A neuroimaging investigation of bipolar disorder and the neurocognitive effects of 5-HT7 antagonists

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ABSTRACT

Bipolar disorder is a psychiatric disorder characterised by pathological mood states, but there is growing recognition of the role of cognitive impairment and dysfunction of emotional processes, which has a profound impact on quality of life. Many people with bipolar disorders exhibit brain volume impairment associated with cognitive dysfunction and an increased risk of dementia.

In this thesis, I conducted a systematic review to understand the relationships between mood disorders and the 5-HT_7 receptor. The 5-HT_7 receptor is related to depression and anxiety, but the relationship between 5-HT_7 and mania remains unclear; in addition, sleep and memory were also related to the 5-HT_7 receptor. Followed by these findings, in the next two chapters, I examined the effects of 5-HT_7 antagonists, using JNJ-18038683, on emotional and cognitive functioning, as well as their neural substrates. I then reported on neuroimaging investigations examining the effects of 5-HT_7 antagonists on emotional processing and cognitive function in healthy volunteers to gain insight into their potential mode of action and utility for bipolar disorder. In fMRI analyses, the drug acted on 5-HT_7 receptors potentially improving cognitive performance by modulating the function of the Cognitive Control Network in healthy controls.

In the above-mentioned chapters, I gained a better understanding of the 5-HT_7 antagonist, JNJ-18038683, and the putative promising effects for pharmacological treatments. However, the approach taken has some limitations, including a small sample size, potential participant bias, and a lack of systematic control of medication dose and duration of administration.

In addition, in Chapter 5, I explored the brain basis of bipolar disorder and its links to cognitive and emotional dysfunction using a new 'brain age' approach. Individuals with bipolar disorder were found to have increased brain age compared to healthy controls.

I hope that these findings can be applied to pharmacological treatment for individuals with bipolar disorder, ultimately allowing patients to benefit from the drug in the future.

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Personal Contribution

This thesis encompasses data obtained from a clinical trial funded by the National Institute for Health and Care Research, titled 'Translational Validation of 5-HT_7 Antagonists as a treatment for cognitive impairment in bipolar disorder, a proof of principle neuroimaging study (SIMBA)' (ClinicalTrials.gov Identifier: NCT03633357). The study design was crafted by the SIMBA study team, led by Prof Allan Young as the principal investigator, and supported by Dr Paul Stokes and Prof Mitul Mehta, who served as co-investigators.

Chapter 1 General Introduction: I wrote this chapter, incorporating feedback and guidance provided by Prof Allan Young, Prof Mitul Mehta, and Dr Owen O'Daly.

Chapter 2 Systematic Review: I developed the protocol under Dr Paul Stokes' guidance. During the analysis phase, I collaborated with Dr Natalie Gottlieb on data screening. In the initial stages, I wrote the draft with feedback from Dr Paul Stokes. Subsequently, for the thesis version, I wrote this chapter, incorporating feedback from Prof Allan Young, Prof Mitul Mehta, and Dr Owen O'Daly.

Chapter 3 & 4 fMRI chapters: I was responsible for supporting the post-doctoral researcher, Dr Natalie Gottlieb, in the clinical trial, including recruitment, and screening visits. For the fMRI chapters, primary data were collected by Dr Natalie Gottlieb. I conducted the fMRI preprocessing and analysis, and wrote these chapters, incorporating feedback from Prof Allan Young, Prof Mitul Mehta, and Dr Owen O'Daly.

Chapter 5: In the chapter on brain age, data was input from SIMBA (Translational Validation of 5-HT_7 Antagonists as a treatment for cognitive impairment in bipolar disorder, a proof of principle neuroimaging study), CRiB (Cognitive Remediation in Bipolar), and BRCFMRS (Biomedical Research Centre Functional Magnetic Resonance Spectroscopy) projects at the

Department of Psychological Medicine, King's College London; BLISS (Bipolar Lithium Imaging and Spectroscopy Study) project was from the Newcastle Magnetic Resonance Centre, Newcastle University. The statistical analysis was guided by Dr Kia-Chong Chua. I undertook the analysis and writing of this chapter, with feedback from Dr Paul Stokes in the early stages. After drafting this chapter, I developed it, incorporating feedback from Prof Allan Young, Prof Mitul Mehta, and Dr Owen O'Daly.

Chapter 6 General Discussion: I wrote this chapter, incorporating feedback and guidance provided by Prof Allan Young, Prof Mitul Mehta, and Dr Owen O'Daly.

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Chapter 1 General Introduction

1.1 Bipolar disorders: background

1.1.1 BD symptoms and epidemiology

Bipolar Disorder (BD) is a mental illness which is characterised by recurring episodes of depression and mania, hypomania or mixed states (APA, 2013). In DSM-5, bipolar and related disorders have been separated from depression; bipolar disorder became a bridge between depressive disorders and schizophrenia spectrum disorders due to the differences of symptomology, family history, and genetic features. There are four types of bipolar: bipolar 1, bipolar 2, cyclothymia, and drug-induced bipolar. In manic episodes, the symptoms include abnormally and persistently elevated, euphoric, expansive, and/or irritable mood. The behaviour presents as inflated esteem, decreased need for sleep, more talkative tendencies, distractibility, racing thoughts, poor judgement, grandiosity, and an increase in goal-directed activities. In depressive episodes, the symptoms include abnormally low mood, a general loss of interest, fatigue, feelings of hopelessness and anhedonia. The person presents as struggling with feeling guilt, being fatigued or losing weight, and having thoughts of, or even attempting, suicide (APA, 2013). In addition to altered mood states, 82.9% of people with bipolar disorder had serious psychological, cognitive, and social impairments (Douglas et al., 2018; Kessler et al., 2005; Solé et al., 2017; Xu et al., 2020). Other core symptoms include impairment of cognitive functions, and this may persist in euthymic states (Batinic et al., 2021; Douglas et al., 2020; MacQueen & Memedovich, 2017; Pavlova et al., 2017; Samamé et al., 2012; Tsapekos et al., 2021). Bipolar disorder has no gender difference in lifetime prevalence, the ratio is roughly 1.1:1 (M:F) (Dell'Osso et al., 2021; Merikangas et al., 2007; Weissman et al., 1988).

Some symptoms will develop more with age, individuals with old-age bipolar disorder showing greater neuropsychological deficits (Gildengers et al., 2004; Sajatovic et al., 2015). In a three-year follow-up study, individuals with old-age bipolar disorder tended to experience more cognitive dysfunction and a more rapid decline in cognitive ability than what would be typical for their age and level of education. This impairment and accelerated decline can result in decreased independence, greater reliance on support from family and the community, and potentially even necessitate relocation to assisted living facilities (Gildengers et al., 2009). Individuals with old-age bipolar disorder also have more frequent episodes, more depressive episodes, and exhibit more severe cognitive dysfunctions compared to individuals with depression or healthy controls (Arnold et al., 2021).

1.1.2 BD and its comorbidities

It is widely accepted that bipolar disorder is associated with a considerable number of clinical comorbidities which affect the person's work and interpersonal functioning. In community studies, bipolar disorder is commonly comorbid with a number of psychiatric disorders including anxiety, substance use, and conduct disorders; in clinical samples, it is also comorbid with eating, sexual behaviour problems, attention-deficit hyperactivity disorders and impulse control disorders, as well as autism spectrum disorders and Tourette's disorder (McElroy, 2004). Recently, researchers found that anxiety symptoms are common in individuals with bipolar disorder. At least 50% of individuals with bipolar disorder are likely to meet the diagnostic criteria for anxiety disorders during their lifetime (Cullen et al., 2021; Spoorthy et al., 2019). The lifetime prevalence of these disorders and symptoms does not vary greatly across bipolar disorder subtypes and is estimated to be as high as 86% in bipolar 1 and 89%

in bipolar 2; these prevalence rates are three times higher than in the general population (Merikangas et al., 2007). Eating disorders and bipolar disorders have a high comorbidity, especially bulimia nervosa and binge eating disorder (Álvarez Ruiz & Gutiérrez-Rojas, 2015). A meta-analysis pointed out that attention deficit and hypoactivity disorder and bipolar disorder common co-occur with each other (Schiweck et al., 2021). The prevalence of bipolar disorder in autistic spectrum disorder (ASD) is estimated at 5% to 8%; developing effective diagnostic tools and potential treatments would address a key need in this field (Dunalska et al., 2021).

For children and adolescents with bipolar disorder, the comorbid diagnosis of anxiety, substance use, and disruptive behaviour disorders are commonly reported (Joshi & Wilens, 2009). Bipolar disorder is also seen to be comorbid with conduct disorder in childhood and adolescence (Kovacs & Pollock, 1995).

Some non-psychiatric diseases, such as diabetes and cardiovascular disease, also may co-occur with bipolar disorder (Liu et al., 2022; Miola et al., 2022; Weiner et al., 2011). In a qualitative interview, the quality of life of individuals with bipolar disorder was not satisfactory, which was also influenced by daily routine, independence, stigma and disclosure, identity, social support and spirituality (Michalak et al., 2006).

1.1.3 BD and social burden

Existing studies showed that cognitive impairments might cause poor psychosocial function, especially employment status (Keck et al., 1998; Wingo et al., 2009). In a six-year follow-up study, the authors reported that some main functions, including executive functioning, inhibition, processing speed, and verbal memory, were impaired in euthymic bipolar outpatients. In addition, even though the cognitive deficits were

stable, the deficits had negative impacts on the psychosocial adaptation (Mora et al., 2013). Bipolar disorder may cause long-term inability to work, and approximately half of individuals with bipolar disorder experience persistent work disability, leading to them requiring a disability pension (Arvilommi et al., 2022).

Since individuals with bipolar disorders have poor cognitive functions, it may cause long-term negative outcomes, both in personal and social levels. Bipolar disorder has the highest suicide rate of any mental illness, about 20-30 times that of the general population (Miller & Black, 2020; Novick et al., 2010; Tondo et al., 2007). Individuals with bipolar disorder experience a high incidence of suicidal behaviour, with 4% to 19% ultimately taking their own life, and 20% to 60% attempting suicide at least once during their lifetime (Dome et al., 2019).

Bipolar disorder has impact on social and economic costs. It has been estimated that managing bipolar disorder cost the National Health Service (NHS) £199 million per year, with hospital admissions accounting for 35% of this. In addition, considering the 297,000 people affected, the cost of the disorder to British society was estimated at £2 billion in 1999/2000. Of this total cost, the NHS was responsible for 10%, the use of non-healthcare resources was responsible for 4%, and the remaining 86% were indirect costs (Das Gupta & Guest, 2002).

1.1.4 BD and cognitive impairments

Bipolar disorder features extreme mood swings, and individuals with bipolar disorder experience cognitive functions deficits as well (Douglas et al., 2018; Solé et al., 2017; Xu et al., 2020). There is a growing body of evidence that individuals with bipolar disorder have neurocognitive impairments even during euthymic periods. Verbal

memory, attention, and executive function impairments are the most consistent findings (Arts et al., 2008; Kurtz & Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007). Moreover, a negative association has been shown between neurocognitive functioning and different measures of disability both in cross-sectional (Martínez-Arán et al., 2004; Martino et al., 2008; Sengupta & Jena, 2022; Tabarés-Seisdedos et al., 2008) and longitudinal (Martino et al., 2008; Tabarés-Seisdedos et al., 2008) studies.

Generally, people with bipolar disorder experience cognitive dysfunction; researchers indicated that working memory and attention (9.6% to 51.9% with impairment), speed and reaction time (23.3% to 44.2% with impairment), verbal memory (8.2% to 42.1% with impairment) and visual memory (11.5% to 32.9% with impairment) are impaired (Cullen et al., 2016). In a recent study, around 48% individuals with bipolar disorder have no impairment, 12-40% have some cognitive impairment including verbal memory, working memory, and executive functions, and 12-40% have cognitive impairment including across all cognitive domains (Burdick et al., 2014; Solé et al., 2015; Global Burden of Disease Study 2017, 2018).

According to studies, cognitive deficits have been observed both through cognitive tests, and self-reports by patients (Kurtz & Gerraty, 2009; Peters et al., 2014). These deficits have been linked to various illness factors, and further influence mood symptoms, comorbidity and medical use (Kurtz & Gerraty, 2009). Verbal learning and verbal memory deficits have been reported (Bourne et al., 2013; Thermenos et al., 2011; Vrabie et al., 2015). For prospective memory, both time-based and event-based prospective memory deficits were found in bipolar disorder (Martínez-Arán et al., 2004; Zhou et al., 2018). Clinical factors influence the illness, such as numbers of episodes and duration of illness (Clark et al., 2002). Cognitive impairments were found in

individuals with bipolar disorder, and the symptoms across manic, depressive, and euthymic status, and may last for several years (Martínez-Arán et al., 2004; Tohen et al., 2000).

For attention, sustained attention deficit is present in early episodes, but becomes more pronounced with recurrent episodes (Clark & Goodwin, 2004). Sustained attention impairments were found in euthymic patients when they underwent rapid visual information processing (RVIP) task (Clark et al., 2005), but their first-degree relatives and those with unipolar depression did not have similar problems. Around 20% comorbidity between attention-deficit hyperactivity disorder (ADHD) and bipolar disorder have also been reported: bipolar disorder shares several symptoms, including mood swings, impulsivity, hyperactivity and inattention, with ADHD (Salvi et al., 2021). This association particularly applies to ADHD and bipolar disorder in younger individuals (Moran et al., 2019). During the continuous performance test (CPT), individuals with bipolar disorder exhibited a worse performance in sustained attention comparing to the healthy control group (Najt et al., 2005). For executive functions, people with bipolar disorder had lower executive function in several domains. Bipolar 1 showed moderate to large impairments across all cognitive functions, in Trail Making Test (TMT), Hayling Test, Digit Span Total, and Category tasks, meaning the processing speed and short-term memory were impaired; bipolar 2 showed small-to-medium impairments in TMT and Category Fluency tasks, meaning the processing speed and verbal (lexical access) ability were impaired, and lower cognitive scores were shown in euthymic status (Cotrena et al., 2020; Soraggi-Frez et al., 2017).

For working memory, despite a lack of difference in working memory performance between euthymic patients and healthy controls, reduced activity in areas including

ventromedial and dorsolateral prefrontal cortices in the bipolar disorder group could be seen in a recent meta-analysis (Saldarini et al., 2022).

Generally, neurocognitive deficits are found in bipolar disorder, and in the remission status, patients showed moderate neuropsychological impairment, which was generally distributed across all domains. Patients' verbal learning and short-term memory were significantly affected, with severe impairment occurring during the manic, mixed or depressive episodes.

