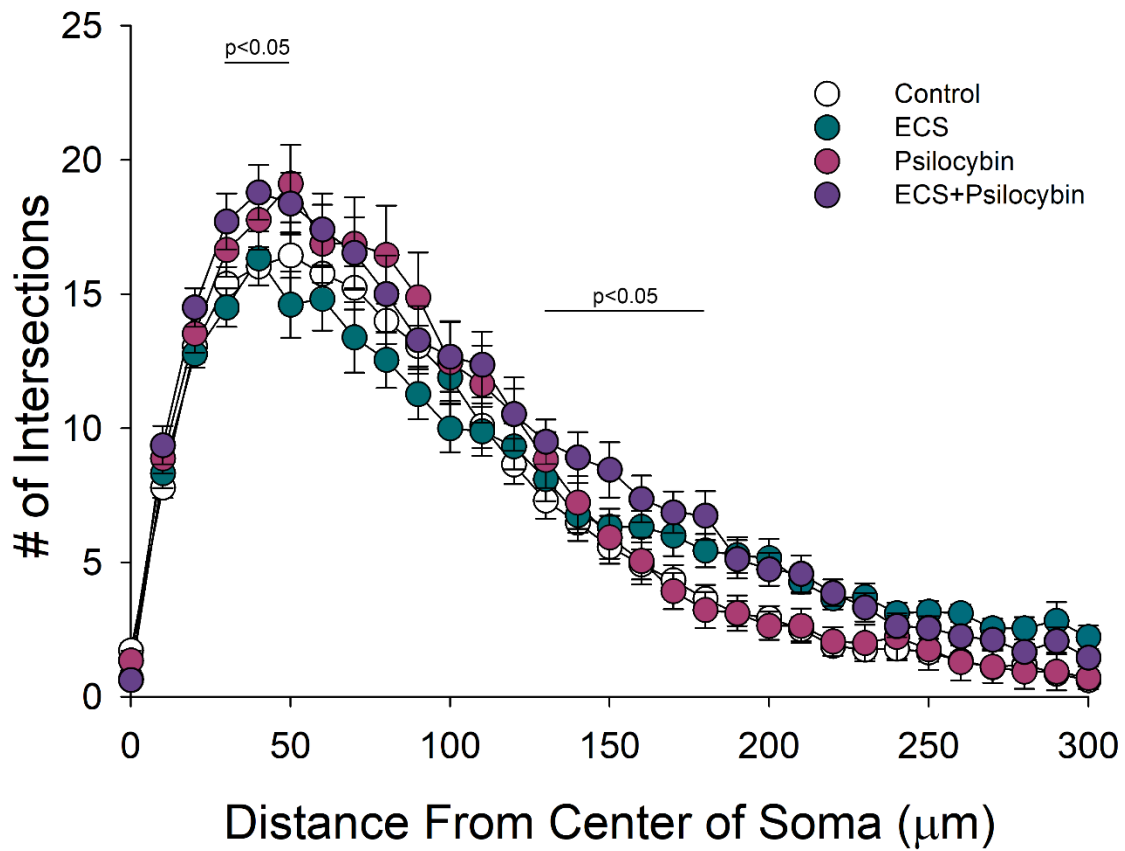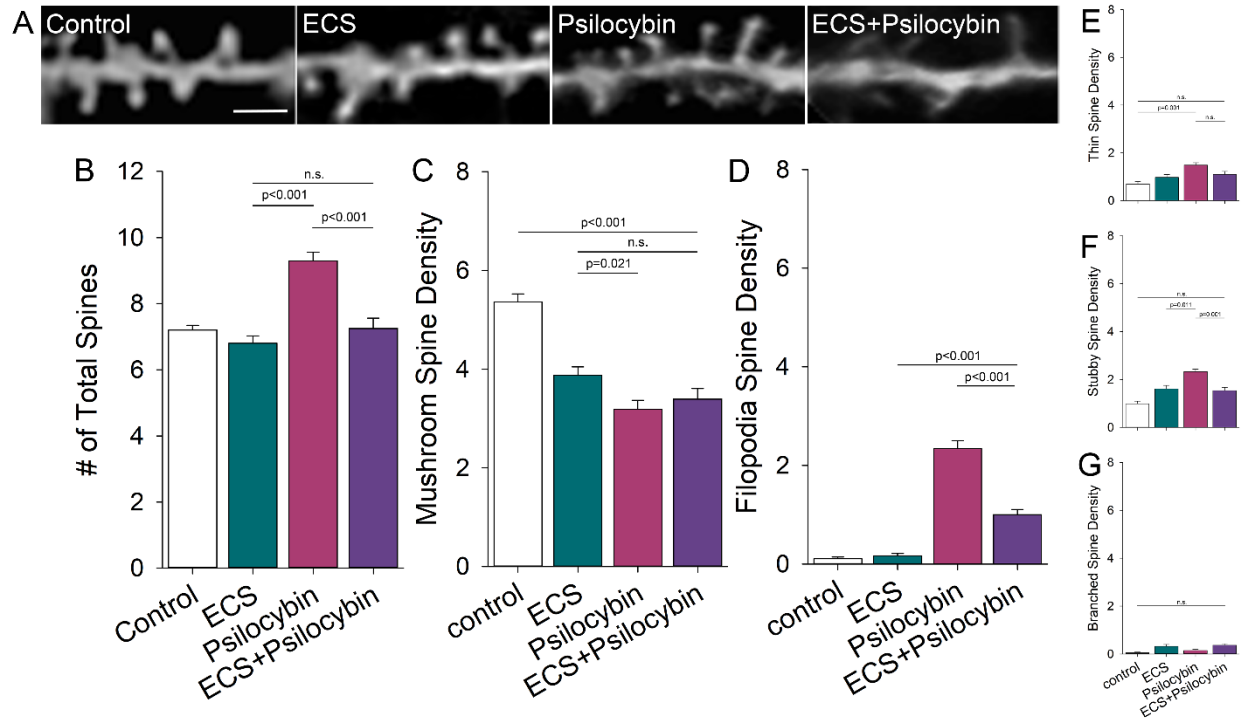**Figure 10: The Effects Following EPT On Dendritic Spine Density And Diversity.** A) Representative images of 10 um sections of neuronal dendrites from control mice and those treated with a low dose of ECS, low dose of Psilocybin, and low dose of ECS + Psilocybin. Scale bar = 2 um B) Quantification of total spine density indicating only the psilocybin-treated group increases total spine density. C) Quantification of mushroom spine density showing all treatments decreased mature spine density. D) Quantification of filopodia spine density showing Psilocybin and ECS+Psilocybin increase filopodia spine density. E) Quantification of thin and stubby spine density indicating that only the psilocybin treatment alone increases the number of thin and stubby spines on dendrites. G) Quantification of branching spines showing no group alters branched spine density. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant

Table 2: Summary of Statistics

Electroconvulsive Shock					
One way analysis of variance for microglia branch count					
Source of Variation	degress of freedom (df)	sum of squares (SS)	mean squares (MS)	F-value	p-value
Between Groups	3	839.961	279.987	16.2	<0.001
Residuals	90	1555.528	17.284		
Total	93	2395.489			
Two way analysis of variance for microglia sholl analysis					
Source of Variation	df	SS	MS	F-value	p-value
Dose	3	711.806	237.269	49.783	<0.001
Distance	15	6098.41	406.561	85.303	<0.001
Dose x Distance	45	1129.763	25.106	5.268	<0.001
Residual	1056	5032.988	4.766		
Total	1119	13908.178	12.429		
One way analysis of variance for microglia endfeet volume					
Source of Variation	df	SS	MS	F-value	p-value
Between Groups	3	1611.672	537.224	3.193	0.034
Residuals	29	6561.424	168.242		
Total	42	8173.096			
One way analysis of variance for microglia total volume					
Source of Variation	df	SS	MS	F-value	p-value
Between Groups	3	2322341.618	774113.873	2.241	0.098
Residuals	42	14508832.27	345448.387		
Total	45	16831173.89			
Two way analysis of variance for sholl analysis					
Source of Variation	df	SS	MS	F-value	p-value
Dose	3	1258.023	419.341	61.877	<0.001
Distance	48	106818.432	2225.384	328.372	<0.001
Dose x Distance	144	1799.449	12.496	1.844	<0.001
Residual	4116	27894.255	6.777		
Total	4311	143616.364	33.314		

One way analysis of variance for dendritic spine total					
Source of Variation	df	SS	MS	F-value	p-value
Between Groups	3	26.27	8.757	3.217	0.023
Residuals	262	713.188	2.722		
Total	265	739.459			
Two way analysis of variance for dendritic spine types					
Source of Variation	df	SS	MS	F-value	p-value
Dose	3	5.07	1.69	1.574	0.194
Spine Type	4	1957.977	489.494	455.771	<0.001
Dose x Spine Type	12	455.289	37.941	35.327	<0.001
Residual	1302	1398.338	1.074		
Total	1321	4016.509	3.041		
Psilocybin					
Two way analysis of variance for sholl analysis					
Source of Variation	df	SS	MS	F-value	p-value
Dose	2	470.718	235.359	24.76	<0.001
Distance	48	104287.93	2172.665	228.567	<0.001
Dose x Distance	96	1952.502	20.339	2.14	<0.001
Residual	3332	31672.695	9.506		
Total	3478	141851.718	40.785		
One way analysis of variance for dendritic spine total					
Source of Variation	df	SS	MS	F-value	p-value
Between Groups	3	265.726	88.575	24.896	<0.001
Residuals	232	825.406	3.558		
Total	235	1091.131			
Two way analysis of variance for dendritic spine types					
Source of Variation	df	SS	MS	F-value	p-value
Dose	2	38.165	19.083	18.23	<0.001
Spine Type	4	1822.016	455.504	435.15	<0.001
Dose x Spine Type	8	456.771	57.096	54.545	<0.001
Residual	1085	1135.75	1.047		
Total	1099	3478.846	3.165		

ECS + Psilocybin					
Two way analysis of variance for sholl analysis					
Source of Variation	df	SS	MS	F-value	p-value
Dose	3	931.726	310.575	34.901	<0.001
Distance	48	127508.88	2656.435	298.514	<0.001
Dose x Distance	144	1888.717	13.116	1.474	<0.001
Residual	4165	37063.736	8.899		
Total	4360	174396743	39.999		
One way analysis of variance for dendritic spine total					
Source of Variation	df	SS	MS	F-value	p-value
Between Groups	3	276.416	92.139	25.482	<0.001
Residuals	266	961.824	3.616		
Total	269	1238.241			
Two way analysis of variance for dendritic spine types					
Source of Variation	df	SS	MS	F-value	p-value
Dose	3	58.132	19.377	17.245	<0.001
Spine Type	4	2428.962	607.24	540.417	<0.001
Dose x Spine Type	12	483.961	40.33	35.892	<0.001
Residual	1465	1646.15	1.124		
Total	1484	4634.182	3.123		

Chapter V: Discussion

There is a limited understanding of the mechanisms underlying the therapeutic effects of ECS and psilocybin. Here, we show the dose-dependent effects of both treatments on dendritic arborization and spine density. ECS regulates microglia activation, promoting changes in neuronal plasticity that can be beneficial at the correct dose. On the other hand, psilocybin is a known psychoplastogen that activates both TrkB and 5-HT2A receptors. Their distinct mechanisms lead us to combine the treatments to understand their mechanism further. Surprisingly, the administration of psilocybin following ECS shows changes to arborization and spine density that are more similar to the effects of ECS than psilocybin.

Possible Mechanism Of Action Of ECS

ECS elicited dose-dependent changes in microglia branching. The change from ramified morphology to ameboid morphology indicates stable changes in microglia activation as ECS amperage increased. ECS has been shown to decrease TGF-β levels in patients with depression (Kartalci et al., 2016). ECS likely works by diminishing levels of TGF-β, and as the amperage of ECS increases, so does its effect on TGF-β expression. TGF-β signaling plays a crucial role in regulating microglial activation and function, promoting a resting state in microglia (Butovsky et al., 2014).

Furthermore, TGF-β induces the transcription of SPARC (Bao et al., 2021). SPARC is an ECM glycoprotein that has garnered attention for its emerging role in synapse formation and regulating microglia activation (Lloyd-Burton et al., 2013; Vincent et al., 2008). SPARC null/CX3CR1-GFP reporter mice show increased microglia arborization. Following a photothrombotic stroke, microglia from the double-transgenic mice had enhanced microgliosis, resulting in enhanced functional recovery time (Lloyd-Burton et al., 2013). Given the morphology changes in microglia following ECS, ECS may regulate TGF-β and SPARC signaling pathways in a dose-dependent manner, increasing the phagocytic properties of microglia. It is also possible that microglia activation could augment the effects by influencing the ECM through

regulatory processes aimed at maintaining tissue homeostasis and responding to changes in their surroundings (Crapser et al., 2021; Nguyen et al., 2020).

Synaptic pruning occurs frequently during critical developmental periods, but instances wane in adulthood. Following ECS, we uncovered dose-dependent dendritic arborization and dendritic spine diversity changes. Results show that ECS was applied at 25 mA, and there was a slight decrease in mature spines but no change in filopodia spines. At the medium dose, we found both a decrease in mature spine types and an increase in immature spine types. At the high dose, we found a significant decrease in mature spines and no change in the immature spine types, further supporting the hypothesis that ECS works by modulating the phagocytic properties of microglia through the TGF-β/SPARC signaling pathway. Microglia exhibit enhanced phagocytosis in SPARC-null mice (Thomas et al., 2015). SPARC influences both pre- and postsynaptic elements. It modulates the composition of the extracellular matrix surrounding synapses, thereby affecting synaptic structure and function (Albrecht et al., 2012; E. V. Jones et al., 2018; Kucukdereli et al., 2011; Velasco & Llobet, 2020). SPARC can regulate the availability of growth factors and neurotransmitters, influencing synaptic transmission and plasticity mechanisms such as LTP and LTD (Lloyd-Burton et al., 2013; Suzuki et al., 2018; Velasco & Llobet, 2020).

Additionally, studies show that ECS can regulate pre- and post-synaptic maturation by modulating the expression of SPARC (Okada-Tsuchioka et al., 2014). The role of SPARC in regulating plasticity in neurons further supports the role SPARC could have in driving the effects of ECS. Furthermore, SPARC's role in regulating synapses could be achieved by interacting with the complement system.

Traditionally recognized as a component of the immune system involved in pathogen recognition and elimination, the complement system has recently emerged as a crucial player in synapse formation and maturation within the central nervous system (Schafer & Stevens, 2015).

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Complement proteins, including C1q, C3, and C4, are now recognized for their active involvement in shaping neural circuits. Complement proteins are expressed temporally and spatially regulated during development, contributing to synapse elimination and refinement (Schafer et al., 2012a; Schafer & Stevens, 2015). C1q is implicated in the tagging of less active or redundant synapses for elimination through a process known as synaptic pruning. The opsonization of synapses by complement proteins facilitates their recognition and removal by microglia, the brain's resident immune cells (Hammond et al., 2018; Hong et al., 2016; Schafer et al., 2012b). The dynamic interplay between the complement system and synaptic elements is not limited to developmental stages; evidence suggests ongoing modulation of synapses in the adult brain. Dysregulation of complement-mediated synaptic pruning has been implicated in neurodevelopmental disorders and neurodegenerative conditions (Hong et al., 2016; Lehrman et al., 2018).

Possbile Mechanism For Psilocybin
Psychedelics like psilocybin are known as psychoplastogens for their ability to cause robust changes in synapses and arborization. Our results show a dose-specific change in dendritic arborization and spine density. A low dose of psilocybin causes an increase in short branches found within 150 um of the soma. The high dose appears to increase those between 120 um and 250 um from the soma. To further our understanding of dose-specific changes, we analyzed the spine density of neurons following administration. When analyzing spine information, we found that it caused similar effects on spine density but to different extents. The low dose of psilocybin seems to cause a more substantial increase in filopodia, thin and stubby spines. Our findings support research attributing the therapeutic potential of psilocybin to its ability to regulate plasticity. The increase in neuroplasticity seen after psilocybin administration is attributed to the activation of 5-HT and TrkB receptors (López-Giménez & González-Maeso, 2018; Madsen et al., 2019; Moliner et al., 2023). Psilocybin allosterically binds to the TrkB receptor, potentiating the actions of endogenous BDNF released at active synapses. BDNF is

necessary for the dimerization of TrkB, which is necessary for its activation (Moliner et al., 2023). Psilocybin binds to 5-HT receptors with relative affinity, activating a cascading effect that increases synaptic plasticity. The plasticity associated with 5-HT could be caused by its interactions with BDNF expression. While BDNF can lead to increases in 5-HT, 5-HT is known to decrease levels of BDNF (Homberg et al., 2014).

Additionally, the 5-HT receptor, 5-HT2A, forms a heteroreceptor with TrkB inhibiting its function (Ilchibaeva et al., 2022). Coupling the role of serotonin on BDNF levels and the inhibiting effect of 5-HT2a on TrkB function could explain why a high dose of psilocybin causes a lessened effect on plasticity. The limiting effect of 5-HT on TrkB signaling and the augmenting effect of psilocybin on TrkB signaling support the notion that psilocybin elicits its therapeutic effects by regulating TrkB signaling.

Possible Mechanism For EPT

When analyzing the effects of EPT on neuron dendritic arborization and spine density, we found that EPT increases dendritic arborization. EPT enhanced the number of short dendrites and increased the number of long dendrites found on neurons, indicating increased neural circuitry. When analyzing the effects of the EPT on spine density, we found that the treatment caused changes in spine density that more closely resembled the effects of ECS on spine density.

The diminished effects of psilocybin following ECS could indicate that the mechanisms behind the two treatments are not as distinct as previously thought. Recent research suggests that psilocybin may modulate microglial activity by interacting with 5-HT receptors, particularly the 5-HT2A receptor (Burmester et al., 2023; Laabi et al., 2024). Psilocybin's ability to bind to 5-HT receptors may influence the release of various signaling molecules, increasing anti-inflammatory cytokines. Additionally, ECS increases microglia-induced BDNF release (Maynard et al., 2018a). We previously discussed the limiting effects of 5-HT on the BDNF/TrkB signaling

pathway. ECS's ability to regulate BDNF and psilocybin to enhance the anti-inflammatory process suggests that ECS could have exhausted either the BDNF signaling pathway or another unknown microglia phagocytic pathway that is also affected by psilocybin. Understanding the interplay between psilocybin and microglia is essential for unraveling the complex mechanisms underlying the psychedelic experience and exploring potential therapeutic applications for mental health conditions associated with neuroinflammation. Our research suggests that psilocybin could enhance microglia activity with a pathway similar to ECS. Still, more research is needed to elucidate the precise mechanisms and consequences of psilocybin's interaction with microglia in the context of brain function and mental health.

Clinical Relevance
Protocol
The clinical protocol for ECT involves a standardized and carefully monitored procedure to ensure its safety and efficacy. Typically administered in a specialized ECT suite within a hospital or outpatient clinic, the protocol begins with a comprehensive pre-treatment evaluation (Association, 2008; Waite & Easton, 2013). The assessment includes a thorough medical history, physical examination, and psychiatric evaluation to determine the appropriateness of ECT for the individual (Thirthalli et al., 2023). Once deemed suitable, patients may undergo routine blood tests, electrocardiogram (ECG), and other baseline assessments. On the day of the procedure, patients are typically required to fast, and general anesthesia, along with muscle relaxants, is administered to induce a controlled seizure (Association, 2008; Thirthalli et al., 2023). Electrodes are strategically placed on the scalp to deliver a brief electrical stimulus, triggering the seizure. Throughout the session, vital signs are closely monitored. A series of ECT sessions is often prescribed, and the frequency varies depending on the nature and severity of the psychiatric condition being treated. Following each session, patients are observed in a recovery area until they regain consciousness. ECT is a collaborative effort involving psychiatrists, anesthesiologists, and nursing staff, ensuring adherence to the clinical

protocol while prioritizing patient safety and well-being. Regular assessments during and after

the treatment course help evaluate its effectiveness and guide further therapeutic decisions

(Association, 2008; Thirthalli et al., 2023; Waite & Easton, 2013). Many studies show that

multiple sessions are required for behavioral changes following ECT (Desfossés et al., 2021;

Jang et al., 2017; Kellner et al., 2016; Mindt et al., 2020; Rasmussen et al., 2002; Subramanian

et al., 2022), but the effects seen when combining ECT and psilocybin indicates the possibility

that psilocybin could diminish the need for multiple sessions when coupled with ECT treatments.

Research suggests that multiple sessions could be necessary to stabilize the proper neural

connections that could be achieved with psilocybin instead of an additional round of ECT.

Type of Stimulation

The pulse type used in ECT has evolved significantly since its inception in the 1930s.

Early forms of ECT employed high-voltage, unmodified, or "straight" sine wave currents (Fink,

2001; Payne & Prudic, 2009a; Sackeim et al., 2008). However, the original methods were

associated with considerable side effects, including severe muscle contractions and fractures.

The development of the brief pulse waveform in the 1950s marked a pivotal shift in ECT

technology. Brief pulse ECT involves the application of electrical stimuli with a shorter duration

and lower charge, resulting in a more controlled seizure (Sackeim et al., 1991, 2008). The

refinement of pulse specifications aimed to reduce the adverse effects associated with the

procedure, such as cognitive impairments and physical injuries related to convulsions. Brief

pulse ECT became the standard for many years, balancing therapeutic efficacy and safety

(Sackeim, 2017). Ultrabrief pulse ECT has gained popularity due to its potential to minimize

cognitive side effects further while maintaining therapeutic benefits. Studies suggest that ultra-

brief pulse ECT is associated with fewer cognitive impairments, including memory deficits,

compared to standard or brief pulse ECT (Loo et al., 2008; Sackeim, 2017; Sackeim et al.,

2008)

The ultra-brief pulse duration, typically in the range of microseconds, allows for more focal and controlled brain stimulation, reducing the risk of neuronal damage and cognitive impairments associated with longer pulse durations (Loo et al., 2008). Ultra-brief pulse induces a local seizure that is therapeutically effective for conditions like severe depression without the extensive spread of electrical activity that might occur with longer pulses. A brief pulse has a lower seizure threshold, resulting in the ability to use a lower amperage during treatment. A result of the lowered seizure threshold increases the efficiency of the treatment while significantly reducing the cognitive adverse effects (Sackeim et al., 2008). The choice of pulse type in ECT is a critical consideration. It is influenced by various factors, including the patient's medical history, the nature of the psychiatric condition, and the desired balance between therapeutic effectiveness and side effect profile. Our study utilizes ultra-brief pulses to enhance the validation of our findings and better mimic the effects seen in humans.

Neuromuscular Blocking Agents

NMBAs are used with ECT to manage the potential risks associated with the procedure. NMBAs are primarily aimed at mitigating the physical manifestations of the seizure, such as motor convulsions (Mirzakhani et al., 2012). By temporarily paralyzing the muscles, NMBAs prevent the intense and often vigorous movements that might occur during a seizure, reducing the risk of fractures or injuries. The neuromuscular blockade also allows for a more controlled and safer administration of the electrical stimulus, minimizing the potential for adverse effects related to muscle contractions. Commonly used neuromuscular blocking agents in ECT include succinylcholine and rocuronium (Bryson et al., 2018; Mirzakhani et al., 2012, 2016). While the use of NMBAs in ECT contributes to the safety and tolerability of the procedure, it is not without considerations. In animal studies involving ECS, the administration of muscle relaxers was avoided to maintain the ability to evaluate the treatment's effectiveness accurately. Our animals were anesthetized during the duration of the ECS to ensure their safety and comfort.

Anesthetics

Anesthesia is crucial to ECT procedure, ensuring patient comfort, safety, and effective seizure induction. The administration of anesthesia aims to minimize awareness and discomfort during the procedure while facilitating the controlled induction of a therapeutic seizure in the brain (Chawla, 2020). Commonly used anesthetics in ECT include short-acting intravenous agents such as propofol and etomidate. Propofol, a widely employed anesthetic in ECT, offers rapid onset and offset of action, making it well-suited for the brief duration of the procedure. Its properties allow for smooth induction and emergence from anesthesia, minimizing the risk of postictal confusion and cognitive side effects (P. M. Haddad & Benbow, 1992; Rasmussen, 2014). Propofol also possesses anti-seizure properties, contributing to the optimization of the therapeutic seizure while ensuring a quick recovery post-ECT (Martin et al., 1998). Etomidate is another intravenous anesthetic used in ECT and is known for its favorable pharmacokinetics. Similar to propofol, etomidate provides rapid onset and short duration of action (Ibrahim & Aldridge, 2006). It is preferred in cases where propofol may not be suitable due to allergy or intolerance. Etomidate's ability to maintain hemodynamic stability during ECT is particularly advantageous, as it helps avoid cardiovascular complications that may arise during the procedure (Gurel et al., 2022; X. Li et al., 2023). In animal research, inhaled anesthetics are frequently employed for their ability to induce and maintain anesthesia in a controlled and reversible manner. Commonly inhaled anesthetics in animal studies include isoflurane, sevoflurane, and desflurane (McAuliffe et al., 2009; Murrell et al., 2008; Schallner et al., 2014). Inhaled anesthetics offer advantages such as rapid onset and offset of anesthesia, precise control over the depth of anesthesia, and minimal metabolism in the body.

Isoflurane, sevoflurane, and desflurane are all volatile agents vaporized and administered through inhalation. They provide a convenient and adjustable means of anesthesia in various animal models, allowing researchers to modulate the depth of anesthesia based on experimental requirements (Eger, 1984). There are notable differences when comparing inhaled

anesthetics used in animal research to the intravenous agents propofol and etomidate commonly employed in ECT. In ECT, the primary goal is to induce a controlled therapeutic seizure while minimizing cognitive side effects. Propofol and etomidate, administered intravenously, offer rapid onset and offset of action, enabling precise control throughout anesthesia during the brief ECT procedure. Intravenous anesthetics are chosen for their favorable pharmacokinetics and the ability to optimize the therapeutic effects of the induced seizure (Chawla, 2020).

Ketamine, a dissociative anesthetic, has gained attention for its unique properties and potential benefits in ECT. Traditionally, ketamine has been utilized as an anesthetic in various medical settings and is known for its rapid onset and short duration of action (Hirota & Lambert, 2022). In recent years, its use in combination with ECT has been explored, and studies suggest that ketamine may offer advantages in enhancing the efficacy and tolerability of the procedure (D.-J. Li et al., 2017). One notable feature of ketamine is its NMDA receptor antagonism, contributing to its dissociative effects and analgesic properties. In the context of ECT, NMDA receptor modulation may influence the seizure threshold and potentially mitigate the cognitive side effects associated with the procedure (Krystal et al., 2003). Additionally, ketamine's antidepressant properties have sparked interest in its potential to augment the therapeutic outcomes of ECT, particularly in individuals with treatment-resistant depression (Okamoto et al., 2010; X. Wang et al., 2012).

When used as an adjunct to standard anesthetic agents like propofol, ketamine can provide a smoother induction of anesthesia and reduce the overall dose of anesthetics required contributing to a more controlled and well-tolerated ECT session (X. Wang et al., 2012). While ketamine is a viable anesthetic for ECT, our study did not include ketamine since it would alter the effects of ECT and Psilocybin, making distinguishing the effects caused by ECT or psilocybin and those caused by ketamine difficult. Research on ketamine's role in ECT is

ongoing, and its unique pharmacological profile suggests promising avenues for optimizing the procedure's safety and efficacy. The potential neuroprotective effects and antidepressant properties of ketamine make it an intriguing candidate for further exploration in refining the administration of ECT and improving outcomes for individuals undergoing ECT.

Prefrontal Cortex

Alterations in dendritic arborization and spine density within the prefrontal cortex further following administration of ECS, psilocybin, and electro-psychedelic treatment further hint at the therapeutic potential of these drugs at their respective dosages. The prefrontal cortex, a region at the front of the brain, is integral to regulating mood and cognition. Often referred to as the brain's executive center, the prefrontal cortex plays a crucial role in decision-making, emotional control, and social behavior. The prefrontal cortex evaluates emotional stimuli, processes social cues, and modulates emotional responses to external stimuli (Dixon et al., 2017). Additionally, the prefrontal cortex is crucial for cognitive functions such as attention, working memory, and problem-solving. It integrates information from various brain regions, allowing for higher-order cognitive processes, including planning and goal-directed behavior (Friedman & Robbins, 2022). Disruptions in prefrontal cortex function are associated with mood disorders such as depression and cognitive impairments seen in conditions like schizophrenia (Callicott et al., 2000; Domingos et al., 2024; J. Li et al., 2024; Tran et al., 2024).

In MDD, alterations in prefrontal cortex function, particularly in emotional regulation and decision-making, are observed (M.-M. Zhang et al., 2022). Dysregulation of mood-related circuits contributes to the manifestation of depressive symptoms. In PTSD, abnormalities in the prefrontal cortex, particularly in regions responsible for fear extinction and emotional processing, are implicated (Alexandra Kredlow et al., 2022). Changes in the prefrontal cortex may contribute to the persistence of traumatic memories and heightened emotional responses. In Schizophrenia, disruptions in the prefrontal cortex are associated with cognitive deficits and

impaired executive functions, contributing to the characteristic cognitive symptoms of the

disorder (Zhou et al., 2007). Exploring the effects of treatments in the prefrontal cortex for

neuropsychiatric conditions is essential for advancing our understanding of these disorders and

developing more effective, personalized treatment approaches to improve patient outcomes.

Future Directions

Exploring the collective impact of ECS and psilocybin creates an opportunity to delve

into additional research on how other 5-HT psychedelics may influence ECS. 5-HT psychedelics

exhibit varying affinities for different 5-HT receptor subtypes, contributing to the diverse range of

effects associated with psychedelics. Among the 5-HT receptor subtypes, the 5-HT2A receptor

is particularly crucial for the hallucinogenic properties of psychedelics like psilocybin, lysergic

acid diethylamide (LSD), mescaline, and 25I-NBOH (Nutt et al., n.d.). 5-HTpsychedelics act as

agonists at the 5-HT2A receptor, binding with high affinity and initiating a cascade of

neurobiological events leading to altered perception and cognition. While the 5-HT2A receptor is

a primary target, psychedelics also interact with other 5-HT receptor subtypes to varying

degrees, including 5-HT1A, 5-HT2C, and 5-HT1B receptors (Canal & Murnane, 2017; Fierro et

al., 2021). The differential affinities for the different 5-HT receptors contribute to the complex

and multifaceted nature of the psychedelic experience. The specific levels of activation influence

perceptual distortions, hallucinations, mood, anxiety, and cognitive processes (Canal &

Murnane, 2017). The activation of 5-HT receptors, especially the 5-HT2A subtype, has also

been linked to neuroplasticity alterations and spine density changes in preclinical studies (Canal

& Morgan, 2012; K. A. Jones et al., 2009; Roppongi et al., 2013; Vargas et al., 2023; Xu et al.,

2016).

LSD is a powerful hallucinogenic substance that belongs to the class of psychedelics.

Discovered in 1938 by Swiss chemist Albert Hofmann, LSD gained notoriety in the 1960s as a

symbol of counterculture and experimentation. LSD induces profound alterations in perception,

cognition, and mood, often resulting in vivid hallucinations, intensified sensory experiences, and a distorted sense of time. LSD's effects are highly dose-dependent, with even small amounts causing noticeable perceptual changes. Some investigations suggest that LSD, when administered in a controlled and supportive setting, may have positive outcomes for individuals dealing with anxiety or depression (Lewis et al., 2023; Lowe et al., 2022). LSD is generally considered to be more potent than psilocybin. A typical dose of LSD is in the microgram range, whereas a dose of psilocybin is usually measured in milligrams. The duration of effects differs between psilocybin and LSD. Psilocybin trips typically last around 4 to 6 hours, while LSD trips can last up to 12 hours or more. Psilocybin is metabolized into psilocin in the body, the primary psychoactive compound responsible for its effects. LSD's exact mechanism of action is more complex and involves interactions with serotonin receptors in the brain (De Gregorio et al., 2016; Ling et al., 2022). Differences in metabolism, mechanism, and duration of effects indicate differences in their therapeutic potential. Understanding how combining other psychedelics with ECT would expand our understanding of their mechanisms of action and expand the therapeutic potential for psychedelics.

Transcranial Magnetic Stimulation (TMS) and ECT are both neuromodulation techniques used in psychiatry, each with distinct mechanisms and applications. TMS involves the application of magnetic fields to induce electrical currents in specific brain regions non-invasively(Lisanby & Belmaker, 2000). It is often employed for conditions like MDD and offers a more targeted approach than ECT (Brys et al., 2016; Heath et al., 2018; Luber et al., 2017). ECT, on the other hand, is a more invasive procedure that induces controlled seizures through the administration of electrical currents, typically reserved for severe mental disorders.

