A LOW DOSE OF ELECTRO-PSYCHEDELIC TREATMENT INCREASES NEURONAL DENDRITIC ARBORIZATION AND FILOPODIC SPINE DENSITY

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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.

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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.

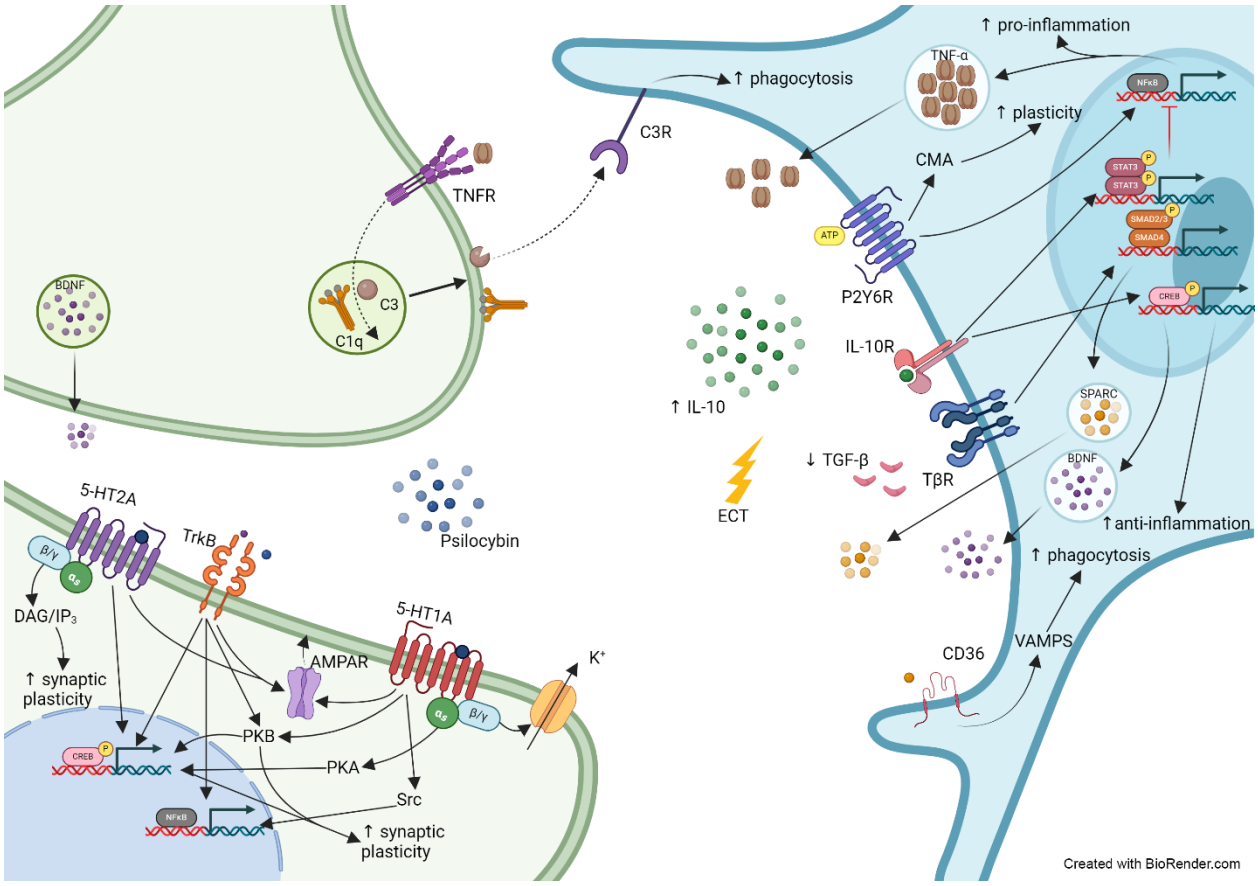

Figure 1: Proposed Mechanism for ECT vs Psilocybin Acronyms: 5-HT1/2A (serotonin 1A/2A receptor); AMPAR (AMPA receptor); ATP (adenosine triphosphate); BDNF(brain-derived neurotrophic factor); C1q (complement component 1q); C3 (complement component 3); C3R (C3 receptor); CD36 (platelet glycoprotein 4); 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

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).