1.2 Brain abnormalities of BD

1.2.1 Grey and white matter abnormalities in individuals with BD

Brain abnormalities are found in individuals with bipolar disorder. When conducting post-mortems, brain abnormalities in the grey and white matters in the prefrontal cortex were found (Clark & Sahakian, 2008; Cotter et al., 2002; Rajkowska et al., 2001), specifically reductions of cell density. Researchers using voxel-based morphometry (VBM) found that grey matter density is decreased in the prefrontal cortex in people with bipolar 1 (Barysheva et al., 2013; Clark & Sahakian, 2008; Lyoo et al., 2004; Masuda et al., 2020) and also in the areas that are associated with executive functions (Menon, 2011; Seeley et al., 2007; Siegel-Ramsay et al., 2022). Research on neurocognitive function showed that individuals with bipolar disorder displayed three core areas of impairments: attention, executive function, and emotion processing, and studies have revealed that the underlying pathophysiology of the condition involves multiple neural circuits, including the prefrontal and anterior cingulate cortex, as well as the subcortical limbic system (Clark & Sahakian, 2008). One further study reported that individuals with bipolar disorders had lower white matter volumes when conducting a meta-analysis of coordinate data, statistical maps, and raw Magnetic

Resonance Imaging (MRI) datasets (Pezzoli et al., 2018). A large meta-analysis elucidated widespread patterns of reduced cortical thickness, lower subcortical volume, and disrupted white matter integrity closely linked to bipolar disorders (Ching et al., 2022).

1.2.2 Abnormalities in brain areas

Abnormalities in specific brain areas have been reported (Jones & Graff-Radford, 2021; Takahashi et al., 2010). When using MRI analysis, researchers reported that individuals with bipolar disorder had a significantly larger pituitary volume than their relatives and healthy controls (Takahashi et al., 2010). The ventral lateral prefrontal cortex plays a role in inhibition, response selection, and monitoring; the medial prefrontal cortex in self-knowledge, motivation, emotional regulation, and updating goal-directed behaviour; and the orbitofrontal cortex in personality, inhibition, and emotional and social reasoning, and many of these processes are impaired in bipolar disorder (Jones & Graff-Radford, 2021). In addition, one study identified that neuronal and glial density decreased in the dorsolateral prefrontal area 9 (Rajkowska et al., 2001). Abnormalities including decreased cortical thickness and glial density in the subgenual anterior cingulate cortex, reduced neuronal density in some amygdala nuclei, and decreased calbindin-positive neuron density in the prefrontal cortex were identified (Harrison et al., 2020).

1.2.3 Brain abnormalities in family studies

In family studies, researchers have investigated the interaction of gene and environment. The first controlled study was conducted in 1975, and the risk of having bipolar disorder in first-degree relatives with bipolar was higher than unipolar and healthy controls

(Gershon, 1975). Over the past few decades, researchers have found that the risk of developing bipolar disorder was higher for relatives of individuals with bipolar disorder compared to controls. Additionally, relatives of individuals with unipolar disorder also had a significantly higher risk of developing bipolar disorder compared to healthy controls (Gershon et al., 1982; Maier et al., 1993; Smoller & Finn, 2003). Recently, researchers reported that first-degree relatives of individuals with bipolar disorder had widespread larger cortical surface area (de Zwarte et al., 2022). They had larger intracranial volume (volume within the cranium, including the brain, meninges, and cerebrospinal fluid); smaller cortical grey matter, cerebral white matter, cerebellar grey, and white matter, and thalamus volumes; and the cortex was thinner; and larger third ventricle (de Zwarte et al., 2019). Increased surface area was found in left pars triangularis, and in the superior temporal cortex of first-degree siblings of bipolar 1 euthymic patients (Yalin et al., 2019).

1.2.4 Emotion and ACC & limbic system

Individuals with bipolar disorder show emotional dysregulation, difficulty with emotional processing, and unstable affective empathy (e.g., over empathising in manic episodes) (Bodnar & Rybakowski, 2017; Shamay-Tsoory et al., 2009; Wessa & Linke, 2009). Of note for daily life impact, individuals with bipolar disorder present with deficits in cognitive empathy and theory of mind, and impaired cognitive empathy was associated with poor performances on neurocognitive tasks that require cognitive flexibility. It is also suggested that prefrontal cortical dysfunction may be a contributing factor to this deficit in bipolar disorder (Shamay-Tsoory et al., 2009). For the emotional tests, in the emotional faces recognition task, individuals with bipolar disorder showed poor performances, including less accuracy or emotion mislabelling, and greater

reaction times (Furlong et al., 2022). One study indicated that individuals with bipolar disorder made the wrong identification (i.e., sad emotion was identified as anger) (Furlong et al., 2022), and another study showed they had over identification (i.e., neutral or happy emotion was identified as anger or fear) (Priyesh et al., 2022). Individuals with bipolar disorder performed less accurately in recognising positive faces expression (Ruihua et al., 2021).

Emotional processing dysfunction may be associated with brain abnormalities; individuals with bipolar disorder showed dysfunction in the ventral-limbic brain network, including the amygdala, insula, striatum, inferior root cingulate cortex, lateral prefrontal cortex, and orbitofrontal cortex, in response to emotional stimuli (Wessa & Linke, 2009). In most studies, patients showed lower activities in dorsolateral brain structures, including the dorsolateral prefrontal cortex, dorsal anterior cingulate, and posterior cingulate cortex (Wessa & Linke, 2009). The anterior cingulate cortex is involved in emotional processes and can be divided into two parts: emotion and cognition. The regions most strongly associated with emotional functioning includes areas 25, 33, and rostral area 24 regions extensively connected to the amygdala and perirhinal cortex (Devinsky et al., 1995). Furthermore, researchers found reduced glial density in subgenual anterior cingulate cortex and reduced glial number in individuals with bipolar disorder (Drevets et al., 1998; Ongür et al., 1998).

A correlation was found between the manic and increased activity in the left dorsal anterior cingulate and the left caudate. This finding suggested that the frontal cortico-subcortical nervous system, including the anterior cingulate and caudate may be involved in the neurobiology during manic episodes (Blumberg et al., 2000). In addition, researchers found that individuals with bipolar disorder had decreased left anterior

cingulate volumes compared with healthy controls, and the cingulate abnormalities also relate to gender differences (Blumberg et al., 2000). Abnormalities in the anterior cingulate cortex are associated with the initial psychotic episode in bipolar disorder (Fornito et al., 2009).

In general, the abnormalities reported in bipolar disorder include ventral and dorsal frontal regions (Fornito et al., 2009), as well as reduced density of grey and white matters volumes in core areas in prefrontal cortex were found (Clark & Sahakian, 2008; Cotter et al., 2002; Rajkowska et al., 2001). However, abnormal intracranial volumes, pituitary volume, and dorsolateral prefrontal, are also strongly associated with emotional, cognitive, and psychosocial functions, and hugely impact life quality (Clark & Sahakian, 2008). Beyond structural or functional abnormalities, cognitive dysfunction is associated with, and exacerbated by, having a lower social-economic status (Eid et al., 2013; Lahelma et al., 2006). Thus, finding suitable treatments to reduce symptoms and improve impairments can also enhance both in personal and social levels: for personal wellbeing and social burden (Fagiolini et al., 2013; Ogilvie et al., 2005; Simon, 2003).

1.2.5 Working memory and DLPFC

Individuals with bipolar disorder show poor working memory and executive functions (Arts et al., 2008; Barnes-Scheufler et al., 2021; Cotrena et al., 2020; Dickinson et al., 2017; Martínez-Arán et al., 2004; Vrabie et al., 2015). A commonly used task is the N-back working memory task which requires sustained attention and comparing information held online from the current trial to those immediately before. When analysing behaviour performance with the N-back working memory task, researchers found individuals with bipolar disorder had less accuracy (Adler et al., 2004; Drapier

et al., 2008; Thermenos et al., 2011). However, when analysing the reaction time, there were some conflicting results: some studies indicated there was no difference between individual with bipolar disorder and controls, but some indicated slower (Thermenos et al., 2011) or faster (Drapier et al., 2008) reaction time for bipolar people. These findings generally showed individuals with bipolar disorder showed poor working memory performance in N-back tasks (Cremaschi et al., 2013).

The involvement of the DLPFC in working memory tasks has been well established through extensive investigations encompassing lesion studies and neuroimaging techniques (Owen et al., 1996; Owen et al., 2005; Yaple & Yu, 2019).

The DLPFC is strongly implicated in working memory task performance both in animal and human studies (Arnsten & Jin, 2014; Miller & Cohen, 2001; Yang et al., 2014). In the early stage, the relationships between frontal cortex and working memory were found in positron emission tomography (PET) research (Owen et al., 1996); specifically, using a task involving the retention and execution of spatial motor sequences in working memory. These researchers found significant blood flow changes in the right and left frontal cortex (specifically area 47), while in a task that required active monitoring and manipulation of spatial information in working memory, additional activation sites were found in the mid-dorsolateral frontal cortex, specifically areas 46 and 9 (Owen et al., 1996). In addition, researchers have found neuropsychological evidence highlighting the role of the DLPFC in the manipulation of verbal and spatial information. This was demonstrated on various cognitive assessments such as the Wechsler Memory Scale (WMS), the Wechsler Adult Intelligence Scale (WAIS), and the N-back task, in which people showed DLPFC damage displayed impairment in manipulating verbal and spatial information processing (Barbey et al., 2013).

In one neuroimaging study there was prefrontal hypoactivation during a working memory task in bipolar 2 depression (Brooks et al., 2015). A review specifically investigated the effects of repetitive transcranial magnetic stimulation (rTMS) to stimulate the DLPFC in individuals with neuropsychiatric diseases or healthy controls, and whether this approach could improve working memory performance with a higher percentage of correct responses and a lower percentage of error responses (Brunoni & Vanderhasselt, 2014). When refocusing on bipolar disorder, a meta-analysis showed that bipolar disorder had higher activation in areas such as the right amygdala, parahippocampal gyrus, medial prefrontal cortex (PFC), left ventral striatum and cerebellum, and lower activation in the right ventrolateral PFC (VLPFC) and DLPFC (Lee et al., 2014). Another meta-analysis showed that bilateral transcranial magnetic stimulation on the DLPFC changed resting state networks and cognitive function among people with bipolar depression (Kazemi et al., 2018). Similar findings were found in children and adolescents, that a group with paediatric bipolar disorder patients showed substantially higher levels of activation in areas including the right DLPFC, insula, parietal cortex and cerebellum than the group with normal development.

1.3 Treatment approaches for BD

Since bipolar disorder severely impacts patients' emotional and cognitive functions, there has been a large and committed effort in basic and clinical research to find effective treatments. Currently, there are two main approaches of treatment for people with bipolar disorder: psychological therapy, and pharmacological treatment (Harrison et al., 2016; Miklowitz et al., 2021).

1.3.1 Psychological therapy and limitations

In psychological therapy, approaches that are well-established and evaluated by researchers include cognitive behavioural therapy, family or conjoint therapy, interpersonal therapy, and psychoeducational therapy (Miklowitz et al., 2021; Oud et al., 2016; Scott, 1995). Empirical studies have demonstrated that psychosocial interventions can yield substantial advantages for individuals with bipolar disorder as well as their families (Scott, 1995), and specific treatment approaches like family therapy and interpersonal and social rhythm therapy indicate that these interventions may exhibit some efficacy in managing episodes (Swartz & Frank, 2001).

1.3.2 Pharmacological treatment and side effects

Pharmacological treatment is the mainstream treatment for bipolar disorder (Geddes & Miklowitz, 2013). Mood stabilisers (Bauer et al., 2013; Karanti et al., 2016; Prabhavalkar et al., 2015; Simonetti et al., 2020), antipsychotics (Bowden, 2005; Pacchiarotti et al., 2019; Yatham, 2005), and some antidepressants (Goldberg et al., 2021; Sidor & MacQueen, 2012) are widely prescribed. Mood stabilisers, including lithium (Fountoulakis et al., 2022; Rakofsky et al., 2022; Akkouh et al., 2020; Gubert et al., 2021) and valproate (Fontana et al., 2020; Yee et al., 2021) have been shown to be effective for acute mania, concomitant psychotic symptoms and prevention of mania.

However, these medications produce side effects. The most common mood stabiliser, lithium, may cause some issues with renal function (Gupta & Khastgir, 2017; Van Alphen et al., 2021); patients who take lithium also need regular blood tests to ensure there are no toxic levels in the blood (Fountoulakis et al., 2022). Lithium has a distinct negative impact on psychomotor speed in participants with bipolar disorder (Paterson

& Parker, 2017). Valproate taken during pregnancy may cause birth defects, and up to 40% of babies whose mothers took valproate during pregnancy are at risk of neurodevelopmental disorders, such as ASD or ADHD (Christensen et al., 2013; Meador et al., 2008; Meador et al., 2009). Using antidepressants may increase the risk of manic episodes (Patel et al., 2015; Tondo et al., 2010). In a review, approximately 20% to 40% of bipolar patients experienced antidepressant-induced manias (Goldberg & Truman, 2003).

Emotional dysregulation and cognitive deficits are tremendous challenges that people with bipolar disorder face; both need more focus and effective treatments. Generally, people with mania present poorer verbal memory, verbal fluency, and cognitive estimation skills than depressed or remitted patients (Dickinson et al., 2017; Dixon et al., 2004; Goswami et al., 2006; Levy et al., 2012; Torres et al., 2007). Researchers have made attempts to find clinically efficient treatments for the cognitive impairments of bipolar disorder (Torres et al., 2010; Vrabie et al., 2015), but there is no effective pharmacological treatment for cognitive impairment (Solé et al., 2017). Currently, although there is a lack of effective treatments, either psychological or pharmacological, for cognitive deficits, and the common side effects of current treatments there is a growing drive to develop innovative and effective medications, and several new potential treatment avenues are gaining interest. Researchers are striving to find efficient treatment approaches, but it still needs time and money for effective interventions (Bonnín et al., 2019; Brickman & Fristad, 2022; Yildiz, 2021).

Since the psychotherapy and pharmacological treatments ae not effective on cognitive functions improvement, this thesis focused on new target of treatment of bipolar

disorder. I used a 5-HT$_7$ antagonist, JNJ-18038683, to test if this drug could improve behavioural performance and modulate the brain activation in healthy controls.

1.3.3 The 5-HT$_7$ antagonists for treatment of BD

5-HT$_7$ may be a promising target to develop novel treatments aimed at improving bipolar patients' cognitive functions. Even though the exact mechanism has not yet been fully identified, some early animal studies indicated that 5-HT$_7$ receptor function is highly associated with anxiety and depression (Peter B. Hedlund et al., 2005; Peter B. Hedlund & J. Gregor Sutcliffe, 2007). There is some evidence to support the 5-HT$_7$ receptor being related to mood disorder and that it may have a potential role in therapeutic strategies, especially with antidepressant property (P. B. Hedlund et al., 2005; Sarkisyan et al., 2010) and anxiolytic effects (Hedlund, 2009; P. B. Hedlund & J. G. Sutcliffe, 2007).

5-hydroxtryptamine (5-HT, serotonin) is a multifunctional chemical messenger which transmits signals between neurons; 5-HT$_7$ was the latest 5-HT receptor to be discovered in 1993 (Bard et al., 1993; Lovenberg et al., 1993; Ruat et al., 1993). The 5-HT$_7$ receptor gene is located on human chromosome 10q23.3-q24.3 (Bard et al., 1993), and the receptor is coupled by G-protein-coupled-receptor (GPCR) which can activate adenylyl cyclase and intracellular signalling pathways (Gellynck et al., 2013; Guseva et al., 2014; Kusek et al., 2021).