Combining psilocybin with TMS introduces a novel avenue for exploration. Psilocybin primarily interacts with 5-HT receptors, while TMS modulates neuronal activity through magnetic fields. Theoretically, the combination could enhance the neuromodulatory effects of TMS by

influencing serotonergic systems, potentially leading to synergistic therapeutic outcomes. Psilocybin's ability to induce altered states of consciousness and modulate mood might complement TMS in addressing conditions like depression. However, careful consideration must be given to the potential interactions. Research is essential to explore the interactions between varying doses of TMS and psilocybin, aiming to reveal the most effective and optimal dosage.

Limitations

While changes in microglia morphology are observed in response to various stimuli or conditions, it is crucial to recognize that alterations in cellular shape do not necessarily equate to specific microglial functions. Microglia are highly dynamic cells capable of adopting various morphological states, including ramified, amoeboid, or intermediate forms, in response to different signals. Morphological changes alone may not provide a comprehensive understanding of the functional states of microglia, as multiple factors can influence their appearance. Functional diversity among microglia is evident through their roles in immune response, synaptic pruning, and maintenance of homeostasis.

Iba1 is a well-established marker in neuroscience utilized for visualizing and quantifying microglial cells, the immune cells of the central nervous system. As a cytoplasmic protein, Iba1 is highly expressed in activated microglia, making it a reliable indicator of microglial activation and reactivity. Immunohistochemical staining for Iba1 is commonly employed in research to visualize microglial morphology and distribution in brain tissues (Jinno & Kosaka, 2008; Sasaki et al., 2001). Iba1 works by forming a complex with L-fimbrin and binding to action, thus aiding the reorganization of actin during an alteration in microglia morphology (Sasaki et al., 2001). The upregulation of Iba1 is associated with various physiological and pathological conditions, reflecting the dynamic nature of microglial responses to changes in their microenvironment (Y.-L. Wang et al., 2018; Yirmiya et al., 2015). Using Iba1 as a marker facilitates the study of microglial activation morphological patterns.

Microglia display a dynamic and multifaceted range of morphologies, adapting their

shapes based on their functional states. Microglia exhibit a vigilant "surveillance state" in the

central nervous system, reflecting their crucial role as resident immune cells responsible for

monitoring and maintaining brain homeostasis. In their baseline, or resting state, microglia

extend numerous ramified processes, constantly surveying their microenvironment for any signs

of disturbance or abnormalities (Hanisch & Kettenmann, 2007b). Surveillance involves

continuously sensing neuronal activity, synaptic connections, and the surrounding extracellular

matrix. Microglia's intricate processes are equipped with various receptors, allowing them to

detect changes in their surroundings, including alterations in neurotransmitter levels, cellular

damage, or pathogens. Biomarkers that are upregulated during microglia surveillance include

those associated with immune response and inflammation, chemokines (e.g., CCL2, CXCL10),

and cell surface markers (e.g., CD11b, CD68) (Tremblay et al., 2011). The constant surveillance

enables microglia to respond to any potential threats or disruptions swiftly, facilitating their role

in immune defense, synaptic maintenance, and tissue repair. DAMPs (Damage-Associated

Molecular Patterns) and PAMPs (Pathogen-Associated Molecular Patterns) are molecules that

can activate microglia, the resident immune cells of the central nervous system, by binding to

pattern recognition receptors (PRRs) on their surface. DAMPs are endogenous molecules

released from damaged or dying cells, indicating tissue injury or stress, while PAMPs are

molecules derived from pathogens such as bacteria, viruses, or fungi (Garaschuk &

Verkhratsky, 2019; Kettenmann et al., 2011). The surveillance state of microglia underscores

their dynamic nature and highlights their essential function in promptly addressing perturbations

within the brain to ensure its optimal functioning and protection against potential threats.

Recognition of DAMPs or PAMPs by microglial PRRs, such as TLRs or NOD-like

receptors (NLRs), triggers signaling pathways that lead to microglial activation (Garaschuk &

Verkhratsky, 2019). Microglia undergo morphological changes upon activation in response to

injury, infection, or other stimuli. Activated microglia can become hyper-ramified with an increase in end-feet volume, indicating changes in their phagocytic function. Microglia undergo dynamic changes in their morphology, including alterations in their endfeet, which are specialized structures at the outermost regions of their processes (Paolicelli et al., 2022). Microglial endfeet is crucial in interacting with blood vessels and the surrounding neural environment. Changes in endfeet morphology are often associated with microglial activation in response to various stimuli, such as injury, infection, or neuroinflammation. Activated microglia may exhibit an enlargement or retraction of end feet, reflecting their involvement in modulating neurovascular interactions and responding to changes in the brain microenvironment. Our results show that 35 mA of ECS causes changes to microglia morphology indicative of cell activation in the early stages. The decreased branches and enlarged end feet suggest that following ECS at 35 mA, microglia have enhanced phagocytic properties.

Phagocytosis is a fundamental cellular process crucial for the maintenance of tissue homeostasis and immune response. Microglial phagocytosis is a finely tuned mechanism that eliminates cellular debris, pathogens, and dysfunctional neurons, contributing to brain health (Fu et al., 2014). Under normal physiological conditions, microglia continually survey their surroundings with their ramified processes. When encountering cellular debris or distress signals, microglia transition into an activated state, characterized by changes in morphology and increased phagocytic activity (Westman et al., 2020). The transition is vital for clearing apoptotic cells, damaged neurons, and extracellular aggregates, preventing the accumulation of potentially harmful substances. The dynamic process is crucial for immune defense and tissue repair in the central nervous system.

CD68 and CD11b are integral biomarkers that significantly assess phagocytic activity in microglia (Lee et al., 2002; Waller et al., 2019). CD68, a glycoprotein associated with the lysosomal membrane, is a reliable marker for activated microglia engaged in phagocytosis. Its

upregulation indicates microglial involvement in clearing cellular debris and apoptotic cells (Waller et al., 2019; Yeo et al., 2019). Similarly, CD11b, also known as complement receptor 3 (CR3), is a cell surface marker associated with microglial activation and phagocytic functions. It plays a crucial role in recognizing and binding to complement-coated particles, facilitating the engulfment of targeted materials (Lee et al., 2002). As stimulation becomes more detrimental, microglia can transition to an amoeboid or amoeboid-like morphology, involving a retraction of processes and a more rounded appearance. In the activated state, microglia become more motile and phagocytic, enabling them to migrate toward the site of injury or inflammation and participate in tissue repair, clearance of cellular debris, and immune responses.

Microglia morphology provides valuable insights into their functional states and contributions to neuroinflammation, synaptic pruning, and overall brain health. The expression of CD11b is mainly associated with the amoeboid morphology assumed by microglia during active phagocytosis (Roy et al., 2006, 2008). Phagocytic biomarkers serve as essential tools in both research and clinical settings, allowing for identifying and characterizing activated microglia engaged in phagocytic functions, contributing to a deeper comprehension of the intricate immune responses within the central nervous system. Impaired or excessive phagocytosis by microglia can contribute to accumulating pathological protein aggregates, exacerbating neuroinflammation and neuronal dysfunction seen in many neurodegenerative diseases (Hou et al., 2020; Kinugawa et al., 2013; Matsumura et al., 2015; Streit et al., 2014). Understanding the intricacies of microglial phagocytosis and biomarkers involved elicited by ECS in our experiments would benefit our understanding of the dose-dependent changes seen to microglia morphology and refinement of protocol to minimize adverse effects. Psilocybin primarily acts on serotonin receptors in the brain, particularly the 5-HT2A receptor. Activation of 5-HT receptors has been linked to anti-inflammatory effects in some contexts (Laabi et al., 2024). Clinical studies investigating the therapeutic effects of psilocybin for conditions like depression and

anxiety have reported changes in cytokine levels in some patients (Burmester et al., 2023).

Investigation of phagocytic markers following psilocybin administration would further our

understanding of the mechanisms of psilocybin and promote the refinement of treatment

protocols.

Neuroinflammation, an intricate immune response within the central nervous system,

involves the activation of various cellular components, with microglia emerging as pivotal

players in orchestrating the complex phenomenon. Activated amoeboid microglia release pro-

inflammatory cytokines, including TNF-α, IL-1β, and ROS, contributing to the neuroinflammatory

milieu (Y. Wang et al., 2022). Pro-inflammatory molecules serve as signaling mediators that

attract other immune cells to the site of injury or pathology, amplifying the immune response.

While neuroinflammation is an adaptive response to remove threats and initiate repair

processes, dysregulated or chronic microglia activation can lead to harmful consequences.

Prolonged release of pro-inflammatory mediators can result in collateral damage to surrounding

neurons, exacerbating neurodegenerative processes implicated in many neuropsychiatric

disorders (Fakhoury, 2020; Ito et al., 2001; Yirmiya et al., 2015).

Translocator Protein (TSPO), TNF-α, and IL-1β play crucial roles in the intricate

landscape of neuroinflammation, contributing to both protective and deleterious aspects of the

immune response within the central nervous system. TSPO, primarily located on the outer

mitochondrial membrane, is a neuroinflammation biomarker (Beckers et al., 2018). Its

upregulation is associated with microglia activation, reflecting an immune response to various

insults. TSPO ligands are utilized in positron emission tomography (PET) imaging to visualize

and quantify neuroinflammatory processes in conditions such as neurodegenerative diseases

and brain injuries (Dimitrova-Shumkovska et al., 2020). The expression of TSPO provides

insights into the extent of microglial activation and the spatial distribution of neuroinflammation

in the brain. TNF-α and IL-1β are pro-inflammatory cytokines released by activated microglia

and other immune cells during neuroinflammation. Pro-inflammatory cytokines play dual roles, serving protective functions in acute responses while potentially contributing to neuronal damage in chronic or dysregulated states. TNF-α and IL-1β modulate the immune response by promoting the recruitment of immune cells to the site of injury or infection (Hanisch, 2002). However, sustained release of pro-inflammatory cytokines can lead to excitotoxicity, oxidative stress, and synaptic dysfunction, contributing to the progression of neurodegenerative disorders.

The intricate interplay between TSPO, TNF-α, and IL-1β underscores their collective impact on the neuroinflammatory cascade. TSPO acts as a marker for microglial activation, while TNF-α and IL-1β mediate inflammatory signaling, influencing the extent and duration of neuroinflammation. Targeting pro-inflammatory molecules has become a focal point in therapeutic strategies to modulate neuroinflammatory responses. Understanding the intricate roles of TSPO, TNF-α, and IL-1β in neuroinflammation provides valuable insights into the underlying mechanisms of ECS. It opens avenues for developing targeted interventions to regulate immune responses and mitigate the detrimental effects of chronic inflammation in the brain.

Upon intake, psilocybin undergoes metabolic conversion to psilocin, which interacts primarily with 5-HT receptors in the brain. The interaction results in altered perception, sensory experiences, and profound changes in consciousness. The hallucinogenic trip induced by psilocybin is characterized by vivid visual distortions, enhanced sensory perception, and a profound sense of interconnectedness with one's surroundings (Kometer et al., 2015). The hallucinogenic trip induced by psilocybin holds significant potential for therapeutic applications, offering a unique avenue for exploring novel approaches to mental health treatment. Research suggests that the subjective experience during a psilocybin trip, characterized by altered perception and a sense of interconnectedness, may have therapeutic benefits. Psilocybin has

shown promise in the treatment of various mental health conditions, including depression, anxiety, and PTSD (Davis et al., 2021; A. J. Khan et al., 2022).

Psilocybin is known for its ability to induce hallucinogenic trips characterized by alterations in perception, mood, and consciousness. The hallucinogenic trip is believed to facilitate introspective insights and emotional processing, allowing individuals to confront and reevaluate aspects of their lives. Additionally, the compound may promote neuroplasticity and alter patterns of brain connectivity, contributing to sustained positive changes in mood and cognition (Kometer et al., 2015; Skosnik et al., 2023). The subjective nature of the experience can vary widely among individuals, influenced by factors such as dosage, set, and setting. The careful and controlled administration of psilocybin in therapeutic settings, guided by trained professionals, is a critical consideration in harnessing its potential benefits (Johnson et al., 2008). As the field of psychedelic-assisted therapy continues to evolve, the therapeutic role of the hallucinogenic trip of psilocybin is becoming a focal point in the exploration of alternative and effective treatments for mental health disorders.

The head-twitch response (HTR) in mice is a well-established behavioral marker used to study the effects of hallucinogenic compounds, including psilocybin. After psilocybin administration, mice often exhibit a characteristic side-to-side head movement, referred to as the HTR. The HTR is considered a 5-HT receptor-mediated response involving the 5-HT2A receptor (Canal & Morgan, 2012). The HTR is commonly used in preclinical research to assess the hallucinogenic and serotonergic properties of substances like psilocybin. The frequency and duration of head twitches is a quantitative measure of the hallucinogenic effects of psilocybin and related compounds in mice (Halberstadt & Geyer, 2013). A limitation of our study is that we failed to look at changes to the HTR following co-administration of ECS and psilocybin. A single session of ECS reduces HTR to 5-HT agonists, but repeated sessions enhance 5-HT (Wielosz, 1985). Our results indicate that a single dose of ECS preceding psilocybin administration could

impact hallucinogenic trip. Psilocybin significantly affects synapses, enhancing filopodial spine

density and increasing serotonin receptor activity. It is plausible that the reduced impact on

filopodial spines observed after EPT could signify a decrease in serotonin receptor response.

The therapeutic role of the controlled induction of seizures using ECT is a multifaceted

aspect of psychiatric intervention that has demonstrated efficacy in the management of severe

mental disorders (Sackeim et al., 1991). ECT's ability to induce therapeutic seizures is thought

to bring neurobiological changes contributing to its clinical benefits. The controlled nature of the

procedure allows for precise modulation of neural circuits, leading to alterations in

neurotransmitter systems and increased neuroplasticity (Maynard et al., 2018a). The controlled

nature of ECT, in turn, has been associated with a rapid and robust alleviation of symptoms,

particularly in cases of treatment-resistant conditions such as severe depression. The

therapeutic role of ECT extends beyond symptom relief, encompassing improvements in overall

cognitive functioning and quality of life for specific individuals. The additive effects of the

combined administration of ECT and psilocybin suggest that psilocybin could affect the seizure

induction properties of ECT.

The effects of serotonergic psychedelics on seizures represent a complex and still-

evolving area of research within the realm of psychopharmacology. Substances such as

psilocybin, LSD, and DMT, which primarily exert their effects through the 5-HT receptor system,

have demonstrated both pro- and anti-convulsive properties in preclinical studies. On the one

hand, there is evidence suggesting that certain serotonergic psychedelics may lower seizure

thresholds, potentially posing risks for individuals with a predisposition to epilepsy (Chiao et al.,

2020). On the other hand, emerging research indicates that serotonergic psychedelics might

have anti-convulsant effects under specific conditions. For example, studies in animal models

have shown that psychedelics like psilocybin could attenuate seizure activity through the

modulation of 5-HT receptors and other neurotransmitter systems (Tyagi et al., 2023). However,

the translation of findings to human populations and the clinical implications for individuals with epilepsy remain areas of ongoing investigation. It is crucial to note that the effects of serotonergic psychedelics on seizures are nuanced and context-dependent and warrant further exploration to inform both potential therapeutic applications and considerations for safety in vulnerable populations (Freidel et al., 2023). As research progresses, understanding the nuanced mechanisms through which controlled seizures impact the brain holds promise for refining ECT protocols, minimizing side effects, and expanding its therapeutic applications in the evolving landscape of psychiatric care.

The relationship between seizure threshold and psychedelics, particularly psilocybin, is an area of interest in neuroscience. Seizure threshold refers to the minimum stimulation level required to induce a seizure. While traditional psychedelics, such as psilocybin, are not generally known for lowering seizure thresholds, the complex interactions between psychedelics and neural circuits warrant investigation. Studies have explored the impact of psilocybin on neuronal activity and seizure susceptibility, with some suggesting that, under certain conditions, psychedelics may modulate seizure thresholds (Freidel et al., 2023). The potential of psilocybin to lower seizure threshold raises intriguing questions about its interaction with ECT, as understanding how ECS and psilocybin may influence each other is crucial for optimizing their effectiveness and ensuring the safety of individuals undergoing combined therapeutic approaches.

By examining the interaction between ECT, a well-established treatment for severe depression and other mental illnesses, and psilocybin, a psychedelic compound with emerging therapeutic promise, on microglia and dendritic spines, the study sheds light on the intricate mechanisms underlying brain plasticity and synaptic remodeling. Understanding the combined effects of ECT and psilocybin on microglia and dendritic spines holds promise for the development of more effective and targeted treatments for depression, anxiety, and related

psychiatric disorders. By elucidating the molecular and cellular mechanisms through which Ecs and psilocybin exert their therapeutic effects, the study opens new avenues for the rational design of interventions that harness the brain's innate capacity for plasticity and repair. Moreover, by exploring the synergistic effects of ECT and psilocybin, the research paves the way for innovative approaches that integrate conventional and psychedelic therapies to optimize treatment outcomes and enhance patient well-being. Overall, our results suggest the potential for combining psychedelics with ECS to enhance therapeutic effectiveness. It may be possible to achieve therapeutic benefits once the protocol has been clarified by administering low doses of each treatment.

Chapter VI: Conclusion

Here, we investigated the dose-dependent changes in microglia morphology and neuronal dendritic arborization following electroconvulsive shock and psilocybin to verify a dose for each treatment to use for combination therapy. Our experiments revealed essential insights into the dose-dependent effects of electroconvulsive shock and psilocybin on microglia morphology and neuronal dendritic arborization. The findings suggest that ECS with high amperage can be detrimental, and too little has no effect on therapeutic effect. Additionally, psilocybin has significant and distinct impacts on dendrites and spines, highlighting the potential for further research in understanding the mechanisms underlying their effects. Based on the results, we can assert that combining electroconvulsive shock and psilocybin at low doses may have therapeutic efficacy due to their ability to promote changes in microglia morphology and neuronal dendritic arborization, potentially enhancing neural communication and diminishing potential adverse effects. Our results contribute to the growing knowledge surrounding the neurobiological effects of psilocybin and ECS and have implications for their potential therapeutic applications. Further exploration into the specific pathways and molecular mechanisms involved in dose-dependent changes will be crucial for fully elucidating their potential impact on neurological and psychiatric conditions.

References

Aben, B., Stapert, S., & Blokland, A. (2012). About the Distinction between Working Memory and Short-Term Memory. *Frontiers in Psychology*, *3*. https://doi.org/10.3389/fpsyg.2012.00301

Abhyankar, R. (1985). REEVALUATION OF ECT. *Indian Journal of Psychiatry*, *27*(1), 35–49.

Abu-Hijleh, F. A., Prashar, S., Joshi, H., Sharma, R., Frey, B. N., & Mishra, R. K. (2021). Novel mechanism of action for the mood stabilizer lithium. *Bipolar Disorders*, *23*(1), 76–83. https://doi.org/10.1111/bdi.13019

Adams, C. E., Awad, G. A., Rathbone, J., Thornley, B., & Soares-Weiser, K. (2014). Chlorpromazine versus placebo for schizophrenia. *The Cochrane Database of Systematic Reviews*, *2014*(1), CD000284. https://doi.org/10.1002/14651858.CD000284.pub3

Adwas, A. A., Jbireal, J. M., & Azab, A. E. (2019). *Anxiety: Insights into Signs, Symptoms, Etiology, Pathophysiology, and Treatment*. 2.

Agranoff, B. W., & Fisher, S. K. (2001). Inositol, lithium, and the brain. *Psychopharmacology Bulletin*, *35*(3), 5–18.

Albertini, G., D'andrea, I., Druart, M., Béchade, C., Nieves-Rivera, N., Etienne, F., Le Magueresse, C., Rebsam, A., Heck, N., Maroteaux, L., & Roumier, A. (2023). Serotonin sensing by microglia conditions the proper development of neuronal circuits and of social and adaptive skills. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-023-02048-5

Albrecht, D., López-Murcia, F. J., Pérez-González, A. P., Lichtner, G., Solsona, C., & Llobet, A. (2012). SPARC prevents maturation of cholinergic presynaptic terminals. *Molecular and Cellular Neurosciences*, *49*(3), 364–374. https://doi.org/10.1016/j.mcn.2012.01.005

Alexandra Kredlow, M., Fenster, R. J., Laurent, E. S., Ressler, K. J., & Phelps, E. A. (2022). Prefrontal cortex, amygdala, and threat processing: Implications for PTSD. *Neuropsychopharmacology*, *47*(1), 247–259. https://doi.org/10.1038/s41386-021-01155-7

Allswede, D. M., & Cannon, T. D. (2018). Prenatal inflammation and risk for schizophrenia: A role for immune proteins in neurodevelopment. *Development and Psychopathology*, *30*(3), 1157–1178. https://doi.org/10.1017/S0954579418000317

Aloisi, F. (2001). Immune function of microglia. *Glia*, *36*(2), 165–179. https://doi.org/10.1002/glia.1106

Amad, A. (2023). Electroconvulsive Therapy Restores Higher-Level Cognition in Catatonia. *The Journal of ECT*, *39*(3), e2. https://doi.org/10.1097/YCT.0000000000000907

Andersen, G., Marcinek, P., Sulzinger, N., Schieberle, P., & Krautwurst, D. (2019). Food sources and biomolecular targets of tyramine. *Nutrition Reviews*, *77*(2), 107–115. https://doi.org/10.1093/nutrit/nuy036

Andoh, M., Ikegaya, Y., & Koyama, R. (2019). Synaptic Pruning by Microglia in Epilepsy. *Journal of Clinical Medicine*, *8*(12), 2170. https://doi.org/10.3390/jcm8122170

Andrade, C., Arumugham, S. S., & Thirthalli, J. (2016). Adverse Effects of Electroconvulsive Therapy. *Psychiatric Clinics of North America*, *39*(3), 513–530. https://doi.org/10.1016/j.psc.2016.04.004

Andrade, C., Sandarsh, S., Chethan, K. B., & Nagesh, K. S. (2010). Serotonin reuptake inhibitor antidepressants and abnormal bleeding: A review for clinicians and a reconsideration of mechanisms. *The Journal of Clinical Psychiatry*, *71*(12), 1565–1575. https://doi.org/10.4088/JCP.09r05786blu

Andreasen, N. C., & Carpenter, W. T., Jr. (1993). Diagnosis and Classification of Schizophrenia. *Schizophrenia Bulletin*, *19*(2), 199–214. https://doi.org/10.1093/schbul/19.2.199

Andreasen, N. C., Nopoulos, P., Schultz, S., Miller, D., Gupta, S., Swayze, V., & Flaum, M. (1994). Positive and negative symptoms of schizophrenia: Past, present, and future. *Acta Psychiatrica Scandinavica*, *90*(s384), 51–59. https://doi.org/10.1111/j.1600-0447.1994.tb05891.x

Anis, N. A., Berry, S. C., Burton, N. R., & Lodge, D. (1983). The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *British Journal of Pharmacology*, *79*(2), 565–575.

Ansseau, M., Von Frenckell, R., Papart, P., Mertens, C., De Wilde, J., Botte, L., Devoitille, J.-M., Evrard, J.-L., De Nayer, A., Koch-Bourdouxhe, S., Darimont, P., Lecoq, A., Mirel, J., Couzinier, J. P., Demarez, J.-P., & Serre, C. (1989). Controlled comparison of milnacipran (F2207) 200 mg and amitriptyline in endogenous depressive inpatients. *Human Psychopharmacology: Clinical and Experimental*, *4*(3), 221–227. https://doi.org/10.1002/hup.470040308

Aoki, R., Sato, H., Katura, T., Utsugi, K., Koizumi, H., Matsuda, R., & Maki, A. (2011). Relationship of negative mood with prefrontal cortex activity during working memory tasks: An optical topography study. *Neuroscience Research*, *70*(2), 189–196. https://doi.org/10.1016/j.neures.2011.02.011

Araragi, N., & Lesch, K.-P. (2013). Serotonin (5-HT) in the Regulation of Depression-Related Emotionality: Insight from 5-HT Transporter and Tryptophan Hydroxylase-2 Knockout Mouse Models. *Current Drug Targets*, *14*(5), 549–570.

Arnold, S. E., Kahn, R. J., Faldetta, L. L., Laing, R. A., & McNair, D. M. (1981). Tricyclic antidepressants and peripheral anticholinergic activity. *Psychopharmacology*, *74*(4), 325–328. https://doi.org/10.1007/BF00432740

Asnis, G. M., Chakraburtty, A., DuBoff, E. A., Krystal, A., Londborg, P. D., Rosenberg, R., Roth-Schechter, B., Scharf, M. B., & Walsh, J. K. (1999). Zolpidem for persistent insomnia in

SSRI-treated depressed patients. *The Journal of Clinical Psychiatry*, *60*(10), 668–676. https://doi.org/10.4088/jcp.v60n1005

Asnis, G. M., Kohn, S. R., Henderson, M., & Brown, N. L. (2004). SSRIs versus Non-SSRIs in Post-traumatic Stress Disorder. *Drugs*, *64*(4), 383–404. https://doi.org/10.2165/00003495-200464040-00004

Association, A. P. (2008). *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging (A Task Force Report of the American Psychiatric Association)*. American Psychiatric Pub.

Atmaca, M. (2020). Selective Serotonin Reuptake Inhibitor-Induced Sexual Dysfunction: Current Management Perspectives. *Neuropsychiatric Disease and Treatment*, *16*, 1043–1050. https://doi.org/10.2147/NDT.S185757

Attal, N. (2019). Pharmacological treatments of neuropathic pain: The latest recommendations. *Revue Neurologique*, *175*(1), 46–50. https://doi.org/10.1016/j.neurol.2018.08.005

Baciu, I., Maghiar, A., Teodorescu, A., & Junie, M. (1995). The effects of electroconvulsant shocks on phagocytic activity and on phagocytic response. *Romanian Journal of Physiology: Physiological Sciences*, *32*(1–4), 77–81.

Baddeley, A. (1992). Working Memory: The Interface between Memory and Cognition. *Journal of Cognitive Neuroscience*, *4*(3), 281–288. https://doi.org/10.1162/jocn.1992.4.3.281

Badimon, A., Strasburger, H. J., Ayata, P., Chen, X., Nair, A., Ikegami, A., Hwang, P., Chan, A. T., Graves, S. M., Uweru, J. O., Ledderose, C., Kutlu, M. G., Wheeler, M. A., Kahan, A., Ishikawa, M., Wang, Y.-C., Loh, Y.-H. E., Jiang, J. X., Surmeier, D. J., … Schaefer, A. (2020). Negative feedback control of neuronal activity by microglia. *Nature*, *586*(7829), Article 7829. https://doi.org/10.1038/s41586-020-2777-8

Baghai, T. C., Marcuse, A., Brosch, M., Schüle, C., Eser, D., Nothdurfter, C., Steng, Y., Noack, I., Pietschmann, K., Möller, H.-J., & Rupprecht, R. (2006). The influence of concomitant antidepressant medication on safety, tolerability and clinical effectiveness of electroconvulsive therapy. *The World Journal of Biological Psychiatry*, *7*(2), 82–90. https://doi.org/10.1080/15622970500213871

Bai, Y.-M., Su, T.-P., Tsai, S.-J., Wen-Fei, C., Li, C.-T., Pei-Chi, T., & Mu-Hong, C. (2014). Comparison of inflammatory cytokine levels among type I/type II and manic/hypomanic/euthymic/depressive states of bipolar disorder. *Journal of Affective Disorders*, *166*, 187–192. https://doi.org/10.1016/j.jad.2014.05.009

Bao, J.-M., Dang, Q., Lin, C.-J., Lo, U.-G., Feldkoren, B., Dang, A., Hernandez, E., Li, F., Panwar, V., Lee, C.-F., Cen, J.-J., Guan, B., Margulis, V., Kapur, P., Brekken, R. A., Luo, J.-H., Hsieh, J.-T., & Tan, W.-L. (2021). SPARC is a key mediator of TGF-β-induced renal cancer metastasis. *Journal of Cellular Physiology*, *236*(3), 1926–1938. https://doi.org/10.1002/jcp.29975

Barber, G. S., & Aaronson, S. T. (2022). The Emerging Field of Psychedelic Psychotherapy. *Current Psychiatry Reports*, *24*(10), 583–590. https://doi.org/10.1007/s11920-022-01363-y

Barbut Siva, J., Barba, T., Kettner, H., Kuc, J., Nutt, D. J., Carhart-Harris, R., & Erritzoe, D. (2024). Interactions between classic psychedelics and serotonergic antidepressants: Effects on the acute psychedelic subjective experience, well-being and depressive symptoms from a prospective survey study. *Journal of Psychopharmacology (Oxford, England)*, *38*(2), 145–155. https://doi.org/10.1177/02698811231224217

Bauer, M., & Pfennig, A. (2005). Epidemiology of Bipolar Disorders. *Epilepsia*, *46*(s4), 8–13. https://doi.org/10.1111/j.1528-1167.2005.463003.x

Baxter, A. J., Scott, K. M., Vos, T., & Whiteford, H. A. (2013). Global prevalence of anxiety disorders: A systematic review and meta-regression. *Psychological Medicine*, *43*(5), 897–910. https://doi.org/10.1017/S003329171200147X

Becher, B., Spath, S., & Goverman, J. (2017). Cytokine networks in neuroinflammation. *Nature Reviews Immunology*, *17*(1), 49–59. https://doi.org/10.1038/nri.2016.123

Beckers, L., Ory, D., Geric, I., Declercq, L., Koole, M., Kassiou, M., Bormans, G., & Baes, M. (2018). Increased Expression of Translocator Protein (TSPO) Marks Pro-inflammatory Microglia but Does Not Predict Neurodegeneration. *Molecular Imaging and Biology*, *20*(1), 94–102. https://doi.org/10.1007/s11307-017-1099-1

Beckett, C. W., & Niklison-Chirou, M. V. (2022). The role of immunomodulators in treatment-resistant depression: Case studies. *Cell Death Discovery*, *8*, 367. https://doi.org/10.1038/s41420-022-01147-6

Benedetti, F., Aggio, V., Pratesi, M. L., Greco, G., & Furlan, R. (2020). Neuroinflammation in Bipolar Depression. *Frontiers in Psychiatry*, *11*. https://doi.org/10.3389/fpsyt.2020.00071

Benjamin, J., Ben-Zion, I. Z., Karbofsky, E., & Dannon, P. (2000). Double-blind placebo-controlled pilot study of paroxetine for specific phobia. *Psychopharmacology*, *149*(2), 194–196. https://doi.org/10.1007/s002130000372

Berk, M., Dodd, S., Kauer-Sant'Anna, M., Malhi, G. S., Bourin, M., Kapczinski, F., & Norman, T. (2007). Dopamine dysregulation syndrome: Implications for a dopamine hypothesis of bipolar disorder. *Acta Psychiatrica Scandinavica*, *116*(s434), 41–49. https://doi.org/10.1111/j.1600-0447.2007.01058.x

Bhalla, S., Mehan, S., Khan, A., & Rehman, M. U. (2022). Protective role of IGF-1 and GLP-1 signaling activation in neurological dysfunctions. *Neuroscience and Biobehavioral Reviews*, *142*, 104896. https://doi.org/10.1016/j.neubiorev.2022.104896

Bienemann, B., Ruschel, N. S., Campos, M. L., Negreiros, M. A., & Mograbi, D. C. (2020). Self-reported negative outcomes of psilocybin users: A quantitative textual analysis. *PLOS ONE*, *15*(2), e0229067. https://doi.org/10.1371/journal.pone.0229067

Bird, C. I. V., Modlin, N. L., & Rucker, J. J. H. (2021). Psilocybin and MDMA for the treatment of trauma-related psychopathology. *International Review of Psychiatry*, *33*(3), 229–249. https://doi.org/10.1080/09540261.2021.1919062

Birkenhäger, T. K., & Mulder, P. G. (n.d.). *Efficacy and Tolerability of Tranylcypromine Versus Phenelzine: A Double-Blind Study in Antidepressant-Refractory Depressed Inpatients*.