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

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 (2^{nd} 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.

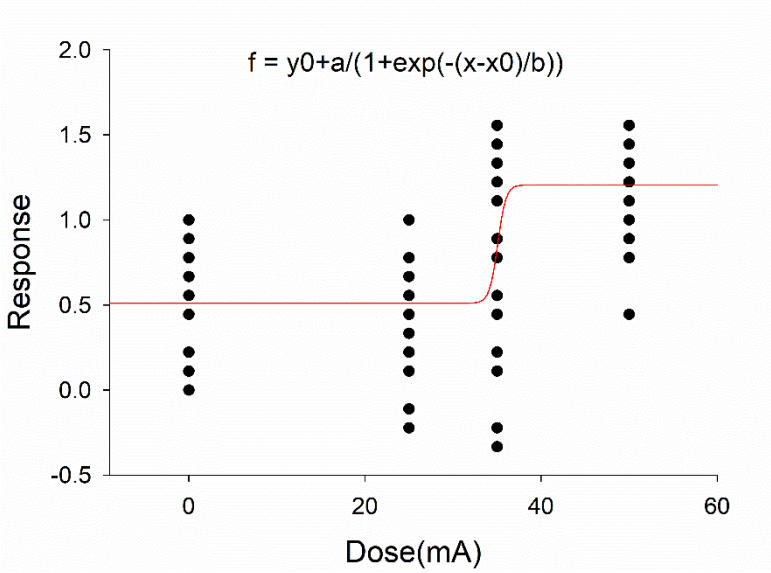

Figure 2: Dose Respone Curve Electroconvulsive Shock

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.

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)