5-HT$_7$ receptors are expressed with the highest density in the thalamus and hypothalamus, with also significant densities in the hippocampus and the cerebral cortex in the brain (Sarkisyan and Hedlund, 2009; Meneses et al., 2015; Hedlund et al.,

2007). Specifically, they are expressed in CA1, CA2, and CA3 areas in the hippocampus (Bonaventure et al., 2012; Solas et al., 2021). Some researchers have also identified that intermediate receptor levels are in the hypothalamus, anterior cingulate gyrus, hippocampus, amygdala, and certain brainstem nuclei (Varnas et al., 2004). Due to where the 5-HT_7 receptors are expressed, they may be related to many physical and psychological functions and pathology, including mood, sleep, learning, memory, stress, and thermoregulation (Hedlund et al., 2004; Hedlund et al., 2003), which also renders them strong potential target for treating mood disorders, including bipolar disorder.

As noted above, 5-HT_7 receptors may have potential as a therapeutic target for the treatment of mood disorders: animal studies show the potential of 5-HT_7 antagonists for treating anxiety and depressive disorders (Takeda et al., 2005; Hedlund et al., 2005; Wesolowska et al., 2006a, b, 2007; Hedlund et al., 2007; Bonaventure et al., 2007; Sarkisyan et al., 2010; Mnie-Filai et al., 2011; Medina et al., 2014; Zhang et al., 2015; Canale et al., 2016; Maxwell et al., 2019). Meanwhile, regarding current treatments, many second-generation antipsychotic drugs show high affinity to the 5-HT_7 receptor; thus, several researchers have focussed on this receptor (Canale et al., 2016; Hedlund et al., 2005; Maxwell et al., 2019; Zhang et al., 2015). This evidence leads to 5-HT_7 being one of the new targets for the treatment of mood disorders.

The 5-HT_7 receptor may influence emotional and cognitive function in individuals with bipolar disorder. The 5-HT_7 receptors are located in the limbic system and also support the role of modulating functions of mood regulation, memory processing, and emotional association with memory (Berumen et al., 2012; Hannon & Hoyer, 2008;

Stiedl et al., 2015). Therefore, administering drugs with 5-HT$_7$ properties, such as lurasidone, enhanced cognitive functions of patients with bipolar disorder (Loebel et al., 2014); similarly, amisulpiride has shown potential benefits for bipolar depression (Loebel et al., 2020); while vortioxetine is a treatment for major depressive disorder (McIntyre et al., 2014).

Consistent findings in neuroimaging research suggest that an aetiological model for bipolar disorder involves abnormalities in the structure and function of the amygdala. Since 5-HT neurons are densely distributed in the hippocampus and in the main target structures of the frontal cortex, it is not surprising that 5-HT is involved in learning and memory processes (Cifariello et al., 2008). Dysregulation of serotonergic transmission would be expected to lead to both emotional and cognitive function impairments, something supported by recent animal studies (Bacqué-Cazenave et al., 2020); in humans, learning and memory deficits are common symptoms of bipolar disorder (Cowen & Sherwood, 2013; Stiedl et al., 2015; Švob Štrac et al., 2016), but the 5-HT$_{1A}$ receptor and 5-HT$_7$ receptor have been found to be associated with cognitive function improving which may be linked to mechanisms of emotional learning and memory (Stiedl et al., 2015).

In addition to emotional memory, 5-HT$_7$ showed a relationship with working memory in pre-clinical data: in a study, an antidepressant with 5-HT$_7$ antagonism, vortioxetine, prevented stress and enhanced short-term episodic memory in rats; in another study, blockade of the 5-HT$_7$ receptor reversed working memory deficits in rats by normalizing cortical glutamate neurotransmission. In a third study, a selective 5-HT$_7$ compound, SB-269970 (vortioxetine), was found to modulate working and reference

memory in rats; some other studies presented similar results (Bétry et al., 2015; Bonaventure et al., 2011; Gasbarri et al., 2008; Jeltsch et al., 2004). In these studies, the focus was on 5-HT_7 and how it improved cognitive functions; however, all of them were preclinical studies in animals (Cifariello et al., 2008; Gasbarri & Pompili, 2014).

1.4 Knowledge gap and study aims

1.4.1 The relationship between emotion and cognition

To investigate the relationships between emotion and cognition, we have to start from the state of integration of emotion and cognition. The theories of emotions have been developed in the past several decades. In the early stages, from a review, Darwin suggested that human facial expression is universal, and the basic emotions are cross-cultural (Ekman, 1992). Ekman also investigated facial expressions and emotions (Ekman, 1992, 2003; Ekman, 2008; Ekman & Cordaro, 2011). However, this theory has been challenged recently (Lindquist et al., 2012; Pessoa, 2017; Shaffer et al., 2022). Pessoa and his colleagues have stated that emotion and cognition are integrated; in other words, there is a complex network in the brain instead of simply pure emotion or cognition (Jungilligens et al., 2022; Misra et al., 2021; Pessoa, 2015, 2017, 2023). Researchers need to see the interactional complexity of the brain, not only the categorial regions (e.g., the amygdala is responsible for emotional response, or the DLPFC is for working memory). Pessoa (2015) suggested that the function of the amygdala went beyond the conventional understanding of its role in emotion in rodent and human studies, and the cognitive-emotional interactions observed within the human prefrontal cortex encompass a wide range of expressions and were not limited to mutual suppression.

Nonetheless, emotional facial expressions are a commonly used stimulus set for studying emotional recognition. In healthy volunteers, some visual, limbic, temporoparietal and prefrontal areas, as well as the putamen and cerebellum, showed increased activation when processing emotional face stimuli. Specifically, the amygdala was activated in response to happy, fearful, and sad faces, whereas angry or disgusted faces did not have a significant effect on this brain region. In addition, the amygdala was significantly more sensitive to fearful faces compared to happy or sad faces and link to negative memory (Duyser et al., 2022; Siegle et al., 2002). Individuals with bipolar disorder show impairments in cognitive empathy and theory of mind, which have significant implications for their daily lives. Deficits in cognitive empathy are associated with poor performance on neurocognitive tasks that require cognitive flexibility, indicating a link between impaired cognitive empathy and the ability to adapt and switch between different mental states. Research suggests that dysfunction in the prefrontal cortex may contribute to these deficits in bipolar disorder (Shamay-Tsoory et al., 2009). In cognitive tests, individuals with bipolar disorder demonstrate suboptimal performance in emotional face recognition tasks. They exhibit lower accuracy in identifying emotions and are more likely to mislabel emotions or take longer to response (Furlong et al., 2022; Priyesh et al., 2022; Ruihua et al., 2021).

With the imaging studies using emotional faces recognition tasks, researchers have found individuals with bipolar disorder show abnormalities in frontal-limbic regions, as well as fewer activations in the orbitofrontal cortex during mania (Altshuler et al., 2005). Fearful emotions were related to cortico-limbic responses (Killgore et al., 2014). In a review, the amygdala and the ventrolateral frontal cortex were shown to be involved in mania, and the ventrolateral frontal cortex was shown to be involved in bipolar depression and euthymia (Townsend & Altshuler, 2012).

In addition to fMRI analysis, some studies explored emotional face tasks with electroencephalogram (EEG) or positron emission tomography (PET). A study using positive and negative emotional faces showed changes in some brain areas, which means emotional expressions significantly affected shifts of attention (Kulke et al., 2021). Furthermore, when responding to happy and disgusted faces, participants' responses differed from those when emotionally neutral faces were presented, and the researchers reported distinct EEG responses to observation of positively and negatively emotional faces (Moore et al., 2012). In a review, researchers concluded that facial expression recognition depended highly on perceptual, rather than affective information and mechanisms (Calvo & Nummenmaa, 2016).

1.4.2 Structure of the study

Even though there have been a few studies that mention facial emotional expression and perception, there remains uncertainty as to whether taking medication will improve emotional function and have potential protective effects. The existing studies were conducted in some specific mood states (e.g., mania, depression, or normal status), but the effects between before and after administrating medication are still unclear, suggesting that clinical efficacy is not fully explored. Thus, our project tried to fill this gap, to investigate if the 5-HT_7 antagonist, JNJ-18038683, could change the behavioural performance or modulate brain functions with fMRI analysis. This thesis discussed, in addition to other work, findings from a recent study where we administrated the 5-HT_7 antagonist, JNJ-18038683, to healthy participants who performed several cognitive tasks while undergoing fMRI scanning. In addition, because detecting brain atrophy can help identify dementia, which individuals with bipolar disorder are at high risk for, I will investigate 'brain age' as part of my study.

To reach the aims, the thesis structure is as follows:

Chapter 1: General introduction, introduced bipolar disorder and treatments. An overview of the current understanding of bipolar disorder, such as brain abnormalities, cognitive functions, and pharmacological treatments, were provided. The rationale for exploring the role of 5-HT_7 antagonists was further introduced. The structure of the thesis was also presented in this chapter.

Chapter 2: Systematic review and findings, clarified the relationships between mood disorders and 5-HT_7 receptors. Existing literature on the links between mood disorders and 5-HT_7 receptors is thoroughly reviewed, with key findings from previous studies, including inconsistencies and gaps, summarised.

Chapter 3: fMRI emotion chapter, investigated the 5-HT_7 antagonist, JNJ-18038683, using a gender discrimination emotional faces task (pop-faces). The findings, limitations and future directions are presented and interpreted.

Chapter 4: fMRI cognition chapter, investigated the 5-HT_7 antagonist, JNJ-18038683, using an N-back working memory task. The findings, limitations and future directions are presented and discussed.

Chapter 5: Brain structure abnormalities, investigates potential older brain age (atrophy) in bipolar disorder; and relationships between brain age and cognitive functions. Methods for assessing brain structure, specifically 'brainageR', are described, with correlations between brain age and cognitive functions explored.

Chapter 6: General discussion, summarised main findings and provided evaluation, including strengths and limitations. Key findings from each chapter were summarised and how they further our understanding of bipolar disorder and the 5-HT_7 antagonist, JNJ-18038683, was discussed. Future research directions, including clinical applications and areas needing further exploration, were suggested.

Reference

Adler, C. M., Holland, S. K., Schmithorst, V., Tuchfarber, M. J., & Strakowski, S. M. (2004). Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. *Bipolar Disord*, *6*(6), 540-549. https://doi.org/10.1111/j.1399-5618.2004.00117.x

Altshuler, L. L., Bookheimer, S. Y., Townsend, J., Proenza, M. A., Eisenberger, N., Sabb, F., Mintz, J., & Cohen, M. S. (2005). Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. *Biol Psychiatry*, *58*(10), 763-769. https://doi.org/10.1016/j.biopsych.2005.09.012

Álvarez Ruiz, E. M., & Gutiérrez-Rojas, L. (2015). Comorbidity of bipolar disorder and eating disorders. *Rev Psiquiatr Salud Ment*, *8*(4), 232-241. https://doi.org/10.1016/j.rpsm.2014.12.001

Arnold, I., Dehning, J., Grunze, A., & Hausmann, A. (2021). Old Age Bipolar Disorder-Epidemiology, Aetiology and Treatment. *Medicina (Kaunas)*, *57*(6). https://doi.org/10.3390/medicina57060587

Arnsten, A. F., & Jin, L. E. (2014). Molecular influences on working memory circuits in dorsolateral prefrontal cortex. *Prog Mol Biol Transl Sci*, *122*, 211-231. https://doi.org/10.1016/b978-0-12-420170-5.00008-8

Arts, B., Jabben, N., Krabbendam, L., & van Os, J. (2008). Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychol Med*, *38*(6), 771-785. https://doi.org/10.1017/s0033291707001675

Arvilommi, P., Pallaskorpi, S., Linnaranta, O., Suominen, K., Leppämäki, S., Valtonen, H., & Isometsä, E. (2022). Long-term work disability due to type I and II bipolar disorder: findings of a six-year prospective study. *Int J Bipolar Disord*, *10*(1), 19. https://doi.org/10.1186/s40345-022-00264-6

Bacqué-Cazenave, J., Bharatiya, R., Barrière, G., Delbecque, J. P., Bouguiyoud, N., Di Giovanni, G., Cattaert, D., & De Deurwaerdère, P. (2020). Serotonin in Animal Cognition and Behavior. *Int J Mol Sci*, *21*(5). https://doi.org/10.3390/ijms21051649

Barbey, A. K., Koenigs, M., & Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. *Cortex*, *49*(5), 1195-1205. https://doi.org/10.1016/j.cortex.2012.05.022

Bard, J. A., Zgombick, J., Adham, N., Vaysse, P., Branchek, T. A., & Weinshank, R. L. (1993). Cloning of a novel human serotonin receptor (5-HT7) positively linked to adenylate

cyclase. *The Journal of biological chemistry*, *268*(31), 23422-23426. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=8226867

Barnes-Scheufler, C. V., Passow, C., Rösler, L., Mayer, J. S., Oertel, V., Kittel-Schneider, S., Matura, S., Reif, A., & Bittner, R. A. (2021). Transdiagnostic comparison of visual working memory capacity in bipolar disorder and schizophrenia. *Int J Bipolar Disord*, *9*(1), 12. https://doi.org/10.1186/s40345-020-00217-x

Barysheva, M., Jahanshad, N., Foland-Ross, L., Altshuler, L. L., & Thompson, P. M. (2013). White matter microstructural abnormalities in bipolar disorder: A whole brain diffusion tensor imaging study. *Neuroimage Clin*, *2*, 558-568. https://doi.org/10.1016/j.nicl.2013.03.016

Batinic, B., Djokic, V., & Ivkovic, M. (2021). Assessment of Cognitive Function, Social Disability and Basic Life Skills in Euthymic Patients with Bipolar Disorder. *Psychiatr Danub*, *33*(3), 320-327. https://doi.org/10.24869/psyd.2021.320

Bauer, M., Glenn, T., Alda, M., Sagduyu, K., Marsh, W., Grof, P., Munoz, R., Baethge, C., Lewitzka, U., Pilhatsch, M., Bauer, R., & Whybrow, P. C. (2013). Regularity in daily mood stabilizer dosage taken by patients with bipolar disorder. *Pharmacopsychiatry*, *46*(5), 163-168. https://doi.org/10.1055/s-0033-1343398

Berumen, L. C., Rodríguez, A., Miledi, R., & García-Alcocer, G. (2012). Serotonin receptors in hippocampus. *ScientificWorldJournal*, *2012*, 823493. https://doi.org/10.1100/2012/823493

Bétry, C., Etiévant, A., Pehrson, A., Sánchez, C., & Haddjeri, N. (2015). Effect of the multimodal acting antidepressant vortioxetine on rat hippocampal plasticity and recognition memory. *Prog Neuropsychopharmacol Biol Psychiatry*, *58*, 38-46. https://doi.org/10.1016/j.pnpbp.2014.12.002

Blumberg, H. P., Stern, E., Martinez, D., Ricketts, S., de Asis, J., White, T., Epstein, J., McBride, P. A., Eidelberg, D., Kocsis, J. H., & Silbersweig, D. A. (2000). Increased anterior cingulate and caudate activity in bipolar mania. *Biol Psychiatry*, *48*(11), 1045-1052. https://doi.org/10.1016/s0006-3223(00)00962-8

Bodnar, A., & Rybakowski, J. K. (2017). Increased affective empathy in bipolar patients during a manic episode. *Braz J Psychiatry*, *39*(4), 342-345. https://doi.org/10.1590/1516-4446-2016-2101

Bonaventure, P., Aluisio, L., Shoblock, J., Boggs, J. D., Fraser, I. C., Lord, B., Lovenberg, T. W., & Galici, R. (2011). Pharmacological blockade of serotonin 5-HT$_7$ receptor

reverses working memory deficits in rats by normalizing cortical glutamate neurotransmission. *PLoS One*, *6*(6), e20210. https://doi.org/10.1371/journal.pone.0020210

Bonnín, C. D. M., Reinares, M., Martínez-Arán, A., Jiménez, E., Sánchez-Moreno, J., Solé, B., Montejo, L., & Vieta, E. (2019). Improving Functioning, Quality of Life, and Well-being in Patients With Bipolar Disorder. *Int J Neuropsychopharmacol*, *22*(8), 467-477. https://doi.org/10.1093/ijnp/pyz018

Bourne, C., Aydemir, Ö., Balanzá-Martínez, V., Bora, E., Brissos, S., Cavanagh, J. T., Clark, L., Cubukcuoglu, Z., Dias, V. V., Dittmann, S., Ferrier, I. N., Fleck, D. E., Frangou, S., Gallagher, P., Jones, L., Kieseppä, T., Martínez-Aran, A., Melle, I., Moore, P. B., . . . Goodwin, G. M. (2013). Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatr Scand*, *128*(3), 149-162. https://doi.org/10.1111/acps.12133

Bowden, C. L. (2005). Atypical antipsychotic augmentation of mood stabilizer therapy in bipolar disorder. *J Clin Psychiatry*, *66 Suppl 3*, 12-19.