Birmaher, B., Axelson, D. A., Monk, K., Kalas, C., Clark, D. B., Ehmann, M., Bridge, J., Heo, J., & Brent, D. A. (2003). Fluoxetine for the Treatment of Childhood Anxiety Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, *42*(4), 415–423. https://doi.org/10.1097/01.CHI.0000037049.04952.9F

Blackburn-Munro, G., & Blackburn-Munro, R. E. (2001). Chronic Pain, Chronic Stress and Depression: Coincidence or Consequence? *Journal of Neuroendocrinology*, *13*(12), 1009–1023. https://doi.org/10.1046/j.0007-1331.2001.00727.x

Bolwig, T. G., & Jørgensen, O. S. (1986). Electroconvulsive Therapy Effects on Synaptic Proteins. *Annals of the New York Academy of Sciences*, *462*(1), 140–146. https://doi.org/10.1111/j.1749-6632.1986.tb51248.x

Boullerne, A. I., & Feinstein, D. L. (2020). History of Neuroscience I. Pío del Río-Hortega (1882–1945): The Discoverer of Microglia and Oligodendroglia. *ASN Neuro, 12*, 1759091420953259. https://doi.org/10.1177/1759091420953259

Bowden, C. L. (2005). Atypical Antipsychotic Augmentation of Mood Stabilizer Therapy in Bipolar Disorder. *The Journal of Clinical Psychiatry*, *66*(suppl 3), 1627.

Bowden, C. L., & Singh, V. (2012). Lamotrigine (Lamictal IR) for the treatment of bipolar disorder. *Expert Opinion on Pharmacotherapy*, *13*(17), 2565–2571. https://doi.org/10.1517/14656566.2012.741590

Bowie, C. R., Reichenberg, A., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2006). Determinants of Real-World Functional Performance in Schizophrenia Subjects: Correlations With Cognition, Functional Capacity, and Symptoms. *American Journal of Psychiatry*, *163*(3), 418–425. https://doi.org/10.1176/appi.ajp.163.3.418

Boyd-Kimball, D., Gonczy, K., Lewis, B., Mason, T., Siliko, N., & Wolfe, J. (2019). Classics in Chemical Neuroscience: Chlorpromazine. *ACS Chemical Neuroscience*, *10*(1), 79–88. https://doi.org/10.1021/acschemneuro.8b00258

Boyer Edward W. & Shannon Michael. (2005). The Serotonin Syndrome. *New England Journal of Medicine*, *352*(11), 1112–1120. https://doi.org/10.1056/NEJMra041867

Boylan, L. S., Haskett, R. F., Mulsant, B. H., Greenberg, R. M., Prudic, J., Spicknall, K., Lisanby, S. H., & Sackeim, H. A. (2000). Determinants of Seizure Threshold in ECT: Benzodiazepine Use, Anesthetic Dosage, and Other Factors. *The Journal of ECT*, *16*(1), 3.

Bracci-Laudiero, L., & De Stefano, M. E. (2016). NGF in Early Embryogenesis, Differentiation, and Pathology in the Nervous and Immune Systems. *Current Topics in Behavioral Neurosciences*, *29*, 125–152. https://doi.org/10.1007/7854_2015_420

Brady, K. T. (n.d.). Posttraumatic Stress Disorder and Comorbidity: Recognizing the Many Faces of PTSD. *J Clin Psychiatry*.

Braff, D. L., & Light, G. A. (2004). Preattentional and attentional cognitive deficits as targets for treating schizophrenia. *Psychopharmacology*, *174*(1), 75–85. https://doi.org/10.1007/s00213-004-1848-0

Braga, R. J., Reynolds, G. P., & Siris, S. G. (2013). Anxiety comorbidity in schizophrenia. *Psychiatry Research*, *210*(1), 1–7. https://doi.org/10.1016/j.psychres.2013.07.030

Briggs, S. W., & Galanopoulou, A. S. (2011). Altered GABA Signaling in Early Life Epilepsies. *Neural Plasticity*, *2011*, e527605. https://doi.org/10.1155/2011/527605

Brown, A. S. (2012). Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. *Developmental Neurobiology*, *72*(10), 1272–1276. https://doi.org/10.1002/dneu.22024

Brown, A. S., & Patterson, P. H. (2011). Maternal Infection and Schizophrenia: Implications for Prevention. *Schizophrenia Bulletin*, *37*(2), 284–290. https://doi.org/10.1093/schbul/sbq146

Brown, A. S., Vinogradov, S., Kremen, W. S., Poole, J. H., Deicken, R. F., Penner, J. D., McKeague, I. W., Kochetkova, A., Kern, D., & Schaefer, C. A. (2009). Prenatal Exposure to Maternal Infection and Executive Dysfunction in Adult Schizophrenia. *American Journal of Psychiatry*, *166*(6), 683–690. https://doi.org/10.1176/appi.ajp.2008.08010089

Brus, O., Cao, Y., Hammar, Å., Landén, M., Lundberg, J., Nordanskog, P., & Nordenskjöld, A. (2019). Lithium for suicide and readmission prevention after electroconvulsive therapy for unipolar depression: Population-based register study. *BJPsych Open*, *5*(3), e46. https://doi.org/10.1192/bjo.2019.37

Brys, M., Fox, M. D., Agarwal, S., Biagioni, M., Dacpano, G., Kumar, P., Pirraglia, E., Chen, R., Wu, A., Fernandez, H., Shukla, A. W., Lou, J.-S., Gray, Z., Simon, D. K., Di Rocco, A., & Pascual-Leone, A. (2016). Multifocal repetitive TMS for motor and mood symptoms of Parkinson disease. *Neurology*, *87*(18), 1907–1915. https://doi.org/10.1212/WNL.0000000000003279

Bryson, E. O., Kellner, C. H., Li, E. H., Aloysi, A. S., & Majeske, M. (2018). Extreme variability in succinylcholine dose for muscle relaxation in electroconvulsive therapy. *Australasian Psychiatry*, *26*(4), 391–393. https://doi.org/10.1177/1039856218761301

Buoli, M., Dell'Osso, B., Bosi, M. F., & Altamura, C. (2010). Slow vs standard up-titration of paroxetine in the treatment of panic disorder: A prospective randomized trial. *Psychiatry and Clinical Neurosciences*, *64*(6), 612–619. https://doi.org/10.1111/j.1440-1819.2010.02136.x

Burmester, D. R., Madsen, M. K., Szabo, A., Aripaka, S. S., Stenbæk, D. S., Frokjaer, V. G., Elfving, B., Mikkelsen, J. D., Knudsen, G. M., & Fisher, P. M. (2023). Subacute effects of a single dose of psilocybin on biomarkers of inflammation in healthy humans: An open-label preliminary investigation. *Comprehensive Psychoneuroendocrinology*, *13*, 100163. https://doi.org/10.1016/j.cpnec.2022.100163

Butovsky, O., Jedrychowski, M. P., Moore, C. S., Cialic, R., Lanser, A. J., Gabriely, G., Koeglsperger, T., Dake, B., Wu, P. M., Doykan, C. E., Fanek, Z., Liu, L., Chen, Z., Rothstein, J. D., Ransohoff, R. M., Gygi, S. P., Antel, J. P., & Weiner, H. L. (2014). Identification of a Unique TGF-β Dependent Molecular and Functional Signature in Microglia. *Nature Neuroscience*, *17*(1), 131–143. https://doi.org/10.1038/nn.3599

Caddy, C., Amit, B. H., McCloud, T. L., Rendell, J. M., Furukawa, T. A., McShane, R., Hawton, K., & Cipriani, A. (2015). Ketamine and other glutamate receptor modulators for depression in adults. *Cochrane Database of Systematic Reviews*, *9*. https://doi.org/10.1002/14651858.CD011612.pub2

Calder, A., & Hasler, G. (2023). Extrapharmacological Safety Topics in Psychedelic-Assisted Psychotherapy. *JAMA Psychiatry*, *80*(8), 761–762. https://doi.org/10.1001/jamapsychiatry.2023.1031

Caldiroli, A., Capuzzi, E., Tagliabue, I., Capellazzi, M., Marcatili, M., Mucci, F., Colmegna, F., Clerici, M., Buoli, M., & Dakanalis, A. (2021). Augmentative Pharmacological Strategies in Treatment-Resistant Major Depression: A Comprehensive Review. *International Journal of Molecular Sciences*, *22*(23), 13070. https://doi.org/10.3390/ijms222313070

Caldwell, P. H., Sureshkumar, P., & Wong, W. C. (2016). Tricyclic and related drugs for nocturnal enuresis in children. *The Cochrane Database of Systematic Reviews*, *2016*(1), CD002117. https://doi.org/10.1002/14651858.CD002117.pub2

Callicott, J. H., Bertolino, A., Mattay, V. S., Langheim, F. J. P., Duyn, J., Coppola, R., Goldberg, T. E., & Weinberger, D. R. (2000). Physiological Dysfunction of the Dorsolateral Prefrontal Cortex in Schizophrenia Revisited. *Cerebral Cortex*, *10*(11), 1078–1092. https://doi.org/10.1093/cercor/10.11.1078

Canal, C. E., & Morgan, D. (2012). Head-twitch response in rodents induced by the hallucinogen 2,5-dimethoxy-4-iodoamphetamine: A comprehensive history, a re-evaluation of mechanisms, and its utility as a model. *Drug Testing and Analysis*, *4*(7–8), 556–576. https://doi.org/10.1002/dta.1333

Canal, C. E., & Murnane, K. S. (2017). The serotonin 5-HT2C receptor and the non-addictive nature of classic hallucinogens. *Journal of Psychopharmacology (Oxford, England)*, *31*(1), 127–143. https://doi.org/10.1177/0269881116677104

Cano, M., & Camprodon, J. A. (2023). Understanding the Mechanisms of Action of Electroconvulsive Therapy: Revisiting Neuroinflammatory and Neuroplasticity Hypotheses. *JAMA Psychiatry*, *80*(6), 643–644. https://doi.org/10.1001/jamapsychiatry.2023.0728

Carbon, M., & Correll, C. U. (2014). Thinking and acting beyond the positive: The role of the cognitive and negative symptoms in schizophrenia. *CNS Spectrums*, *19*(S1), 35–53. https://doi.org/10.1017/S1092852914000601

Carbonaro, T. M., Johnson, M. W., & Griffiths, R. R. (2020). Subjective features of the psilocybin experience that may account for its self-administration by humans: A double-blind comparison of psilocybin and dextromethorphan. *Psychopharmacology*, *237*(8), 2293–2304. https://doi.org/10.1007/s00213-020-05533-9

Cardozo, P. L., de Lima, I. B. Q., Maciel, E. M. A., Silva, N. C., Dobransky, T., & Ribeiro, F. M. (2019). Synaptic Elimination in Neurological Disorders. *Current Neuropharmacology*, *17*(11), 1071–1095. https://doi.org/10.2174/1570159X17666190603170511

Case, K. C., Beltman, R. J., Pflum, M. K. H., & Greenberg, M. L. (2023). Valproate regulates inositol synthesis by reducing expression of myo-inositol-3-phosphate synthase. *Scientific Reports*, *13*(1), 14844. https://doi.org/10.1038/s41598-023-41936-2

Chamberlain, S. R., & Baldwin, D. S. (2021). Monoamine Oxidase Inhibitors (MAOIs) in Psychiatric Practice: How to Use them Safely and Effectively. *CNS Drugs*, *35*(7), 703–716. https://doi.org/10.1007/s40263-021-00832-x

Chan, R. C. K., Chen, E. Y. H., & Law, C. W. (2006). Specific executive dysfunction in patients with first-episode medication-naïve schizophrenia. *Schizophrenia Research*, *82*(1), 51–64. https://doi.org/10.1016/j.schres.2005.09.020

Charney, D. S., Krystal, J. J., Southwick, S. M., Nagy, L. M., Woods, S. W., & Heninger, G. R. (1990). Serotonin Function in Panic and Generalized Anxiety Disorders. *Psychiatric Annals*, *20*(10), 593–602. https://doi.org/10.3928/0048-5713-19901001-11

Chatham, A. N., Shafi, H., & Hermida, A. P. (2022). The Use of ECT in the Elderly—Looking Beyond Depression. *Current Psychiatry Reports*, *24*(9), 451–461. https://doi.org/10.1007/s11920-022-01353-0

Chawla, N. (2020). Anesthesia for Electroconvulsive Therapy. *Anesthesiology Clinics*, *38*(1), 183–195. https://doi.org/10.1016/j.anclin.2019.10.007

Chen, C.-K., Yang, S.-Y., Park, S.-C., Jang, O.-J., Zhu, X., Xiang, Y.-T., Ouyang, W.-C., Javed, A., Khan, M. N. S., Grover, S., Avasthi, A., Kallivayalil, R. A., Chee, K. Y., Chemi, N., Kato, T. A., Hayakawa, K., Pariwatcharakul, P., Maramis, M., Seneviratne, L., … Lin, S.-K. (2023). Clinical use of mood stabilizers beyond treatment for bipolar disorder: The REAP-MS study. *Asian Journal of Psychiatry*, *85*, 103613. https://doi.org/10.1016/j.ajp.2023.103613

Chen, Q., Ren, L., Min, S., Hao, X., Chen, H., & Deng, J. (2018). Changes in synaptic plasticity are associated with electroconvulsive shock-induced learning and memory impairment in rats with depression-like behavior. *Neuropsychiatric Disease and Treatment*, *Volume 14*, 1737–1746. https://doi.org/10.2147/NDT.S163756

Chen, Z., & Trapp, B. D. (2016). Microglia and neuroprotection. *Journal of Neurochemistry*, *136 Suppl 1*, 10–17. https://doi.org/10.1111/jnc.13062

Cheslack-Postava, K., & Brown, A. S. (2022). Prenatal infection and schizophrenia: A decade of further progress. *Schizophrenia Research*, *247*, 7–15. https://doi.org/10.1016/j.schres.2021.05.014

Chiao, S., Isenberg, K., & North, C. S. (2020). Psychotropic Medication Effects on Seizure Threshold and Seizure Duration During Electroconvulsive Therapy Stimulus Titration. *The Journal of ECT*, *36*(2), 115. https://doi.org/10.1097/YCT.0000000000000621

Chien, H.-C., Ku, C.-H., Lu, R.-B., Chu, H., Tao, Y.-H., & Chou, K.-R. (2003). Effects of social skills training on improving social skills of patients with schizophrenia. *Archives of Psychiatric Nursing*, *17*(5), 228–236. https://doi.org/10.1016/S0883-9417(03)00095-5

Chiesa, A., Chierzi, F., De Ronchi, D., & Serretti, A. (2012). Quetiapine for bipolar depression: A systematic review and meta-analysis. *International Clinical Psychopharmacology*, *27*(2), 76. https://doi.org/10.1097/YIC.0b013e32834e4c56

Chinchilla Alfaro, K., van Hunsel, F., & Ekhart, C. (2022). Persistent sexual dysfunction after SSRI withdrawal: A scoping review and presentation of 86 cases from the Netherlands. *Expert Opinion on Drug Safety*, *21*(4), 553–561. https://doi.org/10.1080/14740338.2022.2007883

Cipriani, A., Furukawa, T. A., Salanti, G., Geddes, J. R., Higgins, J. P., Churchill, R., Watanabe, N., Nakagawa, A., Omori, I. M., McGuire, H., Tansella, M., & Barbui, C. (2009). Comparative efficacy and acceptability of 12 new-generation antidepressants: A multiple-treatments meta-analysis. *The Lancet*, *373*(9665), 746–758. https://doi.org/10.1016/S0140-6736(09)60046-5

Clark, L., Iversen, S. D., & Goodwin, G. M. (2002). Sustained attention deficit in bipolar disorder. *The British Journal of Psychiatry*, *180*(4), 313–319. https://doi.org/10.1192/bjp.180.4.313

Clayton, A. H., El Haddad, S., Iluonakhamhe, J.-P., Ponce Martinez, C., & Schuck, A. E. (2014). Sexual dysfunction associated with major depressive disorder and antidepressant treatment. *Expert Opinion on Drug Safety*, *13*(10), 1361–1374. https://doi.org/10.1517/14740338.2014.951324

Cole, C. E., Patterson, R. M., Craig, J. B., Thomas, W. E., Ristine, L. P., Stahly, M., & Pasamanick, B. (1959). A controlled study of efficacy of iproniazid in treatment of depression. *A.M.A. Archives of General Psychiatry*, *1*, 513–518. https://doi.org/10.1001/archpsyc.1959.03590050081010

Collingridge, G. L., & Peineau, S. (2014). Strippers Reveal Their Depressing Secrets: Removing AMPA Receptors. *Neuron*, *82*(1), 3–6. https://doi.org/10.1016/j.neuron.2014.03.019

Colucci-D'Amato, L., Speranza, L., & Volpicelli, F. (2020). Neurotrophic Factor BDNF, Physiological Functions and Therapeutic Potential in Depression, Neurodegeneration and Brain Cancer. *International Journal of Molecular Sciences*, *21*(20), 7777. https://doi.org/10.3390/ijms21207777

Comer, A. L., Carrier, M., Tremblay, M.-È., & Cruz-Martín, A. (2020). The Inflamed Brain in Schizophrenia: The Convergence of Genetic and Environmental Risk Factors That Lead

to Uncontrolled Neuroinflammation. *Frontiers in Cellular Neuroscience*, *14*. https://doi.org/10.3389/fncel.2020.00274

Cooper, C., Jones, L., Dunn, E., Forty, L., Haque, S., Oyebode, F., Craddock, N., & Jones, I. (2007). Clinical presentation of postnatal and non-postnatal depressive episodes. *Psychological Medicine*, *37*(9), 1273–1280. https://doi.org/10.1017/S0033291707000116

Corekli Kaymakci, E., Kok Kendirlioglu, B., & Kucukgoncu, S. (2023). Parkinsonism Symptoms After Exposure to Low-Dose Aripiprazole. *Journal of Clinical Psychopharmacology*, *43*(1), 69. https://doi.org/10.1097/JCP.0000000000001641

Cosci, F., & Fava, G. A. (2021). When Anxiety and Depression Coexist: The Role of Differential Diagnosis Using Clinimetric Criteria. *Psychotherapy and Psychosomatics*, *90*(5), 308–317. https://doi.org/10.1159/000517518

Coskuner, E. R., Culha, M. G., Ozkan, B., & Kaleagasi, E. O. (2018). Post-SSRI Sexual Dysfunction: Preclinical to Clinical. Is It Fact or Fiction? *Sexual Medicine Reviews*, *6*(2), 217–223. https://doi.org/10.1016/j.sxmr.2017.11.004

Costello, E. J., Pine, D. S., Hammen, C., March, J. S., Plotsky, P. M., Weissman, M. M., Biederman, J., Goldsmith, H. H., Kaufman, J., Lewinsohn, P. M., Hellander, M., Hoagwood, K., Koretz, D. S., Nelson, C. A., & Leckman, J. F. (2002). Development and natural history of mood disorders. *Biological Psychiatry*, *52*(6), 529–542. https://doi.org/10.1016/S0006-3223(02)01372-0

Cousins, D. A., Butts, K., & Young, A. H. (2009). The role of dopamine in bipolar disorder. *Bipolar Disorders*, *11*(8), 787–806. https://doi.org/10.1111/j.1399-5618.2009.00760.x

Crapser, J. D., Arreola, M. A., Tsourmas, K. I., & Green, K. N. (2021). Microglia as hackers of the matrix: Sculpting synapses and the extracellular space. *Cellular & Molecular Immunology*, *18*(11), 2472–2488. https://doi.org/10.1038/s41423-021-00751-3

Cumper, S. K., Ahle, G. M., Liebman, L. S., & Kellner, C. H. (2014). Electroconvulsive Therapy (ECT) in Parkinson's Disease: ECS and Dopamine Enhancement. *The Journal of ECT*, *30*(2), 122. https://doi.org/10.1097/YCT.0000000000000142

Cyrino, L. A. R., Delwing-de Lima, D., Ullmann, O. M., & Maia, T. P. (2021). Concepts of Neuroinflammation and Their Relationship With Impaired Mitochondrial Functions in Bipolar Disorder. *Frontiers in Behavioral Neuroscience*, *15*. https://doi.org/10.3389/fnbeh.2021.609487

Dannon, P. N., Lowengrub, K., Iancu, I., & Kotler, M. (2004). Paroxetine in panic disorder: Clinical management and long-term follow-up. *Expert Review of Neurotherapeutics*, *4*(2), 191–198. https://doi.org/10.1586/14737175.4.2.191

Darowski, A., Chambers, S.-A. C. F., & Chambers, D. J. (2009). Antidepressants and Falls in the Elderly. *Drugs & Aging*, *26*(5), 381–394. https://doi.org/10.2165/00002512-200926050-00002

Das, S. K., Sampath, A., Zaman, S. U., Pati, A. K., & Atal, S. (2023). Genetic predisposition for the development of lamotrigine-induced Stevens–Johnson syndrome/toxic epidermal necrolysis: A systematic review and meta-analysis. *Personalized Medicine*, *20*(2), 201–213. https://doi.org/10.2217/pme-2022-0126

Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, *78*(5), 481–489. https://doi.org/10.1001/jamapsychiatry.2020.3285

De Gregorio, D., Comai, S., Posa, L., & Gobbi, G. (2016). d-Lysergic Acid Diethylamide (LSD) as a Model of Psychosis: Mechanism of Action and Pharmacology. *International Journal of Molecular Sciences*, *17*(11), 1953. https://doi.org/10.3390/ijms17111953

De La Fuente-Sandoval, C., León-Ortiz, P., Azcárraga, M., Stephano, S., Favila, R., Díaz-Galvis, L., Alvarado-Alanis, P., Ramírez-Bermúdez, J., & Graff-Guerrero, A. (2013). Glutamate Levels in the Associative Striatum Before and After 4 Weeks of Antipsychotic Treatment in First-Episode Psychosis: A Longitudinal Proton Magnetic Resonance Spectroscopy Study. *JAMA Psychiatry*, *70*(10), 1057. https://doi.org/10.1001/jamapsychiatry.2013.289

De Vane, C. L., Liston, H. L., & Markowitz, J. S. (2002). Clinical Pharmacokinetics of Sertraline. *Clinical Pharmacokinetics*, *41*(15), 1247–1266. https://doi.org/10.2165/00003088-200241150-00002

DeBattista, C. (2005). Executive dysfunction in major depressive disorder. *Expert Review of Neurotherapeutics*, *5*(1), 79–83. https://doi.org/10.1586/14737175.5.1.79

DeGeorge, K. C., Grover, M., & Streeter, G. S. (2022). Generalized Anxiety Disorder and Panic Disorder in Adults. *American Family Physician*, *106*(2), 157–164.

Degraff, Z., Souza, G. S., Santos, N. A., Shoshina, I. I., Felisberti, F. M., Fernandes, T. P., & Sigurdsson, G. (2023). Brain atrophy and cognitive decline in bipolar disorder: Influence of medication use, symptomatology and illness duration. *Journal of Psychiatric Research*, *163*, 421–429. https://doi.org/10.1016/j.jpsychires.2023.05.074

Delamarre, L., Galvao, F., Gohier, B., Poulet, E., & Brunelin, J. (2019). How Much Do Benzodiazepines Matter for Electroconvulsive Therapy in Patients With Major Depression? *The Journal of ECT*, *35*(3), 184. https://doi.org/10.1097/YCT.0000000000000574

Deng, Z.-D., Robins, P. L., Regenold, W., Rohde, P., Dannhauer, M., & Lisanby, S. H. (2024). How electroconvulsive therapy works in the treatment of depression: Is it the seizure, the electricity, or both? *Neuropsychopharmacology*, *49*(1), Article 1. https://doi.org/10.1038/s41386-023-01677-2

Derecki, N. C., Cronk, J. C., Lu, Z., Xu, E., Abbott, S. B. G., Guyenet, P. G., & Kipnis, J. (2012). Wild type microglia arrest pathology in a mouse model of Rett syndrome. *Nature*, *484*(7392), 105–109. https://doi.org/10.1038/nature10907

Desfossés, C.-Y., Peredo, R., Chabot, A., Carmel, J.-P., Tremblay, P.-M., Mérette, C., Picher, G., Lachance, I., Patry, S., & Lemasson, M. (2021). The Pattern of Change in Depressive Symptoms and Inflammatory Markers After Electroconvulsive Therapy: A Systematic Review. *The Journal of ECT*, *37*(4), 291. https://doi.org/10.1097/YCT.0000000000000782

Dey, A., & Hankey Giblin, P. A. (2018). Insights into Macrophage Heterogeneity and Cytokine-Induced Neuroinflammation in Major Depressive Disorder. *Pharmaceuticals*, *11*(3), Article 3. https://doi.org/10.3390/ph11030064

Dilsaver, S. C., & Alessi, N. E. (1988). Antipsychotic withdrawal symptoms: Phenomenology and pathophysiology. *Acta Psychiatrica Scandinavica*, *77*(3), 241–246. https://doi.org/10.1111/j.1600-0447.1988.tb05116.x

Dimitrova-Shumkovska, J., Krstanoski, L., & Veenman, L. (2020). Diagnostic and Therapeutic Potential of TSPO Studies Regarding Neurodegenerative Diseases, Psychiatric Disorders, Alcohol Use Disorders, Traumatic Brain Injury, and Stroke: An Update. *Cells*, *9*(4), 870. https://doi.org/10.3390/cells9040870

Ding, H., Chen, J., Su, M., Lin, Z., Zhan, H., Yang, F., Li, W., Xie, J., Huang, Y., Liu, X., Liu, B., & Zhou, X. (2020). BDNF promotes activation of astrocytes and microglia contributing to neuroinflammation and mechanical allodynia in cyclophosphamide-induced cystitis. *Journal of Neuroinflammation*, *17*(1), 19. https://doi.org/10.1186/s12974-020-1704-0

Dinwiddie, S. H., Huo, D., & Gottlieb, O. (2010). The Course of Myalgia and Headache After Electroconvulsive Therapy. *The Journal of ECT*, *26*(2), 116. https://doi.org/10.1097/YCT.0b013e3181b07c0a

DiSabato, D. J., Quan, N., & Godbout, J. P. (2016). Neuroinflammation: The devil is in the details. *Journal of Neurochemistry*, *139*(S2), 136–153. https://doi.org/10.1111/jnc.13607

Discussion: Investigation of Outcome of Treatment of Depression [Abridged]. (1959). *Proceedings of the Royal Society of Medicine*, *52*(8), 583–587.

Divac, N., Prostran, M., Jakovcevski, I., & Cerovac, N. (2014). Second-Generation Antipsychotics and Extrapyramidal Adverse Effects. *BioMed Research International*, *2014*, e656370. https://doi.org/10.1155/2014/656370

Dixon, M. L., Thiruchselvam, R., Todd, R., & Christoff, K. (2017). Emotion and the prefrontal cortex: An integrative review. *Psychological Bulletin*, *143*(10), 1033–1081. https://doi.org/10.1037/bul0000096

Dols, A., Sienaert, P., van Gerven, H., Schouws, S., Stevens, A., Kupka, R., & Stek, M. L. (2013). The prevalence and management of side effects of lithium and anticonvulsants as mood stabilizers in bipolar disorder from a clinical perspective: A review. *International Clinical Psychopharmacology*, *28*(6), 287. https://doi.org/10.1097/YIC.0b013e32836435e2

Domingos, L. B., Müller, H. K., da Silva, N. R., Filiou, M. D., Nielsen, A. L., Guimarães, F. S., Wegener, G., & Joca, S. (2024). Repeated cannabidiol treatment affects neuroplasticity

and endocannabinoid signaling in the prefrontal cortex of the Flinders Sensitive Line (FSL) rat model of depression. *Neuropharmacology*, *248*, 109870. https://doi.org/10.1016/j.neuropharm.2024.109870

Domino, G. (1983). Impact of the Film, "One Flew over the Cuckoo's Nest," on Attitudes towards Mental Illness. *Psychological Reports*, *53*(1), 179–182. https://doi.org/10.2466/pr0.1983.53.1.179

dos Santos, R. G., Hallak, J. E., Baker, G., & Dursun, S. (2021). Hallucinogenic/psychedelic 5HT2A receptor agonists as rapid antidepressant therapeutics: Evidence and mechanisms of action. *Journal of Psychopharmacology*, *35*(4), 453–458. https://doi.org/10.1177/0269881120986422

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A Meta-Analysis of Cytokines in Major Depression. *Biological Psychiatry*, *67*(5), 446–457. https://doi.org/10.1016/j.biopsych.2009.09.033

Du, Y., Li, Y., Zhao, X., Yao, Y., Wang, B., Zhang, L., & Wang, G. (2023). Psilocybin facilitates fear extinction in mice by promoting hippocampal neuroplasticity. *Chinese Medical Journal*, *136*(24), 2983–2992. https://doi.org/10.1097/CM9.0000000000002647

Duma, A., Maleczek, M., Panjikaran, B., Herkner, H., Karrison, T., & Nagele, P. (2019). Major Adverse Cardiac Events and Mortality Associated with Electroconvulsive Therapy: A Systematic Review and Meta-analysis. *Anesthesiology*, *130*(1), 83–91. https://doi.org/10.1097/ALN.0000000000002488

Duman, C. H., & Duman, R. S. (2015). Spine synapse remodeling in the pathophysiology and treatment of depression. *Neuroscience Letters*, *601*, 20–29. https://doi.org/10.1016/j.neulet.2015.01.022

Duman, R. S., Aghajanian, G. K., Sanacora, G., & Krystal, J. H. (2016). Synaptic plasticity and depression: New insights from stress and rapid-acting antidepressants. *Nature Medicine*, *22*(3), Article 3. https://doi.org/10.1038/nm.4050

Dunn, A. L., Trivedi, M. H., Kampert, J. B., Clark, C. G., & Chambliss, H. O. (2005). Exercise treatment for depression: Efficacy and dose response. *American Journal of Preventive Medicine*, *28*(1), 1–8. https://doi.org/10.1016/j.amepre.2004.09.003

Eaton, W. W., Bienvenu, O. J., & Miloyan, B. (2018). Specific phobias. *The Lancet Psychiatry*, *5*(8), 678–686. https://doi.org/10.1016/S2215-0366(18)30169-X

Edinoff, A., Wu, N., deBoisblanc, C., Feltner, C. O., Norder, M., Tzoneva, V., Kaye, A. M., Cornett, E. M., Kaye, A. D., Viswanath, O., & Urits, I. (2020). Lumateperone for the Treatment of Schizophrenia. *Psychopharmacology Bulletin*, *50*(4), 32–59.

Efficacy and safety of electroconvulsive therapy in depressive disorders: A systematic review and meta-analysis. (2003). *The Lancet*, *361*(9360), 799–808. https://doi.org/10.1016/S0140-6736(03)12705-5

Eger, E. I. (1984). The pharmacology of isoflurane. *British Journal of Anaesthesia*, *56 Suppl 1*, 71S-99S.

Emsley, R., Chiliza, B., Asmal, L., & Harvey, B. H. (2013). The nature of relapse in schizophrenia. *BMC Psychiatry*, *13*(1), 50. https://doi.org/10.1186/1471-244X-13-50

Espinoza, R. T., & Kellner, C. H. (2022). Electroconvulsive Therapy. *The New England Journal of Medicine*, *386*(7), 667–672. https://doi.org/10.1056/NEJMra2034954

Fakhoury, M. (2020). Inflammation in Alzheimer's Disease. *Current Alzheimer Research*, *17*(11), 959–961. https://doi.org/10.2174/1567205017112102101110513

Fava, G. A., Gatti, A., Belaise, C., Guidi, J., & Offidani, E. (2015). Withdrawal Symptoms after Selective Serotonin Reuptake Inhibitor Discontinuation: A Systematic Review. *Psychotherapy and Psychosomatics*, *84*(2), 72–81. https://doi.org/10.1159/000370338

Fava, M. (2000). Weight gain and antidepressants. *The Journal of Clinical Psychiatry*, *61 Suppl 11*, 37–41.

Feighner, J. P. (1999). Mechanism of Action of Antidepressant Medications. *The Journal of Clinical Psychiatry*, *60*(suppl 4), 4–11.