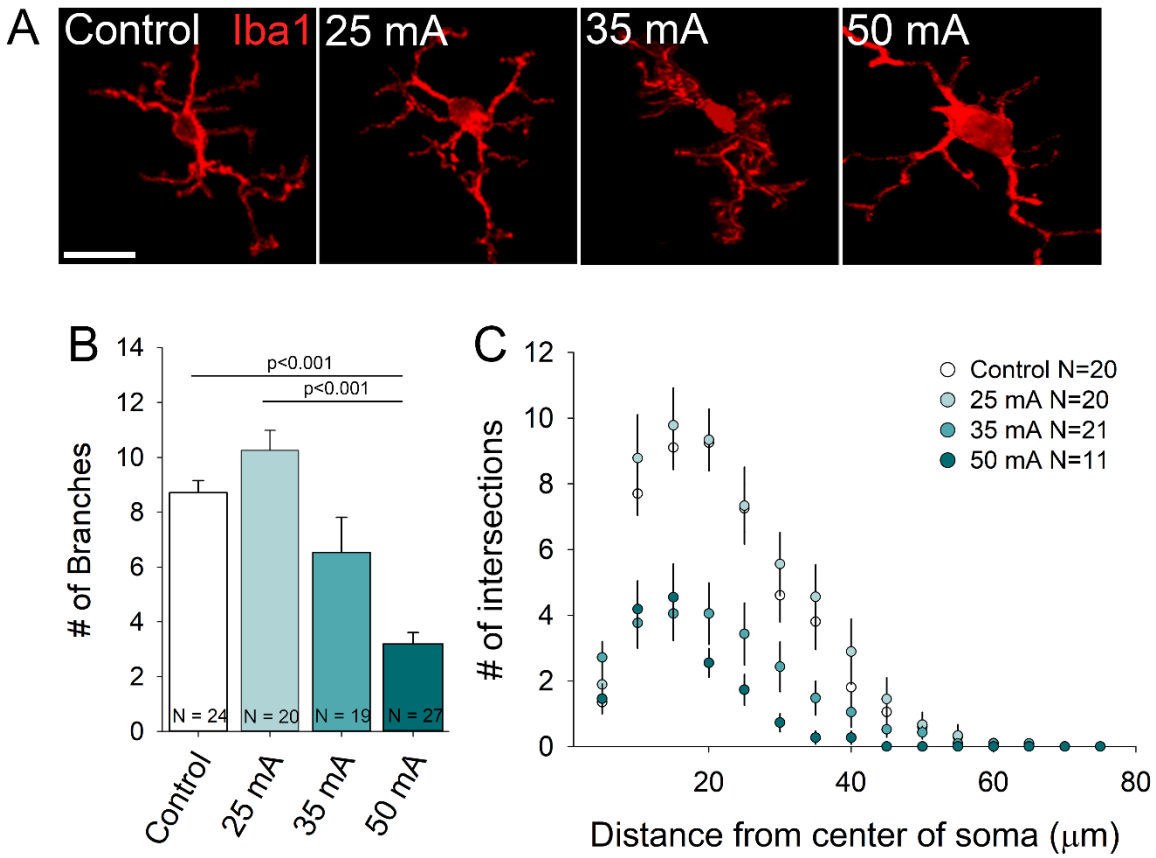

Figure 3: Changes In Microglia Morphology Following ECS Administration At Different Amperages. A) Representative confocal images of immunohistochemically stained Iba1+ cells. Scale bar = 20 um B) Quantification of the average number of branches each IBA1+ cell has indicates that as the dose of ECS increases, 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

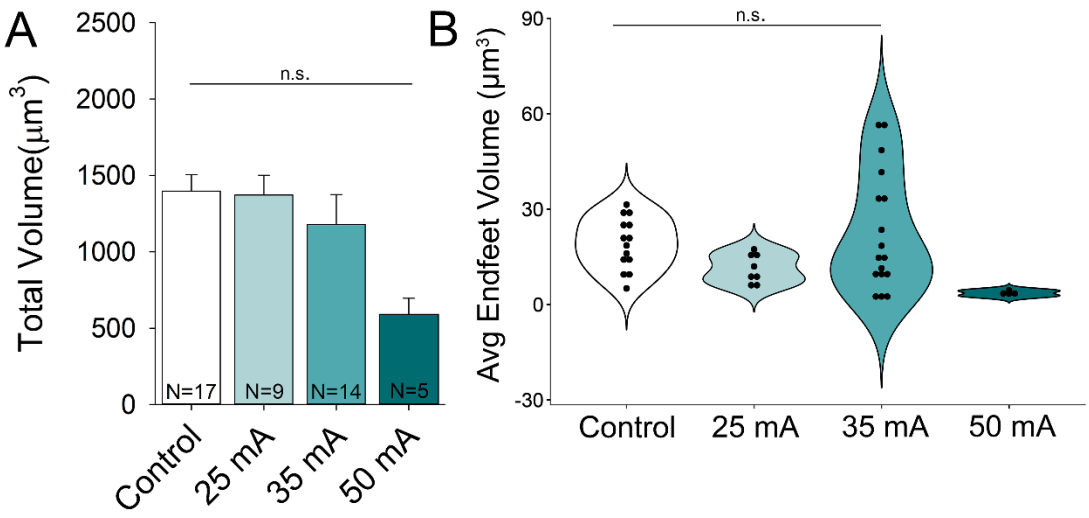

Figure 4: Microglia Volume Changes Following Administration Of ECS At Different Amperages. A) Quantificaiton of total cell volume showing ECS does not change the total cell volume of microglia. B) Quantification of the average endfeet volume showing endfeet volume does not change following administration of ECS at different doses. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant

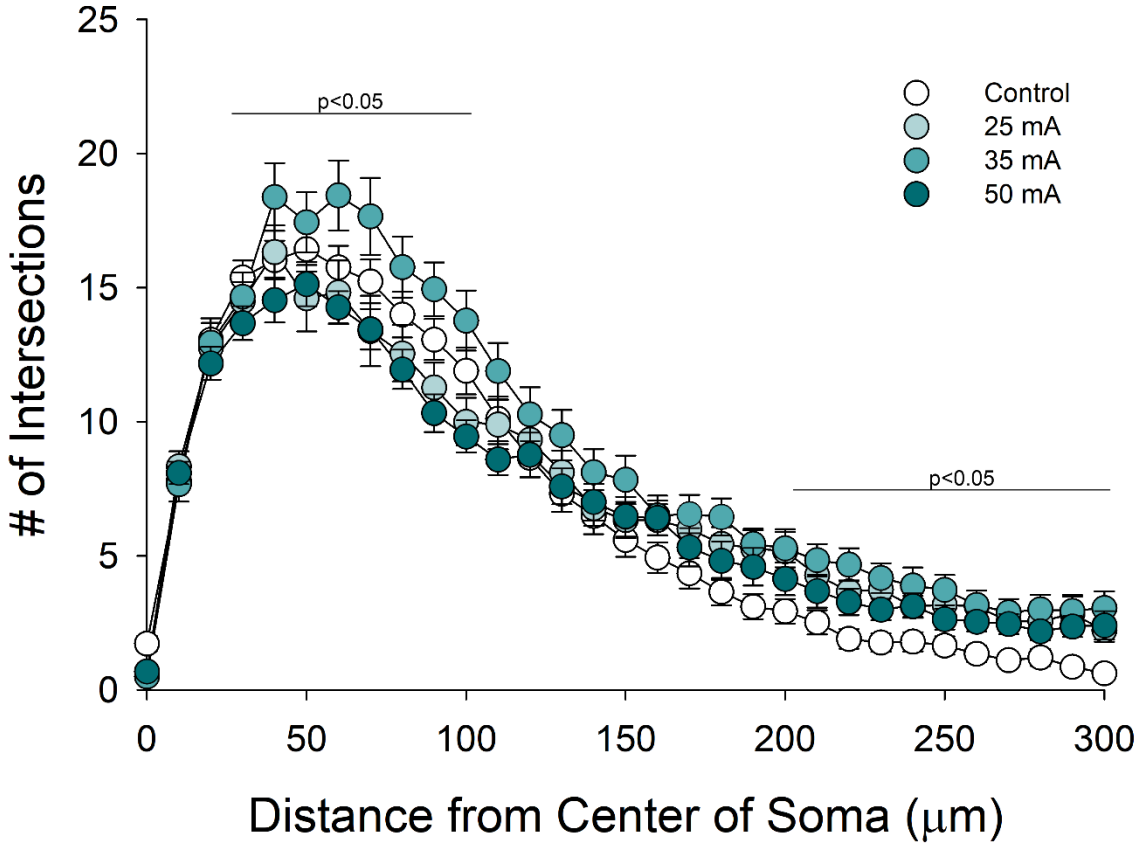

Figure 5: Changes In Dendritic Arborization Following ECS At Different Amperages. A) Sholl analysis of neurons indicating that all doses of ECS increases dendritic length and 35mA also increases the number of short dendrities. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant

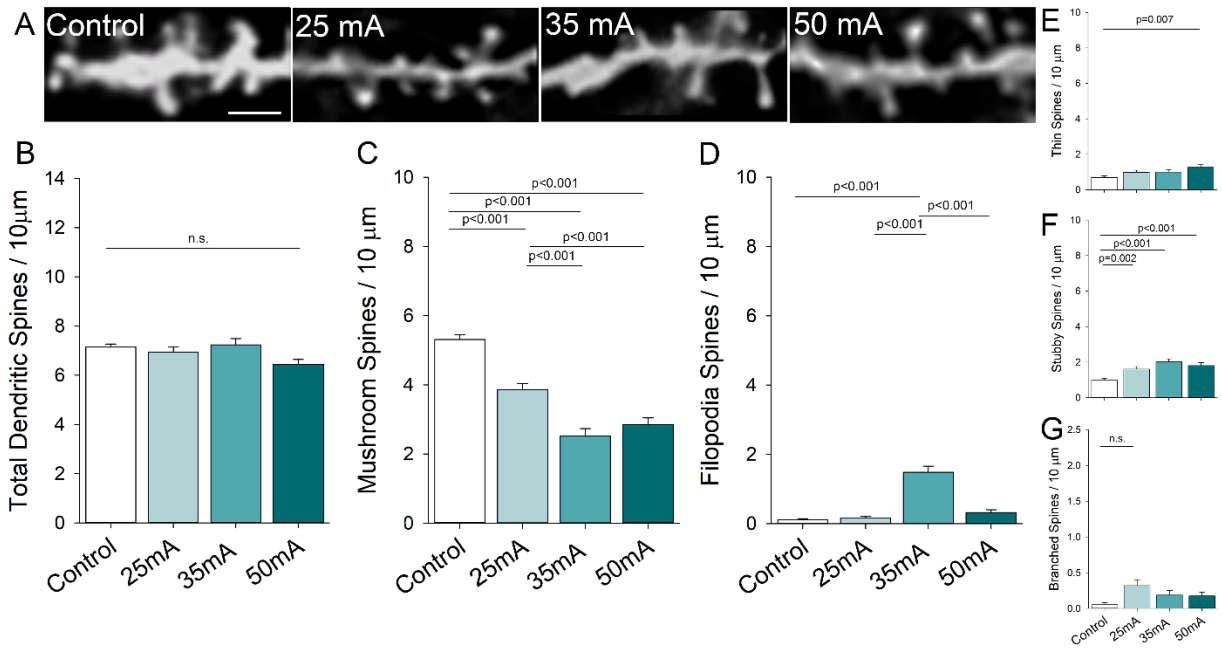

Figure 6: Changes In Dendritic Spine Density And Diversity Following ECS At Different Amperages. A) Representative images of 10 um sections of neuronal dendrites from control mice and those treated with ECS at 25, 35 and 50 mA. Scale bar = 2 um B) Quantification of total spine density within 10 um dendritic 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).