Brickman, H. M., & Fristad, M. A. (2022). Psychosocial Treatments for Bipolar Disorder in Children and Adolescents. *Annu Rev Clin Psychol*, *18*, 291-327. https://doi.org/10.1146/annurev-clinpsy-072220-021237

Brooks, J. O., 3rd, Vizueta, N., Penfold, C., Townsend, J. D., Bookheimer, S. Y., & Altshuler, L. L. (2015). Prefrontal hypoactivation during working memory in bipolar II depression. *Psychol Med*, *45*(8), 1731-1740. https://doi.org/10.1017/s0033291714002852

Brunoni, A. R., & Vanderhasselt, M. A. (2014). Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain Cogn*, *86*, 1-9. https://doi.org/10.1016/j.bandc.2014.01.008

Burdick, K. E., Russo, M., Frangou, S., Mahon, K., Braga, R. J., Shanahan, M., & Malhotra, A. K. (2014). Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. *Psychol Med*, *44*(14), 3083-3096. https://doi.org/10.1017/s0033291714000439

Calvo, M. G., & Nummenmaa, L. (2016). Perceptual and affective mechanisms in facial expression recognition: An integrative review. *Cogn Emot*, *30*(6), 1081-1106. https://doi.org/10.1080/02699931.2015.1049124

Ching, C. R. K., Hibar, D. P., Gurholt, T. P., Nunes, A., Thomopoulos, S. I., Abé, C., Agartz, I., Brouwer, R. M., Cannon, D. M., de Zwarte, S. M. C., Eyler, L. T., Favre, P., Hajek, T., Haukvik, U. K., Houenou, J., Landén, M., Lett, T. A., McDonald, C., Nabulsi, L., . . .

Andreassen, O. A. (2022). What we learn about bipolar disorder from large-scale neuroimaging: Findings and future directions from the ENIGMA Bipolar Disorder Working Group. *Hum Brain Mapp*, *43*(1), 56-82. https://doi.org/10.1002/hbm.25098

Christensen, J., Grønborg, T. K., Sørensen, M. J., Schendel, D., Parner, E. T., Pedersen, L. H., & Vestergaard, M. (2013). Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *Jama*, *309*(16), 1696-1703. https://doi.org/10.1001/jama.2013.2270

Cifariello, A., Pompili, A., & Gasbarri, A. (2008). 5-HT(7) receptors in the modulation of cognitive processes. *Behav Brain Res*, *195*(1), 171-179. https://doi.org/10.1016/j.bbr.2007.12.012

Clark, L., & Goodwin, G. M. (2004). State- and trait-related deficits in sustained attention in bipolar disorder. *Eur Arch Psychiatry Clin Neurosci*, *254*(2), 61-68. https://doi.org/10.1007/s00406-004-0460-y

Clark, L., Iversen, S. D., & Goodwin, G. M. (2002). Sustained attention deficit in bipolar disorder. *Br J Psychiatry*, *180*, 313-319. https://doi.org/10.1192/bjp.180.4.313

Clark, L., Kempton, M. J., Scarnà, A., Grasby, P. M., & Goodwin, G. M. (2005). Sustained attention-deficit confirmed in euthymic bipolar disorder but not in first-degree relatives of bipolar patients or euthymic unipolar depression. *Biol Psychiatry*, *57*(2), 183-187. https://doi.org/10.1016/j.biopsych.2004.11.007

Clark, L., & Sahakian, B. J. (2008). Cognitive neuroscience and brain imaging in bipolar disorder. *Dialogues Clin Neurosci*, *10*(2), 153-163. https://doi.org/10.31887/DCNS.2008.10.2/lclark

Cotrena, C., Damiani Branco, L., Ponsoni, A., Samamé, C., Milman Shansis, F., & Paz Fonseca, R. (2020). Executive functions and memory in bipolar disorders I and II: new insights from meta-analytic results. *Acta Psychiatr Scand*, *141*(2), 110-130. https://doi.org/10.1111/acps.13121

Cotter, D., Mackay, D., Chana, G., Beasley, C., Landau, S., & Everall, I. P. (2002). Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cereb Cortex*, *12*(4), 386-394. https://doi.org/10.1093/cercor/12.4.386

Cowen, P., & Sherwood, A. C. (2013). The role of serotonin in cognitive function: evidence from recent studies and implications for understanding depression. *J Psychopharmacol*, *27*(7), 575-583. https://doi.org/10.1177/0269881113482531

Cremaschi, L., Penzo, B., Palazzo, M., Dobrea, C., Cristoffanini, M., Dell'Osso, B., & Altamura, A. C. (2013). Assessing working memory via N-back task in euthymic bipolar I disorder patients: a review of functional magnetic resonance imaging studies. *Neuropsychobiology*, *68*(2), 63-70. https://doi.org/10.1159/000352011

Cullen, B., Ward, J., Graham, N. A., Deary, I. J., Pell, J. P., Smith, D. J., & Evans, J. J. (2016). Prevalence and correlates of cognitive impairment in euthymic adults with bipolar disorder: A systematic review. *J Affect Disord*, *205*, 165-181. https://doi.org/10.1016/j.jad.2016.06.063

Cullen, C., Kappelmann, N., Umer, M., Abdolizadeh, A., Husain, M. O., Bonato, S., Sharma, G., Xue, S., Ortiz, A., Kloiber, S. M., Mulsant, B. H., & Husain, M. I. (2021). Efficacy and acceptability of pharmacotherapy for comorbid anxiety symptoms in bipolar disorder: A systematic review and meta-analysis. *Bipolar Disord*, *23*(8), 754-766. https://doi.org/10.1111/bdi.13125

Das Gupta, R., & Guest, J. F. (2002). Annual cost of bipolar disorder to UK society. *Br J Psychiatry*, *180*, 227-233. https://doi.org/10.1192/bjp.180.3.227

de Zwarte, S. M. C., Brouwer, R. M., Agartz, I., Alda, M., Aleman, A., Alpert, K. I., Bearden, C. E., Bertolino, A., Bois, C., Bonvino, A., Bramon, E., Buimer, E. E. L., Cahn, W., Cannon, D. M., Cannon, T. D., Caseras, X., Castro-Fornieles, J., Chen, Q., Chung, Y., . . . van Haren, N. E. M. (2019). The Association Between Familial Risk and Brain Abnormalities Is Disease Specific: An ENIGMA-Relatives Study of Schizophrenia and Bipolar Disorder. *Biol Psychiatry*, *86*(7), 545-556. https://doi.org/10.1016/j.biopsych.2019.03.985

de Zwarte, S. M. C., Brouwer, R. M., Agartz, I., Alda, M., Alonso-Lana, S., Bearden, C. E., Bertolino, A., Bonvino, A., Bramon, E., Buimer, E. E. L., Cahn, W., Canales-Rodríguez, E. J., Cannon, D. M., Cannon, T. D., Caseras, X., Castro-Fornieles, J., Chen, Q., Chung, Y., De la Serna, E., . . . van Haren, N. E. M. (2022). Intelligence, educational attainment, and brain structure in those at familial high-risk for schizophrenia or bipolar disorder. *Hum Brain Mapp*, *43*(1), 414-430. https://doi.org/10.1002/hbm.25206

Dell'Osso, B., Cafaro, R., & Ketter, T. A. (2021). Has Bipolar Disorder become a predominantly female gender related condition? Analysis of recently published large sample studies. *Int J Bipolar Disord*, *9*(1), 3. https://doi.org/10.1186/s40345-020-00207-z

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain*, *118 (Pt 1)*, 279-306. https://doi.org/10.1093/brain/118.1.279

Dickinson, T., Becerra, R., & Coombes, J. (2017). Executive functioning deficits among adults with Bipolar Disorder (types I and II): A systematic review and meta-analysis. *J Affect Disord*, *218*, 407-427. https://doi.org/10.1016/j.jad.2017.04.010

Dixon, T., Kravariti, E., Frith, C., Murray, R. M., & McGuire, P. K. (2004). Effect of symptoms on executive function in bipolar illness. *Psychol Med*, *34*(5), 811-821. https://doi.org/10.1017/s0033291703001570

Dome, P., Rihmer, Z., & Gonda, X. (2019). Suicide Risk in Bipolar Disorder: A Brief Review. *Medicina (Kaunas)*, *55*(8). https://doi.org/10.3390/medicina55080403

Douglas, K. M., Gallagher, P., Robinson, L. J., Carter, J. D., McIntosh, V. V., Frampton, C. M., Watson, S., Young, A. H., Ferrier, I. N., & Porter, R. J. (2018). Prevalence of cognitive impairment in major depression and bipolar disorder. *Bipolar Disord*, *20*(3), 260-274. https://doi.org/10.1111/bdi.12602

Douglas, K. M., Porter, R. J., & Young, A. H. (2020). Cognition in mood disorders. *BJPsych Open*, *7*(1), e16. https://doi.org/10.1192/bjo.2020.149

Drapier, D., Surguladze, S., Marshall, N., Schulze, K., Fern, A., Hall, M. H., Walshe, M., Murray, R. M., & McDonald, C. (2008). Genetic liability for bipolar disorder is characterized by excess frontal activation in response to a working memory task. *Biol Psychiatry*, *64*(6), 513-520. https://doi.org/10.1016/j.biopsych.2008.04.038

Drevets, W. C., Ongür, D., & Price, J. L. (1998). Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. *Mol Psychiatry*, *3*(3), 220-226, 190-221. https://doi.org/10.1038/sj.mp.4000370

Dunalska, A., Rzeszutek, M., Dębowska, Z., & Bryńska, A. (2021). Comorbidity of bipolar disorder and autism spectrum disorder - review paper. *Psychiatr Pol*, *55*(6), 1421-1431. https://doi.org/10.12740/PP/OnlineFirst/122350 (Współwystępowanie choroby afektywnej dwubiegunowej i zaburzeń ze spektrum autyzmu – przegląd badań.)

Duyser, F. A., Vrijsen, J. N., van Oort, J., Collard, R. M., Schene, A. H., Tendolkar, I., & van Eijndhoven, P. F. (2022). Amygdala sensitivity for negative information as a neural marker for negative memory bias across psychiatric diagnoses. *Psychiatry Res Neuroimaging*, *323*, 111481. https://doi.org/10.1016/j.pscychresns.2022.111481

Eid, L., Heim, K., Doucette, S., McCloskey, S., Duffy, A., & Grof, P. (2013). Bipolar disorder and socioeconomic status: what is the nature of this relationship? *Int J Bipolar Disord*, *1*, 9. https://doi.org/10.1186/2194-7511-1-9

Ekman, P. (1992). Are there basic emotions? *Psychol Rev*, *99*(3), 550-553. https://doi.org/10.1037/0033-295x.99.3.550

Ekman, P. (2003). Emotions inside out. 130 Years after Darwin's "The Expression of the Emotions in Man and Animal". *Ann N Y Acad Sci*, *1000*, 1-6. https://doi.org/10.1196/annals.1280.002

Ekman, P. (2008). An argument for basic emotions. *Cognition and Emotion*, *6*(3-4), 169-200. https://doi.org/10.1080/02699939208411068

Ekman, P., & Cordaro, D. (2011). What is Meant by Calling Emotions Basic. *Emotion Review*, *3*(4), 364-370. https://doi.org/10.1177/1754073911410740

Fagiolini, A., Forgione, R., Maccari, M., Cuomo, A., Morana, B., Dell'Osso, M. C., Pellegrini, F., & Rossi, A. (2013). Prevalence, chronicity, burden and borders of bipolar disorder. *J Affect Disord*, *148*(2-3), 161-169. https://doi.org/10.1016/j.jad.2013.02.001

Fontana, E., Mandolini, G. M., Delvecchio, G., Bressi, C., Soares, J. C., & Brambilla, P. (2020). Intravenous valproate in the treatment of acute manic episode in bipolar disorder: A review. *J Affect Disord*, *260*, 738-743. https://doi.org/10.1016/j.jad.2019.08.071

Fornito, A., Yücel, M., Wood, S. J., Bechdolf, A., Carter, S., Adamson, C., Velakoulis, D., Saling, M. M., McGorry, P. D., & Pantelis, C. (2009). Anterior cingulate cortex abnormalities associated with a first psychotic episode in bipolar disorder. *Br J Psychiatry*, *194*(5), 426-433. https://doi.org/10.1192/bjp.bp.107.049205

Fountoulakis, K. N., Tohen, M., & Zarate, C. A., Jr. (2022). Lithium treatment of Bipolar disorder in adults: A systematic review of randomized trials and meta-analyses. *Eur Neuropsychopharmacol*, *54*, 100-115. https://doi.org/10.1016/j.euroneuro.2021.10.003

Furlong, L. S., Rossell, S. L., Karantonis, J. A., Cropley, V. L., Hughes, M., & Van Rheenen, T. E. (2022). Characterization of facial emotion recognition in bipolar disorder: Focus on emotion mislabelling and neutral expressions. *J Neuropsychol*, *16*(2), 353-372. https://doi.org/10.1111/jnp.12267

Gasbarri, A., Cifariello, A., Pompili, A., & Meneses, A. (2008). Effect of 5-HT(7) antagonist SB-269970 in the modulation of working and reference memory in the rat. *Behav Brain Res*, *195*(1), 164-170. https://doi.org/10.1016/j.bbr.2007.12.020

Gasbarri, A., & Pompili, A. (2014). Serotonergic 5-HT7 receptors and cognition. *Rev Neurosci*, *25*(3), 311-323. https://doi.org/10.1515/revneuro-2013-0066

Geddes, J. R., & Miklowitz, D. J. (2013). Treatment of bipolar disorder. *Lancet*, *381*(9878), 1672-1682. https://doi.org/10.1016/s0140-6736(13)60857-0