Ferensztajn-Rochowiak, E., & Rybakowski, J. K. (2023). Long-Term Lithium Therapy: Side Effects and Interactions. *Pharmaceuticals*, *16*(1), Article 1. https://doi.org/10.3390/ph16010074

Ferensztajn-Rochowiak, E., Szczepankiewicz, A., & Rybakowski, J. (2022). Lithium treatment and stress response in bipolar disorder. *Pharmacotherapy in Psychiatry and Neurology/Farmakoterapia w Psychiatrii i Neurologii*, *37*(3), 235–243. https://doi.org/10.5114/fpn.2021.115646

Fernstrom, M. H., & Kupfer, D. J. (1988). Antidepressant-induced weight gain: A comparison study of four medications. *Psychiatry Research*, *26*(3), 265–271. https://doi.org/10.1016/0165-1781(88)90120-5

Ferraguti, G., Terracina, S., Micangeli, G., Lucarelli, M., Tarani, L., Ceccanti, M., Spaziani, M., D'Orazi, V., Petrella, C., & Fiore, M. (2023). NGF and BDNF in pediatrics syndromes. *Neuroscience and Biobehavioral Reviews*, *145*, 105015. https://doi.org/10.1016/j.neubiorev.2022.105015

Fiaturi, N., & Greenblatt, D. J. (2019). Therapeutic Drug Monitoring of Antidepressants. In M. Macaluso & S. H. Preskorn (Eds.), *Antidepressants: From Biogenic Amines to New Mechanisms of Action* (pp. 115–133). Springer International Publishing. https://doi.org/10.1007/164_2018_161

Fico, G., Anmella, G., Pacchiarotti, I., Verdolini, N., Sagué-Vilavella, M., Corponi, F., Manchia, M., Vieta, E., & Murru, A. (2020). The biology of aggressive behavior in bipolar disorder: A systematic review. *Neuroscience & Biobehavioral Reviews*, *119*, 9–20. https://doi.org/10.1016/j.neubiorev.2020.09.015

Fierro, A., Matthies, D. J., Cassels, B. K., Jaque, P., & Zapata-Torres, G. (2021). 5-HT2 Receptor Subfamily and the Halogen Bond Promise. *Journal of Chemical Information and Modeling*, *61*(10), 5001–5012. https://doi.org/10.1021/acs.jcim.1c00466

Fink, M. (2001). Convulsive therapy: A review of the first 55 years. *Journal of Affective Disorders*, *63*(1), 1–15. https://doi.org/10.1016/S0165-0327(00)00367-0

Flaum, M., & Schultz, S. K. (1996). The Core Symptoms of Schizophrenia. *Annals of Medicine*, *28*(6), 525–531. https://doi.org/10.3109/07853899608999116

Fonseka, L. N., & Woo, B. K. (2023). Therapeutic role of psilocybin and 3,4-methylenedioxymethamphetamine in trauma: A literature review. *World Journal of Psychiatry*, *13*(5), 182–190. https://doi.org/10.5498/wjp.v13.i5.182

Foong, A.-L., Grindrod, K. A., Patel, T., & Kellar, J. (2018). Demystifying serotonin syndrome (or serotonin toxicity). *Canadian Family Physician*, *64*(10), 720–727.

Franklin, R., Zorowitz, S., Corse, A. K., Widge, A. S., & Deckersbach, T. (2015). Lurasidone for the treatment of bipolar depression: An evidence-based review. *Neuropsychiatric Disease and Treatment*, *11*, 2143–2152. https://doi.org/10.2147/NDT.S50961

Freidel, N., Kreuder, L., Rabinovitch, B. S., Chen, F. Y., Huang, R. S. T., & Lewis, E. C. (2023). Psychedelics, epilepsy, and seizures: A review. *Frontiers in Pharmacology*, *14*, 1326815. https://doi.org/10.3389/fphar.2023.1326815

Friedman, N. P., & Robbins, T. W. (2022). The role of prefrontal cortex in cognitive control and executive function. *Neuropsychopharmacology*, *47*(1), 72–89. https://doi.org/10.1038/s41386-021-01132-0

Fu, R., Shen, Q., Xu, P., Luo, J. J., & Tang, Y. (2014). Phagocytosis of microglia in the central nervous system diseases. *Molecular Neurobiology*, *49*(3), 1422–1434. https://doi.org/10.1007/s12035-013-8620-6

Fuente-Sandoval, C. D. L., León-Ortiz, P., Favila, R., Stephano, S., Mamo, D., Ramírez-Bermúdez, J., & Graff-Guerrero, A. (2011). Higher Levels of Glutamate in the Associative-Striatum of Subjects with Prodromal Symptoms of Schizophrenia and Patients with First-Episode Psychosis. *Neuropsychopharmacology*, *36*(9), 1781–1791. https://doi.org/10.1038/npp.2011.65

Gallagher, D., Norman, A. A., Woodard, C. L., Yang, G., Gauthier-Fisher, A., Fujitani, M., Vessey, J. P., Cancino, G. I., Sachewsky, N., Woltjen, K., Fatt, M. P., Morshead, C. M., Kaplan, D. R., & Miller, F. D. (2013). Transient Maternal IL-6 Mediates Long-Lasting Changes in Neural Stem Cell Pools by Deregulating an Endogenous Self-Renewal Pathway. *Cell Stem Cell*, *13*(5), 564–576. https://doi.org/10.1016/j.stem.2013.10.002

Gandhi, K., Nguyen, K., Driscoll, M., Islam, Z., & Maru, S. (2023). Catatonia, Pregnancy, and Electroconvulsive Therapy (ECT). *Case Reports in Psychiatry*, *2023*, e9601642. https://doi.org/10.1155/2023/9601642

Gao, K., Kemp, D. E., Wu, R., & Calabrese, J. R. (2015). Mood Stabilizers. In *Psychiatry* (pp. 2129–2158). John Wiley & Sons, Ltd. https://doi.org/10.1002/9781118753378.ch105

Garakani, A., Buono, F. D., Salehi, M., Funaro, M. C., Klimowicz, A., Sharma, H., Faria, C. G. F., Larkin, K., & Freire, R. C. (n.d.). Antipsychotic agents in anxiety disorders: An umbrella review. *Acta Psychiatrica Scandinavica*, *n/a*(n/a). https://doi.org/10.1111/acps.13669

Garaschuk, O., & Verkhratsky, A. (2019). Physiology of Microglia. In O. Garaschuk & A. Verkhratsky (Eds.), *Microglia: Methods and Protocols* (pp. 27–40). Springer. https://doi.org/10.1007/978-1-4939-9658-2_3

Garg, K., Rajan, R., & Singh, M. (2021). Drug-Induced Parkinsonism. *Neurology India*, *69*(2), 437. https://doi.org/10.4103/0028-3886.314567

Gärtner, M., Ghisu, M. E., Scheidegger, M., Bönke, L., Fan, Y., Stippl, A., Herrera-Melendez, A.-L., Metz, S., Winnebeck, E., Fissler, M., Henning, A., Bajbouj, M., Borgwardt, K., Barnhofer, T., & Grimm, S. (2018). Aberrant working memory processing in major depression: Evidence from multivoxel pattern classification. *Neuropsychopharmacology*, *43*(9), 1972. https://doi.org/10.1038/s41386-018-0081-1

Gashi, L., Sandberg, S., & Pedersen, W. (2021). Making "bad trips" good: How users of psychedelics narratively transform challenging trips into valuable experiences. *International Journal of Drug Policy*, *87*, 102997. https://doi.org/10.1016/j.drugpo.2020.102997

Gattuso, J. J., Perkins, D., Ruffell, S., Lawrence, A. J., Hoyer, D., Jacobson, L. H., Timmermann, C., Castle, D., Rossell, S. L., Downey, L. A., Pagni, B. A., Galvão-Coelho, N. L., Nutt, D., & Sarris, J. (2023). Default Mode Network Modulation by Psychedelics: A Systematic Review. *International Journal of Neuropsychopharmacology*, *26*(3), 155–188. https://doi.org/10.1093/ijnp/pyac074

Gay, F., Romeo, B., Martelli, C., Benyamina, A., & Hamdani, N. (2021). Cytokines changes associated with electroconvulsive therapy in patients with treatment-resistant depression: A Meta-analysis. *Psychiatry Research*, *297*, 113735. https://doi.org/10.1016/j.psychres.2021.113735

Geloso, M. C., & D'Ambrosi, N. (2021). Microglial Pruning: Relevance for Synaptic Dysfunction in Multiple Sclerosis and Related Experimental Models. *Cells*, *10*(3), 686. https://doi.org/10.3390/cells10030686

Germann, M., Brederoo, S. G., & Sommer, I. E. C. (2021). Abnormal synaptic pruning during adolescence underlying the development of psychotic disorders. *Current Opinion in Psychiatry*, *34*(3), 222–227. https://doi.org/10.1097/YCO.0000000000000696

Geyer, M. A. (2023). A Brief Historical Overview of Psychedelic Research. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. https://doi.org/10.1016/j.bpsc.2023.11.003

Ghaemi, S. N., & Goodwin, F. K. (1999). Use of Atypical Antipsychotic Agents in Bipolar and Schizoaffective Disorders: Review of the Empirical Literature. *Journal of Clinical Psychopharmacology*, *19*(4), 354.

Gibb, R., & Kolb, B. (1998). A method for vibratome sectioning of Golgi–Cox stained whole rat brain. *Journal of Neuroscience Methods*, *79*(1), 1–4. https://doi.org/10.1016/S0165-0270(97)00163-5

Gideons, E. S., Lin, P.-Y., Mahgoub, M., Kavalali, E. T., & Monteggia, L. M. (2017). Chronic lithium treatment elicits its antimanic effects via BDNF-TrkB dependent synaptic downscaling. *eLife*, *6*, e25480. https://doi.org/10.7554/eLife.25480

Gillman, P. K. (2005). Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *BJA: British Journal of Anaesthesia*, *95*(4), 434–441. https://doi.org/10.1093/bja/aei210

Gillman, P. K. (2007). Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *British Journal of Pharmacology*, *151*(6), 737–748. https://doi.org/10.1038/sj.bjp.0707253

Ginhoux, F., Lim, S., Hoeffel, G., Low, D., & Huber, T. (2013). Origin and differentiation of microglia. *Frontiers in Cellular Neuroscience*, *7*. https://doi.org/10.3389/fncel.2013.00045

Ginsberg, S. D., Hemby, S. E., & Smiley, J. F. (2012). Expression profiling in neuropsychiatric disorders: Emphasis on glutamate receptors in bipolar disorder. *Pharmacology Biochemistry and Behavior*, *100*(4), 705–711. https://doi.org/10.1016/j.pbb.2011.09.015

Gitlin, M. (2016). Lithium side effects and toxicity: Prevalence and management strategies. *International Journal of Bipolar Disorders*, *4*(1), 27. https://doi.org/10.1186/s40345-016-0068-y

Gjerde, P. F. (1983). Attentional capacity dysfunction and arousal in schizophrenia. *Psychological Bulletin*, *93*(1), 57–72. https://doi.org/10.1037/0033-2909.93.1.57

Glebov, K., Löchner, M., Jabs, R., Lau, T., Merkel, O., Schloss, P., Steinhäuser, C., & Walter, J. (2015). Serotonin stimulates secretion of exosomes from microglia cells. *Glia*, *63*(4), 626–634. https://doi.org/10.1002/glia.22772

Glue, P., Gostello, M. J., Pert, A., Mele, A., & Nutt, D. J. (1990). Regional neurotransmitter responses after acute and chronic electroconvulsive shock. *Psychopharmacology*, *100*(1), 60–65. https://doi.org/10.1007/BF02245791

Godlewska, B. R., Norbury, R., Selvaraj, S., Cowen, P. J., & Harmer, C. J. (2012). Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. *Psychological Medicine*, *42*(12), 2609–2617. https://doi.org/10.1017/S0033291712000591

Goff, D. C., & Coyle, J. T. (2001). The Emerging Role of Glutamate in the Pathophysiology and Treatment of Schizophrenia. *American Journal of Psychiatry*, *158*(9), 1367–1377. https://doi.org/10.1176/appi.ajp.158.9.1367

Goldberg, J. F. (2024). Valproate and Weight Gain: A New Look at an Old Problem. *The Journal of Clinical Psychiatry*, *85*(2), 53864. https://doi.org/10.4088/JCP.23com15213

Gonda, X., Pompili, M., Serafini, G., Montebovi, F., Campi, S., Dome, P., Duleba, T., Girardi, P., & Rihmer, Z. (2012). Suicidal behavior in bipolar disorder: Epidemiology, characteristics and major risk factors. *Journal of Affective Disorders*, *143*(1), 16–26. https://doi.org/10.1016/j.jad.2012.04.041

Gong, R., Wang, P., & Dworkin, L. (2016). What we need to know about the effect of lithium on the kidney. *American Journal of Physiology - Renal Physiology*, *311*(6), F1168–F1171. https://doi.org/10.1152/ajprenal.00145.2016

Goodwin, G. M., Aaronson, S. T., Alvarez, O., Arden, P. C., Baker, A., Bennett, J. C., Bird, C., Blom, R. E., Brennan, C., Brusch, D., Burke, L., Campbell-Coker, K., Carhart-Harris, R., Cattell, J., Daniel, A., DeBattista, C., Dunlop, B. W., Eisen, K., Feifel, D., … Malievskaia, E. (2022). Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. *The New England Journal of Medicine*, *387*(18), 1637–1648. https://doi.org/10.1056/NEJMoa2206443

Goschke, T. (2014). *Dysfunctions of decision‐making and cognitive control as transdiagnostic mechanisms of mental disorders: Advances, gaps, and needs in current research*. https://doi.org/10.1002/mpr.1410

Gotlib, I. H., Krasnoperova, E., Yue, D. N., & Joormann, J. (2004). Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of Abnormal Psychology*, *113*(1), 121–135. https://doi.org/10.1037/0021-843X.113.1.121

Graeber, M. B., & Streit, W. J. (2010). Microglia: Biology and pathology. *Acta Neuropathologica*, *119*(1), 89–105. https://doi.org/10.1007/s00401-009-0622-0

Grandjean, J., Buehlmann, D., Buerge, M., Sigrist, H., Seifritz, E., Vollenweider, F. X., Pryce, C. R., & Rudin, M. (2021). Psilocybin exerts distinct effects on resting state networks associated with serotonin and dopamine in mice. *NeuroImage*, *225*, 117456. https://doi.org/10.1016/j.neuroimage.2020.117456

Granholm, E., Twamley, E. W., Mahmood, Z., Keller, A. V., Lykins, H. C., Parrish, E. M., Thomas, M. L., Perivoliotis, D., & Holden, J. L. (2022). Integrated Cognitive-Behavioral Social Skills Training and Compensatory Cognitive Training for Negative Symptoms of Psychosis: Effects in a Pilot Randomized Controlled Trial. *Schizophrenia Bulletin*, *48*(2), 359–370. https://doi.org/10.1093/schbul/sbab126

Green, M. F. (2016). Impact of Cognitive and Social Cognitive Impairment on Functional Outcomes in Patients With Schizophrenia. *The Journal of Clinical Psychiatry*, 77(suppl 2), 8569. https://doi.org/10.4088/JCP.14074su1c.02

Greil, W., de Bardeci, M., Müller-Oerlinghausen, B., Nievergelt, N., Stassen, H., Hasler, G., Erfurth, A., Cattapan, K., Rüther, E., Seifert, J., Toto, S., Bleich, S., & Schoretsanitis, G. (2023). Controversies regarding lithium-associated weight gain: Case–control study of real-world drug safety data. *International Journal of Bipolar Disorders*, *11*, 34. https://doi.org/10.1186/s40345-023-00313-8

Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., McCann, U., & Jesse, R. (2011). Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related effects. *Psychopharmacology*, *218*(4), 649–665. https://doi.org/10.1007/s00213-011-2358-5

Griffiths, R. R., Richards, W. A., McCann, U., & Jesse, R. (2006). Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology*, *187*(3), 268–283. https://doi.org/10.1007/s00213-006-0457-5

Gruenbaum, B. F., Zlotnik, A., Oleshko, A., Matalon, F., Shiyntum, H. N., Frenkel, A., & Boyko, M. (2024). The Relationship between Post-Traumatic Stress Disorder Due to Brain Injury and Glutamate Intake: A Systematic Review. *Nutrients*, *16*(6), Article 6. https://doi.org/10.3390/nu16060901

Grunze, A., Amann, B. L., & Grunze, H. (2021). Efficacy of Carbamazepine and Its Derivatives in the Treatment of Bipolar Disorder. *Medicina*, *57*(5), 433. https://doi.org/10.3390/medicina57050433

Guilherme Graeff, F., & Zangrossi Jr., H. (2010). The Dual Role of Serotonin in Defense and the Mode of Action of Antidepressants on Generalized Anxiety and Panic Disorders. *Central Nervous System Agents in Medicinal ChemistryChemistry - Central Nervous System Agents)*, *10*(3), 207–217.

Guloksuz, S., Rutten, B. P. F., Arts, B., van Os, J., & Kenis, G. (2014). The Immune System and Electroconvulsive Therapy for Depression. *The Journal of ECT*, *30*(2), 132. https://doi.org/10.1097/YCT.0000000000000127

Guo, Q., Wang, Y., Guo, L., Li, X., Ma, X., He, X., Li, J., Zhang, X., & Shang, S. (2024). Long-term cognitive effects of electroconvulsive therapy in major depressive disorder: A systematic review and meta-analysis. *Psychiatry Research*, *331*, 115611. https://doi.org/10.1016/j.psychres.2023.115611

Gurba, K. N., Chaudhry, R., & Haroutounian, S. (2022). Central Neuropathic Pain Syndromes: Current and Emerging Pharmacological Strategies. *CNS Drugs*, *36*(5), 483–516. https://doi.org/10.1007/s40263-022-00914-4

Gurel, S. C., Ozden, H. C., Karahan, S., & Ayhan, Y. (2022). The superiority of ketofol and etomidate against propofol or thiopental anesthesia for ECT. *Asian Journal of Psychiatry*, *72*, 103090. https://doi.org/10.1016/j.ajp.2022.103090

Haarman, B. C. M. (Benno), Riemersma-Van der Lek, R. F., de Groot, J. C., Ruhé, H. G. (Eric), Klein, H. C., Zandstra, T. E., Burger, H., Schoevers, R. A., de Vries, E. F. J., Drexhage, H. A., Nolen, W. A., & Doorduin, J. (2014). Neuroinflammation in bipolar disorder – A [11C]-(*R*)-PK11195 positron emission tomography study. *Brain, Behavior, and Immunity*, *40*, 219–225. https://doi.org/10.1016/j.bbi.2014.03.016

Haas, G. L., & Sweeney, J. A. (1992). Premorbid and Onset Features of First-Episode Schizophrenia. *Schizophrenia Bulletin*, *18*(3), 373–386. https://doi.org/10.1093/schbul/18.3.373

Haddad, P. (1998). The SSRI discontinuation syndrome. *Journal of Psychopharmacology*, *12*(3), 305–313. https://doi.org/10.1177/026988119801200311

Haddad, P. M., & Benbow, S. M. (1992). Propofol and ECT. *The British Journal of Psychiatry: The Journal of Mental Science*, *161*, 277–278. https://doi.org/10.1192/bjp.161.2.277

Hageman, I., Nielsen, M., Wortwein, G., Diemer, N. H., & Jorgensen, M. B. (2008). Electroconvulsive stimulations prevent stress-induced morphological changes in the hippocampus. *Stress*, *11*(4), 282–289. https://doi.org/10.1080/10253890701783794

Haghighi, M., Sedighinejad, A., Naderi Nabi, B., Emiralavi, C., Biazar, G., Mirmozaffari, K., Zahedan, C., & Jafari, M. (2016). The Incidence and Predictors of Headache and Myalgia in Patients After Electroconvulsive Therapy (ECT). *Anesthesiology and Pain Medicine*, *6*(3), e33724. https://doi.org/10.5812/aapm.33724

Halberstadt, A. L., & Geyer, M. A. (2013). Characterization of the head-twitch response induced by hallucinogens in mice. *Psychopharmacology*, *4*(227), 727–739. https://doi.org/10.1007/s00213-013-3006-z

Hammershøj, L. G., Petersen, J. Z., Jensen, H. M., Jørgensen, M. B., & Miskowiak, K. W. (2022). Cognitive Adverse Effects of Electroconvulsive Therapy: A Discrepancy Between Subjective and Objective Measures? *The Journal of ECT*, *38*(1), 30. https://doi.org/10.1097/YCT.0000000000000797

Hammond, T. R., Robinton, D., & Stevens, B. (2018). Microglia and the Brain: Complementary Partners in Development and Disease. *Annual Review of Cell and Developmental Biology*, *34*(1), 523–544. https://doi.org/10.1146/annurev-cellbio-100616-060509

Hanisch, U.-K. (2002). Microglia as a source and target of cytokines. *Glia*, *40*(2), 140–155. https://doi.org/10.1002/glia.10161

Hanisch, U.-K., & Kettenmann, H. (2007a). Microglia: Active sensor and versatile effector cells in the normal and pathologic brain. *Nature Neuroscience*, *10*(11), 1387–1394. https://doi.org/10.1038/nn1997

Hanisch, U.-K., & Kettenmann, H. (2007b). Microglia: Active sensor and versatile effector cells in the normal and pathologic brain. *Nature Neuroscience*, *10*(11), Article 11. https://doi.org/10.1038/nn1997

Harrison, T. S., & Goa, K. L. (2004). Long-Acting Risperidone. *CNS Drugs*, *18*(2), 113–132. https://doi.org/10.2165/00023210-200418020-00005

Haruwaka, K., Ikegami, A., Tachibana, Y., Ohno, N., Konishi, H., Hashimoto, A., Matsumoto, M., Kato, D., Ono, R., Kiyama, H., Moorhouse, A. J., Nabekura, J., & Wake, H. (2019). Dual microglia effects on blood brain barrier permeability induced by systemic inflammation. *Nature Communications*, *10*(1), 5816. https://doi.org/10.1038/s41467-019-13812-z

Hashimoto, K. (2008). Microglial activation in schizophrenia and minocycline treatment. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(7), 1758–1759. https://doi.org/10.1016/j.pnpbp.2008.06.012

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*, *75*(4), 336–346. https://doi.org/10.1001/jamapsychiatry.2017.4602

Haskett, R. F. (2014). Electroconvulsive Therapy's Mechanism of Action: Neuroendocrine Hypotheses. *The Journal of ECT*, *30*(2), 107. https://doi.org/10.1097/YCT.0000000000000143

Haskett, R. F., & Loo, C. (2010). Adjunctive Psychotropic Medications During Electroconvulsive Therapy in the Treatment of Depression, Mania, and Schizophrenia. *The Journal of ECT*, *26*(3), 196. https://doi.org/10.1097/YCT.0b013e3181eee13f

Hassija, C. M., & Gray, M. J. (2010). Are cognitive techniques and interventions necessary? A case for the utility of cognitive approaches in the treatment of PTSD. *Clinical Psychology: Science and Practice*, *17*(2), 112–127. https://doi.org/10.1111/j.1468-2850.2010.01201.x

Hayakawa, H., Yokota, N., Kawai, K., Okamoto, Y., Osada, M., Kikumoto, O., Motohashi, N., Yamawaki, S., Nishida, A., & Shimizu, M. (1993). Effects of Electroconvulsive Shock on the Serotonin Metabolism and Serotonin1A Receptors in the Rat Brain. *Psychiatry and Clinical Neurosciences*, *47*(2), 418–419. https://doi.org/10.1111/j.1440-1819.1993.tb02129.x

He, Y., Gao, Y., Zhang, Q., Zhou, G., Cao, F., & Yao, S. (2020). IL-4 Switches Microglia/macrophage M1/M2 Polarization and Alleviates Neurological Damage by Modulating the JAK1/STAT6 Pathway Following ICH. *Neuroscience*, *437*, 161–171. https://doi.org/10.1016/j.neuroscience.2020.03.008

Heath, A., Lindberg, D. R., Makowiecki, K., Gray, A., Asp, A. J., Rodger, J., Choi, D.-S., & Croarkin, P. E. (2018). Medium- and high-intensity rTMS reduces psychomotor agitation with distinct neurobiologic mechanisms. *Translational Psychiatry*, *8*. https://doi.org/10.1038/s41398-018-0129-3

Heijnen, W. T., Birkenhäger, T. K., Wierdsma, A. I., & van den Broek, W. W. (2010). Antidepressant Pharmacotherapy Failure and Response to Subsequent Electroconvulsive Therapy: A Meta-Analysis. *Journal of Clinical Psychopharmacology*, *30*(5), 616. https://doi.org/10.1097/JCP.0b013e3181ee0f5f

Hemmati, S., Astaneh, A. N., Solemani, F., Vameghi, R., Sajedi, F., & Tabibi, N. (2010). A Survey of the Tardive Dyskinesia Induced by Antipsychotic Drugs in Patients with Schizophrenia. *Iranian Journal of Psychiatry*, *5*(4), 159–163.

Herbon, N., Werner, M., Braig, C., Gohlke, H., Dütsch, G., Illig, T., Altmüller, J., Hampe, J., Lantermann, A., Schreiber, S., Bonifacio, E., Ziegler, A., Schwab, S., Wildenauer, D., van den Boom, D., Braun, A., Knapp, M., Reitmeir, P., & Wjst, M. (2003). High-resolution

snp scan of chromosome 6p21 in pooled samples from patients with complex diseases. *Genomics*, *81*(5), 510–518. https://doi.org/10.1016/S0888-7543(02)00035-6

Hermida, A. P., Mohsin, M., Marques Pinheiro, A. P., McCord, E., Lisko, J. C., & Head, L. W. (2022). The Cardiovascular Side Effects of Electroconvulsive Therapy and Their Management. *The Journal of ECT*, *38*(1), 2. https://doi.org/10.1097/YCT.0000000000000802

Hertzberg, M. A., Butterfield, M. I., Feldman, M. E., Beckham, J. C., Sutherland, S. M., Connor, K. M., & Davidson, J. R. T. (1999). A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biological Psychiatry*, *45*(9), 1226–1229. https://doi.org/10.1016/S0006-3223(99)00011-6

Hesselgrave, N., Troppoli, T. A., Wulff, A. B., Cole, A. B., & Thompson, S. M. (2021). Harnessing psilocybin: Antidepressant-like behavioral and synaptic actions of psilocybin are independent of 5-HT2R activation in mice. *Proceedings of the National Academy of Sciences*, *118*(17), e2022489118. https://doi.org/10.1073/pnas.2022489118

Higgins, G. A., & Sellers, E. M. (2021). 5-HT2A and 5-HT2C receptors as potential targets for the treatment of nicotine use and dependence. *Progress in Brain Research*, *259*, 229–263. https://doi.org/10.1016/bs.pbr.2021.01.007

Hillhouse, T. M., & Porter, J. H. (2015). A brief history of the development of antidepressant drugs: From monoamines to glutamate. *Experimental and Clinical Psychopharmacology*, *23*(1), 1–21. https://doi.org/10.1037/a0038550

Hilton, S. E., Maradit, H., & Möller, H. J. (1997). Serotonin syndrome and drug combinations: Focus on MAOI and RIMA. *European Archives of Psychiatry and Clinical Neuroscience*, *247*(3), 113–119. https://doi.org/10.1007/BF03033064

Hirota, K., & Lambert, D. G. (2022). Ketamine; history and role in anesthetic pharmacology. *Neuropharmacology*, *216*, 109171. https://doi.org/10.1016/j.neuropharm.2022.109171

Hirschfeld, R. M. A. (n.d.). *The Comorbidity of Major Depression and Anxiety Disorders: Recognition and Management in Primary Care*.

Hirschfeld, R. M. A. (1999). *Efficacy of SSRIs and Newer Antidepressants in Severe Depression: Comparison With TCAs*.

Hirschfeld, R. M. A., Calabrese, J. R., Weissman, M. M., Reed, M., Davies, M. A., Frye, M. A., Keck, P. E., Lewis, L., McElroy, S. L., McNulty, J. P., & Wagner, K. D. (2003). Screening for Bipolar Disorder in the Community. *The Journal of Clinical Psychiatry*, *64*(1), 53–59. https://doi.org/10.4088/JCP.v64n0111

Hofmann, S. G., & Gómez, A. F. (2017). Mindfulness-Based Interventions for Anxiety and Depression. *Psychiatric Clinics*, *40*(4), 739–749. https://doi.org/10.1016/j.psc.2017.08.008

Hogarty, G. E., Anderson, C. M., Reiss, D. J., Kornblith, S. J., Greenwald, D. P., Javna, C. D., & Madonia, M. J. (1986). Family Psychoeducation, Social Skills Training, and Maintenance Chemotherapy in the Aftercare Treatment of Schizophrenia: I. One-Year Effects of a Controlled Study on Relapse and Expressed Emotion. *Archives of General Psychiatry*, *43*(7), 633–642. https://doi.org/10.1001/archpsyc.1986.01800070019003

Homberg, J. R., Molteni, R., Calabrese, F., & Riva, M. A. (2014). The serotonin–BDNF duo: Developmental implications for the vulnerability to psychopathology. *Neuroscience & Biobehavioral Reviews*, *43*, 35–47. https://doi.org/10.1016/j.neubiorev.2014.03.012

Hong, S., Beja-Glasser, V. F., Nfonoyim, B. M., Frouin, A., Li, S., Ramakrishnan, S., Merry, K. M., Shi, Q., Rosenthal, A., Barres, B. A., Lemere, C. A., Selkoe, D. J., & Stevens, B. (2016). Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science (New York, N.Y.)*, *352*(6286), 712–716. https://doi.org/10.1126/science.aad8373

Hong, S., & Stevens, B. (2016). Microglia: Phagocytosing to Clear, Sculpt, and Eliminate. *Developmental Cell*, *38*(2), 126–128. https://doi.org/10.1016/j.devcel.2016.07.006

Horowitz, M. A., Jauhar, S., Natesan, S., Murray, R. M., & Taylor, D. (2021). A Method for Tapering Antipsychotic Treatment That May Minimize the Risk of Relapse. *Schizophrenia Bulletin*, *47*(4), 1116–1129. https://doi.org/10.1093/schbul/sbab017

Horowitz, M. A., & Taylor, D. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. *The Lancet Psychiatry*, *6*(6), 538–546. https://doi.org/10.1016/S2215-0366(19)30032-X

Horwitz, T., Lam, K., Chen, Y., Xia, Y., & Liu, C. (2019). A Decade in Psychiatric GWAS Research. *Molecular Psychiatry*, *24*(3), 378–389. https://doi.org/10.1038/s41380-018-0055-z

Hou, L., Qu, X., Qiu, X., Huang, R., Zhao, X., & Wang, Q. (2020). Integrin CD11b mediates locus coeruleus noradrenergic neurodegeneration in a mouse Parkinson's disease model. *Journal of Neuroinflammation*, *17*(1), 148. https://doi.org/10.1186/s12974-020-01823-3

Howes, O. D., Thase, M. E., & Pillinger, T. (2022). Treatment resistance in psychiatry: State of the art and new directions. *Molecular Psychiatry*, *27*(1), Article 1. https://doi.org/10.1038/s41380-021-01200-3

Hunter, R., Kennedy, E., Song, F., Gadon, L., & Irving, C. B. (2003). Risperidone versus typical antipsychotic medication for schizophrenia. *The Cochrane Database of Systematic Reviews*, *2003*(2), CD000440. https://doi.org/10.1002/14651858.CD000440

Husain, M. M., Rush, A. J., Fink, M., Knapp, R., Petrides, G., Rummans, T., Biggs, M. M., O'Connor, K., Rasmussen, K., & Litle, M. (2004). Speed of Response and Remission in Major Depressive Disorder With Acute Electroconvulsive Therapy (ECT): A Consortium for Research in ECT (CORE) Report. *The Journal of Clinical Psychiatry*, *65*(4), 485–491.