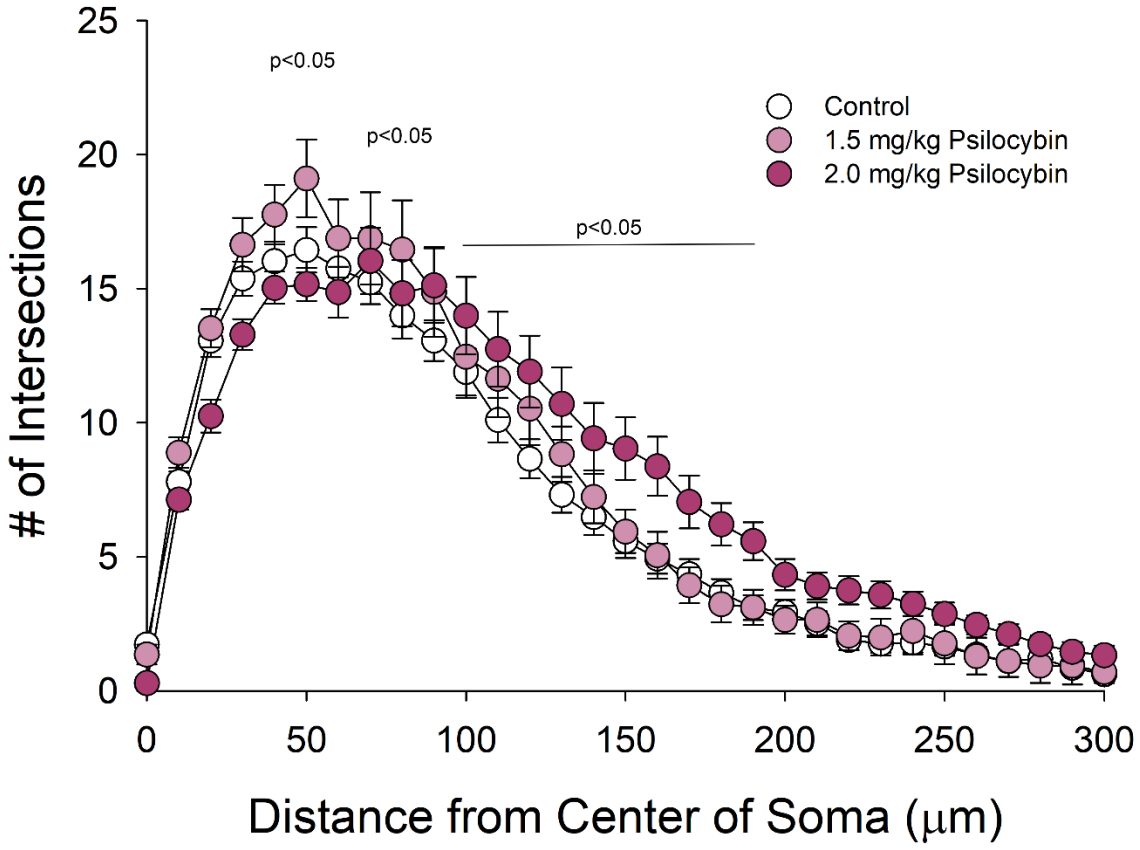

Figure 7: Changes In Dendritic Arborization Following Psilocybin Administration At Different Doses A) Sholl analysis of neurons indicating that 1.5 mg/kg of Psilocybin increases the number of dendrites under 100 um and 2.0 mg/kg of Psilocybin increased the number of dendrites between 100 and 200 um. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant

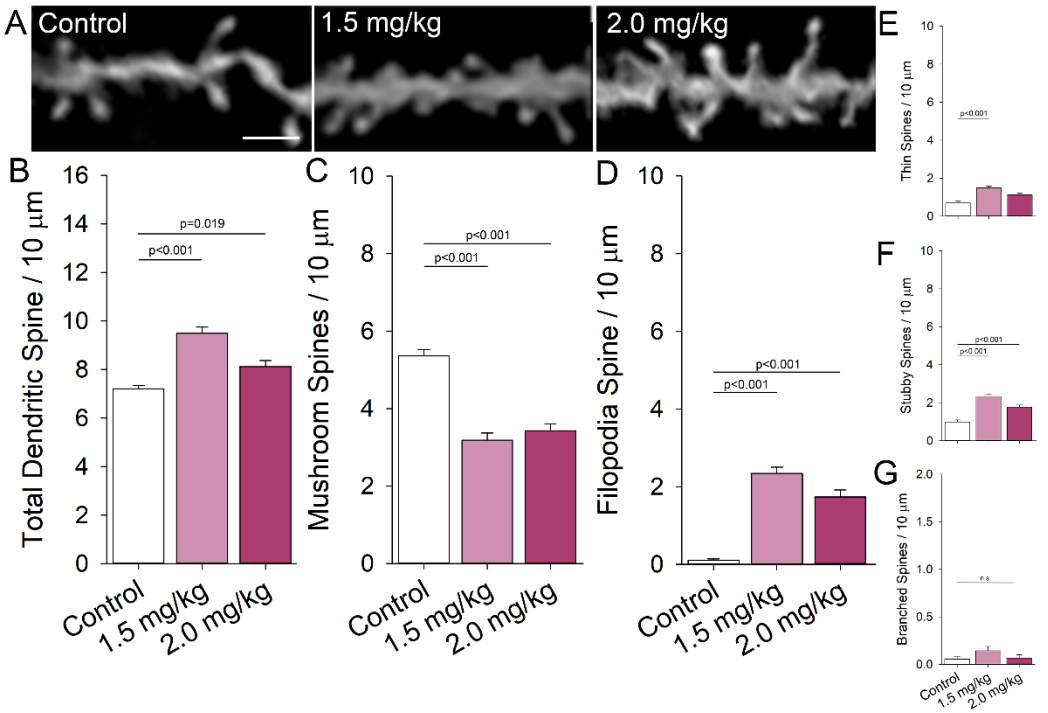

Figure 8: Changes In Dendritic Spine Density And Diversity Following Psilocybin Administration At Different Doses. A) Representative images of 10 um sections of neuronal dendrites from control mice and those treated with low, medium, and high doses of Psilocybin. Scale bar = 2 um B) Quantification of 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).

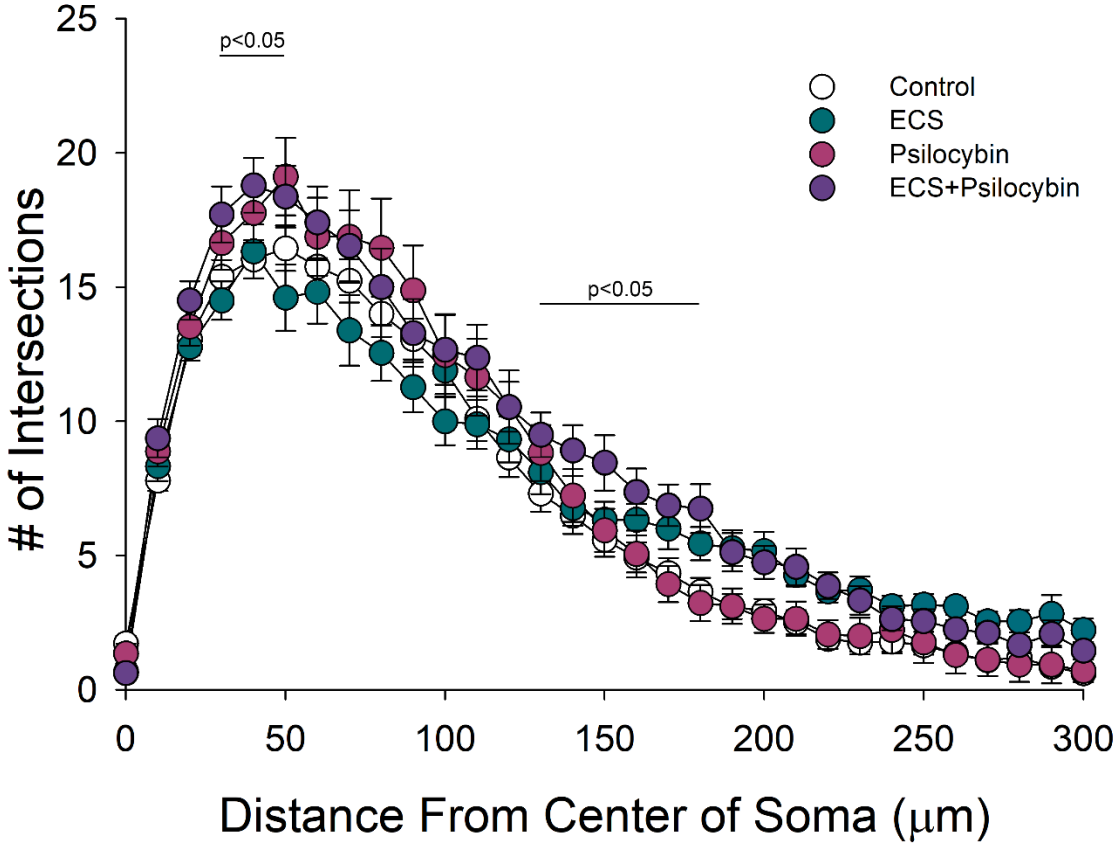

Figure 9: The Effects Following EPT On Neuronal Dendritic Arborization. A) Sholl analysis of neurons indicating that EPTincreases the number dendrites between 30 - 50 um and 130-180 um from the soma. All graphs plot mean and standard error. P values from ANOVA or subsequent t-test. n.s. = not significant