Gershon, E. S., Hamovit, J., Guroff, J. J., Dibble, E., Leckman, J. F., Sceery, W., Targum, S. D., Nurnberger, J. I., Jr., Goldin, L. R., & Bunney, W. E., Jr. (1982). A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen*

Psychiatry, *39*(10), 1157-1167. https://doi.org/10.1001/archpsyc.1982.04290100031006

Gershon, E. S., Mark, A., Cohen, N., Belizon, N., Baron, M., & Knobe, K. E. (1975). Transmitted factors in the morbid risk of Affective Disorders: A Controlled Study. . *Journal of Psychiatric Research*, *12*(4), 283-299. https://doi.org/10.1016/0022-3956(75)90007-2

Gildengers, A. G., Butters, M. A., Seligman, K., McShea, M., Miller, M. D., Mulsant, B. H., Kupfer, D. J., & Reynolds, C. F., 3rd. (2004). Cognitive functioning in late-life bipolar disorder. *Am J Psychiatry*, *161*(4), 736-738. https://doi.org/10.1176/appi.ajp.161.4.736

Gildengers, A. G., Mulsant, B. H., Begley, A., Mazumdar, S., Hyams, A. V., Reynolds Iii, C. F., Kupfer, D. J., & Butters, M. A. (2009). The longitudinal course of cognition in older adults with bipolar disorder. *Bipolar Disord*, *11*(7), 744-752. https://doi.org/10.1111/j.1399-5618.2009.00739.x

Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. (2018). *Lancet*, *392*(10159), 1789-1858. https://doi.org/10.1016/s0140-6736(18)32279-7

Goldberg, J. F., Nierenberg, A. A., & Iosifescu, D. V. (2021). Wrestling With Antidepressant Use in Bipolar Disorder: The Ongoing Debate. *J Clin Psychiatry*, *82*(1). https://doi.org/10.4088/JCP.19ac13181

Goldberg, J. F., & Truman, C. J. (2003). Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord*, *5*(6), 407-420. https://doi.org/10.1046/j.1399-5618.2003.00067.x

Goswami, U., Sharma, A., Khastigir, U., Ferrier, I. N., Young, A. H., Gallagher, P., Thompson, J. M., & Moore, P. B. (2006). Neuropsychological dysfunction, soft neurological signs and social disability in euthymic patients with bipolar disorder. *Br J Psychiatry*, *188*, 366-373. https://doi.org/10.1192/bjp.188.4.366

Gupta, S., & Khastgir, U. (2017). Drug information update. Lithium and chronic kidney disease: debates and dilemmas. *BJPsych Bull*, *41*(4), 216-220. https://doi.org/10.1192/pb.bp.116.054031

Hannon, J., & Hoyer, D. (2008). Molecular biology of 5-HT receptors. *Behav Brain Res*, *195*(1), 198-213. https://doi.org/10.1016/j.bbr.2008.03.020

Harrison, P. J., Cipriani, A., Harmer, C. J., Nobre, A. C., Saunders, K., Goodwin, G. M., & Geddes, J. R. (2016). Innovative approaches to bipolar disorder and its treatment. *Ann N Y Acad Sci*, *1366*(1), 76-89. https://doi.org/10.1111/nyas.13048

Harrison, P. J., Colbourne, L., & Harrison, C. H. (2020). The neuropathology of bipolar disorder: systematic review and meta-analysis. *Mol Psychiatry*, *25*(8), 1787-1808. https://doi.org/10.1038/s41380-018-0213-3

Hedlund, P. B. (2009). The 5-HT7 receptor and disorders of the nervous system: an overview. *Psychopharmacology (Berl)*, *206*(3), 345-354. https://doi.org/10.1007/s00213-009-1626-0

Hedlund, P. B., Huitron-Resendiz, S., Henriksen, S. J., & Sutcliffe, J. G. (2005). 5-HT7 receptor inhibition and inactivation induce antidepressantlike behavior and sleep pattern. *Biological psychiatry*, *58*(10), 831-837. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=16018977

Hedlund, P. B., Huitron-Resendiz, S., Henriksen, S. J., & Sutcliffe, J. G. (2005). 5-HT7 receptor inhibition and inactivation induce antidepressantlike behavior and sleep pattern. *Biol Psychiatry*, *58*(10), 831-837. https://doi.org/10.1016/j.biopsych.2005.05.012

Hedlund, P. B., & Sutcliffe, J. G. (2007). The 5-HT7 receptor influences stereotypic behavior in a model of obsessive-compulsive disorder. *Neurosci Lett*, *414*(3), 247-251. https://doi.org/10.1016/j.neulet.2006.12.054

Hedlund, P. B., & Sutcliffe, J. G. (2007). The 5-HT7 receptor influences stereotypic behavior in a model of obsessive-compulsive disorder. *Neuroscience letters*, *414*(3), 247-251. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=17267119

Jeltsch, H., Bertrand, F., Galani, R., Lazarus, C., Schimchowitsch, S., & Cassel, J. C. (2004). Intraseptal injection of the 5-HT1A/5-HT7 agonist 8-OH-DPAT and working memory in rats. *Psychopharmacology (Berl)*, *175*(1), 37-46. https://doi.org/10.1007/s00213-004-1783-0

Jones, D. T., & Graff-Radford, J. (2021). Executive Dysfunction and the Prefrontal Cortex. *Continuum (Minneap Minn)*, *27*(6), 1586-1601. https://doi.org/10.1212/con.0000000000001009

Joshi, G., & Wilens, T. (2009). Comorbidity in pediatric bipolar disorder. *Child Adolesc Psychiatr Clin N Am*, *18*(2), 291-319, vii-viii. https://doi.org/10.1016/j.chc.2008.12.005

Jungilligens, J., Paredes-Echeverri, S., Popkirov, S., Barrett, L. F., & Perez, D. L. (2022). A new science of emotion: implications for functional neurological disorder. *Brain*, *145*(8), 2648-2663. https://doi.org/10.1093/brain/awac204

Karanti, A., Kardell, M., Lundberg, U., & Landén, M. (2016). Changes in mood stabilizer prescription patterns in bipolar disorder. *J Affect Disord*, *195*, 50-56. https://doi.org/10.1016/j.jad.2016.01.043

Kazemi, R., Rostami, R., Khomami, S., Baghdadi, G., Rezaei, M., Hata, M., Aoki, Y., Ishii, R., Iwase, M., & Fitzgerald, P. B. (2018). Bilateral Transcranial Magnetic Stimulation on DLPFC Changes Resting State Networks and Cognitive Function in Patients With Bipolar Depression. *Front Hum Neurosci*, *12*, 356. https://doi.org/10.3389/fnhum.2018.00356

Keck, P. E., Jr., McElroy, S. L., Strakowski, S. M., West, S. A., Sax, K. W., Hawkins, J. M., Bourne, M. L., & Haggard, P. (1998). 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. *Am J Psychiatry*, *155*(5), 646-652. https://doi.org/10.1176/ajp.155.5.646

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, Severity, and Comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617-627. https://doi.org/10.1001/archpsyc.62.6.617

Killgore, W. D., Britton, J. C., Schwab, Z. J., Price, L. M., Weiner, M. R., Gold, A. L., Rosso, I. M., Simon, N. M., Pollack, M. H., & Rauch, S. L. (2014). Cortico-limbic responses to masked affective faces across ptsd, panic disorder, and specific phobia. *Depress Anxiety*, *31*(2), 150-159. https://doi.org/10.1002/da.22156

Kovacs, M., & Pollock, M. (1995). Bipolar disorder and comorbid conduct disorder in childhood and adolescence. *J Am Acad Child Adolesc Psychiatry*, *34*(6), 715-723. https://doi.org/10.1097/00004583-199506000-00011

Kulke, L., Brümmer, L., Pooresmaeili, A., & Schacht, A. (2021). Overt and covert attention shifts to emotional faces: Combining EEG, eye tracking, and a go/no-go paradigm. *Psychophysiology*, *58*(8), e13838. https://doi.org/10.1111/psyp.13838

Kurtz, M. M., & Gerraty, R. T. (2009). A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. *Neuropsychology*, *23*(5), 551-562. https://doi.org/10.1037/a0016277

Lahelma, E., Laaksonen, M., Martikainen, P., Rahkonen, O., & Sarlio-Lähteenkorva, S. (2006). Multiple measures of socioeconomic circumstances and common mental disorders. *Soc Sci Med*, *63*(5), 1383-1399. https://doi.org/10.1016/j.socscimed.2006.03.027

Lee, M. S., Anumagalla, P., Talluri, P., & Pavuluri, M. N. (2014). Meta-analyses of developing brain function in high-risk and emerged bipolar disorder. *Front Psychiatry*, *5*, 141. https://doi.org/10.3389/fpsyt.2014.00141

Levy, B., Manove, E., & Weiss, R. D. (2012). Recovery of cognitive functioning in patients with co-occurring bipolar disorder and alcohol dependence during early remission from an acute mood episode. *Ann Clin Psychiatry*, *24*(2), 143-154.

Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., & Barrett, L. F. (2012). The brain basis of emotion: a meta-analytic review. *Behav Brain Sci*, *35*(3), 121-143. https://doi.org/10.1017/s0140525x11000446

Liu, Y. K., Ling, S., Lui, L. M. W., Ceban, F., Vinberg, M., Kessing, L. V., Ho, R. C., Rhee, T. G., Gill, H., Cao, B., Mansur, R. B., Lee, Y., Rosenblat, J., Teopiz, K. M., & McIntyre, R. S. (2022). Prevalence of type 2 diabetes mellitus, impaired fasting glucose, general obesity, and abdominal obesity in patients with bipolar disorder: A systematic review and meta-analysis. *J Affect Disord*, *300*, 449-461. https://doi.org/10.1016/j.jad.2021.12.110

Loebel, A., Cucchiaro, J., Silva, R., Kroger, H., Hsu, J., Sarma, K., & Sachs, G. (2014). Lurasidone Monotherapy in the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study. *American Journal of Psychiatry*, *171*(2), 160-168. https://doi.org/doi: 10.1176/appi.ajp.2013.13070984

Loebel, A., Koblan, K., Kent, J., Tsai, J., Ozol-Godfrey, A., Fava, M., & Hopkins, S. (2020). A randomized, double-blind, placebo-controlled study of SEP-4199 for the treatment of patients with bipolar depression. *Neuropsychopharmacology*, *45*, 95-96. https://doi.org/http://dx.doi.org/10.1038/s41386-020-00890-7 (59th Annual Meeting of the American College of Neuropsychopharmacology, ACNP 2020.)

Lovenberg, T. W., Baron, B. M., de Lecea, L., Miller, J. D., Prosser, R. A., Rea, M. A., Foye, P. E., Racke, M., Slone, A. L., & Siegel, B. W. (1993). A novel adenylyl cyclase-activating serotonin receptor (5-HT7) implicated in the regulation of mammalian circadian rhythms. *Neuron*, *11*(3), 449-458.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=8398139

Lyoo, I. K., Kim, M. J., Stoll, A. L., Demopulos, C. M., Parow, A. M., Dager, S. R., Friedman, S. D., Dunner, D. L., & Renshaw, P. F. (2004). Frontal lobe gray matter density decreases in bipolar I disorder. *Biol Psychiatry*, *55*(6), 648-651. https://doi.org/10.1016/j.biopsych.2003.10.017

MacQueen, G. M., & Memedovich, K. A. (2017). Cognitive dysfunction in major depression and bipolar disorder: Assessment and treatment options. *Psychiatry Clin Neurosci*, *71*(1), 18-27. https://doi.org/10.1111/pcn.12463

Maier, W., Lichtermann, D., Minges, J., Hallmayer, J., Heun, R., Benkert, O., & Levinson, D. F. (1993). Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. *Arch Gen Psychiatry*, *50*(11), 871-883. https://doi.org/10.1001/archpsyc.1993.01820230041004

Martínez-Arán, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sánchez-Moreno, J., Benabarre, A., Goikolea, J. M., Comes, M., & Salamero, M. (2004). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry*, *161*(2), 262-270. https://doi.org/10.1176/appi.ajp.161.2.262

Martino, D. J., Strejilevich, S. A., Scápola, M., Igoa, A., Marengo, E., Ais, E. D., & Perinot, L. (2008). Heterogeneity in cognitive functioning among patients with bipolar disorder. *J Affect Disord*, *109*(1-2), 149-156. https://doi.org/10.1016/j.jad.2007.12.232

Masuda, Y., Okada, G., Takamura, M., Shibasaki, C., Yoshino, A., Yokoyama, S., Ichikawa, N., Okuhata, S., Kobayashi, T., Yamawaki, S., & Okamoto, Y. (2020). White matter abnormalities and cognitive function in euthymic patients with bipolar disorder and major depressive disorder. *Brain Behav*, *10*(12), e01868. https://doi.org/10.1002/brb3.1868

McElroy, S. L. (2004). Diagnosing and treating comorbid (complicated) bipolar disorder. *J Clin Psychiatry*, *65 Suppl 15*, 35-44.

McIntyre, R. S., Lophaven, S., & Olsen, C. K. (2014). A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*, *17*(10), 1557-1567. https://doi.org/10.1017/s1461145714000546

Meador, K., Reynolds, M. W., Crean, S., Fahrbach, K., & Probst, C. (2008). Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published

pregnancy registries and cohorts. *Epilepsy Res*, *81*(1), 1-13. https://doi.org/10.1016/j.eplepsyres.2008.04.022

Meador, K. J., Penovich, P., Baker, G. A., Pennell, P. B., Bromfield, E., Pack, A., Liporace, J. D., Sam, M., Kalayjian, L. A., Thurman, D. J., Moore, E., & Loring, D. W. (2009). Antiepileptic drug use in women of childbearing age. *Epilepsy Behav*, *15*(3), 339-343. https://doi.org/10.1016/j.yebeh.2009.04.026

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci*, *15*(10), 483-506. https://doi.org/10.1016/j.tics.2011.08.003

Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M., Petukhova, M., & Kessler, R. C. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*, *64*(5), 543-552. https://doi.org/10.1001/archpsyc.64.5.543

Michalak, E. E., Yatham, L. N., Kolesar, S., & Lam, R. W. (2006). Bipolar disorder and quality of life: a patient-centered perspective. *Qual Life Res*, *15*(1), 25-37. https://doi.org/10.1007/s11136-005-0376-7

Miklowitz, D. J., Efthimiou, O., Furukawa, T. A., Scott, J., McLaren, R., Geddes, J. R., & Cipriani, A. (2021). Adjunctive Psychotherapy for Bipolar Disorder: A Systematic Review and Component Network Meta-analysis. *JAMA Psychiatry*, *78*(2), 141-150. https://doi.org/10.1001/jamapsychiatry.2020.2993

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*, *24*, 167-202. https://doi.org/10.1146/annurev.neuro.24.1.167

Miller, J. N., & Black, D. W. (2020). Bipolar Disorder and Suicide: a Review. *Curr Psychiatry Rep*, *22*(2), 6. https://doi.org/10.1007/s11920-020-1130-0

Miola, A., De Filippis, E., Veldic, M., Ho, A. M., Winham, S. J., Mendoza, M., Romo-Nava, F., Nunez, N. A., Gardea Resendez, M., Prieto, M. L., McElroy, S. L., Biernacka, J. M., Frye, M. A., & Cuellar-Barboza, A. B. (2022). The genetics of bipolar disorder with obesity and type 2 diabetes. *J Affect Disord*, *313*, 222-231. https://doi.org/10.1016/j.jad.2022.06.084

Misra, J., Surampudi, S. G., Venkatesh, M., Limbachia, C., Jaja, J., & Pessoa, L. (2021). Learning brain dynamics for decoding and predicting individual differences. *PLoS Comput Biol*, *17*(9), e1008943. https://doi.org/10.1371/journal.pcbi.1008943

Moore, A., Gorodnitsky, I., & Pineda, J. (2012). EEG mu component responses to viewing emotional faces. *Behav Brain Res*, *226*(1), 309-316. https://doi.org/10.1016/j.bbr.2011.07.048

Mora, E., Portella, M. J., Forcada, I., Vieta, E., & Mur, M. (2013). Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study. *Psychol Med*, *43*(6), 1187-1196. https://doi.org/10.1017/s0033291712001948

Moran, L. V., Guvenek-Cokol, P. E., & Perlis, R. H. (2019). Attention-Deficit/Hyperactivity Disorder, Hypomania, and Bipolar Disorder in Youth. *JAMA Psychiatry*, *76*(11), 1119-1121. https://doi.org/10.1001/jamapsychiatry.2019.1926

Najt, P., Glahn, D., Bearden, C. E., Hatch, J. P., Monkul, E. S., Kaur, S., Villarreal, V., Bowden, C., & Soares, J. C. (2005). Attention deficits in bipolar disorder: a comparison based on the Continuous Performance Test. *Neuroscience letters*, *379*(2), 122–126. https://doi.org/10.1016/j.neulet.2004.12.051.