Hwang, J., Zheng, L. T., Ock, J., Lee, M. G., Kim, S.-H., Lee, H.-W., Lee, W.-H., Park, H.-C., & Suk, K. (2008). Inhibition of glial inflammatory activation and neurotoxicity by tricyclic antidepressants. *Neuropharmacology*, *55*(5), 826–834. https://doi.org/10.1016/j.neuropharm.2008.06.045

Hwang, Y. M., Roper, R. T., Piekos, S. N., Enquobahrie, D. A., Hebert, M. F., Paquette, A. G., Baloni, P., Price, N. D., Hood, L., & Hadlock, J. J. (2024). Timing of selective serotonin reuptake inhibitor use and risk for preterm birth and related adverse events: With a consideration of the COVID-19 pandemic period. *The Journal of Maternal-Fetal & Neonatal Medicine*, *37*(1), 2313364. https://doi.org/10.1080/14767058.2024.2313364

Ibrahim, F. I., & Aldridge, C. (2006). Etomidate and ECT. *Anaesthesia*, *61*(2), 192. https://doi.org/10.1111/j.1365-2044.2005.04519_2.x

Ilchibaeva, T., Tsybko, A., Zeug, A., Müller, F. E., Guseva, D., Bischoff, S., Ponimaskin, E., & Naumenko, V. (2022). Serotonin Receptor 5-HT2A Regulates TrkB Receptor Function in Heteroreceptor Complexes. *Cells*, *11*(15), 2384. https://doi.org/10.3390/cells11152384

Iovino, L., Tremblay, M. E., & Civiero, L. (2020). Glutamate-induced excitotoxicity in Parkinson's disease: The role of glial cells. *Journal of Pharmacological Sciences*, *144*(3), 151–164. https://doi.org/10.1016/j.jphs.2020.07.011

I.P., L. (2003). Neurokynurenines (Neky) as Common Neurochemical Links of Stress and Anxiety. In G. Allegri, C. V. L. Costa, E. Ragazzi, H. Steinhart, & L. Varesio (Eds.), *Developments in Tryptophan and Serotonin Metabolism* (pp. 121–125). Springer US. https://doi.org/10.1007/978-1-4615-0135-0_14

Ito, D., Tanaka, K., Suzuki, S., Dembo, T., & Fukuuchi, Y. (2001). Enhanced Expression of Iba1, Ionized Calcium-Binding Adapter Molecule 1, After Transient Focal Cerebral Ischemia In Rat Brain. *Stroke*, *32*(5), 1208–1215. https://doi.org/10.1161/01.STR.32.5.1208

Jackson, J. L., O'Malley, P. G., & Kroenke, K. (2006). Antidepressants and Cognitive-Behavioral Therapy for Symptom Syndromes. *CNS Spectrums*, *11*(3), 212–222. https://doi.org/10.1017/S1092852900014383

Jackson, W. K., Roose, S. P., & Glassman, A. H. (2010). Cardiovascular Toxicity of Antidepressant Medications. *Psychopathology*, *20*(Suppl. 1), 64–74. https://doi.org/10.1159/000284525

Jacobsen, P. L., Mahableshwarkar, A. R., Chen, Y., Chrones, L., & Clayton, A. H. (2015). Effect of Vortioxetine vs. Escitalopram on Sexual Functioning in Adults with Well-Treated Major Depressive Disorder Experiencing SSRI-Induced Sexual Dysfunction. *The Journal of Sexual Medicine*, *12*(10), 2036–2048. https://doi.org/10.1111/jsm.12980

Jang, S.-S., Jeong, H. G., & Chung, H. J. (2017). Electroconvulsive Seizures in Rats and Fractionation of Their Hippocampi to Examine Seizure-induced Changes in Postsynaptic Density Proteins. *Journal of Visualized Experiments: JoVE*, *126*, 56016. https://doi.org/10.3791/56016

Janiri, L., D'Ambrosio, F., & Di Lorenzo, C. (2021). Combined treatment of myo-inositol and d-chiro-inositol (80:1) as a therapeutic approach to restore inositol eumetabolism in patients with bipolar disorder taking lithium and valproic acid. *European Review for Medical and Pharmacological Sciences*, *25*(17), 5483–5489. https://doi.org/10.26355/eurrev_202109_26657

Janjua, A. U., Dhingra, A. L., Greenberg, R., & McDonald, W. M. (2020). The Efficacy and Safety of Concomitant Psychotropic Medication and Electroconvulsive Therapy (ECT). *CNS Drugs*, *34*(5), 509–520. https://doi.org/10.1007/s40263-020-00729-1

Jansson, L., Wennström, M., Johanson, A., & Tingström, A. (2009). Glial cell activation in response to electroconvulsive seizures. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *33*(7), 1119–1128. https://doi.org/10.1016/j.pnpbp.2009.06.007

Järventausta, K., Sorri, A., Kampman, O., Björkqvist, M., Tuohimaa, K., Hämäläinen, M., Moilanen, E., Leinonen, E., Peltola, J., & Lehtimäki, K. (2017). Changes in interleukin-6 levels during electroconvulsive therapy may reflect the therapeutic response in major depression. *Acta Psychiatrica Scandinavica*, *135*(1), 87–92. https://doi.org/10.1111/acps.12665

Jefferson, J. W. (1975). A Review of the Cardiovascular Effects and Toxicity of Tricyclic Antidepressants. *Psychosomatic Medicine*, *37*(2), 160.

Jha, A., & Stein, G. (1996). Decreased efficacy of combined benzodiazepines and unilateral ECT in treatment of depression. *Acta Psychiatrica Scandinavica*, *94*(2), 101–104. https://doi.org/10.1111/j.1600-0447.1996.tb09832.x

Jinno, S., & Kosaka, T. (2008). Reduction of Iba1-expressing microglial process density in the hippocampus following electroconvulsive shock. *Experimental Neurology*, *212*(2), 440–447. https://doi.org/10.1016/j.expneurol.2008.04.028

Johns, C., & Thompson, J. W. (1995). Adjunctive Treatments in Schizophrenia: Pharmacotherapies and Electroconvulsive Therapy. *Schizophrenia Bulletin*, *21*(4), 607–619. https://doi.org/10.1093/schbul/21.4.607

Johnson, M. W. (2022). Classic Psychedelics in Addiction Treatment: The Case for Psilocybin in Tobacco Smoking Cessation. *Current Topics in Behavioral Neurosciences*, *56*, 213–227. https://doi.org/10.1007/7854_2022_327

Johnson, M. W., Garcia-Romeu, A., & Griffiths, R. R. (2017). Long-term follow-up of psilocybin-facilitated smoking cessation. *The American Journal of Drug and Alcohol Abuse*, *43*(1), 55–60. https://doi.org/10.3109/00952990.2016.1170135

Johnson, M. W., Hendricks, P. S., Barrett, F. S., & Griffiths, R. R. (2019). Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function. *Pharmacology & Therapeutics*, *197*, 83–102. https://doi.org/10.1016/j.pharmthera.2018.11.010

Johnson, M. W., Richards, W. A., & Griffiths, R. R. (2008). Human Hallucinogen Research: Guidelines for Safety. *Journal of Psychopharmacology (Oxford, England)*, *22*(6), 603–620. https://doi.org/10.1177/0269881108093587

Johnson, M. W., Sewell, R. A., & Griffiths, R. R. (2012). Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers. *Drug and Alcohol Dependence*, *123*(1–3), 132–140. https://doi.org/10.1016/j.drugalcdep.2011.10.029

Jones, A. L., Mowry, B. J., Pender, M. P., & Greer, J. M. (2005). Immune dysregulation and self-reactivity in schizophrenia: Do some cases of schizophrenia have an autoimmune basis? *Immunology & Cell Biology*, *83*(1), 9–17. https://doi.org/10.1111/j.1440-1711.2005.01305.x

Jones, E. V., Bernardinelli, Y., Zarruk, J. G., Chierzi, S., & Murai, K. K. (2018). SPARC and GluA1-Containing AMPA Receptors Promote Neuronal Health Following CNS Injury. *Frontiers in Cellular Neuroscience*, *12*, 22. https://doi.org/10.3389/fncel.2018.00022

Jones, K. A., Srivastava, D. P., Allen, J. A., Strachan, R. T., Roth, B. L., & Penzes, P. (2009). Rapid modulation of spine morphology by the 5-HT2A serotonin receptor through kalirin-7 signaling. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(46), 19575–19580. https://doi.org/10.1073/pnas.0905884106

Jun, C., Choi, Y., Lim, S. M., Bae, S., Hong, Y. S., Kim, J. E., & Lyoo, I. K. (2014). Disturbance of the Glutamatergic System in Mood Disorders. *Experimental Neurobiology*, *23*(1), 28–35. https://doi.org/10.5607/en.2014.23.1.28

Kakunje, A., Prabhu, A., Sindhu Priya, E., Karkal, R., Kumar, P., Gupta, N., & Rahyanath, P. (2018). Valproate: It's Effects on Hair. *International Journal of Trichology*, *10*(4), 150–153. https://doi.org/10.4103/ijt.ijt_10_18

Kaliora, S. C., Zervas, I. M., & Papadimitriou, G. N. (2018). [Electroconvulsive therapy: 80 years of use in psychiatry]. *Psychiatrike = Psychiatriki*, *29*(4), 291–302. https://doi.org/10.22365/jpsych.2018.294.291

Kara, N. Z., Karpel, O., Toker, L., Agam, G., Belmaker, R. H., & Einat, H. (2014). Chronic oral carbamazepine treatment elicits mood-stabilising effects in mice. *Acta Neuropsychiatrica*, *26*(1), 29–34. https://doi.org/10.1017/neu.2013.23

Karlsgodt, K. H., Bachman, P., Winkler, A. M., Bearden, C. E., & Glahn, D. C. (2011). Genetic influence on the working memory circuitry: Behavior, structure, function and extensions to illness. *Behavioural Brain Research*, *225*(2), 610–622. https://doi.org/10.1016/j.bbr.2011.08.016

Kartalci, S., Karabulut, A. B., Erbay, L. G., & Acar, C. (2016). Effects of Electroconvulsive Therapy on Some Inflammatory Factors in Patients With Treatment-Resistant Schizophrenia. *The Journal of ECT*, *32*(3), 174. https://doi.org/10.1097/YCT.0000000000000303

Kato, M., Baba, H., Takekita, Y., Naito, M., Koshikawa, Y., Bandou, H., & Kinoshita, T. (2023). Usefulness of mirtazapine and SSRIs in late-life depression: Post hoc analysis of the

GUNDAM study. *European Journal of Clinical Pharmacology*, *79*(11), 1515–1524. https://doi.org/10.1007/s00228-023-03563-8

Katz, I. R., Rogers, M. P., Lew, R., Thwin, S. S., Doros, G., Ahearn, E., Ostacher, M. J., DeLisi, L. E., Smith, E. G., Ringer, R. J., Ferguson, R., Hoffman, B., Kaufman, J. S., Paik, J. M., Conrad, C. H., Holmberg, E. F., Boney, T. Y., Huang, G. D., & Liang, M. H. (2022). Lithium Treatment in the Prevention of Repeat Suicide-Related Outcomes in Veterans With Major Depression or Bipolar Disorder. *JAMA Psychiatry*, *79*(1), 1–10. https://doi.org/10.1001/jamapsychiatry.2021.3170

Kaur, C., Hao, A.-J., Wu, C.-H., & Ling, E.-A. (2001). Origin of microglia. *Microscopy Research and Technique*, *54*(1), 2–9. https://doi.org/10.1002/jemt.1114

Kaur, G., & Singh, N. K. (2021). The Role of Inflammation in Retinal Neurodegeneration and Degenerative Diseases. *International Journal of Molecular Sciences*, *23*(1), 386. https://doi.org/10.3390/ijms23010386

Keck, P. E., McElroy, S. L., Strakowski, S. M., & Soutullo, C. A. (2000). Antipsychotics in the treatment of mood disorders and risk of tardive dyskinesia. *The Journal of Clinical Psychiatry*, *61 Suppl 4*, 33–38.

Keefe, R. S. E., Lobelc, D. S., Mohs, R. C., Silverman, J. M., Harvey, P. D., Davidson, M., Losonczy, M. F., & Davis, K. L. (1991). Diagnostic issues in chronic schizophrenia: Kraepelinian schizophrenia, undifferentiated schizophrenia, and state-independent negative symptoms. *Schizophrenia Research*, *4*(2), 71–79. https://doi.org/10.1016/0920-9964(91)90026-N

Kellner, C. H., Husain, M. M., Knapp, R. G., McCall, W. V., Petrides, G., Rudorfer, M. V., Young, R. C., Sampson, S., McClintock, S. M., Mueller, M., Prudic, J., Greenberg, R. M., Weiner, R. D., Bailine, S. H., Rosenquist, P. B., Raza, A., Kaliora, S., Latoussakis, V., Tobias, K. G., … Lisanby, S. H. (2016). A Novel Strategy for Continuation ECT in Geriatric Depression: Phase 2 of the PRIDE Study. *American Journal of Psychiatry*, *173*(11), 1110–1118. https://doi.org/10.1176/appi.ajp.2016.16010118

Kellner, C. H., Knapp, R. G., Petrides, G., Rummans, T. A., Husain, M. M., Rasmussen, K., Mueller, M., Bernstein, H. J., O'Connor, K., Smith, G., Biggs, M., Bailine, S. H., Malur, C., Yim, E., McClintock, S., Sampson, S., & Fink, M. (2006). Continuation Electroconvulsive Therapy vs Pharmacotherapy for Relapse Prevention in Major Depression: A Multisite Study From the Consortium for Research in Electroconvulsive Therapy (CORE). *Archives of General Psychiatry*, *63*(12), 1337–1344. https://doi.org/10.1001/archpsyc.63.12.1337

Kerr, N., Scott, J., & Phillips, M. L. (2005). Patterns of attentional deficits and emotional bias in bipolar and major depressive disorder. *British Journal of Clinical Psychology*, *44*(3), 343–356. https://doi.org/10.1348/014466505X57755

Kettenmann, H., Hanisch, U.-K., Noda, M., & Verkhratsky, A. (2011). Physiology of Microglia. *Physiol Rev*, *91*, 93.

Khan, A. J., Bradley, E., O'Donovan, A., & Woolley, J. (2022). Psilocybin for Trauma-Related Disorders. *Current Topics in Behavioral Neurosciences*, *56*, 319–332. https://doi.org/10.1007/7854_2022_366

Khan, S. J., Fersh, M. E., Ernst, C., Klipstein, K., Albertini, E. S., & Lusskin, S. I. (2016). Bipolar Disorder in Pregnancy and Postpartum: Principles of Management. *Current Psychiatry Reports*, *18*(2), 13. https://doi.org/10.1007/s11920-015-0658-x

Khan, Y. S., Khoodoruth, M. A. S., Albobali, Y., & Haddad, P. M. (2023). SSRI withdrawal syndrome in children and adolescents: A narrative literature review. *Expert Opinion on Drug Safety*, *22*(5), 381–390. https://doi.org/10.1080/14740338.2023.2224557

Khandaker, G. M., Zimbron, J., Lewis, G., & Jones, P. B. (2013). Prenatal maternal infection, neurodevelopment and adult schizophrenia: A systematic review of population-based studies. *Psychological Medicine*, *43*(2), 239–257. https://doi.org/10.1017/S0033291712000736

Khanna, R. (2024). Psilocybin for the treatment of posttraumatic stress disorder: A magic to treat a harmony of illusions? *Journal of Indira Gandhi Institute Of Medical Science*, *10*(1), 24. https://doi.org/10.4103/jigims.jigims_60_23

Khwanchuea, R., Mulvany, M. J., & Jansakul, C. (2008). Cardiovascular effects of tyramine: Adrenergic and cholinergic interactions. *European Journal of Pharmacology*, *579*(1), 308–317. https://doi.org/10.1016/j.ejphar.2007.10.029

Kierdorf, K., Erny, D., Goldmann, T., Sander, V., Schulz, C., Perdiguero, E. G., Wieghofer, P., Heinrich, A., Riemke, P., Hölscher, C., Müller, D. N., Luckow, B., Brocker, T., Debowski, K., Fritz, G., Opdenakker, G., Diefenbach, A., Biber, K., Heikenwalder, M., … Prinz, M. (2013). Microglia emerge from erythromyeloid precursors via Pu.1- and Irf8-dependent pathways. *Nature Neuroscience*, *16*(3), 273–280. https://doi.org/10.1038/nn.3318

Kim, T., Xu, C., & Amsterdam, J. D. (2019). Relative effectiveness of tricyclic antidepressant versus monoamine oxidase inhibitor monotherapy for treatment-resistant depression. *Journal of Affective Disorders*, *250*, 199–203. https://doi.org/10.1016/j.jad.2019.03.028

Kim, Y.-K., & Na, K.-S. (2016). Role of glutamate receptors and glial cells in the pathophysiology of treatment-resistant depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *70*, 117–126. https://doi.org/10.1016/j.pnpbp.2016.03.009

Kim, Y.-K., Na, K.-S., Myint, A.-M., & Leonard, B. E. (2016). The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *64*, 277–284. https://doi.org/10.1016/j.pnpbp.2015.06.008

King, S., Jelen, L. A., Horne, C. M., Cleare, A., Pariante, C. M., Young, A. H., & Stone, J. M. (2019). Inflammation, Glutamate, and Cognition in Bipolar Disorder Type II: A Proof of Concept Study. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00066

Kinugawa, K., Monnet, Y., Béchade, C., Alvarez-Fischer, D., Hirsch, E. C., Bessis, A., & Hunot, S. (2013). DAP12 and CD11b contribute to the microglial-induced death of dopaminergic neurons in vitro but not in vivo in the MPTP mouse model of Parkinson's disease. *Journal of Neuroinflammation*, *10*(1), 854. https://doi.org/10.1186/1742-2094-10-82

Koch-Weser, J., & Hollister, L. E. (1978). Tricyclic Antidepressants. *New England Journal of Medicine*, *299*(20), 1106–1109. https://doi.org/10.1056/NEJM197811162992004

Kohno, M., Link, J., Dennis, L. E., McCready, H., Huckans, M., Hoffman, W. F., & Loftis, J. M. (2019). Neuroinflammation in addiction: A review of neuroimaging studies and potential immunotherapies. *Pharmacology Biochemistry and Behavior*, *179*, 34–42. https://doi.org/10.1016/j.pbb.2019.01.007

Kolodziejczak, M., Béchade, C., Gervasi, N., Irinopoulou, T., Banas, S., Cordier, C., Rebsam, A., Roumier, A., & Maroteaux, L. (2015). Serotonin Modulates Developmental Microglia via 5-HT2B Receptors: Potential Implication during Synaptic Refinement of Retinogeniculate Projections. *ACS Chemical Neuroscience*, *6*(7), 1219–1230. https://doi.org/10.1021/cn5003489

Kometer, M., Pokorny, T., Seifritz, E., & Volleinweider, F. X. (2015). Psilocybin-induced spiritual experiences and insightfulness are associated with synchronization of neuronal oscillations. *Psychopharmacology*, *232*(19), 3663–3676. https://doi.org/10.1007/s00213-015-4026-7

Kremen, W. S., Seidman, L. J., Faraone, S. V., Toomey, R., & Tsuang, M. T. (2004). Heterogeneity of schizophrenia: A study of individual neuropsychological profiles. *Schizophrenia Research*, *71*(2), 307–321. https://doi.org/10.1016/j.schres.2004.02.022

Kronfol, Z., Hamdan-Allen, G., Goel, K., & Hill, E. M. (1991). Effects of single and repeated electroconvulsive therapy sessions on plasma ACTH, prolactin, growth hormone and cortisol concentrations. *Psychoneuroendocrinology*, *16*(4), 345–352. https://doi.org/10.1016/0306-4530(91)90020-t

Krystal, A. D., Weiner, R. D., Dean, M. D., Lindahl, V. H., Tramontozzi III, L. A., Falcone, G., & Coffey, C. E. (2003). Comparison of Seizure Duration, Ictal EEG, and Cognitive Effects of Ketamine and Methohexital Anesthesia With ECT. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *15*(1), 27–34. https://doi.org/10.1176/jnp.15.1.27

Kucukdereli, H., Allen, N. J., Lee, A. T., Feng, A., Ozlu, M. I., Conatser, L. M., Chakraborty, C., Workman, G., Weaver, M., Sage, E. H., Barres, B. A., & Eroglu, C. (2011). Control of excitatory CNS synaptogenesis by astrocyte-secreted proteins Hevin and SPARC. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(32), E440-449. https://doi.org/10.1073/pnas.1104977108

Laabi, S., LeMmon, C., Vogel, C., Chacon, M., & Jimenez, V. M. (2024). Deciphering psilocybin: Cytotoxicity, anti-inflammatory effects, and mechanistic insights. *International Immunopharmacology*, *130*, 111753. https://doi.org/10.1016/j.intimp.2024.111753

Lahti, A. C., Koffel, B., LaPorte, D., & Tamminga, C. A. (1995). Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology*, *13*(1), 9–19. https://doi.org/10.1016/0893-133X(94)00131-I

Lally, J., & MacCabe, J. H. (2015). Antipsychotic medication in schizophrenia: A review. *British Medical Bulletin*, *114*(1), 169–179. https://doi.org/10.1093/bmb/ldv017

Lambert, R. A. (2015). Intervention in Panic and Anxiety Disorders Through Lifestyle Modification. In I. Söderback (Ed.), *International Handbook of Occupational Therapy Interventions* (pp. 541–551). Springer International Publishing. https://doi.org/10.1007/978-3-319-08141-0_37

Lambrichts, S., Detraux, J., Vansteelandt, K., Nordenskjöld, A., Obbels, J., Schrijvers, D., & Sienaert, P. (2021). Does lithium prevent relapse following successful electroconvulsive therapy for major depression? A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *143*(4), 294–306. https://doi.org/10.1111/acps.13277

Landau, A. M., Chakravarty, M. M., Clark, C. M., Zis, A. P., & Doudet, D. J. (2011). Electroconvulsive Therapy Alters Dopamine Signaling in the Striatum of Non-human Primates. *Neuropsychopharmacology*, *36*(2), 511–518. https://doi.org/10.1038/npp.2010.182

Laskaris, L. E., Di Biase, M. A., Everall, I., Chana, G., Christopoulos, A., Skafidas, E., Cropley, V. L., & Pantelis, C. (2016). Microglial activation and progressive brain changes in schizophrenia. *British Journal of Pharmacology*, *173*(4), 666–680. https://doi.org/10.1111/bph.13364

Lauritzen, L., Odgaard, K., Clemmesen, L., Lunde, M., Öhrström, J., Black, C., & Bech, P. (1996). Relapse prevention by means of paroxetine in ECT-treated patients with major depression: A comparison with imipramine and placebo in medium-term continuation therapy. *Acta Psychiatrica Scandinavica*, *94*(4), 241–251. https://doi.org/10.1111/j.1600-0447.1996.tb09856.x

Lee, Y. B., Nagai, A., & Kim, S. U. (2002). Cytokines, chemokines, and cytokine receptors in human microglia. *Journal of Neuroscience Research*, *69*(1), 94–103. https://doi.org/10.1002/jnr.10253

Lehrman, E. K., Wilton, D. K., Litvina, E. Y., Welsh, C. A., Chang, S. T., Frouin, A., Walker, A. J., Heller, M. D., Umemori, H., Chen, C., & Stevens, B. (2018). CD47 Protects Synapses from Excess Microglia-Mediated Pruning during Development. *Neuron*, *100*(1), 120-134.e6. https://doi.org/10.1016/j.neuron.2018.09.017

Lehtimäki, K., Keränen, T., Huuhka, M., Palmio, J., Hurme, M., Leinonen, E., & Peltola, J. (2008). Increase in Plasma Proinflammatory Cytokines After Electroconvulsive Therapy in Patients With Depressive Disorder. *The Journal of ECT*, *24*(1), 88. https://doi.org/10.1097/YCT.0b013e3181571abb

Leonard, B. E. (2003). *Fundamentals of Psychopharmacology*. John Wiley & Sons.

Lett, T. A., Voineskos, A. N., Kennedy, J. L., Levine, B., & Daskalakis, Z. J. (2014). Treating Working Memory Deficits in Schizophrenia: A Review of the Neurobiology. *Biological Psychiatry*, *75*(5), 361–370. https://doi.org/10.1016/j.biopsych.2013.07.026

Leucht, S., Huhn, M., & Davis, J. M. (2021). Should 'typical', first-generation antipsychotics no longer be generally used in the treatment of schizophrenia? *European Archives of Psychiatry and Clinical Neuroscience*, *271*(8), 1411–1413. https://doi.org/10.1007/s00406-021-01335-y

Lewis, V., Bonniwell, E. M., Lanham, J. K., Ghaffari, A., Sheshbaradaran, H., Cao, A. B., Calkins, M. M., Bautista-Carro, M. A., Arsenault, E., Telfer, A., Taghavi-Abkuh, F.-F., Malcolm, N. J., El Sayegh, F., Abizaid, A., Schmid, Y., Morton, K., Halberstadt, A. L., Aguilar-Valles, A., & McCorvy, J. D. (2023). A non-hallucinogenic LSD analog with therapeutic potential for mood disorders. *Cell Reports*, *42*(3), 112203. https://doi.org/10.1016/j.celrep.2023.112203

Leyhe, T., Eschweiler, G. W., Stransky, E., Gasser, T., Annas, P., Basun, H., & Laske, C. (2009). Increase of BDNF serum concentration in lithium treated patients with early Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, *16*(3), 649–656. https://doi.org/10.3233/JAD-2009-1004

Li, D.-J., Wang, F.-C., Chu, C.-S., Chen, T.-Y., Tang, C.-H., Yang, W.-C., Chow, P. C., Wu, C.-K., Tseng, P.-T., & Lin, P.-Y. (2017). Significant treatment effect of add-on ketamine anesthesia in electroconvulsive therapy in depressive patients: A meta-analysis. *European Neuropsychopharmacology*, *27*(1), 29–41. https://doi.org/10.1016/j.euroneuro.2016.11.008

Li, J., Zhao, R., Wang, C., Song, J., Guo, X., Ge, Y., & Chu, X. (2024). Structural and functional abnormalities in the medial prefrontal cortex were associated with pain and depressive symptoms in patients with adhesive capsulitis. *Pain Reports*, *9*(2), e1139. https://doi.org/10.1097/PR9.0000000000001139

Li, W., Liu, L., Liu, Y., Luo, J., Lin, J., Li, X., Wang, B., & Min, S. (2012). Effects of Electroconvulsive Stimulation on Long-Term Potentiation and Synaptophysin in the Hippocampus of Rats With Depressive Behavior. *The Journal of ECT*, *28*(2), 111. https://doi.org/10.1097/YCT.0b013e31824a47ca

Li, X., Hu, J., Zang, X., Xing, J., Mo, X., Hei, Z., Gong, C., Chen, C., & Zhou, S. (2023). Etomidate Improves the Antidepressant Effect of Electroconvulsive Therapy by Suppressing Hippocampal Neuronal Ferroptosis via Upregulating BDNF/Nrf2. *Molecular Neurobiology*, *60*(11), 6584–6597. https://doi.org/10.1007/s12035-023-03499-1

Liao, X., Ye, H., & Si, T. (2021). A Review of Switching Strategies for Patients with Schizophrenia Comorbid with Metabolic Syndrome or Metabolic Abnormalities. *Neuropsychiatric Disease and Treatment*, *17*, 453–469. https://doi.org/10.2147/NDT.S294521

Licht, C. M. M., de Geus, E. J. C., Seldenrijk, A., van Hout, H. P. J., Zitman, F. G., van Dyck, R., & Penninx, B. W. J. H. (2009). Depression Is Associated With Decreased Blood

Pressure, but Antidepressant Use Increases the Risk for Hypertension. *Hypertension*, *53*(4), 631–638. https://doi.org/10.1161/HYPERTENSIONAHA.108.126698

Limoa, E., Hashioka, S., Miyaoka, T., Tsuchie, K., Arauchi, R., Azis, I. A., Wake, R., Hayashida, M., Araki, T., Furuya, M., Liaury, K., Tanra, A. J., & Horiguchi, J. (2016). Electroconvulsive shock attenuated microgliosis and astrogliosis in the hippocampus and ameliorated schizophrenia-like behavior of Gunn rat. *Journal of Neuroinflammation*, *13*(1). https://doi.org/10.1186/s12974-016-0688-2

Lin, C.-H., Chen, C.-C., & Huang, C.-J. (2020). Electroconvulsive Therapy Versus Fluoxetine in Suicidal Resolution for Patients With Major Depressive Disorder. *The Journal of ECT*, *36*(4), 234. https://doi.org/10.1097/YCT.0000000000000676

Ling, S., Ceban, F., Lui, L. M. W., Lee, Y., Teopiz, K. M., Rodrigues, N. B., Lipsitz, O., Gill, H., Subramaniapillai, M., Mansur, R. B., Lin, K., Ho, R., Rosenblat, J. D., Castle, D., & McIntyre, R. S. (2022). Molecular Mechanisms of Psilocybin and Implications for the Treatment of Depression. *CNS Drugs*, *36*(1), 17–30. https://doi.org/10.1007/s40263-021-00877-y

Lisanby, S. H., & Belmaker, R. H. (2000). Animal models of the mechanisms of action of repetitive transcranial magnetic stimulation (RTMS): Comparisons with electroconvulsive shock (ECS). *Depression and Anxiety*, *12*(3), 178–187. https://doi.org/10.1002/1520-6394(2000)12:3<178::AID-DA10>3.0.CO;2-N

Liu, C., Min, S., Wei, K., Liu, D., Dong, J., Luo, J., & Liu, X. (2012). Effect of electroconvulsive shock on the glutamate level and the hyperphosphorylation of protein tau in depression rat models whose olfactory bulbs were removed. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao. Acta Academiae Medicinae Sinicae*, *34*(3), 216–221. https://doi.org/10.3881/j.issn.1000-503X.2012.03.005

Liu, L.-R., Liu, J.-C., Bao, J.-S., Bai, Q.-Q., & Wang, G.-Q. (2020). Interaction of Microglia and Astrocytes in the Neurovascular Unit. *Frontiers in Immunology*, *11*, 1024. https://doi.org/10.3389/fimmu.2020.01024

Livingston, R., Wu, C., Mu, K., & Coffey, M. J. (2018). Regulation of Electroconvulsive Therapy: A Systematic Review of US State Laws. *The Journal of ECT*, *34*(1), 60. https://doi.org/10.1097/YCT.0000000000000460

Lloyd, J. R., Silverman, E. R., Kugler, J. L., & Cooper, J. J. (2020). Electroconvulsive Therapy for Patients with Catatonia: Current Perspectives. *Neuropsychiatric Disease and Treatment*, *16*, 2191–2208. https://doi.org/10.2147/NDT.S231573

Lloyd-Burton, S. M., York, E. M., Anwar, M. A., Vincent, A. J., & Roskams, A. J. (2013). SPARC regulates microgliosis and functional recovery following cortical ischemia. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *33*(10), 4468–4481. https://doi.org/10.1523/JNEUROSCI.3585-12.2013

Lochmann, D., & Richardson, T. (2019). Selective Serotonin Reuptake Inhibitors. In M. Macaluso & S. H. Preskorn (Eds.), *Antidepressants: From Biogenic Amines to New*

Mechanisms of Action (pp. 135–144). Springer International Publishing. https://doi.org/10.1007/164_2018_172

Lock, T. (1994). Advances in the practice of electroconvulsive therapy. *Advances in Psychiatric Treatment*, *1*(2), 47–56. https://doi.org/10.1192/apt.1.2.47

Loo, C. K., Sainsbury, K., Sheehan, P., & Lyndon, B. (2008). A comparison of RUL ultrabrief pulse (0.3 ms) ECT and standard RUL ECT. *International Journal of Neuropsychopharmacology*, *11*(7), 883–890. https://doi.org/10.1017/S1461145708009292

Loonen, A. J., & Ivanova, S. A. (2021). Neurobiological mechanisms associated with antipsychotic drug-induced dystonia. *Journal of Psychopharmacology (Oxford, England)*, *35*(1), 3–14. https://doi.org/10.1177/0269881120944156

López-Giménez, J. F., & González-Maeso, J. (2018). Hallucinogens and Serotonin 5-HT2A Receptor-Mediated Signaling Pathways. *Current Topics in Behavioral Neurosciences*, *36*, 45–73. https://doi.org/10.1007/7854_2017_478

Lopez-Munoz, F., & Alamo, C. (2009). Monoaminergic Neurotransmission: The History of the Discovery of Antidepressants from 1950s Until Today. *Current Pharmaceutical Design*, *15*(14), 1563–1586. https://doi.org/10.2174/138161209788168001

López-Muñoz, F., Shen, W. W., D'Ocon, P., Romero, A., & Álamo, C. (2018). A History of the Pharmacological Treatment of Bipolar Disorder. *International Journal of Molecular Sciences*, *19*(7), 2143. https://doi.org/10.3390/ijms19072143

Lorenz, T., Rullo, J., & Faubion, S. (2016). Antidepressant-Induced Female Sexual Dysfunction. *Mayo Clinic Proceedings*, *91*(9), 1280–1286. https://doi.org/10.1016/j.mayocp.2016.04.033

Lowe, H., Toyang, N., Steele, B., Grant, J., Ali, A., Gordon, L., & Ngwa, W. (2022). Psychedelics: Alternative and Potential Therapeutic Options for Treating Mood and Anxiety Disorders. *Molecules (Basel, Switzerland)*, *27*(8), 2520. https://doi.org/10.3390/molecules27082520

Lu, J., Zhang, C., Lv, J., Zhu, X., Jiang, X., Lu, W., Lu, Y., Tang, Z., Wang, J., & Shen, X. (2021). Antiallergic drug desloratadine as a selective antagonist of 5HT2A receptor ameliorates pathology of Alzheimer's disease model mice by improving microglial dysfunction. *Aging Cell*, *20*(1), e13286. https://doi.org/10.1111/acel.13286

Luber, B. M., Davis, S., Bernhardt, E., Neacsiu, A., Kwapil, L., Lisanby, S. H., & Strauman, T. J. (2017). Using neuroimaging to individualize TMS treatment for depression: Toward a new paradigm for imaging-guided intervention. *NeuroImage*, *148*, 1–7. https://doi.org/10.1016/j.neuroimage.2016.12.083