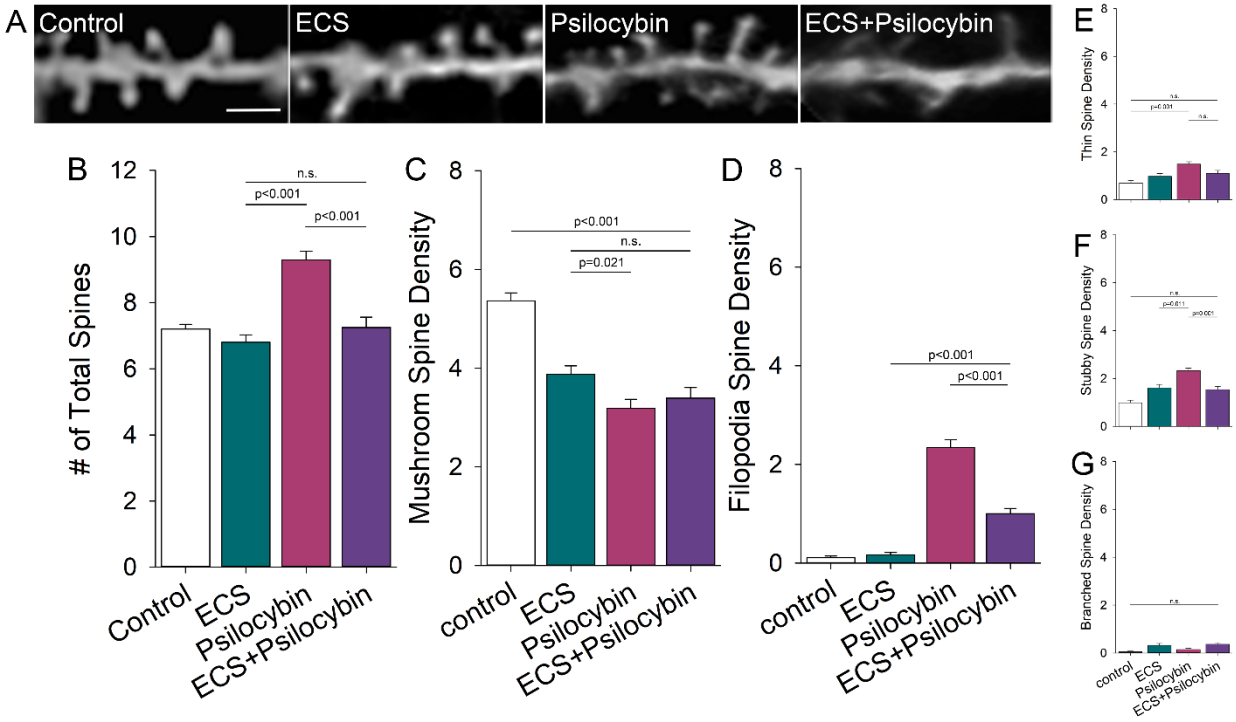

Figure 10: The Effects Following EPT On Dendritic Spine Density And Diversity. A) Representative images of 10 um sections of neuronal dendrites from control mice and those treated with a low dose of ECS, low dose of Psilocybin, and low dose of ECS + Psilocybin. Scale bar = 2 um B) Quantification of total 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).

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.

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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

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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-Present
Department of Psychology, University of Nevada, Las Vegas
- 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 – Spring 2018
Department of Psychology, University of Nevada, Las Vegas
- Worked with Dr. Dustin Hines to assess changes in microglia 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-Spring 2022
Department of Psychology, University of Nevada, Las Vegas
- 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: AI assisted morphological, electroencephalographic, and behavioral signatures of diverse psychedelics.* Nanosymposium presentation 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.* 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-Spring 2021

Interdisciplinary Neuroscience Executive Committee, University of Nevada, 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