Novick, D. M., Swartz, H. A., & Frank, E. (2010). Suicide attempts in bipolar I and bipolar II disorder: a review and meta-analysis of the evidence. *Bipolar Disord*, *12*(1), 1-9. https://doi.org/10.1111/j.1399-5618.2009.00786.x

Ogilvie, A. D., Morant, N., & Goodwin, G. M. (2005). The burden on informal caregivers of people with bipolar disorder. *Bipolar Disord*, *7 Suppl 1*, 25-32. https://doi.org/10.1111/j.1399-5618.2005.00191.x

Ongür, D., Drevets, W. C., & Price, J. L. (1998). Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci U S A*, *95*(22), 13290-13295. https://doi.org/10.1073/pnas.95.22.13290

Oud, M., Mayo-Wilson, E., Braidwood, R., Schulte, P., Jones, S. H., Morriss, R., Kupka, R., Cuijpers, P., & Kendall, T. (2016). Psychological interventions for adults with bipolar disorder: systematic review and meta-analysis. *Br J Psychiatry*, *208*(3), 213-222. https://doi.org/10.1192/bjp.bp.114.157123

Owen, A. M., Evans, A. C., & Petrides, M. (1996). Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. *Cereb Cortex*, *6*(1), 31-38. https://doi.org/10.1093/cercor/6.1.31

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp*, *25*(1), 46-59. https://doi.org/10.1002/hbm.20131

Pacchiarotti, I., Tiihonen, J., Kotzalidis, G. D., Verdolini, N., Murru, A., Goikolea, J. M., Valentí, M., Aedo, A., & Vieta, E. (2019). Long-acting injectable antipsychotics (LAIs) for maintenance treatment of bipolar and schizoaffective disorders: A systematic

review. *Eur Neuropsychopharmacol*, *29*(4), 457-470. https://doi.org/10.1016/j.euroneuro.2019.02.003

Patel, R., Reiss, P., Shetty, H., Broadbent, M., Stewart, R., McGuire, P., & Taylor, M. (2015). Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study. *BMJ Open*, *5*(12), e008341. https://doi.org/10.1136/bmjopen-2015-008341

Paterson, A., & Parker, G. (2017). Lithium and cognition in those with bipolar disorder. *Int Clin Psychopharmacol*, *32*(2), 57-62. https://doi.org/10.1097/yic.0000000000000152

Pavlova, B., Perlis, R. H., Mantere, O., Sellgren, C. M., Isometsä, E., Mitchell, P. B., Alda, M., & Uher, R. (2017). Prevalence of current anxiety disorders in people with bipolar disorder during euthymia: a meta-analysis. *Psychol Med*, *47*(6), 1107-1115. https://doi.org/10.1017/s0033291716003135

Pessoa, L. (2015). Précis on The Cognitive-Emotional Brain. *Behav Brain Sci*, *38*, e71. https://doi.org/10.1017/s0140525x14000120

Pessoa, L. (2017). A Network Model of the Emotional Brain. *Trends Cogn Sci*, *21*(5), 357-371. https://doi.org/10.1016/j.tics.2017.03.002

Pessoa, L. (2023). The Entangled Brain. *J Cogn Neurosci*, *35*(3), 349-360. https://doi.org/10.1162/jocn_a_01908

Peters, A. T., Peckham, A. D., Stange, J. P., Sylvia, L. G., Hansen, N. S., Salcedo, S., Rauch, S. L., Nierenberg, A. A., Dougherty, D. D., & Deckersbach, T. (2014). Correlates of real world executive dysfunction in bipolar I disorder. *J Psychiatr Res*, *53*, 87-93. https://doi.org/10.1016/j.jpsychires.2014.02.018

Pezzoli, S., Emsell, L., Yip, S. W., Dima, D., Giannakopoulos, P., Zarei, M., Tognin, S., Arnone, D., James, A., Haller, S., Frangou, S., Goodwin, G. M., McDonald, C., & Kempton, M. J. (2018). Meta-analysis of regional white matter volume in bipolar disorder with replication in an independent sample using coordinates, T-maps, and individual MRI data. *Neurosci Biobehav Rev*, *84*, 162-170. https://doi.org/10.1016/j.neubiorev.2017.11.005

Prabhavalkar, K. S., Poovanpallil, N. B., & Bhatt, L. K. (2015). Management of bipolar depression with lamotrigine: an antiepileptic mood stabilizer. *Front Pharmacol*, *6*, 242. https://doi.org/10.3389/fphar.2015.00242

Priyesh, C., Suryavanshi, C. A., Sasidharan, A., Bhandary, R., Behere, R. V., & Nayak, K. R. (2022). Facial Emotion Recognition, Misattribution, and Response Time in

Schizophrenia and Bipolar Disorder. *Neurophysiology*, *53*(2), 120-131. https://doi.org/10.1007/s11062-022-09923-x

Rajkowska, G., Halaris, A., & Selemon, L. D. (2001). Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol Psychiatry*, *49*(9), 741-752. https://doi.org/10.1016/s0006-3223(01)01080-0

Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., & Moore, P. B. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord*, *93*(1-3), 105-115. https://doi.org/10.1016/j.jad.2006.02.016

Ruat, M., Traiffort, E., Leurs, R., Tardivel-Lacombe, J., Diaz, J., Arrang, J. M., & Schwartz, J. C. (1993). Molecular cloning, characterization, and localization of a high-affinity serotonin receptor (5-HT7) activating cAMP formation. *Proceedings of the National Academy of Sciences of the United States of America*, *90*(18), 8547-8551. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=8397408

Ruihua, M., Meng, Z., Nan, C., Panqi, L., Hua, G., Sijia, L., Jing, S., Ke, Z., Yunlong, T., Shuping, T., Fude, Y., Li, T., & Zhiren, W. (2021). Differences in Facial Expression Recognition Between Unipolar and Bipolar Depression. *Front Psychol*, *12*, 619368. https://doi.org/10.3389/fpsyg.2021.619368

Sajatovic, M., Strejilevich, S. A., Gildengers, A. G., Dols, A., Al Jurdi, R. K., Forester, B. P., Kessing, L. V., Beyer, J., Manes, F., Rej, S., Rosa, A. R., Schouws, S. N., Tsai, S. Y., Young, R. C., & Shulman, K. I. (2015). A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disord*, *17*(7), 689-704. https://doi.org/10.1111/bdi.12331

Saldarini, F., Gottlieb, N., & Stokes, P. R. A. (2022). Neural correlates of working memory function in euthymic people with bipolar disorder compared to healthy controls: A systematic review and meta-analysis. *J Affect Disord*, *297*, 610-622. https://doi.org/10.1016/j.jad.2021.10.084

Salvi, V., Ribuoli, E., Servasi, M., Orsolini, L., & Volpe, U. (2021). ADHD and Bipolar Disorder in Adulthood: Clinical and Treatment Implications. *Medicina (Kaunas)*, *57*(5). https://doi.org/10.3390/medicina57050466

Samamé, C., Martino, D. J., & Strejilevich, S. A. (2012). Social cognition in euthymic bipolar disorder: systematic review and meta-analytic approach. *Acta Psychiatr Scand*, *125*(4), 266-280. https://doi.org/10.1111/j.1600-0447.2011.01808.x

Sarkisyan, G., Roberts, A. J., & Hedlund, P. B. (2010). The 5-HT(7) receptor as a mediator and modulator of antidepressant-like behavior. *Behav Brain Res*, *209*(1), 99-108. https://doi.org/10.1016/j.bbr.2010.01.022

Schiweck, C., Arteaga-Henriquez, G., Aichholzer, M., Edwin Thanarajah, S., Vargas-Cáceres, S., Matura, S., Grimm, O., Haavik, J., Kittel-Schneider, S., Ramos-Quiroga, J. A., Faraone, S. V., & Reif, A. (2021). Comorbidity of ADHD and adult bipolar disorder: A systematic review and meta-analysis. *Neurosci Biobehav Rev*, *124*, 100-123. https://doi.org/10.1016/j.neubiorev.2021.01.017

Scott, J. (1995). Psychotherapy for bipolar disorder. *Br J Psychiatry*, *167*(5), 581-588. https://doi.org/10.1192/bjp.167.5.581

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*, *27*(9), 2349-2356. https://doi.org/10.1523/jneurosci.5587-06.2007

Sengupta, G., & Jena, S. (2022). Disability in Patients With Bipolar Disorder in Full or Partial Remission: A Cross-Sectional Study. *Prim Care Companion CNS Disord*, *24*(5). https://doi.org/10.4088/PCC.21m03183

Shaffer, C., Westlin, C., Quigley, K. S., Whitfield-Gabrieli, S., & Barrett, L. F. (2022). Allostasis, Action, and Affect in Depression: Insights from the Theory of Constructed Emotion. *Annu Rev Clin Psychol*, *18*, 553-580. https://doi.org/10.1146/annurev-clinpsy-081219-115627

Shamay-Tsoory, S., Harari, H., Szepsenwol, O., & Levkovitz, Y. (2009). Neuropsychological evidence of impaired cognitive empathy in euthymic bipolar disorder. *J Neuropsychiatry Clin Neurosci*, *21*(1), 59-67. https://doi.org/10.1176/jnp.2009.21.1.59

Sidor, M. M., & MacQueen, G. M. (2012). An update on antidepressant use in bipolar depression. *Curr Psychiatry Rep*, *14*(6), 696-704. https://doi.org/10.1007/s11920-012-0323-6

Siegel-Ramsay, J. E., Bertocci, M. A., Wu, B., Phillips, M. L., Strakowski, S. M., & Almeida, J. R. C. (2022). Distinguishing between depression in bipolar disorder and unipolar depression using magnetic resonance imaging: a systematic review. *Bipolar Disord*, *24*(5), 474-498. https://doi.org/10.1111/bdi.13176

Siegle, G. J., Steinhauer, S. R., Thase, M. E., Stenger, V. A., & Carter, C. S. (2002). Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in

response to emotional information in depressed individuals. *Biol Psychiatry*, *51*(9), 693-707. https://doi.org/10.1016/s0006-3223(02)01314-8

Simon, G. E. (2003). Social and economic burden of mood disorders. *Biol Psychiatry*, *54*(3), 208-215. https://doi.org/10.1016/s0006-3223(03)00420-7

Simonetti, A., Koukopoulos, A. E., Kotzalidis, G. D., Janiri, D., De Chiara, L., Janiri, L., & Sani, G. (2020). Stabilization Beyond Mood: Stabilizing Patients With Bipolar Disorder in the Various Phases of Life. *Front Psychiatry*, *11*, 247. https://doi.org/10.3389/fpsyt.2020.00247

Smoller, J. W., & Finn, C. T. (2003). Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet C Semin Med Genet*, *123c*(1), 48-58. https://doi.org/10.1002/ajmg.c.20013

Solé, B., Bonnin, C. M., Mayoral, M., Amann, B. L., Torres, I., González-Pinto, A., Jimenez, E., Crespo, J. M., Colom, F., Tabarés-Seisdedos, R., Reinares, M., Ayuso-Mateos, J. L., Soria, S., Garcia-Portilla, M. P., Ibañez, Á., Vieta, E., Martinez-Aran, A., & Torrent, C. (2015). Functional remediation for patients with bipolar II disorder: improvement of functioning and subsyndromal symptoms. *Eur Neuropsychopharmacol*, *25*(2), 257-264. https://doi.org/10.1016/j.euroneuro.2014.05.010

Solé, B., Jiménez, E., Torrent, C., Reinares, M., Bonnin, C. D. M., Torres, I., Varo, C., Grande, I., Valls, E., Salagre, E., Sanchez-Moreno, J., Martinez-Aran, A., Carvalho, A. F., & Vieta, E. (2017). Cognitive Impairment in Bipolar Disorder: Treatment and Prevention Strategies. *Int J Neuropsychopharmacol*, *20*(8), 670-680. https://doi.org/10.1093/ijnp/pyx032

Soraggi-Frez, C., Santos, F. H., Albuquerque, P. B., & Malloy-Diniz, L. F. (2017). Disentangling Working Memory Functioning in Mood States of Bipolar Disorder: A Systematic Review. *Front Psychol*, *8*, 574. https://doi.org/10.3389/fpsyg.2017.00574

Spoorthy, M. S., Chakrabarti, S., & Grover, S. (2019). Comorbidity of bipolar and anxiety disorders: An overview of trends in research. *World J Psychiatry*, *9*(1), 7-29. https://doi.org/10.5498/wjp.v9.i1.7

Stiedl, O., Pappa, E., Konradsson-Geuken, Å., & Ögren, S. O. (2015). The role of the serotonin receptor subtypes 5-HT1A and 5-HT7 and its interaction in emotional learning and memory. *Front Pharmacol*, *6*, 162. https://doi.org/10.3389/fphar.2015.00162

Švob Štrac, D., Pivac, N., & Mück-Šeler, D. (2016). The serotonergic system and cognitive function. *Transl Neurosci*, *7*(1), 35-49. https://doi.org/10.1515/tnsci-2016-0007

Swartz, H. A., & Frank, E. (2001). Psychotherapy for bipolar depression: a phase-specific treatment strategy? *Bipolar Disord*, *3*(1), 11-22. https://doi.org/10.1034/j.1399-5618.2001.030102.x

Tabarés-Seisdedos, R., Balanzá-Martínez, V., Sánchez-Moreno, J., Martinez-Aran, A., Salazar-Fraile, J., Selva-Vera, G., Rubio, C., Mata, I., Gómez-Beneyto, M., & Vieta, E. (2008). Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *J Affect Disord*, *109*(3), 286-299. https://doi.org/10.1016/j.jad.2007.12.234