Lurie, I., & Levine, S. Z. (2010). Meta-Analysis of Dropout Rates in SSRIs Versus Placebo in Randomized Clinical Trials of PTSD. *The Journal of Nervous and Mental Disease*, *198*(2), 116. https://doi.org/10.1097/NMD.0b013e3181cc41b6

Lye, M.-S., Tey, Y.-Y., Tor, Y.-S., Shahabudin, A. F., Ibrahim, N., Ling, K.-H., Stanslas, J., Loh, S.-P., Rosli, R., Lokman, K. A., Badamasi, I. M., Faris-Aldoghachi, A., & Abdul Razak, N. A. (2020). Predictors of recurrence of major depressive disorder. *PLoS ONE*, *15*(3), e0230363. https://doi.org/10.1371/journal.pone.0230363

Lyman, M., Lloyd, D. G., Ji, X., Vizcaychipi, M. P., & Ma, D. (2014). Neuroinflammation: The role and consequences. *Neuroscience Research*, *79*, 1–12. https://doi.org/10.1016/j.neures.2013.10.004

Ma, P., & Ou, Y. (2023). Correlation between the dopaminergic system and inflammation disease: A review. *Molecular Biology Reports*, *50*(8), 7043–7053. https://doi.org/10.1007/s11033-023-08610-2

Macritchie, K., Geddes, J., Scott, J., Haslam, D. R., Lima, M. S. de, & Goodwin, G. (2003). Valproate for acute mood episodes in bipolar disorder. *Cochrane Database of Systematic Reviews*, *1*. https://doi.org/10.1002/14651858.CD004052

Madsen, M. K., Fisher, P. M., Burmester, D., Dyssegaard, A., Stenbæk, D. S., Kristiansen, S., Johansen, S. S., Lehel, S., Linnet, K., Svarer, C., Erritzoe, D., Ozenne, B., & Knudsen, G. M. (2019). Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *44*(7), 1328–1334. https://doi.org/10.1038/s41386-019-0324-9

Maeda, J., Higuchi, M., Inaji, M., Ji, B., Haneda, E., Okauchi, T., Zhang, M.-R., Suzuki, K., & Suhara, T. (2007). Phase-dependent roles of reactive microglia and astrocytes in nervous system injury as delineated by imaging of peripheral benzodiazepine receptor. *Brain Research*, *1157*, 100–111. https://doi.org/10.1016/j.brainres.2007.04.054

Magnusson, A., & Boivin, D. (2003). Seasonal Affective Disorder: An Overview: REVIEW. *Chronobiology International*, *20*(2), 189–207. https://doi.org/10.1081/CBI-120019310

Magruder, K. M., McLaughlin, K. A., & Elmore Borbon, D. L. (2017). Trauma is a public health issue. *European Journal of Psychotraumatology*, *8*(1), 1375338. https://doi.org/10.1080/20008198.2017.1375338

Mahmoudi, E., Faizi, M., Hajiaghaee, R., & Razmi*, A. (2018). Alteration of Depressive-like Behaviors by Psilocybe cubensis Alkaloid Extract in Mice: The Role of Glutamate Pathway. *Research Journal of Pharmacognosy*, *5*(2), 17–24. https://doi.org/10.22127/rjp.2018.58486

Malhi, G. S., Ivanovski, B., Hadzi-Pavlovic, D., Mitchell, P. B., Vieta, E., & Sachdev, P. (2007). Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. *Bipolar Disorders*, *9*(1–2), 114–125. https://doi.org/10.1111/j.1399-5618.2007.00324.x

Mamo, D. C., Sweet, R. A., & Keshavan, M. S. (1999). Managing Antipsychotic-Induced Parkinsonism. *Drug Safety*, *20*(3), 269–275. https://doi.org/10.2165/00002018-199920030-00006

Mansouri, F. A., Rosa, M. G. P., & Atapour, N. (2015). Working Memory in the Service of Executive Control Functions. *Frontiers in Systems Neuroscience*, *9*, 166. https://doi.org/10.3389/fnsys.2015.00166

Maron, E., & Shlik, J. (2006). Serotonin Function in Panic Disorder: Important, But Why? *Neuropsychopharmacology*, *31*(1), 1–11. https://doi.org/10.1038/sj.npp.1300880

Marshall, R. D., Lewis-Fernandez, R., Blanco, C., Simpson, H. B., Lin, S.-H., Vermes, D., Garcia, W., Schneier, F., Neria, Y., Sanchez-Lacay, A., & Liebowitz, M. R. (2007). A controlled trial of paroxetine for chronic PTSD, dissociation, and interpersonal problems in mostly minority adults. *Depression and Anxiety*, *24*(2), 77–84. https://doi.org/10.1002/da.20176

Martin, B. A., Cooper, R. M., & Parikh, S. V. (1998). Propofol anesthesia, seizure duration, and ECT: A case report and literature review. *The Journal of ECT*, *14*(2), 99–108.

Matheson, E., & Hainer, B. L. (2017). Insomnia: Pharmacologic Therapy. *American Family Physician*, *96*(1), 29–35.

Mathieson, S., Lin, C.-W. C., Underwood, M., & Eldabe, S. (2020). Pregabalin and gabapentin for pain. *BMJ*, *369*, m1315. https://doi.org/10.1136/bmj.m1315

Matsumura, A., Suzuki, S., Iwahara, N., Hisahara, S., Kawamata, J., Suzuki, H., Yamauchi, A., Takata, K., Kitamura, Y., & Shimohama, S. (2015). Temporal Changes of CD68 and α7 Nicotinic Acetylcholine Receptor Expression in Microglia in Alzheimer's Disease-Like Mouse Models. *Journal of Alzheimer's Disease*, *44*(2), 409–423. https://doi.org/10.3233/JAD-141572

Maynard, Kristen. R., Hobbs, J. W., Rajpurohit, S. K., & Martinowich, K. (2018a). Electroconvulsive seizures influence dendritic spine morphology and BDNF expression in a neuroendocrine model of depression. *Brain Stimulation*, *11*(4), 856–859. https://doi.org/10.1016/j.brs.2018.04.003

Maynard, Kristen. R., Hobbs, J. W., Rajpurohit, S., & Martinowich, K. (2018b). Electroconvulsive seizures influence dendritic spine morphology and BDNF expression in a neuroendocrine model of depression. *Brain Stimulation*, *11*(4), 856–859. https://doi.org/10.1016/j.brs.2018.04.003

Mayur, P. M., Gangadhar, B. N., Subbakrishna, D. K., & Janakiramaiah, N. (2000). Discontinuation of antidepressant drugs during electroconvulsive therapy: A controlled study. *Journal of Affective Disorders*, *58*(1), 37–41. https://doi.org/10.1016/S0165-0327(99)00096-8

McAuliffe, J. J., Loepke, A. W., Miles, L., Joseph, B., Hughes, E., & Vorhees, C. V. (2009). Desflurane, isoflurane, and sevoflurane provide limited neuroprotection against neonatal hypoxia-ischemia in a delayed preconditioning paradigm. *Anesthesiology*, *111*(3), 533–546. https://doi.org/10.1097/ALN.0b013e3181b060d3

McEwen, B. S. (2005). Glucocorticoids, depression, and mood disorders: Structural remodeling in the brain. *Metabolism*, *54*(5, Supplement), 20–23. https://doi.org/10.1016/j.metabol.2005.01.008

McKiernan, P. (2014). Acute liver failure after valproate exposure: Liver transplantation may be indicated beyond childhood. *Liver Transplantation*, *20*(11), 1287–1289. https://doi.org/10.1002/lt.23988

Mei, Y.-Y., Wu, D. C., & Zhou, N. (2018). Astrocytic Regulation of Glutamate Transmission in Schizophrenia. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00544

Meltzer, H. Y. (1991). The Mechanism of Action of Novel Antipsychotic Drugs. *Schizophrenia Bulletin*, *17*(2), 263–287. https://doi.org/10.1093/schbul/17.2.263

Meltzer, H. Y., & Stahl, S. M. (1976). The dopamine hypothesis of schizophrenia: A review. *Schizophrenia Bulletin*, *2*(1), 19–76. https://doi.org/10.1093/schbul/2.1.19

Merens, W., Willem Van der Does, A. J., & Spinhoven, P. (2007). The effects of serotonin manipulations on emotional information processing and mood. *Journal of Affective Disorders*, *103*(1), 43–62. https://doi.org/10.1016/j.jad.2007.01.032

Metastasio, A., & Dodwell, D. (2013). A translation of "L´Elettroshock" by Cerletti & Bini, with an introduction. *The European Journal of Psychiatry*, *27*(4), 231–239. https://doi.org/10.4321/S0213-61632013000400001

Meyer, D., & Halfin, V. (1981). Toxicity Secondary to Meperidine in Patients on Monoamine Oxidase Inhibitors: A Case Report and Critical Review. *Journal of Clinical Psychopharmacology*, *1*(5), 319.

Meyers, K. T., Damphousse, C. C., Ozols, A. B., Campbell, J. M., Newbern, J. M., Hu, C., Marrone, D. F., & Gallitano, A. L. (2023). Serial electroconvulsive Seizure alters dendritic complexity and promotes cellular proliferation in the mouse dentate gyrus; a role for Egr3. *Brain Stimulation*, *16*(3), 889–900. https://doi.org/10.1016/j.brs.2023.04.022

Michael, T., Zetsche, U., & Margraf, J. (2007). Epidemiology of anxiety disorders. *Psychiatry*, *6*(4), 136–142. https://doi.org/10.1016/j.mppsy.2007.01.007

Mickey, B. J., Ginsburg, Y., Sitzmann, A. F., Grayhack, C., Sen, S., Kirschbaum, C., Maixner, D. F., & Abelson, J. L. (2018). Cortisol trajectory, melancholia, and response to electroconvulsive therapy. *Journal of Psychiatric Research*, *103*, 46–53. https://doi.org/10.1016/j.jpsychires.2018.05.007

Mindt, S., Neumaier, M., Hoyer, C., Sartorius, A., & Kranaster, L. (2020). Cytokine-mediated cellular immune activation in electroconvulsive therapy: A CSF study in patients with treatment-resistant depression. *The World Journal of Biological Psychiatry*, *21*(2), 139–147. https://doi.org/10.1080/15622975.2019.1618494

Miranda, A. S. de, Miranda, A. S. de, & Teixeira, A. L. (2019). Lamotrigine as a mood stabilizer: Insights from the pre-clinical evidence. *Expert Opinion on Drug Discovery*, *14*(2), 179–190. https://doi.org/10.1080/17460441.2019.1553951

Mirzakhani, H., Guchelaar, H.-J., Welch, C. A., Cusin, C., Doran, M. E., MacDonald, T. O., Bittner, E. A., Eikermann, M., & Nozari, A. (2016). Minimum Effective Doses of Succinylcholine and Rocuronium During Electroconvulsive Therapy: A Prospective, Randomized, Crossover Trial. *Anesthesia & Analgesia*, *123*(3), 587. https://doi.org/10.1213/ANE.0000000000001218

Mirzakhani, H., Welch, C. A., Eikermann, M., & Nozari, A. (2012). Neuromuscular blocking agents for electroconvulsive therapy: A systematic review. *Acta Anaesthesiologica Scandinavica*, *56*(1), 3–16. https://doi.org/10.1111/j.1399-6576.2011.02520.x

Mizutani, M., Pino, P. A., Saederup, N., Charo, I. F., Ransohoff, R. M., & Cardona, A. E. (2012). The Fractalkine Receptor but Not CCR2 Is Present on Microglia from Embryonic Development throughout Adulthood. *The Journal of Immunology*, *188*(1), 29–36. https://doi.org/10.4049/jimmunol.1100421

Modestin, J., Stephan, P. L., Erni, T., & Umari, T. (2000). Prevalence of extrapyramidal syndromes in psychiatric inpatients and the relationship of clozapine treatment to tardive dyskinesia. *Schizophrenia Research*, *42*(3), 223–230. https://doi.org/10.1016/S0920-9964(99)00133-4

Mohamadian, M., Fallah, H., Ghofrani-Jahromi, Z., Rahimi-Danesh, M., Shokouhi Qare Saadlou, M.-S., & Vaseghi, S. (2023). Mood and behavior regulation: Interaction of lithium and dopaminergic system. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *396*(7), 1339–1359. https://doi.org/10.1007/s00210-023-02437-1

Moliner, R., Girych, M., Brunello, C. A., Kovaleva, V., Biojone, C., Enkavi, G., Antenucci, L., Kot, E. F., Goncharuk, S. A., Kaurinkoski, K., Kuutti, M., Fred, S. M., Elsilä, L. V., Sakson, S., Cannarozzo, C., Diniz, C. R. A. F., Seiffert, N., Rubiolo, A., Haapaniemi, H., … Castrén, E. (2023). Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. *Nature Neuroscience*, *26*(6), Article 6. https://doi.org/10.1038/s41593-023-01316-5

Monji, A., Kato, T., & Kanba, S. (2009). Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. *Psychiatry and Clinical Neurosciences*, *63*(3), 257–265. https://doi.org/10.1111/j.1440-1819.2009.01945.x

Monteiro, L. C., & Ferreira, F. (2018). Ecological assessment of executive dysfunction in anxiety. *Clinical and Biomedical Research*, *38*(1), Article 1. https://seer.ufrgs.br/index.php/hcpa/article/view/76288

Moon, C.-M., Sundaram, T., Choi, N.-G., & Jeong, G.-W. (2016). Working memory dysfunction associated with brain functional deficits and cellular metabolic changes in patients with generalized anxiety disorder. *Psychiatry Research: Neuroimaging*, *254*, 137–144. https://doi.org/10.1016/j.pscychresns.2016.06.013

Moore, R. A., Derry, S., Aldington, D., Cole, P., & Wiffen, P. J. (2015). Amitriptyline for neuropathic pain in adults. *The Cochrane Database of Systematic Reviews*, *2015*(7), CD008242. https://doi.org/10.1002/14651858.CD008242.pub3

Moraczewski, J., Awosika, A. O., & Aedma, K. K. (2023). Tricyclic Antidepressants. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK557791/

Morcos, N., Maixner, S., & Maixner, D. F. (2021). Electroconvulsive Therapy for Bipolar Depression in Older Adults. *The Journal of ECT*, *37*(3), 182. https://doi.org/10.1097/YCT.0000000000000755

Morgan, J. T., Chana, G., Pardo, C. A., Achim, C., Semendeferi, K., Buckwalter, J., Courchesne, E., & Everall, I. P. (2010). Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. *Biological Psychiatry*, *68*(4), 368–376. https://doi.org/10.1016/j.biopsych.2010.05.024

Moritz, S., Silverstein, S. M., Dietrichkeit, M., & Gallinat, J. (2020). Neurocognitive deficits in schizophrenia are likely to be less severe and less related to the disorder than previously thought. *World Psychiatry*, *19*(2), 254–255. https://doi.org/10.1002/wps.20759

Mukherjee, S. (1993). Combined ECT and Lithium Therapy. *The Journal of ECT*, *9*(4), 274.

Müller, N. (2008). Inflammation and the glutamate system in schizophrenia: Implications for therapeutic targets and drug development. *Expert Opinion on Therapeutic Targets*, *12*(12), 1497–1507. https://doi.org/10.1517/14728220802507852

Müller, N., & Schwarz, M. J. (2007). The immune-mediated alteration of serotonin and glutamate: Towards an integrated view of depression. *Molecular Psychiatry*, *12*(11), 988–1000. https://doi.org/10.1038/sj.mp.4002006

Muratore, A. F., & Attia, E. (2022). Psychopharmacologic Management of Eating Disorders. *Current Psychiatry Reports*, *24*(7), 345–351. https://doi.org/10.1007/s11920-022-01340-5

Murrell, J. C., Waters, D., & Johnson, C. B. (2008). Comparative effects of halothane, isoflurane, sevoflurane and desflurane on the electroencephalogram of the rat. *Laboratory Animals*, *42*(2), 161–170. https://doi.org/10.1258/la.2007.06019e

Musholt, K., Cirillo, G., Cavaliere, C., Rosaria Bianco, M., Bock, J., Helmeke, C., Braun, K., & Papa, M. (2009). Neonatal separation stress reduces glial fibrillary acidic protein- and S100β-immunoreactive astrocytes in the rat medial precentral cortex. *Developmental Neurobiology*, *69*(4), 203–211. https://doi.org/10.1002/dneu.20694

Nair, J., & Ajit, S. S. (2008). The Role of the Glutamatergic System in Posttraumatic Stress Disorder. *CNS Spectrums*, *13*(7), 585–591. https://doi.org/10.1017/S1092852900016862

Nayak, S. M., Jackson, H., Sepeda, N. D., Mathai, D. S., So, S., Yaffe, A., Zaki, H., Brasher, T. J., Lowe, M. X., Jolly, D. R. P., Barrett, F. S., Griffiths, R. R., Strickland, J. C., Johnson, M. W., Jackson, H., & Garcia-Romeu, A. (2023). Naturalistic psilocybin use is associated

with persisting improvements in mental health and wellbeing: Results from a prospective, longitudinal survey. *Frontiers in Psychiatry*, *14*, 1199642. https://doi.org/10.3389/fpsyt.2023.1199642

Nemeroff, C. B., & Owens, M. J. (2002). Treatment of mood disorders. *Nature Neuroscience*, *5*(11), 1068–1070. https://doi.org/10.1038/nn943

Nguyen, P. T., Dorman, L. C., Pan, S., Vainchtein, I. D., Han, R. T., Nakao-Inoue, H., Taloma, S. E., Barron, J. J., Molofsky, A. B., Kheirbek, M. A., & Molofsky, A. V. (2020). Microglial Remodeling of the Extracellular Matrix Promotes Synapse Plasticity. *Cell*, *182*(2), 388-403.e15. https://doi.org/10.1016/j.cell.2020.05.050

Nichols, D. E. (2004). Hallucinogens. *Pharmacology & Therapeutics*, *101*(2), 131–181. https://doi.org/10.1016/j.pharmthera.2003.11.002

Nichols, D. E. (2020). Psilocybin: From ancient magic to modern medicine. *The Journal of Antibiotics*, *73*(10), 679–686. https://doi.org/10.1038/s41429-020-0311-8

Nobler, M. S., & Sackeim, H. A. (1993). Augmentation Strategies in Electroconvulsive Therapy: A Synthesis. *The Journal of ECT*, *9*(4), 331.

Noda, M. (n.d.). Dysfunction of Glutamate Receptors in Microglia May Cause Neurodegeneration. *Current Alzheimer Research*, *13*(4), 381–386.

Nøhr, A. K., Eriksson, H., Hobart, M., Moltke, I., Buller, R., Albrechtsen, A., & Lindgreen, S. (2021). Predictors and trajectories of treatment response to SSRIs in patients suffering from PTSD. *Psychiatry Research*, *301*, 113964. https://doi.org/10.1016/j.psychres.2021.113964

Nuñez, N. A., Joseph, B., Pahwa, M., Kumar, R., Resendez, M. G., Prokop, L. J., Veldic, M., Seshadri, A., Biernacka, J. M., Frye, M. A., Wang, Z., & Singh, B. (2022). Augmentation strategies for treatment resistant major depression: A systematic review and network meta-analysis. *Journal of Affective Disorders*, *302*, 385–400. https://doi.org/10.1016/j.jad.2021.12.134

Nutt, D. J., Peill, J. M., Weiss, B., Godfrey, K., Carhart-Harris, R. L., & Erritzoe, D. (n.d.). *Psilocybin and Other Classic Psychedelics in Depression* (pp. 1–26). Springer. https://doi.org/10.1007/7854_2023_451

Nygren, A., Reutfors, J., Brandt, L., Bodén, R., Nordenskjöld, A., & Tiger, M. (2023). Response to electroconvulsive therapy in treatment-resistant depression: Nationwide observational follow-up study. *BJPsych Open*, *9*(2), e35. https://doi.org/10.1192/bjo.2023.5

Obata, H. (2017). Analgesic Mechanisms of Antidepressants for Neuropathic Pain. *International Journal of Molecular Sciences*, *18*(11), Article 11. https://doi.org/10.3390/ijms18112483

Okada-Tsuchioka, M., Segawa, M., Kajitani, N., Hisaoka-Nakashima, K., Shibasaki, C., Morinobu, S., & Takebayashi, M. (2014). Electroconvulsive seizure induces thrombospondin-1 in the adult rat hippocampus. *Progress in Neuro-*

Psychopharmacology and Biological Psychiatry, *48*, 236–244.
https://doi.org/10.1016/j.pnpbp.2013.10.001

Okamoto, N., Nakai, T., Sakamoto, K., Nagafusa, Y., Higuchi, T., & Nishikawa, T. (2010). Rapid
Antidepressant Effect of Ketamine Anesthesia During Electroconvulsive Therapy of
Treatment-Resistant Depression: Comparing Ketamine and Propofol Anesthesia. *The
Journal of ECT*, *26*(3), 223. https://doi.org/10.1097/YCT.0b013e3181c3b0aa

Olvera, R. L. (2002). Intermittent Explosive Disorder. *CNS Drugs*, *16*(8), 517–526.
https://doi.org/10.2165/00023210-200216080-00002

O'Neill, J. R., & Stephenson, C. (2022). Antipsychotic-Induced Laryngeal Dystonia.
Psychopharmacology Bulletin, *52*(1), 61–67.

Orellana, G., & Slachevsky, A. (2013). Executive Functioning in Schizophrenia. *Frontiers in
Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00035

Orihuela, R., McPherson, C. A., & Harry, G. J. (2016). Microglial M1/M2 polarization and
metabolic states. *British Journal of Pharmacology*, *173*(4), 649–665.
https://doi.org/10.1111/bph.13139

Orsolini, L., Pompili, S., Tempia Valenta, S., Salvi, V., & Volpe, U. (2022). C-Reactive Protein as
a Biomarker for Major Depressive Disorder? *International Journal of Molecular Sciences*,
23(3), Article 3. https://doi.org/10.3390/ijms23031616

Orzelska-Górka, J., Mikulska, J., Wiszniewska, A., & Biała, G. (2022). New Atypical
Antipsychotics in the Treatment of Schizophrenia and Depression. *International Journal
of Molecular Sciences*, *23*(18), Article 18. https://doi.org/10.3390/ijms231810624

Owens, M. J. (2004). *Selectivity of Antidepressants: From the Monoamine Hypothesis of
Depression to the SSRI Revolution and Beyond*.

Pace, M., Heckendorn, M., Aouizerate, B., Hanon, C., Seigneurie, A.-S., Lavaud, P., Hozer, F.,
Raykeer, R. P. D., Guerin-Langlois, C., Cormier, L., Raucourt, H. P. D., Limosin, F., &
Hoertel, N. (2021). Management of panic disorder in the elderly. *Geriatrie Et Psychologie
Neuropsychiatrie Du Vieillissement*. https://doi.org/10.1684/pnv.2021.0965

Pacholko, A. G., & Bekar, L. K. (2021). Lithium orotate: A superior option for lithium therapy?
Brain and Behavior, *11*(8), e2262. https://doi.org/10.1002/brb3.2262

Pacitti, F., Iannitelli, A., Caredda, M., Marconi, D., Limpido, L., & Bersani, G. (2011). Immediate
serum growth hormone decrease as a potential index of dopamine-related response to
electroconvulsive therapy in schizophrenic patients. *The Journal of ECT*, *27*(2), 119–
122. https://doi.org/10.1097/YCT.0b013e3181e4812e

Pagnin, D., de Queiroz, V., Pini, S., & Cassano, G. B. (2004). Efficacy of ECT in Depression: A
Meta-Analytic Review. *The Journal of ECT*, *20*(1), 13.

Pajares, M., I. Rojo, A., Manda, G., Boscá, L., & Cuadrado, A. (2020). Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. *Cells*, *9*(7), Article 7. https://doi.org/10.3390/cells9071687

Paolicelli, R. C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., Giustetto, M., Ferreira, T. A., Guiducci, E., Dumas, L., Ragozzino, D., & Gross, C. T. (2011). Synaptic Pruning by Microglia Is Necessary for Normal Brain Development. *Science*, *333*(6048), 1456–1458. https://doi.org/10.1126/science.1202529

Paolicelli, R. C., Sierra, A., Stevens, B., Tremblay, M.-E., Aguzzi, A., Ajami, B., Amit, I., Audinat, E., Bechmann, I., Bennett, M., Bennett, F., Bessis, A., Biber, K., Bilbo, S., Blurton-Jones, M., Boddeke, E., Brites, D., Brône, B., Brown, G. C., … Wyss-Coray, T. (2022). Microglia states and nomenclature: A field at its crossroads. *Neuron*, *110*(21), 3458–3483. https://doi.org/10.1016/j.neuron.2022.10.020

Parker, et al. (2001). Assessing the Comparative Effectiveness of Antidepressant Therapies: A Prospective Clinical Practice Study. *J Clin Psychiatry*.

Parkhurst, C. N., Yang, G., Ninan, I., Savas, J. N., Yates, J. R., Lafaille, J. J., Hempstead, B. L., Littman, D. R., & Gan, W.-B. (2013). Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell*, *155*(7), 1596–1609. https://doi.org/10.1016/j.cell.2013.11.030

Parrott, A. C. (2015). Why all stimulant drugs are damaging to recreational users: An empirical overview and psychobiological explanation. *Human Psychopharmacology*, *30*(4), 213–224. https://doi.org/10.1002/hup.2468

Patel, K. R., Cherian, J., Gohil, K., & Atkinson, D. (2014). Schizophrenia: Overview and Treatment Options. *Pharmacy and Therapeutics*, *39*(9), 638–645.

Patel, M., Patel, S., Hardy, D. W., Benzies, B. J., & Tare, V. (2006). Should Electroconvulsive Therapy Be an Early Consideration for Suicidal Patients? *The Journal of ECT*, *22*(2), 113.

Payne, N. A., & Prudic, J. (2009a). Electroconvulsive Therapy Part I: A Perspective on the Evolution and Current Practice of ECT. *Journal of Psychiatric Practice*, *15*(5), 346–368. https://doi.org/10.1097/01.pra.0000361277.65468.ef

Payne, N. A., & Prudic, J. (2009b). Electroconvulsive Therapy Part II: A Biopsychosocial Perspective. *Journal of Psychiatric Practice*, *15*(5), 369–390. https://doi.org/10.1097/01.pra.0000361278.73092.85

Pearlman, C. (1991). Electroconvulsive therapy: Current concepts. *General Hospital Psychiatry*, *13*(2), 128–137. https://doi.org/10.1016/0163-8343(91)90024-Q

Pearlstein, T. (2015). Depression during Pregnancy. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *29*(5), 754–764. https://doi.org/10.1016/j.bpobgyn.2015.04.004

Peleg, L. C., Rabinovitch, D., Lavie, Y., Rabbie, D. M., Horowitz, I., Fruchter, E., & Gruenwald, I. (2022). Post-SSRI Sexual Dysfunction (PSSD): Biological Plausibility, Symptoms, Diagnosis, and Presumed Risk Factors. *Sexual Medicine Reviews*, *10*(1), 91–98. https://doi.org/10.1016/j.sxmr.2021.07.001

Pereira, V. S., & Hiroaki-Sato, V. A. (2018). A brief history of antidepressant drug development: From tricyclics to beyond ketamine. *Acta Neuropsychiatrica*, *30*(6), 307–322. https://doi.org/10.1017/neu.2017.39

Perez-Caballero, L., Torres-Sanchez, S., Bravo, L., Mico, J. A., & Berrocoso, E. (2014). Fluoxetine: A case history of its discovery and preclinical development. *Expert Opinion on Drug Discovery*, *9*(5), 567–578. https://doi.org/10.1517/17460441.2014.907790

Pérez-Cano, L., Azidane Chenlo, S., Sabido-Vera, R., Sirci, F., Durham, L., & Guney, E. (2023). Translating precision medicine for autism spectrum disorder: A pressing need. *Drug Discovery Today*, *28*(3), 103486. https://doi.org/10.1016/j.drudis.2023.103486

Perrotta, G. (2019). Panic Disorder: Definitions, Contexts, Neural Correlates and Clinical Strategies. *Current Trends in Clinical & Medical Sciences*, *1*. https://doi.org/10.33552/CTCMS.2019.01.000508

Petersen, T. J. (2006). Enhancing the efficacy of antidepressants with psychotherapy. *Journal of Psychopharmacology*, *20*(3_suppl), 19–28. https://doi.org/10.1177/1359786806064314

Petrides, G., Fink, M., Husain, M. M., Knapp, R. G., Rush, A. J., Mueller, M., Rummans, T. A., O'Connor, K. M., Rasmussen, K. G. J., Bernstein, H. J., Biggs, M., Bailine, S. H., & Kellner, C. H. (2001). ECT Remission Rates in Psychotic Versus Nonpsychotic Depressed Patients: A Report from CORE. *The Journal of ECT*, *17*(4), 244.

Petty, F. (1995). GABA and mood disorders: A brief review and hypothesis. *Journal of Affective Disorders*, *34*(4), 275–281. https://doi.org/10.1016/0165-0327(95)00025-I

Pigott, H. E., Leventhal, A. M., Alter, G. S., & Boren, J. J. (2010). Efficacy and Effectiveness of Antidepressants: Current Status of Research. *Psychotherapy and Psychosomatics*, *79*(5), 267–279. https://doi.org/10.1159/000318293

Pike, A. F., Longhena, F., Faustini, G., van Eik, J.-M., Gombert, I., Herrebout, M. A. C., Fayed, M. M. H. E., Sandre, M., Varanita, T., Teunissen, C. E., Hoozemans, J. J. M., Bellucci, A., Veerhuis, R., & Bubacco, L. (2022). Dopamine signaling modulates microglial NLRP3 inflammasome activation: Implications for Parkinson's disease. *Journal of Neuroinflammation*, *19*(1), 50. https://doi.org/10.1186/s12974-022-02410-4

Pluijms, E. M., Kamperman, A. M., Hoogendijk, W. J., Birkenhäger, T. K., & van den Broek, W. W. (2021). Influence of an adjuvant antidepressant on the efficacy of electroconvulsive therapy: A systematic review and meta-analysis. *Australian & New Zealand Journal of Psychiatry*, *55*(4), 366–380. https://doi.org/10.1177/0004867420952543

Popiolek, K., Brus, O., Elvin, T., Landén, M., Lundberg, J., Nordanskog, P., & Nordenskjöld, A. (2018). Rehospitalization and suicide following electroconvulsive therapy for bipolar

depression-A population-based register study. *Journal of Affective Disorders*, *226*, 146–154. https://doi.org/10.1016/j.jad.2017.09.030

Popova, N. K., Tsybko, A. S., & Naumenko, V. S. (2022). The Implication of 5-HT Receptor Family Members in Aggression, Depression and Suicide: Similarity and Difference. *International Journal of Molecular Sciences*, *23*(15), Article 15. https://doi.org/10.3390/ijms23158814

Price, L. H., Charney, D. S., Delgado, P. L., & Heninger, G. R. (1990). Lithium and serotonin function: Implications for the serotonin hypothesis of depression. *Psychopharmacology*, *100*(1), 3–12. https://doi.org/10.1007/BF02245781

Prinsloo, S., & Pretorius, P. J. (2004). Electroconvulsive therapy and its use in modern-day psychiatry. *South African Journal of Psychiatry*, *10*(2), Article 2. https://doi.org/10.4102/sajpsychiatry.v10i2.142

Proença, C. R., Markowitz, J. C., Coimbra, B. M., Cogo-Moreira, H., Maciel, M. R., Mello, A. F., & Mello, M. F. (n.d.). Interpersonal psychotherapy versus sertraline for women with posttraumatic stress disorder following recent sexual assault: A randomized clinical trial. *European Journal of Psychotraumatology*, *13*(2), 2127474. https://doi.org/10.1080/20008066.2022.2127474

Quagliato, L. A., Freire, R. C., & Nardi, A. E. (2018). Risks and benefits of medications for panic disorder: A comparison of SSRIs and benzodiazepines. *Expert Opinion on Drug Safety*, *17*(3), 315–324. https://doi.org/10.1080/14740338.2018.1429403

Rahman, T., & Lauriello, J. (2016). Schizophrenia: An Overview. *FOCUS*, *14*(3), 300–307. https://doi.org/10.1176/appi.focus.20160006

Ram, R., Bromet, E. J., Eaton, W. W., Pato, C., & Schwartz, J. E. (1992). The Natural Course of Schizophrenia: A Review of First-admission Studies. *Schizophrenia Bulletin*, *18*(2), 185–207. https://doi.org/10.1093/schbul/18.2.185

Ramachandraih, C. T., Subramanyam, N., Bar, K. J., Baker, G., & Yeragani, V. K. (2011). Antidepressants: From MAOIs to SSRIs and more. *Indian Journal of Psychiatry*, *53*(2), 180. https://doi.org/10.4103/0019-5545.82567

Ramnauth, A. D., Maynard, K. R., Kardian, A. S., Phan, B. N., Tippani, M., Rajpurohit, S., Hobbs, J. W., Cerceo Page, S., Jaffe, A. E., & Martinowich, K. (2022). Induction of Bdnf from promoter I following electroconvulsive seizures contributes to structural plasticity in neurons of the piriform cortex. *Brain Stimulation*, *15*(2), 427–433. https://doi.org/10.1016/j.brs.2022.02.003

Rappaport, L. M., Hunter, M. D., Russell, J. J., Pinard, G., Bleau, P., & Moskowitz, D. S. (2021). Emotional and interpersonal mechanisms in community SSRI treatment of social anxiety disorder. *Journal of Psychiatry & Neuroscience : JPN*, *46*(1), E56–E64. https://doi.org/10.1503/jpn.190164

Rasmussen, K. G. (2014). Propofol for ECT anesthesia a review of the literature. *The Journal of ECT*, *30*(3), 210–215. https://doi.org/10.1097/YCT.0000000000000093

Rasmussen, K. G., Sampson, S. M., & Rummans, T. A. (2002). Electroconvulsive Therapy and Newer Modalities for the Treatment of Medication-Refractory Mental Illness. *Mayo Clinic Proceedings*, *77*(6), 552–556. https://doi.org/10.4065/77.6.552

Ratnayake, U., Quinn, T. A., Castillo-Melendez, M., Dickinson, H., & Walker, D. W. (2012). Behaviour and hippocampus-specific changes in spiny mouse neonates after treatment of the mother with the viral-mimetic Poly I:C at mid-pregnancy. *Brain, Behavior, and Immunity*, *26*(8), 1288–1299. https://doi.org/10.1016/j.bbi.2012.08.011

Ratnayake, U., Quinn, T., LaRosa, D. A., Dickinson, H., & Walker, D. W. (2014). Prenatal Exposure to the Viral Mimetic Poly I:C Alters Fetal Brain Cytokine Expression and Postnatal Behaviour. *Developmental Neuroscience*, *36*(2), 83–94. https://doi.org/10.1159/000362205

Reif Andreas, Bitter Istvan, Buyze Jozefien, Cebulla Kerstin, Frey Richard, Fu Dong-Jing, Ito Tetsuro, Kambarov Yerkebulan, Llorca Pierre-Michel, Oliveira-Maia Albino J., Messer Thomas, Mulhern-Haughey Siobhán, Rive Benoît, von Holt Christian, Young Allan H., & Godinov Yordan. (2023). Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression. *New England Journal of Medicine*, *389*(14), 1298–1309. https://doi.org/10.1056/NEJMoa2304145

Reisman, Y. (2020). Post-SSRI sexual dysfunction. *BMJ*, *368*, m754. https://doi.org/10.1136/bmj.m754

Reitan, R. M., & Wolfson, D. (1997). Emotional disturbances and their interaction with neuropsychological deficits. *Neuropsychology Review*, *7*(1), 3–19. https://doi.org/10.1007/BF02876970

Remington, G., Hahn, M. K., Agarwal, S. M., Chintoh, A., & Agid, O. (2021). Schizophrenia: Antipsychotics and drug development. *Behavioural Brain Research*, *414*, 113507. https://doi.org/10.1016/j.bbr.2021.113507

Rezaie, P., & Male, D. (2002). MESOGLIA & MICROGLIA – A Historical Review of the Concept of Mononuclear Phagocytes Within the Central Nervous System. *Journal of the History of the Neurosciences*, *11*(4), 325–374. https://doi.org/10.1076/jhin.11.4.325.8531

Richtand, N. M., & McNamara, R. K. (2008). Serotonin and dopamine interactions in psychosis prevention. In G. Di Giovann, V. Di Matteo, & E. Esposito (Eds.), *Progress in Brain Research* (Vol. 172, pp. 141–153). Elsevier. https://doi.org/10.1016/S0079-6123(08)00907-2

Riley, S. C. E., & Hayward, E. (2004). Patterns, Trends, and Meanings of Drug Use by Dance-drug Users in Edinburgh, Scotland. *Drugs: Education, Prevention and Policy*, *11*(3), 243–262. https://doi.org/10.1080/09687630310001643111

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T., Farh, K.-H., Holmans, P. A., Lee, P., Bulik-Sullivan, B., Collier, D. A., Huang, H., Pers, T. H., Agartz, I., Agerbo, E., Albus, M., Alexander, M., Amin, F., Bacanu, S. A., Begemann, M., Belliveau, R. A., … O'Donovan, M. C. (2014). Biological Insights From 108 Schizophrenia-Associated Genetic Loci. *Nature*, *511*(7510), 421–427. https://doi.org/10.1038/nature13595

Rizzo, L. F. L., Mana, D. L., & Serra, H. A. (2017). Drug-induced hypothyroidism. *Medicina*, *77*(5), 394–404.

Roberts, C. A., Osborne-Miller, I., Cole, J., Gage, S. H., & Christiansen, P. (2020). Perceived harm, motivations for use and subjective experiences of recreational psychedelic 'magic' mushroom use. *Journal of Psychopharmacology*, *34*(9), 999–1007. https://doi.org/10.1177/0269881120936508

Rodríguez-Carrillo, A., Verheyen, V. J., Van Nuijs, A. L. N., Fernández, M. F., & Remy, S. (2023). Brain-derived neurotrophic factor (BDNF): An effect biomarker of neurodevelopment in human biomonitoring programs. *Frontiers in Toxicology*, *5*, 1319788. https://doi.org/10.3389/ftox.2023.1319788

Rodríguez-Gómez, J. A., Kavanagh, E., Engskog-Vlachos, P., Engskog, M. K. R., Herrera, A. J., Espinosa-Oliva, A. M., Joseph, B., Hajji, N., Venero, J. L., & Burguillos, M. A. (2020). Microglia: Agents of the CNS Pro-Inflammatory Response. *Cells*, *9*(7), Article 7. https://doi.org/10.3390/cells9071717

Roila, F., & Del Favero, A. (1995). Ondansetron clinical pharmacokinetics. *Clinical Pharmacokinetics*, *29*(2), 95–109. https://doi.org/10.2165/00003088-199529020-00004

Ronaldson, P. T., & Davis, T. P. (2020). Regulation of blood-brain barrier integrity by microglia in health and disease: A therapeutic opportunity. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *40*(1_suppl), S6–S24. https://doi.org/10.1177/0271678X20951995

Roppongi, R. T., Kojima, N., Hanamura, K., Yamazaki, H., & Shirao, T. (2013). Selective reduction of drebrin and actin in dendritic spines of hippocampal neurons by activation of 5-HT(2A) receptors. *Neuroscience Letters*, *547*, 76–81. https://doi.org/10.1016/j.neulet.2013.04.061

Rossi, G. N., Hallak, J. E. C., Bouso Saiz, J. C., & Dos Santos, R. G. (2022). Safety issues of psilocybin and LSD as potential rapid acting antidepressants and potential challenges. *Expert Opinion on Drug Safety*, *21*(6), 761–776. https://doi.org/10.1080/14740338.2022.2066650

Rothmore, J. (2020). Antidepressant-induced sexual dysfunction. *Medical Journal of Australia*, *212*(7), 329–334. https://doi.org/10.5694/mja2.50522

Roy, A., Fung, Y. K., Liu, X., & Pahan, K. (2006). Up-regulation of Microglial CD11b Expression by Nitric Oxide *. *Journal of Biological Chemistry*, *281*(21), 14971–14980. https://doi.org/10.1074/jbc.M600236200

Roy, A., Jana, A., Yatish, K., Freidt, M. B., Fung, Y. K., Martinson, J. A., & Pahan, K. (2008). Reactive oxygen species up-regulate CD11b in microglia via nitric oxide: Implications for neurodegenerative diseases. *Free Radical Biology and Medicine*, *45*(5), 686–699. https://doi.org/10.1016/j.freeradbiomed.2008.05.026

Roy-Byrne, P. P., Craske, M. G., & Stein, M. B. (2006). Panic disorder. *The Lancet*, *368*(9540), 1023–1032. https://doi.org/10.1016/S0140-6736(06)69418-X

Rybakowski, J. (2020). Lithium treatment – the state of the art for 2020. *Psychiatria Polska*, *54*(6), 1047–1066. https://doi.org/10.12740/PP/128340

Saari, K. (2004). Hyperlipidemia in Persons Using Antipsychotic Medication: A General Population-Based Birth Cohort Study. *The Journal of Clinical Psychiatry*, *65*(4), 8384.

Sabe, M., Pillinger, T., Kaiser, S., Chen, C., Taipale, H., Tanskanen, A., Tiihonen, J., Leucht, S., Correll, C. U., & Solmi, M. (2022). Half a century of research on antipsychotics and schizophrenia: A scientometric study of hotspots, nodes, bursts, and trends. *Neuroscience & Biobehavioral Reviews*, *136*, 104608. https://doi.org/10.1016/j.neubiorev.2022.104608

Sackeim, H. A. (2017). Modern Electroconvulsive Therapy: Vastly Improved yet Greatly Underused. *JAMA Psychiatry*, *74*(8), 779–780. https://doi.org/10.1001/jamapsychiatry.2017.1670

Sackeim, H. A., Decina, P., Prohovnik, I., Portnoy, S., Kanzler, M., & Malitz, S. (1986, March 1). *Dosage, Seizure Threshold, and the Antidepressant Efficacy of Electroconvulsive Therapya*. Annals of the New York Academy of Sciences. https://doi.org/10.1111/j.1749-6632.1986.tb51274.x

Sackeim, H. A., Devanand, D. P., & Prudic, J. (1991). Stimulus intensity, seizure threshold, and seizure duration: Impact on the efficacy and safety of electroconvulsive therapy. *The Psychiatric Clinics of North America*, *14*(4), 803–843.

Sackeim, H. A., Haskett, R. F., Mulsant, B. H., Thase, M. E., Mann, J. J., Pettinati, H. M., Greenberg, R. M., Crowe, R. R., Cooper, T. B., & Prudic, J. (2001). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: A randomized controlled trial. *JAMA*, *285*(10), 1299–1307. https://doi.org/10.1001/jama.285.10.1299

Sackeim, H. A., Prudic, J., Nobler, M. S., Fitzsimons, L., Lisanby, S. H., Payne, N., Berman, R. M., Brakemeier, E.-L., Perera, T., & Devanand, D. P. (2008). Effects of Pulse Width and Electrode Placement on the Efficacy and Cognitive Effects of Electroconvulsive Therapy. *Brain Stimulation*, *1*(2), 71–83. https://doi.org/10.1016/j.brs.2008.03.001

Sadek, A.-R., Knight, G. E., & Burnstock, G. (2011). Electroconvulsive therapy: A novel hypothesis for the involvement of purinergic signalling. *Purinergic Signalling*, 7(4), 447–452. https://doi.org/10.1007/s11302-011-9242-y

Sarparast, A., Thomas, K., Malcolm, B., & Stauffer, C. S. (2022). Drug-drug interactions between psychiatric medications and MDMA or psilocybin: A systematic review. *Psychopharmacology*, *239*(6), 1945–1976. https://doi.org/10.1007/s00213-022-06083-y

Sasaki, Y., Ohsawa, K., Kanazawa, H., Kohsaka, S., & Imai, Y. (2001). Iba1 Is an Actin-Cross-Linking Protein in Macrophages/Microglia. *Biochemical and Biophysical Research Communications*, *286*(2), 292–297. https://doi.org/10.1006/bbrc.2001.5388

Sastre, E., Nicolay, A., Bruguerolle, B., & Portugal, H. (2005). Effect of lithium on norepinephrine metabolic pathways. *Life Sciences*, *77*(7), 758–767. https://doi.org/10.1016/j.lfs.2004.12.033

Savitz, J., Lucki, I., & Drevets, W. C. (2009). 5-HT1A receptor function in major depressive disorder. *Progress in Neurobiology*, *88*(1), 17–31. https://doi.org/10.1016/j.pneurobio.2009.01.009

Schafer, D. P., Lehrman, E. K., Kautzman, A. G., Koyama, R., Mardinly, A. R., Yamasaki, R., Ransohoff, R. M., Greenberg, M. E., Barres, B. A., & Stevens, B. (2012a). Microglia Sculpt Postnatal Neural Circuits in an Activity and Complement-Dependent Manner. *Neuron*, *74*(4), 691–705. https://doi.org/10.1016/j.neuron.2012.03.026

Schafer, D. P., Lehrman, E. K., Kautzman, A. G., Koyama, R., Mardinly, A. R., Yamasaki, R., Ransohoff, R. M., Greenberg, M. E., Barres, B. A., & Stevens, B. (2012b). Microglia Sculpt Postnatal Neural Circuits in an Activity and Complement-Dependent Manner. *Neuron*, *74*(4), 691–705. https://doi.org/10.1016/j.neuron.2012.03.026

Schafer, D. P., Lehrman, E. K., & Stevens, B. (2013). The "Quad-partite" Synapse: Microglia-Synapse Interactions in the Developing and Mature CNS. *Glia*, *61*(1), 24–36. https://doi.org/10.1002/glia.22389

Schafer, D. P., & Stevens, B. (2015). Microglia Function in Central Nervous System Development and Plasticity. *Cold Spring Harbor Perspectives in Biology*, *7*(10). https://doi.org/10.1101/cshperspect.a020545

Schallner, N., Ulbrich, F., Engelstaedter, H., Biermann, J., Auwaerter, V., Loop, T., & Goebel, U. (2014). Isoflurane but not sevoflurane or desflurane aggravates injury to neurons in vitro and in vivo via p75NTR-NF-κB activation. *Anesthesia and Analgesia*, *119*(6), 1429–1441. https://doi.org/10.1213/ANE.0000000000000488

Scheepstra, K. W. F., van Doorn, J. B., Scheepens, D. S., de Haan, A., Schukking, N., Zantvoord, J. B., & Lok, A. (2022). 'Rapid speed of response to ECT in bipolar depression: A chart review. *Journal of Psychiatric Research*, *147*, 34–38. https://doi.org/10.1016/j.jpsychires.2022.01.008

Schloesser, R. J., Martinowich, K., & Manji, H. K. (2012). Mood-stabilizing drugs: Mechanisms of action. *Trends in Neurosciences*, *35*(1), 36–46. https://doi.org/10.1016/j.tins.2011.11.009

Schmitz, G. P., Chiu, Y.-T., König, G. M., Kostenis, E., Roth, B. L., & Herman, M. A. (2022). *Psychedelic compounds directly excite 5-HT2A Layer 5 Pyramidal Neurons in the Prefrontal Cortex through a 5-HT2A Gq -mediated activation mechanism* (p. 2022.11.15.516655). bioRxiv. https://doi.org/10.1101/2022.11.15.516655

Schneider, J., Patterson, M., & Jimenez, X. F. (2019). Beyond depression: Other uses for tricyclic antidepressants. *Cleveland Clinic Journal of Medicine*, *86*(12), 807–814. https://doi.org/10.3949/ccjm.86a.19005

Schneier, F. R., Campeas, R., Carcamo, J., Glass, A., Lewis-Fernandez, R., Neria, Y., Sanchez-Lacay, A., Vermes, D., & Wall, M. M. (2015). Combined Mirtazapine and SSRI Treatment of PTSD: A Placebo-Controlled Trial. *Depression and Anxiety*, *32*(8), 570–579. https://doi.org/10.1002/da.22384

Schwenkreis, P., & Assion, H. (2004). Atypical antipsychotics and diabetes mellitus. *The World Journal of Biological Psychiatry*, *5*(2), 73–82. https://doi.org/10.1080/15622970410029915

Seeman, P. (1987). Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse*, *1*(2), 133–152. https://doi.org/10.1002/syn.890010203

Sellgren, C. M., Gracias, J., Watmuff, B., Biag, J. D., Thanos, J. M., Whittredge, P. B., Fu, T., Worringer, K., Brown, H. E., Wang, J., Kaykas, A., Karmacharya, R., Goold, C. P., Sheridan, S. D., & Perlis, R. H. (2019). Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. *Nature Neuroscience*, *22*(3), 374–385. https://doi.org/10.1038/s41593-018-0334-7

Semkovska, M., Bédard, M.-A., Godbout, L., Limoge, F., & Stip, E. (2004). Assessment of executive dysfunction during activities of daily living in schizophrenia. *Schizophrenia Research*, *69*(2), 289–300. https://doi.org/10.1016/j.schres.2003.07.005

Senderovich, H., & Jeyapragasan, G. (2018). Is there a role for combined use of gabapentin and pregabalin in pain control? Too good to be true? *Current Medical Research and Opinion*, *34*(4), 677–682. https://doi.org/10.1080/03007995.2017.1391756

Sepúlveda-Lizcano, L., Arenas-Villamizar, V. V., Jaimes-Duarte, E. B., García-Pacheco, H., Paredes, C. S., Bermúdez, V., & Rivera-Porras, D. (2023). Metabolic Adverse Effects of Psychotropic Drug Therapy: A Systematic Review. *European Journal of Investigation in Health, Psychology and Education*, *13*(8), 1505–1520. https://doi.org/10.3390/ejihpe13080110

Sepulveda-Rodriguez, A., Li, P., Khan, T., Ma, J. D., Carlone, C. A., Bozzelli, P. L., Conant, K. E., Forcelli, P. A., & Vicini, S. (2019). Electroconvulsive Shock Enhances Responsive Motility and Purinergic Currents in Microglia in the Mouse Hippocampus. *eNeuro*, *6*(2). https://doi.org/10.1523/ENEURO.0056-19.2019

Shaerzadeh, F., Streit, W. J., Heysieattalab, S., & Khoshbouei, H. (2018). Methamphetamine neurotoxicity, microglia, and neuroinflammation. *Journal of Neuroinflammation*, *15*(1), 341. https://doi.org/10.1186/s12974-018-1385-0

Shaha, D. P. (2023). Insomnia Management: A Review and Update. *The Journal of Family Practice*, *72*(6 Suppl), S31–S36. https://doi.org/10.12788/jfp.0620

Shaltiel, G., Shamir, A., Shapiro, J., Ding, D., Dalton, E., Bialer, M., Harwood, A. J., Belmaker, R. H., Greenberg, M. L., & Agam, G. (2004). Valproate decreases inositol biosynthesis. *Biological Psychiatry*, *56*(11), 868–874. https://doi.org/10.1016/j.biopsych.2004.08.027

Shao, L.-X., Liao, C., Gregg, I., Davoudian, P. A., Savalia, N. K., Delagarza, K., & Kwan, A. C. (2021). Psilocybin induces rapid and persistent growth of dendritic spines in frontal

cortex in vivo. *Neuron, 109*(16), 2535-2544.e4.
https://doi.org/10.1016/j.neuron.2021.06.008

Sheehan, D. V. (2002). The Management of Panic Disorder. *The Journal of Clinical Psychiatry*, *63*(suppl 14), 11106.

Shelton, R. C. (1999). Mood-Stabilizing Drugs in Depression. *The Journal of Clinical Psychiatry*, *60*(suppl 5), 12269.

Shen, W. W. (1999). A history of antipsychotic drug development. *Comprehensive Psychiatry*, *40*(6), 407–414. https://doi.org/10.1016/S0010-440X(99)90082-2

Shi, Z., Atlantis, E., Taylor, A. W., Gill, T. K., Price, K., Appleton, S., Wong, M.-L., & Licinio, J. (2017). SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a 4-year Australian follow-up study. *BMJ Open, 7*(8), e016224. https://doi.org/10.1136/bmjopen-2017-016224

Shiwaku, H., Fujita, M., & Takahashi, H. (2020). Benzodiazepines Reduce Relapse and Recurrence Rates in Patients with Psychotic Depression. *Journal of Clinical Medicine*, *9*(6), Article 6. https://doi.org/10.3390/jcm9061938

Shnayder, N. A., Khasanova, A. K., Strelnik, A. I., Al-Zamil, M., Otmakhov, A. P., Neznanov, N. G., Shipulin, G. A., Petrova, M. M., Garganeeva, N. P., & Nasyrova, R. F. (2022). Cytokine Imbalance as a Biomarker of Treatment-Resistant Schizophrenia. *International Journal of Molecular Sciences, 23*(19), Article 19. https://doi.org/10.3390/ijms231911324

Shulman, K. I., Herrmann, N., & Walker, S. E. (2013). Current Place of Monoamine Oxidase Inhibitors in the Treatment of Depression. *CNS Drugs, 27*(10), 789–797. https://doi.org/10.1007/s40263-013-0097-3

Siemer, M. (2005). Mood-congruent cognitions constitute mood experience. *Emotion, 5*(3), 296–308. https://doi.org/10.1037/1528-3542.5.3.296

Sienaert, P., Brus, O., Lambrichts, S., Lundberg, J., Nordanskog, P., Obbels, J., Verspecht, S., Vansteelandt, K., & Nordenskjöld, A. (2022). Suicidal ideation and ECT, ECT and suicidal ideation: A register study. *Acta Psychiatrica Scandinavica, 146*(1), 74–84. https://doi.org/10.1111/acps.13425

Silverstone, P. H., & McGrath, B. M. (2009). Lithium and valproate and their possible effects on themyo-inositol second messenger system in healthy volunteers and bipolar patients. *International Review of Psychiatry (Abingdon, England), 21*(4), 414–423. https://doi.org/10.1080/09540260902962214

Skeppar, P., & Adolfsson, R. (2006). Bipolar II and the bipolar spectrum. *Nordic Journal of Psychiatry, 60*(1), 7–26. https://doi.org/10.1080/08039480500504685

Skosnik, P. D., Sloshower, J., Safi-Aghdam, H., Pathania, S., Syed, S., Pittman, B., & D'Souza, D. C. (2023). Sub-acute effects of psilocybin on EEG correlates of neural plasticity in

major depression: Relationship to symptoms. *Journal of Psychopharmacology (Oxford, England)*, *37*(7), 687–697. https://doi.org/10.1177/02698811231179800

Sloshower, J., Skosnik, P. D., Safi-Aghdam, H., Pathania, S., Syed, S., Pittman, B., & D'Souza, D. C. (2023). Psilocybin-assisted therapy for major depressive disorder: An exploratory placebo-controlled, fixed-order trial. *Journal of Psychopharmacology*, *37*(7), 698–706. https://doi.org/10.1177/02698811231154852

Smigielski, L., Scheidegger, M., Kometer, M., & Vollenweider, F. X. (2019). Psilocybin-assisted mindfulness training modulates self-consciousness and brain default mode network connectivity with lasting effects. *NeuroImage*, *196*, 207–215. https://doi.org/10.1016/j.neuroimage.2019.04.009

Sobczak, S., Honig, A., Van Duinen, M., & Riedel, W. (2002). Serotonergic dysregulation in bipolar disorders: A literature review of serotonergic challenge studies. *Bipolar Disorders*, *4*(6), 347–356. https://doi.org/10.1034/j.1399-5618.2002.01217.x

Solyom, L., Solyom, C., & Ledwidge, B. (1991). Fluoxetine in Panic Disorder. *The Canadian Journal of Psychiatry*, *36*(5), 378–380. https://doi.org/10.1177/070674379103600512

Song, G.-M., Tian, X., Shuai, T., Yi, L.-J., Zeng, Z., Liu, S., Zhou, J.-G., & Wang, Y. (2015). Treatment of Adults With Treatment-Resistant Depression: Electroconvulsive Therapy Plus Antidepressant or Electroconvulsive Therapy Alone? Evidence From an Indirect Comparison Meta-Analysis. *Medicine*, *94*(26), e1052. https://doi.org/10.1097/MD.0000000000001052

Song, J., Kambari, Y., Amaev, A., Ueno, F., Torres Carmona, E., De Luca, V., Pollock, B., Flint, A., Husain, M. I., Graff-Guerrero, A., & Gerretsen, P. (2023). Psilocybin to promote synaptogenesis in the brains of patients with mild cognitive impairment. *Medical Hypotheses*, *175*, 111068. https://doi.org/10.1016/j.mehy.2023.111068

Spiers, N., Labate, B. C., Ermakova, A. O., Farrell, P., Romero, O. S. G., Gabriell, I., & Olvera, N. (2024). Indigenous psilocybin mushroom practices: An annotated bibliography. *Journal of Psychedelic Studies*, *1*(aop). https://doi.org/10.1556/2054.2023.00297

Srivastava, A. S., & Kumar, R. (2005). Suicidal ideation and attempts in patients with major depression: Sociodemographic and clinical variables. *Indian Journal of Psychiatry*, *47*(4), 225–228. https://doi.org/10.4103/0019-5545.43059

Stahl, S. M. (1998). Mechanism of action of serotonin selective reuptake inhibitors: Serotonin receptors and pathways mediate therapeutic effects and side effects. *Journal of Affective Disorders*, *51*(3), 215–235. https://doi.org/10.1016/S0165-0327(98)00221-3

Stahl, S. M., Entsuah, R., & Rudolph, R. L. (2002). Comparative efficacy between venlafaxine and SSRIs: A pooled analysis of patients with depression. *Biological Psychiatry*, *52*(12), 1166–1174. https://doi.org/10.1016/S0006-3223(02)01425-7

Stahl, S. M., & Li, D. (2003). Escitalopram in the Treatment of Panic Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial. *The Journal of Clinical Psychiatry*, *64*(11), 6601.

Stein, D. J., Seedat, S., van der Linden, G. J., & Zungu-Dirwayi, N. (2000). Selective serotonin reuptake inhibitors in the treatment of post-traumatic stress disorder: A metaanalysis of randomized controlled trials. *International Clinical Psychopharmacology*, *15*, S31.

Stein, M. B., & Sareen, J. (2015). Generalized Anxiety Disorder. *New England Journal of Medicine*, *373*(21), 2059–2068. https://doi.org/10.1056/NEJMcp1502514

Stephan, K. E., Baldeweg, T., & Friston, K. J. (2006). Synaptic Plasticity and Dysconnection in Schizophrenia. *Biological Psychiatry*, *59*(10), 929–939. https://doi.org/10.1016/j.biopsych.2005.10.005

Stevens, A., Fischer, A., Bartels, M., & Buchkremer, G. (1996). Electroconvulsive therapy: A review on indications, methods, risks and medication. *European Psychiatry*, *11*(4), 165–174. https://doi.org/10.1016/0924-9338(96)88386-6

Stevens, B. (2003). Glia: Much more than the neuron's side-kick. *Current Biology*, *13*(12), R469–R472. https://doi.org/10.1016/S0960-9822(03)00404-4

Storm, M. P., & Christensen, K. S. (2021). Comparing treatments for post-traumatic stress disorder—A systematic review. *Danish Medical Journal*, *68*(9). http://www.scopus.com/inward/record.url?scp=85114109349&partnerID=8YFLogxK

Strassman, R. J., & Qualls, C. R. (1994). Dose-Response Study of N,N-Dimethyltryptamine in Humans: I. Neuroendocrine, Autonomic, and Cardiovascular Effects. *Archives of General Psychiatry*, *51*(2), 85–97. https://doi.org/10.1001/archpsyc.1994.03950020009001

Strawn, J. R., Geracioti, L., Rajdev, N., Clemenza, K., & Levine, A. (2018). Pharmacotherapy for Generalized Anxiety Disorder in Adults and Pediatric Patients: An Evidence-Based Treatment Review. *Expert Opinion on Pharmacotherapy*, *19*(10), 1057–1070. https://doi.org/10.1080/14656566.2018.1491966

Strawn, J. R., Prakash, A., Zhang, Q., Pangallo, B. A., Stroud, C. E., Cai, N., & Findling, R. L. (2015). A Randomized, Placebo-Controlled Study of Duloxetine for the Treatment of Children and Adolescents With Generalized Anxiety Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *54*(4), 283–293. https://doi.org/10.1016/j.jaac.2015.01.008

Streit, W. J., Xue, Q.-S., Braak, H., & del Tredici, K. (2014). Presence of severe neuroinflammation does not intensify neurofibrillary degeneration in human brain. *Glia*, *62*(1), 96–105. https://doi.org/10.1002/glia.22589

Subramanian, S., Lopez, R., Zorumski, C. F., & Cristancho, P. (2022). Electroconvulsive therapy in treatment resistant depression. *Journal of the Neurological Sciences*, *434*, 120095. https://doi.org/10.1016/j.jns.2021.120095

Sun, N., Victor, M. B., Park, Y. P., Xiong, X., Scannail, A. N., Leary, N., Prosper, S., Viswanathan, S., Luna, X., Boix, C. A., James, B. T., Tanigawa, Y., Galani, K., Mathys, H., Jiang, X., Ng, A. P., Bennett, D. A., Tsai, L.-H., & Kellis, M. (2023). Human microglial

state dynamics in Alzheimer's disease progression. *Cell*, *186*(20), 4386-4403.e29. https://doi.org/10.1016/j.cell.2023.08.037

Suzuki, R., Fujikawa, A., Komatsu, Y., Kuboyama, K., Tanga, N., & Noda, M. (2018). Enhanced extinction of aversive memories in mice lacking SPARC-related protein containing immunoglobulin domains 1 (SPIG1/FSTL4). *Neurobiology of Learning and Memory*, *152*, 61–70. https://doi.org/10.1016/j.nlm.2018.05.010

Swartz, C. M., & Chen, J.-J. (1985). Electroconvulsive Therapy-Induced Cortisol Release: Changes with Depressive State. *Convulsive Therapy*, *1*(1), 15–21.