Takahashi, T., Walterfang, M., Wood, S. J., Kempton, M. J., Jogia, J., Lorenzetti, V., Soulsby, B., Suzuki, M., Velakoulis, D., Pantelis, C., & Frangou, S. (2010). Pituitary volume in patients with bipolar disorder and their first-degree relatives. *J Affect Disord*, *124*(3), 256-261. https://doi.org/10.1016/j.jad.2009.12.002

Thermenos, H. W., Makris, N., Whitfield-Gabrieli, S., Brown, A. B., Giuliano, A. J., Lee, E. H., Faraone, S. V., Tsuang, M. T., & Seidman, L. J. (2011). A functional MRI study of working memory in adolescents and young adults at genetic risk for bipolar disorder: preliminary findings. *Bipolar Disord*, *13*(3), 272-286. https://doi.org/10.1111/j.1399-5618.2011.00920.x

Tohen, M., Hennen, J., Zarate, C. M., Jr., Baldessarini, R. J., Strakowski, S. M., Stoll, A. L., Faedda, G. L., Suppes, T., Gebre-Medhin, P., & Cohen, B. M. (2000). Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. *Am J Psychiatry*, *157*(2), 220-228. https://doi.org/10.1176/appi.ajp.157.2.220

Tondo, L., Lepri, B., & Baldessarini, R. J. (2007). Suicidal risks among 2826 Sardinian major affective disorder patients. *Acta Psychiatr Scand*, *116*(6), 419-428. https://doi.org/10.1111/j.1600-0447.2007.01066.x

Tondo, L., Vázquez, G., & Baldessarini, R. J. (2010). Mania associated with antidepressant treatment: comprehensive meta-analytic review. *Acta Psychiatr Scand*, *121*(6), 404-414. https://doi.org/10.1111/j.1600-0447.2009.01514.x

Torres, I. J., Boudreau, V. G., & Yatham, L. N. (2007). Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatr Scand Suppl*(434), 17-26. https://doi.org/10.1111/j.1600-0447.2007.01055.x

Torres, I. J., DeFreitas, V. G., DeFreitas, C. M., Kauer-Sant'Anna, M., Bond, D. J., Honer, W. G., Lam, R. W., & Yatham, L. N. (2010). Neurocognitive functioning in patients with

bipolar I disorder recently recovered from a first manic episode. *J Clin Psychiatry*, *71*(9), 1234-1242. https://doi.org/10.4088/JCP.08m04997yel

Townsend, J., & Altshuler, L. L. (2012). Emotion processing and regulation in bipolar disorder: a review. *Bipolar Disord*, *14*(4), 326-339. https://doi.org/10.1111/j.1399-5618.2012.01021.x

Tsapekos, D., Strawbridge, R., Cella, M., Young, A. H., & Wykes, T. (2021). Does cognitive improvement translate into functional changes? Exploring the transfer mechanisms of cognitive remediation therapy for euthymic people with bipolar disorder. *Psychol Med*, 1-9. https://doi.org/10.1017/s0033291721002336

Van Alphen, A. M., Bosch, T. M., Kupka, R. W., & Hoekstra, R. (2021). Chronic kidney disease in lithium-treated patients, incidence and rate of decline. *Int J Bipolar Disord*, *9*(1), 1. https://doi.org/10.1186/s40345-020-00204-2

Vrabie, M., Marinescu, V., Talaşman, A., Tăutu, O., Drima, E., & Micluţia, I. (2015). Cognitive impairment in manic bipolar patients: important, understated, significant aspects. *Ann Gen Psychiatry*, *14*, 41. https://doi.org/10.1186/s12991-015-0080-0

Weiner, M., Warren, L., & Fiedorowicz, J. G. (2011). Cardiovascular morbidity and mortality in bipolar disorder. *Ann Clin Psychiatry*, *23*(1), 40-47.

Weissman, M. M., Leaf, P. J., Tischler, G. L., Blazer, D. G., Karno, M., Bruce, M. L., & Florio, L. P. (1988). Affective disorders in five United States communities. *Psychol Med*, *18*(1), 141-153. https://doi.org/10.1017/s0033291700001975

Wessa, M., & Linke, J. (2009). Emotional processing in bipolar disorder: behavioural and neuroimaging findings. *Int Rev Psychiatry*, *21*(4), 357-367. https://doi.org/10.1080/09540260902962156

Wingo, A. P., Harvey, P. D., & Baldessarini, R. J. (2009). Neurocognitive impairment in bipolar disorder patients: functional implications. *Bipolar Disord*, *11*(2), 113-125. https://doi.org/10.1111/j.1399-5618.2009.00665.x

Xu, N., Huggon, B., & Saunders, K. E. A. (2020). Cognitive Impairment in Patients with Bipolar Disorder: Impact of Pharmacological Treatment. *CNS Drugs*, *34*(1), 29-46. https://doi.org/10.1007/s40263-019-00688-2

Yalin, N., Saricicek, A., Hidiroglu, C., Zugman, A., Direk, N., Ada, E., Cavusoglu, B., Er, A., Isik, G., Ceylan, D., Tunca, Z., Kempton, M. J., & Ozerdem, A. (2019). Cortical thickness and surface area as an endophenotype in bipolar disorder type I patients and their first-degree relatives. *Neuroimage Clin*, *22*, 101695. https://doi.org/10.1016/j.nicl.2019.101695

Yang, S. T., Shi, Y., Wang, Q., Peng, J. Y., & Li, B. M. (2014). Neuronal representation of working memory in the medial prefrontal cortex of rats. *Mol Brain*, *7*, 61. https://doi.org/10.1186/s13041-014-0061-2

Yaple, Z. A., & Yu, R. (2019). Fractionating adaptive learning: A meta-analysis of the reversal learning paradigm. *Neurosci Biobehav Rev*, *102*, 85-94. https://doi.org/10.1016/j.neubiorev.2019.04.006

Yatham, L. N. (2005). Atypical antipsychotics for bipolar disorder. *Psychiatr Clin North Am*, *28*(2), 325-347. https://doi.org/10.1016/j.psc.2005.01.001

Yee, C. S., Vázquez, G. H., Hawken, E. R., Biorac, A., Tondo, L., & Baldessarini, R. J. (2021). Long-Term Treatment of Bipolar Disorder with Valproate: Updated Systematic Review and Meta-analyses. *Harv Rev Psychiatry*, *29*(3), 188-195. https://doi.org/10.1097/hrp.0000000000000292

Yildiz, M. (2021). Psychosocial Rehabilitation Interventions in the Treatment of Schizophrenia and Bipolar Disorder. *Noro Psikiyatr Ars*, *58*(Suppl 1), S77-s82. https://doi.org/10.29399/npa.27430

Zhou, F. C., Wang, Y. Y., Zheng, W., Ungvari, G. S., Ng, C. H., Yuan, Z., & Xiang, Y. T. (2018). Prospective memory in bipolar disorder: A meta-analysis. *Psychiatry Res*, *259*, 184-190. https://doi.org/10.1016/j.psychres.2017.09.073

Chapter 2 The 5-HT$_7$ receptor in mood disorders: a systematic review

2.0 Abstract

Preclinical animal and preliminary human studies indicate that 5-HT$_7$ antagonists may have potential as new treatment approaches for mood and anxiety disorders. In this systematic review, we aimed to review the relationships between the 5-HT$_7$ receptor system and mood disorders, and to further explore the pharmacology and therapeutic potential of medications which target the 5-HT$_7$ receptor for the treatment of mood disorders.

Medline, Cochrane Library, EMBASE, PsycINFO databases, the National Institute of Health website Clinicaltrials.gov, controlled-trials.com, and relevant grey literature were searched to find original research articles; in addition, we hand-searched the reference lists of the included papers.

There were 62 studies that met criteria, including 50 animal studies and 12 human studies. These studies used a variety of preclinical paradigms and questionnaires to assess changes in mood, and few studies examined sleep or cognition, such as memory and attention. Although results were mixed, many found putative anxiolytic and antidepressant properties that warrant further study.

Even though there is a potential for the 5-HT$_7$ receptor system as a treatment target for mood and anxiety disorders, the compounds reviewed in this study also bind to other receptors. To explore the efficacy of drugs that specifically target 5-HT$_7$ receptors, additional research is necessary. Furthermore, to investigate the relationship between 5-HT$_7$ receptors, mood disorders, sleep, and cognition, it would be useful to evaluate sleep patterns and cognitive function.

2.1 Introduction

2.1.1 Mood disorders and pharmacological treatment

A mood disorder is a mental illness characterised by pathological mood changes such as depression or elation as well as a variety of other symptoms (APA, 2013). Individuals with mood disorders experience also often experience impaired social function as well (Batinic et al., 2021; Fagiolini et al., 2013; Goswami et al., 2006; Vlad et al., 2018). Changes in behaviour and social function impairments related to the mood disorder are highly likely to decrease peoples' work productivity which in turn leads to financial losses (Das Gupta & Guest, 2002; Simon, 2003). Pharmacological treatment plays an important role in treating mood disorders, and antidepressants, mood stabilisers, and antipsychotics, are often prescribed as treatments (Correll et al., 2015). Although some individuals with depression benefit after taking selective serotonin reuptake inhibitors (SSRIs) (Ferguson, 2001), about one third remain 'treatment resistant' after two consecutive antidepressant treatments (Thase, 1995). In addition, adverse effects such as gastrointestinal symptoms, drowsiness, sexual dysfunction and emotional blunting are common (Goethe, 2007; Goodwin, 2017), and thus a crucial goal of researchers is to find new treatments for mood disorders that benefit a higher number of patients and have fewer adverse effects.

2.1.2 Treating mood disorders with 5-HT_7 antagonists

5-hydroxtryptamine (5-HT, serotonin) is a neurotransmitter which is widely distributed in the brain and modulates signals between neurons. The main 5-HT receptor subtypes that have been identified include 5-HT_1 (with subtypes 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}), 5-HT_2 (with subtypes 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}), 5-HT_3, 5-HT_4, 5-HT_5 (with subtypes 5-HT_{5A} and 5-HT_{5B}), 5-HT_6, and 5-HT_7 (Pithadia & Jain, 2009).

Selective drugs capable of either stimulating or inhibiting these specific 5-HT receptor subtypes are being developed and the 5-HT_7 receptors play an important role in both body and brain functions. The 5-HT_7 receptor was discovered in 1993, currently the last to be described (Bard et al., 1993; Lovenberg et al., 1993; Ruat et al., 1993). The 5-HT_7 receptors expressed in the cortex have been linked to mood and sleep; in the hippocampus they have been linked to learning, memory, and stress; in the thalamus have been linked to sleep and seizures; and in the hypothalamus have been linked to circadian rhythm and thermoregulation (Horisawa et al., 2013; Martin-Cora & Pazos, 2004; Thomas et al., 2003; To, 1995).

The high-affinity antagonism of many second-generation antipsychotics to the 5-HT_7 receptor has attracted the attention of researchers, leading to the examination of therapeutic applications associated with this receptor. 5-HT_7 antagonists are compounds or drugs that bind to the 5-HT_7 receptors to inhibit their response, while 5-HT_7 agonists are compounds or drugs that activate the 5-HT_7 receptors to initiate a response. For emotional functions some have suggested that the 5-HT_7 receptor may have potential as a treatment for anxiety and depression (Canese et al., 2015; Cates et al., 2013; Hedlund & Sutcliffe, 2007). Animal studies also suggest the potential of 5-HT_7 antagonists for the treatment of anxiety disorders (Hedlund & Sutcliffe, 2007). Even though the mechanism through which 5-HT_7 antagonism may lead to improved therapeutic benefit is not fully understood, some studies indicate that 5-HT_7 receptor function is highly associated with anxiety and depression (Canese et al., 2015; Cates et al., 2013; Hedlund & Sutcliffe, 2007). This chapter aims to update previous reviews to identify the relationship between the 5-HT_7 receptor and mood disorders, and to further

explore the pharmacology and therapeutic potential of medications that target the 5-HT_7 receptor for the treatment of mood disorders.

2.2 Method

2.2.1 Study procedure

A protocol was designed and registered in the International Prospective Register for Systematic Reviews (PROSPERO); number CRD42019138174. In addition, all study procedures were documented and were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (Moher et al., 2015).

The research was conducted by two reviewers (TYL and NG). We conducted independent searches of the previously specified databases and compiled results using Rayyan QCRI software (Ouzzani et al., 2016) and then screened the papers to determine which met the inclusion criteria. We did a basic screen, first looking at titles and abstracts and then carried out a more in-depth screen reviewing full texts of articles where relevance was not immediately clear. A record of included and excluded studies, and reasons for exclusion was kept. Articles were discarded if we found that they met exclusion criteria at any stage. Once both reviewers had screened all papers, we compared included papers. For any disagreements over which papers to include, an additional reviewer (PRS) adjudicated. Once the reviewers had agreed upon the included papers, we moved on to the data extraction stage.

The electronic databases which were interrogated, comprised Medline, Cochrane Library, EMBASE, PsycINFO, the National Institute of Health website Clinicaltrials.gov, controlled-trials.com, and Grey Literature (i.e., Global Heath &

HMIC). They were searched up to March 2021. If papers were not written in English, an effort was made to obtain a translated version. Otherwise, the abstracts of papers written in English were collected.

The search string was:

[(5-HT7 OR serotonin receptor 7 OR 5-hydroxytryptamine 7) AND (depress* OR bipolar disorder OR anxiety disorder)] OR [(5-HT7 OR serotonin receptor 7 OR 5-hydroxytryptamine 7) AND (animals OR humans OR preclinical study OR clinical trial OR experimental medicine)] OR [(5-HT7 OR serotonin receptor 7 OR 5-hydroxytryptamine 7) AND (lurasidone OR vortioxetine)] OR (5-HT7 antagonists OR 5-HT7 agonists)]

2.2.2 Inclusion and exclusion criteria

Data relevant to 5-HT_7 agonists and antagonists, either in animal or human studies, was collected. For animal experiments studies, all models of depression or anxiety disorders were included, particularly rodent (mice, rats, guinea pigs, hamsters, and gerbils) models of a mood or anxiety disorder. 5-HT_7 genetic knockout or pharmacological blockade animal studies were collected if the studies aimed to examine animals' behaviours. 5-HT agonists were defined as the medicines which activate the 5-HT receptors, while the antagonists are defined as the medicines blocking receptors. The selective 5-HT_7 agonists and antagonists were all included.

For human clinical trial studies, males and females over the age of 18 fulfilling an ICD or DSM criteria diagnosis of a major depressive disorder or major depressive episode; or fulfilling ICD or DSM criteria for bipolar affective disorder; or fulfilling ICD or DSM criteria for an anxiety disorder were included. All subtypes of major depressive

disorder or major depressive episodes (e.g., mild, moderate, severe, with/without psychotic features) were included.

Changes from baseline to endpoint in mood status, assessed by change in mood related symptoms measured by validated rating scales such the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959), Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), or Quick Inventory of Depressive Symptomatology (QIDS) (Rush et a., 2003), change in sleep, cognitive or other markers were examined (e.g., neuroimaging or related clinical markers) main outcomes.