Tafet, G. E., & Bernardini, R. (2003). Psychoneuroendocrinological links between chronic stress and depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *27*(6), 893–903. https://doi.org/10.1016/S0278-5846(03)00162-3

Takahashi, K., & Naito, M. (1993). Development, differentiation, and proliferation of macrophages in the rat yolk sac. *Tissue and Cell*, *25*(3), 351–362. https://doi.org/10.1016/0040-8166(93)90077-X

Takeuchi, C., Ishikawa, M., Sawano, T., Shin, Y., Mizuta, N., Hasegawa, S., Tanaka, R., Tsuboi, Y., Nakatani, J., Sugiura, H., Yamagata, K., & Tanaka, H. (2020). Dendritic Spine Density is Increased in Arcadlin-deleted Mouse Hippocampus. *Neuroscience*, *442*, 296–310. https://doi.org/10.1016/j.neuroscience.2020.06.037

Tamminga, C. A., & Carlsson, A. (2002). Partial dopamine agonists and dopaminergic stabilizers, in the treatment of psychosis. *Current Drug Targets. CNS and Neurological Disorders*, *1*(2), 141–147. https://doi.org/10.2174/1568007024606195

Tang, Y., & Le, W. (2016). Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases. *Molecular Neurobiology*, *53*(2), 1181–1194. https://doi.org/10.1007/s12035-014-9070-5

Taub, S. (1987). Electroconvulsive Therapy, Malpractice, and Informed Consent. *The Journal of Psychiatry & Law*, *15*(1), 7–54. https://doi.org/10.1177/009318538701500103

Teychenne, M., Ball, K., & Salmon, J. (2010). Sedentary Behavior and Depression Among Adults: A Review. *International Journal of Behavioral Medicine*, *17*(4), 246–254. https://doi.org/10.1007/s12529-010-9075-z

Tharyan, P., & Adams, C. E. (2002). Electroconvulsive therapy for schizophrenia. *Cochrane Database of Systematic Reviews*, *2*. https://doi.org/10.1002/14651858.CD000076

Thase, M. E., Trivedi, M. H., & Rush, A. J. (1995). MAOIs in the Contemporary Treatment of Depression. *Neuropsychopharmacology*, *12*(3), 185–219. https://doi.org/10.1016/0893-133X(94)00058-8

Thirthalli, J., Sinha, P., & Sreeraj, V. S. (2023). Clinical Practice Guidelines for the Use of Electroconvulsive Therapy. *Indian Journal of Psychiatry*, *65*(2), 258–269. https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_491_22

Thomas, S. L., Schultz, C. R., Mouzon, E., Golembieski, W. A., Naili, R. E., Radakrishnan, A., Lemke, N., Poisson, L. M., Gutiérrez, J. A., Cottingham, S., & Rempel, S. A. (2015). Loss of Sparc in p 53-null Astrocytes Promotes Macrophage Activation and Phagocytosis Resulting in Decreased Tumor Size and Tumor Cell Survival. *Brain Pathology*, *25*(4), 391–400. https://doi.org/10.1111/bpa.12161

Tohen, M., & Vieta, E. (2009). Antipsychotic agents in the treatment of bipolar mania. *Bipolar Disorders*, *11*(s2), 45–54. https://doi.org/10.1111/j.1399-5618.2009.00710.x

Tran, K. H., Luki, J., Hanstock, S., Hanstock, C. C., Seres, P., Aitchison, K., Shandro, T., & Le Melledo, J.-M. (2024). The impact of matching for reproductive status on the comparison of magnetic spectroscopic measurements of glutamate and gamma-aminobutyric acid + in the medial prefrontal cortex of women with major depression. *Journal of Affective Disorders*, *351*, 396–402. https://doi.org/10.1016/j.jad.2024.01.140

Tremblay, M.-È., Stevens, B., Sierra, A., Wake, H., Bessis, A., & Nimmerjahn, A. (2011). The Role of Microglia in the Healthy Brain. *Journal of Neuroscience*, *31*(45), 16064–16069. https://doi.org/10.1523/JNEUROSCI.4158-11.2011

Trépanier, M. O., Hopperton, K. E., Mizrahi, R., Mechawar, N., & Bazinet, R. P. (2016). Postmortem evidence of cerebral inflammation in schizophrenia: A systematic review. *Molecular Psychiatry*, *21*(8), 1009–1026. https://doi.org/10.1038/mp.2016.90

Trifu, S., Sevcenco, A., Stănescu, M., Drăgoi, A. M., & Cristea, M. B. (2021). Efficacy of electroconvulsive therapy as a potential first-choice treatment in treatment-resistant depression (Review). *Experimental and Therapeutic Medicine*, *22*(5), 1281. https://doi.org/10.3892/etm.2021.10716

Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., Brizard, B., El Hage, W., Surget, A., Belzung, C., & Camus, V. (2021). Neuroinflammation and depression: A review. *European Journal of Neuroscience*, *53*(1), 151–171. https://doi.org/10.1111/ejn.14720

Tsao, C.-W., Lin, Y.-S., Chen, C.-C., Bai, C.-H., & Wu, S.-R. (2006). Cytokines and serotonin transporter in patients with major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *30*(5), 899–905. https://doi.org/10.1016/j.pnpbp.2006.01.029

Tse, L., Barr, A. M., Scarapicchia, V., & Vila-Rodriguez, F. (2015). Neuroleptic Malignant Syndrome: A Review from a Clinically Oriented Perspective. *Current Neuropharmacology*, *13*(3), 395–406. https://doi.org/10.2174/1570159X13999150424113345

Tsuang, M. T., Lyons, M. J., & Faraone, S. V. (1990). Heterogeneity of Schizophrenia: Conceptual Models and Analytic Strategies. *The British Journal of Psychiatry*, *156*(1), 17–26. https://doi.org/10.1192/bjp.156.1.17

Tsuji, S., & Kaneko, K. (2023). Management of treatment-resistant nocturnal enuresis. *Pediatrics International*, *65*(1), e15573. https://doi.org/10.1111/ped.15573

Tucker, P., Potter-Kimball, R., Wyatt, D. B., Parker, D. E., Burgin, C., Jones, D. E., & Masters, B. K. (2003). Can physiologic assessment and side effects tease out differences in PTSD trials? A double-blind comparison of citalopram, sertraline, and placebo. *Psychopharmacology Bulletin*, *37*(3), 135–149.

Tucker, P., Zaninelli, R., Yehuda, R., Ruggiero, L., Dillingham, K., & Pitts, C. D. (2001). Paroxetine in the treatment of chronic posttraumatic stress disorder: Results of a placebo-controlled, flexible-dosage trial. *The Journal of Clinical Psychiatry*, *62*(11), 860–868. https://doi.org/10.4088/jcp.v62n1105

Turgay, A. (2004). Aggression and disruptive behavior disorders in children and adolescents. *Expert Review of Neurotherapeutics*, *4*(4), 623–632. https://doi.org/10.1586/14737175.4.4.623

Tyagi, R., Saraf, T. S., & Canal, C. E. (2023). The Psychedelic N,N-Dipropyltryptamine Prevents Seizures in a Mouse Model of Fragile X Syndrome via a Mechanism that Appears Independent of Serotonin and Sigma1 Receptors. *ACS Pharmacology & Translational Science*, *6*(10), 1480–1491. https://doi.org/10.1021/acsptsci.3c00137

Tzioras, M., Stevenson, A. J., Boche, D., & Spires-Jones, T. L. (2021). Microglial contribution to synaptic uptake in the prefrontal cortex in schizophrenia. *Neuropathology and Applied Neurobiology*, *47*(2), 346–351. https://doi.org/10.1111/nan.12660

Unal, A., Altindag, A., Demir, B., & Aksoy, I. (2017). The Use of Lorazepam and Electroconvulsive Therapy in the Treatment of Catatonia: Treatment Characteristics and Outcomes in 60 Patients. *The Journal of ECT*, *33*(4), 290. https://doi.org/10.1097/YCT.0000000000000433

Uno, Y., & Coyle, J. T. (2019). Glutamate hypothesis in schizophrenia. *Psychiatry and Clinical Neurosciences*, *73*(5), 204–215. https://doi.org/10.1111/pcn.12823

Uyanik, V., Tuglu, C., Gorgulu, Y., Kunduracilar, H., & Uyanik, M. S. (2015). Assessment of cytokine levels and hs-CRP in bipolar I disorder before and after treatment. *Psychiatry Research*, *228*(3), 386–392. https://doi.org/10.1016/j.psychres.2015.05.078

Van Der Walt, M., & Keddy, K. H. (2021). The Tuberculosis-Depression Syndemic and Evolution of Pharmaceutical Therapeutics: From Ancient Times to the Future. *Frontiers in Psychiatry*, *12*, 617751. https://doi.org/10.3389/fpsyt.2021.617751

Vargas, M. V., Dunlap, L. E., Dong, C., Carter, S. J., Tombari, R. J., Jami, S. A., Cameron, L. P., Patel, S. D., Hennessey, J. J., Saeger, H. N., McCorvy, J. D., Gray, J. A., Tian, L., & Olson, D. E. (2023). Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors. *Science*, *379*(6633), 700–706. https://doi.org/10.1126/science.adf0435

Vas, C., Jain, A., Trivedi, M., Jha, M. K., & Mathew, S. J. (2023). Pharmacotherapy for Treatment-Resistant Depression. *Psychiatric Clinics of North America*, *46*(2), 261–275. https://doi.org/10.1016/j.psc.2023.02.012

Vázquez, G. H., Bahji, A., Undurraga, J., Tondo, L., & Baldessarini, R. J. (2021). Efficacy and Tolerability of Combination Treatments for Major Depression: Antidepressants plus Second-Generation Antipsychotics vs. Esketamine vs. Lithium. *Journal of Psychopharmacology (Oxford, England)*, *35*(8), 890–900. https://doi.org/10.1177/02698811211013579

Velasco, C. D., & Llobet, A. (2020). Synapse elimination activates a coordinated homeostatic presynaptic response in an autaptic circuit. *Communications Biology*, *3*(1), 260. https://doi.org/10.1038/s42003-020-0963-8

Vidal, P. M., & Pacheco, R. (2020). The Cross-Talk Between the Dopaminergic and the Immune System Involved in Schizophrenia. *Frontiers in Pharmacology*, *11*. https://doi.org/10.3389/fphar.2020.00394

Vincent, A. J., Lau, P. W., & Roskams, A. J. (2008). SPARC is expressed by macroglia and microglia in the developing and mature nervous system. *Developmental Dynamics: An Official Publication of the American Association of Anatomists*, *237*(5), 1449–1462. https://doi.org/10.1002/dvdy.21495

Vollenweider, F., Vontobel, P., Hell, D., & Leenders, K. (1999). 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in man—A PET study with [C-11]raclopride. *Neuropsychopharmacology*, *20*(5), 424–433.

Vollenweider, F. X., & Preller, K. H. (2020). Psychedelic drugs: Neurobiology and potential for treatment of psychiatric disorders. *Nature Reviews Neuroscience*, *21*(11), Article 11. https://doi.org/10.1038/s41583-020-0367-2

Waite, J., & Easton, A. (2013). *The ECT Handbook*. RCPsych Publications.

Walkup John T., Labellarte Michael J., Riddle Mark A., Pine Daniel S., Greenhill Laurence, Klein Rachel, Davies Mark, Sweeney Michael, Abikoff Howard, Hack Sabine, Klee Brian, McCracken James, Bergman Lindsey, Piacentini John, March John, Compton Scott, Robinson James, O'Hara Thomas, Baker Sherryl, … Roper Margaret. (2001). Fluvoxamine for the Treatment of Anxiety Disorders in Children and Adolescents. *New England Journal of Medicine*, *344*(17), 1279–1285. https://doi.org/10.1056/NEJM200104263441703

Waller, R., Baxter, L., Fillingham, D. J., Coelho, S., Pozo, J. M., Mozumder, M., Frangi, A. F., Ince, P. G., Simpson, J. E., & Highley, J. R. (2019). Iba-1-/CD68+ microglia are a prominent feature of age-associated deep subcortical white matter lesions. *PLOS ONE*, *14*(1), e0210888. https://doi.org/10.1371/journal.pone.0210888

Wang, J., & Cosci, F. (2021). Neonatal Withdrawal Syndrome following Late in utero Exposure to Selective Serotonin Reuptake Inhibitors: A Systematic Review and Meta-Analysis of Observational Studies. *Psychotherapy and Psychosomatics*, *90*(5), 299–307. https://doi.org/10.1159/000516031

Wang, R. Z., Vashistha, V., Kaur, S., & Houchens, N. W. (2016). Serotonin syndrome: Preventing, recognizing, and treating it. *Cleveland Clinic Journal of Medicine*, *83*(11), 810–816. https://doi.org/10.3949/ccjm.83a.15129

Wang, W., Liu, W., Duan, D., Bai, H., Wang, Z., & Xing, Y. (2021). Chronic social defeat stress mouse model: Current view on its behavioral deficits and modifications. *Behavioral Neuroscience*, *135*(3), 326–335. https://doi.org/10.1037/bne0000418

Wang, W., Pu, C., Jiang, J., Cao, X., Wang, J., Zhao, M., & Li, C. (2015). Efficacy and safety of treating patients with refractory schizophrenia with antipsychotic medication and adjunctive electroconvulsive therapy: A systematic review and meta-analysis. *Shanghai Archives of Psychiatry*, *27*(4), 206–219. https://doi.org/10.11919/j.issn.1002-0829.215093

Wang, X., Chen, Y., Zhou, X., Liu, F., Zhang, T., & Zhang, C. (2012). Effects of Propofol and Ketamine as Combined Anesthesia for Electroconvulsive Therapy in Patients With Depressive Disorder. *The Journal of ECT*, *28*(2), 128. https://doi.org/10.1097/YCT.0b013e31824d1d02

Wang, X., Xiong, J., Xu, W.-H., Yu, S., Huang, X., Zhang, J., Tian, C., Huang, D., Jia, W., & Lang, S. (2015). Risk of a lamotrigine-related skin rash: Current meta-analysis and postmarketing cohort analysis. *Seizure*, *25*, 52–61. https://doi.org/10.1016/j.seizure.2014.12.001

Wang, X., Zhou, H., & Zhu, X. (2020). Attention deficits in adults with Major depressive disorder: A systematic review and meta-analysis. *Asian Journal of Psychiatry*, *53*, 102359. https://doi.org/10.1016/j.ajp.2020.102359

Wang, Y., Leak, R. K., & Cao, G. (2022). Microglia-mediated neuroinflammation and neuroplasticity after stroke. *Frontiers in Cellular Neuroscience*, *16*, 980722. https://doi.org/10.3389/fncel.2022.980722

Wang, Y.-L., Han, Q.-Q., Gong, W.-Q., Pan, D.-H., Wang, L.-Z., Hu, W., Yang, M., Li, B., Yu, J., & Liu, Q. (2018). Microglial activation mediates chronic mild stress-induced depressive- and anxiety-like behavior in adult rats. *Journal of Neuroinflammation*, *15*(1), 21. https://doi.org/10.1186/s12974-018-1054-3

Ward, H. B., Fromson, J. A., Cooper, J. J., De Oliveira, G., & Almeida, M. (2018). Recommendations for the use of ECT in pregnancy: Literature review and proposed clinical protocol. *Archives of Women's Mental Health*, *21*(6), 715–722. https://doi.org/10.1007/s00737-018-0851-0

Warren, S. L., Heller, W., & Miller, G. A. (2021). The Structure of Executive Dysfunction in Depression and Anxiety. *Journal of Affective Disorders*, *279*, 208–216. https://doi.org/10.1016/j.jad.2020.09.132

Wassef, A., Baker, J., & Kochan, L. D. (2003). GABA and Schizophrenia: A Review of Basic Science and Clinical Studies. *Journal of Clinical Psychopharmacology*, *23*(6), 601. https://doi.org/10.1097/01.jcp.0000095349.32154.a5

Weiden, P. J. (2007). EPS Profiles: The Atypical Antipsychotics: Are Not All the Same. *Journal of Psychiatric Practice®*, *13*(1), 13.

Weiss, F., Caruso, V., De Rosa, U., Beatino, M. F., Barbuti, M., Nicoletti, F., & Perugi, G. (2023). The role of NMDA receptors in bipolar disorder: A systematic review. *Bipolar Disorders*, *25*(8), 624–636. https://doi.org/10.1111/bdi.13335

Werneburg, S., Feinberg, P. A., Johnson, K. M., & Schafer, D. P. (2017). A Microglia-Cytokine Axis to Modulate Synaptic Connectivity and Function. *Current Opinion in Neurobiology*, *47*, 138–145. https://doi.org/10.1016/j.conb.2017.10.002

Westman, J., Grinstein, S., & Marques, P. E. (2020). Phagocytosis of Necrotic Debris at Sites of Injury and Inflammation. *Frontiers in Immunology*, *10*, 3030. https://doi.org/10.3389/fimmu.2019.03030

Wielosz, M. (1985). Increased sensitivity to serotonergic agonists after repeated electroconvulsive shock in rats. *Pharmacology, Biochemistry, and Behavior*, *22*(5), 683–687. https://doi.org/10.1016/0091-3057(85)90513-1

Williams, K., Romero, O. S. G., Braunstein, M., & Brant, S. (2022). Indigenous Philosophies and the "Psychedelic Renaissance." *Anthropology of Consciousness*, *33*(2), 506–527. https://doi.org/10.1111/anoc.12161

Williams, T., Phillips, N. J., Stein, D. J., & Ipser, J. C. (2022). Pharmacotherapy for post traumatic stress disorder (PTSD). *The Cochrane Database of Systematic Reviews*, *2022*(3), CD002795. https://doi.org/10.1002/14651858.CD002795.pub3

Wittchen, H.-U. (2002). Generalized anxiety disorder: Prevalence, burden, and cost to society. *Depression and Anxiety*, *16*(4), 162–171. https://doi.org/10.1002/da.10065

Wojtas, A., Bysiek, A., Wawrzczak-Bargiela, A., Szych, Z., Majcher-Maślanka, I., Herian, M., Maćkowiak, M., & Gołembiowska, K. (2022). Effect of Psilocybin and Ketamine on Brain Neurotransmitters, Glutamate Receptors, DNA and Rat Behavior. *International Journal of Molecular Sciences*, *23*(12), Article 12. https://doi.org/10.3390/ijms23126713

Wolf, S. A., Boddeke, H. W. G. M., & Kettenmann, H. (2017). Microglia in Physiology and Disease. *Annual Review of Physiology*, *79*(1), 619–643. https://doi.org/10.1146/annurev-physiol-022516-034406

Won, E., & Kim, Y.-K. (2017). An Oldie but Goodie: Lithium in the Treatment of Bipolar Disorder through Neuroprotective and Neurotrophic Mechanisms. *International Journal of Molecular Sciences*, *18*(12), 2679. https://doi.org/10.3390/ijms18122679

Won, E., & Kim, Y.-K. (2020). Neuroinflammation-Associated Alterations of the Brain as Potential Neural Biomarkers in Anxiety Disorders. *International Journal of Molecular Sciences*, *21*(18), Article 18. https://doi.org/10.3390/ijms21186546

Woody, S., & Rachman, S. (1994). Generalized anxiety disorder (GAD) as an unsuccessful search for safety. *Clinical Psychology Review*, *14*(8), 743–753. https://doi.org/10.1016/0272-7358(94)90040-X

Wrobel, S. (2007). Science, serotonin, and sadness: The biology of antidepressants. *The FASEB Journal*, *21*(13), 3404–3417. https://doi.org/10.1096/fj.07-1102ufm

Wu, H., Siafis, S., Wang, D., Burschinski, A., Schneider-Thoma, J., Priller, J., Davis, J. M., & Leucht, S. (2023). Antipsychotic-induced akathisia in adults with acute schizophrenia: A systematic review and dose-response meta-analysis. *European Neuropsychopharmacology*, *72*, 40–49. https://doi.org/10.1016/j.euroneuro.2023.03.015

Wulff, A. B., Nichols, C. D., & Thompson, S. M. (2023). Preclinical perspectives on the mechanisms underlying the therapeutic actions of psilocybin in psychiatric disorders. *Neuropharmacology*, *231*, 109504. https://doi.org/10.1016/j.neuropharm.2023.109504

Xu, C., Ma, X.-M., Chen, H.-B., Zhou, M.-H., Qiao, H., & An, S.-C. (2016). Orbitofrontal cortex 5-HT2A receptor mediates chronic stress-induced depressive-like behaviors and alterations of spine density and Kalirin7. *Neuropharmacology*, *109*, 7–17. https://doi.org/10.1016/j.neuropharm.2016.02.020

Yamada, M., & Yasuhara, H. (2004). Clinical Pharmacology of MAO Inhibitors: Safety and Future. *NeuroToxicology*, *25*(1), 215–221. https://doi.org/10.1016/S0161-813X(03)00097-4

Yan, J., Zhang, Y., Wang, L., Li, Z., Tang, S., Wang, Y., Gu, N., Sun, X., & Li, L. (2022). TREM2 activation alleviates neural damage via Akt/CREB/BDNF signalling after traumatic brain injury in mice. *Journal of Neuroinflammation*, *19*(1), 289. https://doi.org/10.1186/s12974-022-02651-3

Yatham, L. N., Kusumakar, V., Parikh, S. V., Haslam, D. R., Matte, R., Sharma, V., & Kennedy, S. (1997). Bipolar depression: Treatment options. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*, *42 Suppl 2*, 87S-91S.

Yeo, H.-G., Hong, J. J., Lee, Y., Yi, K. S., Jeon, C.-Y., Park, J., Won, J., Seo, J., Ahn, Y.-J., Kim, K., Baek, S. H., Hwang, E.-H., Kim, G., Jin, Y. B., Jeong, K.-J., Koo, B.-S., Kang, P., Lim, K. S., Kim, S.-U., … Lee, S.-R. (2019). Increased CD68/TGFβ Co-expressing Microglia/ Macrophages after Transient Middle Cerebral Artery Occlusion in Rhesus Monkeys. *Experimental Neurobiology*, *28*(4), 458–473. https://doi.org/10.5607/en.2019.28.4.458

Yilmaz, A., Schulz, D., Aksoy, A., & Canbeyli, R. (2002). Prolonged effect of an anesthetic dose of ketamine on behavioral despair. *Pharmacology Biochemistry and Behavior*, *71*(1), 341–344. https://doi.org/10.1016/S0091-3057(01)00693-1

Yirmiya, R., Rimmerman, N., & Reshef, R. (2015). Depression as a Microglial Disease. *Trends in Neurosciences*, *38*(10), 637–658. https://doi.org/10.1016/j.tins.2015.08.001

Yrondi, A., Sporer, M., Péran, P., Schmitt, L., Arbus, C., & Sauvaget, A. (2018). Electroconvulsive therapy, depression, the immune system and inflammation: A systematic review. *Brain Stimulation*, *11*(1), 29–51. https://doi.org/10.1016/j.brs.2017.10.013

Yu, Y., Lin, Y., Takasaki, Y., Wang, C., Kimura, H., Xing, J., Ishizuka, K., Toyama, M., Kushima, I., Mori, D., Arioka, Y., Uno, Y., Shiino, T., Nakamura, Y., Okada, T., Morikawa, M., Ikeda, M., Iwata, N., Okahisa, Y., … Ozaki, N. (2018). Rare loss of function mutations in N-methyl-d-aspartate glutamate receptors and their contributions to schizophrenia susceptibility. *Translational Psychiatry*, *8*, 12. https://doi.org/10.1038/s41398-017-0061-y

Yu, Z., Fang, X., Liu, W., Sun, R., Zhou, J., Pu, Y., Zhao, M., Sun, D., Xiang, Z., Liu, P., Ding, Y., Cao, L., & He, C. (2022). Microglia Regulate Blood-Brain Barrier Integrity via MiR-126a-5p/MMP9 Axis during Inflammatory Demyelination. *Advanced Science (Weinheim, Baden-Wurttemberg, Germany)*, *9*(24), e2105442. https://doi.org/10.1002/advs.202105442

Yuan, X., Wang, S., Shi, Y., Yang, Y., Zhang, Y., Xia, L., Zhang, K., & Liu, H. (2022). Pro-inflammatory cytokine levels are elevated in female patients with schizophrenia treated with clozapine. *Psychopharmacology*, *239*(3), 765–771. https://doi.org/10.1007/s00213-022-06067-y

Yudofsky, S. C. (1981). Electroconvulsive therapy in general hospital psychiatry: A focus on new indications and technologies. *General Hospital Psychiatry*, *3*(4), 292–296. https://doi.org/10.1016/0163-8343(81)90035-9

Yüksel, C., & Öngür, D. (2010). Magnetic Resonance Spectroscopy Studies of Glutamate-Related Abnormalities in Mood Disorders. *Biological Psychiatry*, *68*(9), 785–794. https://doi.org/10.1016/j.biopsych.2010.06.016

Zelic, M., Pontarelli, F., Woodworth, L., Zhu, C., Mahan, A., Ren, Y., LaMorte, M., Gruber, R., Keane, A., Loring, P., Guo, L., Xia, T.-H., Zhang, B., Orning, P., Lien, E., Degterev, A., Hammond, T., & Ofengeim, D. (2021). RIPK1 activation mediates neuroinflammation and disease progression in multiple sclerosis. *Cell Reports*, *35*(6), 109112. https://doi.org/10.1016/j.celrep.2021.109112

Zhang, et al. (2004). *Changes in Serum Interleukin-2, -6, and -8 Levels Before and During Treatment With Risperidone and Haloperidol: Relationship to Outcome in Schizophrenia*.

Zhang, G., & Stackman, R. W. (2015). The role of serotonin 5-HT2A receptors in memory and cognition. *Frontiers in Pharmacology*, *6*. https://doi.org/10.3389/fphar.2015.00225

Zhang, J., Rong, P., Zhang, L., He, H., Zhou, T., Fan, Y., Mo, L., Zhao, Q., Han, Y., Li, S., Wang, Y., Yan, W., Chen, H., & You, Z. (2021). IL4-driven microglia modulate stress resilience through BDNF-dependent neurogenesis. *Science Advances*, *7*(12), eabb9888. https://doi.org/10.1126/sciadv.abb9888

Zhang, M.-M., Guo, M.-X., Zhang, Q.-P., Chen, X.-Q., Li, N.-Z., Liu, Q., Cheng, J., Wang, S.-L., Xu, G.-H., Li, C.-F., Zhu, J.-X., & Yi, L.-T. (2022). IL-1R/C3aR signaling regulates synaptic pruning in the prefrontal cortex of depression. *Cell & Bioscience*, *12*(1), 90. https://doi.org/10.1186/s13578-022-00832-4

Zhao, C., Warner-Schmidt, J., Duman, R. S., & Gage, F. H. (2012). Electroconvulsive Seizure Promotes Spine Maturation in Newborn Dentate Granule Cells in Adult Rat. *Developmental Neurobiology*, *72*(6), 937–942. https://doi.org/10.1002/dneu.20986

Zhdanava, M., Pilon, D., Ghelerter, I., Chow, W., Joshi, K., Lefebvre, P., & Sheehan, J. J. (2021). The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. *The Journal of Clinical Psychiatry*, *82*(2), 29169. https://doi.org/10.4088/JCP.20m13699

Zhou, Y., Liang, M., Jiang, T., Tian, L., Liu, Y., Liu, Z., Liu, H., & Kuang, F. (2007). Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI. *Neuroscience Letters*, *417*(3), 297–302. https://doi.org/10.1016/j.neulet.2007.02.081

Curriculum Vitae
ELAINE ALEXANDRA AQUINO VASQUEZ
Aquinoelaine64@gmail.com

EDUCATION

PhD in Neuroscience   May 2024
University of Nevada, Las Vegas
> Dissertation: *Low Dose Of Electropsychedelic Treatment Increases Neuronal Dendritic Arborization And Filopodic Spine Density*

BS in Biology   Spring 2018
University of Nevada, Las Vegas
> Minor: Neuroscience; Psychology

RESEARCH EXPERIENCE

Graduate Research Assistant   Fall 2018-
Department of Psychology, University of Nevada, Las Vegas   Present
- Look at different stimuli and how they affect glial cell activation to determine the pathology and therapeutic effects of stimuli
- Look at the effects of electroconvulsive shock, blast-induced traumatic brain injury, transcranial magnetic stimulation, tactile stimulation, and chronic ultra-mild stress.
- Use histological techniques to assess morphological and functional changes and different behavioral assays to determine detrimental or therapeutic behavioral effects.

Undergraduate Research Assistant   Spring 2017
Department of Psychology, University of Nevada, Las Vegas   – Spring
- Worked with Dr. Dustin Hines to assess changes in microglia   2018
  morphology using immunohistochemistry in response to electroconvulsive shock

CERTIFICATIONS

Programming for Biology   Fall 2022
Cold Spring Harbor Laboratory

TEACHING AND MENTORING EXPERIENCE

Instructor, Introduction to Neuroscience   Fall 2021-
Department of Psychology, University of Nevada, Las Vegas   Spring 2022
- Developed lectures introducing 50 students to basic principles and terminology in neuroscience and connecting how cellular and molecular parts of the nervous system come together to produce behavior and develop into multiple disorders
- Generated assignments that emphasized critical thinking and promoted discussion during class sessions

- Created and graded assessments to ensure students understood topics

Instructor, General Psychology   Fall 2020-
Department of Psychology, University of Nevada, Las Vegas   Spring 2021
- Developed lectures introducing 70 students to basic principles and terminology of psychology emphasizing the role of specific brain regions and cells within the nervous system in the development of behaviors
- Generated assignments that emphasized critical thinking and promoted discussion during class sessions
- Created and graded assessments to ensure students understood topics

Teaching Assistant, Introduction to Statistical Methods   Fall 2019 –
Department of Psychology, University of Nevada, Las Vegas   Spring 2020
- Mentored 110-120 first- and second-year level undergraduate students in statistical methods and analysis
- Graded exams, quizzes, and homework

Graduate Mentor   Fall 2019
Department of Psychology, University of Nevada, Las Vegas
- Mentored two undergraduate students in data collection and analysis of histological images of brain cells
- Aided in the presentation of findings.

Teaching Assistant, Psychopharmacology   Fall 2018 -
Department of Psychology, University of Nevada, Las Vegas   Spring 2019
- Developed lectures focusing on research methods applied in neuroscience research for 30-40 junior and senior-level students
- Created and graded quizzes to ensure students understood topics
- Graded exams and quizzes

Graduate Mentor   Summer
Department of Psychology, University of Nevada, Las Vegas   2019
- Mentored two undergraduate students in data collection and analysis of behavioral assays and histological images of brain cells
- Aided in the presentation of findings.

PUBLICATIONS

Hines RM, Aquino EA, Khumnark MI, Dávila MP, Hines DJ. Comparative Assessment of TSPO Modulators on Electroencephalogram Activity and Exploratory Behavior. Front Pharmacol. 2022 Apr 4;13:750554. doi: 10.3389/fphar.2022.750554. PMID: 35444539; PMCID: PMC9015213.

PRESENTATIONS

Oral Presentations
Contreras, A., Aquino, E.A., Hines, R.M., and Hines, D.J. *The Tripnogram:*   Fall 2023
AI assisted morphological, electroencephalographic, and behavioral
signatures of diverse psychedelics. Nanosymposium presentation at Society
for Neuroscience, Washington, DC.

Aquino, E.A., Contreras, A., Hines, D.J., and Hines, R.M. *Automated Processing of Neuronal Axon Initial Segment.* Graduate & Professional Student Research Forum, UNLV, Las Vegas, NV	Spring 2023
Aquino, E.A, and Hines, D.J., Modulation of Currents in ECS Regulates Microgliosis and Decreases Branch Order, Graduate & Professional Student Research Forum, UNLV, Las Vegas, NV	Spring 2020
Aquino, E.A., and Hines, D.J, *Microglial Branch Order Decreased with Increased Voltage in Murine Model of Electroconvulsive Shock*, Office of Undergraduate Summer Research Symposium, UNLV, Las Vegas, NV.	Fall 2017

Poster Presentations

Aquino, E.A., Contreras, A., Hines, D.J., and Hines, R.M. *Automated Processing of Neuronal Axon Initial Segment.* Poster Session at Society for Neuroscience, Washington, DC.	Fall 2023
Aquino, E.A., Contreras, A., Hines, D.J., and Hines, R.M. *Automated Processing of Neuronal Axon Initial Segment.* Poster Session at Brain Informatics, Hoboken, NJ.	Fall 2023
Aquino, E.A., Strong, H.N., Hines, R.M., and Hines, D.J. *Increased TSPO in Microglia Endfeet aids Cell Survival and Attenuates Gross-Motor Deficits following a Blast-induced Traumatic Brain Injury.* Poster Session at Society for Neuroscience Global Connectome, Virtual.	Spring 2021
Aquino, E.A., Hines, R.M., and Hines, D.J. *Electroconvulsive Shock decreases Microglia Branch Order,* Poster Session at Society for Neuroscience, Chicago, IL.	Fall 2019
Aquino, E.A., and Hines, D.J, *Changes in Glial Cell Morphology Mediated the Antidepressant Effects of Electroconvulsive Shock*, Poster Session at AANAPISI Scholars Summer Research Symposium, UNLV, Las Vegas, NV.	Fall 2017

GRANTS AND AWARDS

Travel Grant, Graduate and Professional Student Association, University of Nevada, Las Vegas	Fall 2023
Travel Grant, Graduate and Professional Student Association, University of Nevada, Las Vegas	Fall 2023
GPSA Annual Graduate Research Forum 1st place winner, Graduate and Professional Student Association, University of Nevada, Las Vegas	Spring 2023
Travel Grant, Graduate and Professional Student Association, University of Nevada, Las Vegas	Fall 2022
Summer Doctoral Fellowship, Graduate College, University of Nevada, Las Vegas	Summer 2022
Patricia Sastaunik Scholarship, Graduate College, University of Nevada, Las Vegas	Fall 2021- Spring 2023
Summer Session Scholarship, Graduate College, University of Nevada, Las Vegas	Summer 2021
Travel Grant, Graduate and Professional Student Association, University of Nevada, Las Vegas	Fall 2019
Graduate Summer Stipend, College of Liberal Arts, University of Nevada, Las Vegas	Summer 2019
Summer Research Stipend, Title III AANAPISI Scholars Summer Research Institute, University of Nevada, Las Vegas	Summer 2017
Millennium Scholarship, Nevada Treasurer's GGMS Office, Las Vegas, NV	Spring 2013 -Fall 2018

UNIVERSITY SERVICE

Neuroscience Graduate Student Representative   Fall 2019-
Interdisciplinary Neuroscience Executive Committee, University of Nevada,   Spring 2021
Las Vegas

- Collaborate with faculty and students on subject matters concerning GA stipend, workload, etc.
- Liaison between graduate students and faculty
- Maintain open communication with students, updating them on IDP issues
- Work to create camaraderie between students within multiple departments

PROFESSIONAL ASSOCIATION AND ORGANIZATION MEMBERSHIP

Society for Neuroscience   Fall 2019 –
                                                                    Current

National Neurotrauma Society   Spring 2022-
                                                                    Current

SKILLS

- Programming languages and mathematical packages: Python, Sigmaplot, SPSS, R
- Histological staining techniques: immunohistochemistry, Golgi-cox
- Image processing and analyzing programs: LSM-5 image browser, ImageJ, ICY Bioimaging software
- Behavioral assays: force swim task, open field task, rung walk task, string pull task, adhesive dot removal task, cylinder exploration task,
- Behavioral analysis software: ANY-maze