2.2.3 Outcome measures

The primary outcome was mood change after pharmacological intervention(s) with 5-HT_7 agonists or antagonists. For animal studies, behavioural changes were evaluated by animal tests, including tests for anxiety (e.g., light/dark transfer test, elevated plus maze test) and tests for depression (e.g., forced swim test (FST) or tail suspension test (TST)). For human studies, the mood status was measured by change (from baseline to endpoint) in mood status, including clinician-based questionnaire (e.g., HAM-A or HAM-D). A secondary outcome was change in sleep or cognitive functions.

2.2.4 Quality Measures

The quality of studies was measured by using the 'Quality Assessment Tool for Quantitative Studies' which was designed by the Effective Public Health Practice Project (EPHPP) (Armijo-Olivo et al., 2012; Thomas et al., 2004). The study data was assessed in several domains, i.e., selecting bias, study design, confounders, blinding, data collection methods, withdrawal and dropout, intervention integrity and analysis. A global quality rating was scored. The disagreements were discussed by reviewers (TYL

and NG) until a consensus was reached. An additional (PRS) reviewer was consulted as needed.

2.2.5 Data collection and analysis

The types of studies included animal experiment studies, and clinical trials (randomised controlled trials and cross-over trials). The titles and abstracts were screened to check whether relevance to the topic. After screening, those directly related to our topic were collated and perused. In data extraction and synthesis stages, tables and figures were designed to manage the results and conclusions. The topic was categorised by several themes, including different kinds of mood disorders. Other relevant themes, such as stress and sleep/awake topics, were not focused on.

2.3 Result

The initial search identified 8096 papers. After removal of duplicates, 4989 studies underwent initial title and abstract screening leaving 109 studies for full text review. Review of full-text articles excluded 47 articles for the following reasons: article type (7 review or meta-analysis papers, 18 conference abstracts or posters), wrong disorder or outcome measure (18), data reported elsewhere (2), not a randomised controlled trial study (1), and article language (1). In total, 62 studies were included (50 animal studies and 12 human studies) and details are outlined in Figure 2-1.

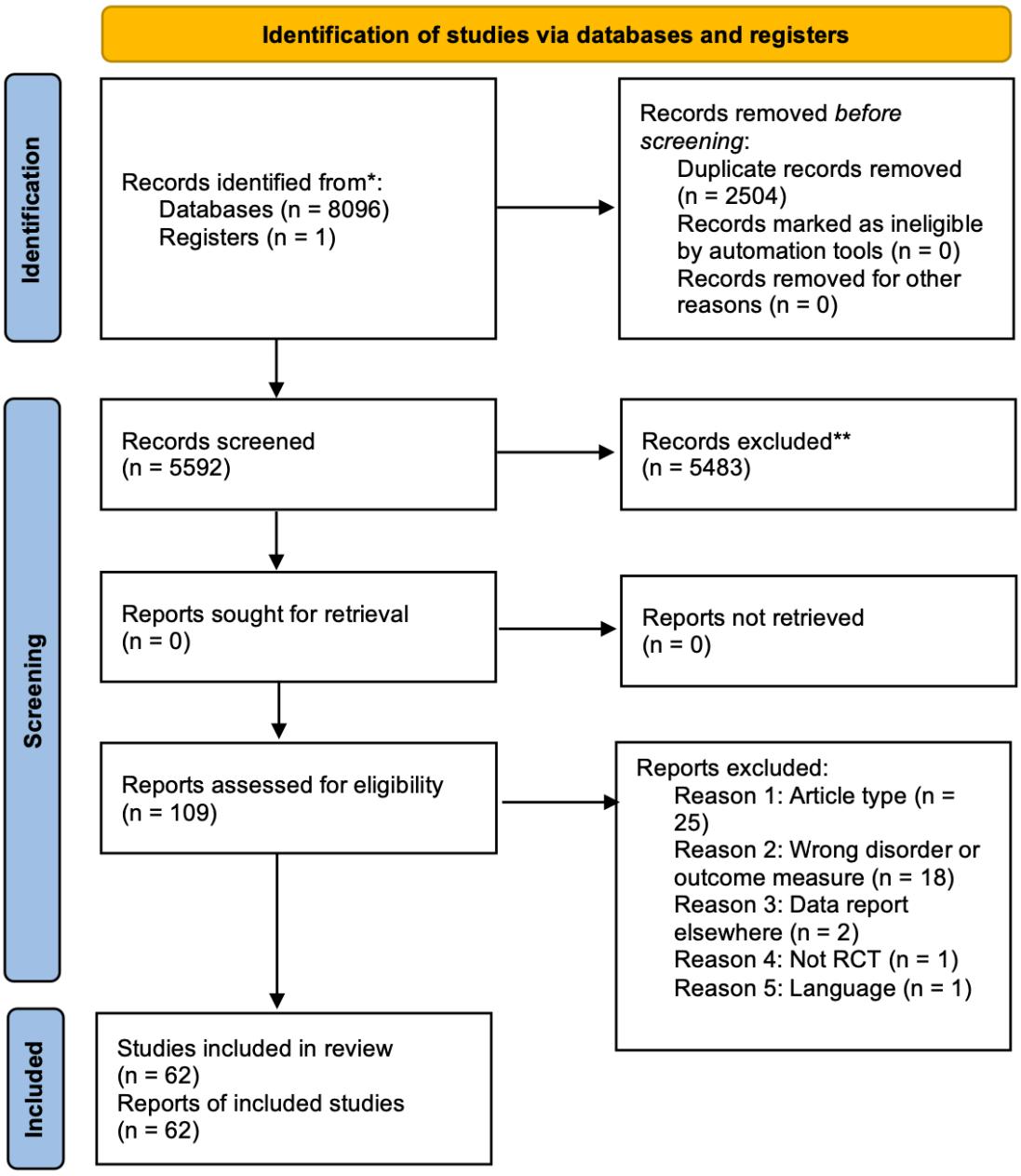

Figure 2-1

PRISMA diagram.

2.3.1 Depression and the 5-HT$_7$ receptor

The preclinical studies and human studies reviewed indicated a role for the 5-HT$_7$ receptor in the treatment of depression. In animal testing, the forced swim test (FST) and the tail suspension test (TST) are used to evaluate antidepressant agents. Even though the FST and TST are not recognised as complete models of depression (i.e., whether FST or TST findings can be applied to human beings), it is used for screening potential antidepressants (Petit-Demouliere et al., 2005). It is important to recognise that the use of animal models is at best an approximation of the human condition. The ability to confidently mimic specific abnormal behaviours in these models and assess their translational effects has been an issue (Stanford, 2020). Therefore, caution is warranted, and one should not overinterpret the results. The details of whether animal studies could transfer to human studies will be discussed in the discussion section in this chapter.

Briefly, in both the FST and TST, selective 5-HT$_7$ antagonists have been shown to induce animals' antidepressant-like activity (Takeda et al., 2005). Animals given SB-269970 (a selective 5-HT$_7$ receptor antagonist) exhibited reduced immobility in the FST or TST (Canale, Kurczab, Partyka, Sataa, et al., 2016; Hedlund et al., 2005; Maxwell et al., 2019; Medina et al., 2014; Mnie-Filali et al., 2011a; Sarkisyan et al., 2010; Wesolowska, Nikiforuk, & Stachowicz, 2006a; Wesolowska, Nikiforuk, Stachowicz, et al., 2006b; Wesolowska et al., 2007; Zhang et al., 2015). When SB-269970 was combined with other drugs, such as citalopram, imipramine, desipramine and moclobemide, it had an anti-immobility effect in rodents (Wesolowska et al., 2007). Another study using intrahippocampal injection of SB-269970, reduced immobility time in the FST, indicating that the hippocampus is one brain region involved in actions

of the antagonist (Wesolowska, Nikiforuk, & Stachowicz, 2006a). A recent animal study also supported that 5-HT_7 antagonist may associate with improving depressive-like behaviours (Bijata et al., 2022).

In addition, researchers found that antipsychotics with antidepressant properties have high affinity to the 5-HT_7 receptor (Abbas et al., 2009; Cates et al., 2013; Delcourte et al., 2017). One antipsychotic, lurasidone, reduced mice immobility in the TST and FST immediately, and was able to reduce the immobility time in the open-space swim test. Another antipsychotic, amisulpiride, an antipsychotic with 5-HT_7 receptor antagonism, has putative antidepressant actions (Abbas et al., 2009). The other antipsychotic, asenapine, may also modulate mood-related behaviours and 5-$HT_{1A/7}$ receptor-mediated neurotransmission (Delcourte et al., 2017; El-Mallakh et al., 2020; Volz, 2011). The 5-HT_7 receptor has been implicated as a potential therapeutic target for both psychosis and depression, as some antipsychotic and antidepressant drugs that affect this receptor have high affinity for it. For example, the antipsychotics lurasidone, amisulpiride, and asenapine, as well as the antidepressant vortioxetine, act on the 5-HT_7 receptors. The results suggest the clinical potential of 5-HT_7 receptor antagonism for these disorders: multiple lines of evidence point to the 5-HT_7 receptor as a therapeutic target for depression, anxiety, and schizophrenia (Balcer et al., 2019).

The 5-HT_7 receptors were found to be associated with major depressive disorder in human studies. LU AA21004 (subsequently named vortioxetine), a compound with 5-HT_{1A}, 5-HT_{1B}, 5-HT_3 and 5-HT_7 receptors and 5-HT transporters, was effective in treating major depressive disorder (Alvarez et al., 2012; Baldwin, 2011; Dragheim et al., 2011; Henigsberg et al., 2011; Katona et al., 2012), and improved mood status in other psychiatric disorders (Kennedy et al., 2016; Mahableshwarkar et al., 2014;

McIntyre et al., 2013; Tomassini et al., 2017). In general, dosing vortioxetine in 5mg, 10mg or 20 mg daily for more than 6 weeks showed positive efficacy when measuring with Montgomery–Åsberg Depression Rating Scale (MADRS) (Alvarez et al., 2012; Clayton et al., 2018), Hamilton Depression Rating Scale (HDRS, also known as the HAM-D) (Henigsberg et al., 2011) and HAM-D (Katona et al., 2012). For elderly people, dosing 5mg vortioxetine for 8 weeks was shown to be efficacious, and their cognitive functions were assessed and showed improvement in the Digital Symbol Substitute Test and Ray Auditory Verbal Learning Test as well (RAVLT) (Katona et al., 2012).

However, one study reported that dosing vortioxetine 2.5mg, 5mg, or 10mg was not statistically significantly different when compared to placebo (Baldwin, 2011). When dosing 8 weeks 2.5mg or 5mg vortioxetine in adults with major depressive disorder, the HAM-D score declined, but the differences were not significant (Mahableshwarkar et al., 2014). This drug has been tested for its usefulness in treating depression, and has demonstrated an antidepressant and anxiolytic property (Guilloux et al., 2013).

In a phase 2 clinical trial, a clinical difference was shown between JNJ-18038683 and the matched placebo; the selective 5-HT_7 antagonist, JNJ-18038683, changed animals' and humans' rapid eye movement sleep, and was effective in improving major depressive disorder (Bonaventure et al., 2012a). There was a statistically significant improvement between JNJ-18038683 and placebo in MADRS (Bonaventure et al., 2012a). At present, JNJ-18038683 is in the process of being tested for efficacy and safety in humans and has shown preliminary effectiveness in treating depression. HBK-15, a compound with 5-HT_7 affinity, reduced mice immobility FST (Pytka et al., 2015b); also, PZ-1417 and PZ-1150, two 5-HT_7 antagonist displayed antidepressant properties

(Canale, Kurczab, Partyka, Satala, Lenda, et al., 2016). In addition, a new 5-HT_7 antagonist, N-biphenyl-2-ylmethyl2-methoxyphenylpiperazinylalkanamidesa, also reduced mice immobility in force swimming, which indicates it may have antidepressant efficacy (Canale, Kurczab, Partyka, Satala, Sloczynska, et al., 2016).

2.3.2 Anxiety and 5-HT_7 receptor

Animal and human studies have suggested that 5-HT_7 receptor antagonists may have anxiolytic-like effects. Anxiety disorder is a widely used term covering various disorders that all relate to fear and anxiety (APA, 2013). There are many animal tests that can putatively evaluate a rodent's (anti-)anxiety behaviour, mostly related to reduction of immobility in an anxious condition. The 5-HT_7 antagonist, SB-269970, was shown to have anxiolytic-like efficacy. SB-269970 reduced anxious behaviours in many tests: in the Vogel conflict drinking test, in which the rodents' tolerance of shock increased. In the elevated plus-maze test, SB-269970 induced an anxiolytic-like effect by increasing the time spent in the task (Wesolowska, Nikiforuk, Stachowicz, et al., 2006a). A similar finding was in the shock threshold test and open-field test (Wesolowska, Nikiforuk, & Stachowicz, 2006b). When being dosed with a 5-HT_7 antagonist, SB-269970, mice showed less anxious behaviour in the marble-burying test, which is a model of obsessive-compulsive like behaviours (Hedlund & Sutcliffe, 2007). At least two 5-HT_7 antagonists decreased rodents' anxiety in the Vogel conflict drinking test and the light-dark transfer test (Volk et al., 2008a; Volk et al., 2011).

For human studies, 5-HT_7 antagonists also demonstrated anti-anxiolytic effects. Administrating vortioxetine 5mg or 10mg for 24-56 weeks was efficacious in preventing relapse and was well tolerated in the maintenance treatment of general

anxiety disorder (GAD) (Baldwin, 2011). However, vortioxetine did not improve symptoms of GAD over 8 weeks of treatment (Rothschild et al., 2011). There was no statistically significant difference in the reduction in HAM-A (Hamilton, 1959; Thompson, 2015) total score from baseline between the vortioxetine and placebo groups. The two results seemed contradict each other, but the dosing duration of 24-56 weeks is much longer than 8 weeks which indicate the dosing duration may influence the effects (Baldwin & Dragheim, 2011; Rothschild et al., 2011).

2.3.3 Antidepressant and anxiolytic effects of 5-HT_7 antagonists

Animal studies suggest that the 5-HT_7 receptor may mediate both antidepressant and anxiolytic effects. Some compounds have both antidepressant-like and anxiolytic-like effects. A compound which displayed antagonistic activity at 5-HT_7, 5-HT_{2A}, D2 postsynaptic sites, produced antidepressant-like effects in the FST and anxiolytic effect in the plus-maze test (Zajdel et al., 2012a). HBK-14 and HBK-15, triple 5-HT_{1A}, 5-HT_7 and 5-HT_3 antagonists, showed antidepressant-like properties and significantly increased serotonin levels in the hippocampus after chronic dosing. HBK-14 showed stronger antidepressant efficacy while HBK-15 had greater anxiolytic effect (Pytka, Gluch-Lutwin, et al., 2017; Pytka, Socala, et al., 2017). Also, rodents given MF-8, a 5-HT_7 antagonist, displayed reduced immobility in FST and had positive behaviours in the four-plate test, which indicated antidepressant-like and anxiolytic-like activity (Latacz, Hogendorf, et al., 2018).

2.3.4 Bipolar disorder and 5-HT_7

Many antipsychotics have high 5-HT_7 affinity, and this suggests that 5-HT_7 receptors may be associated with bipolar disorder. Asenapine, an antipsychotic with 5-HT_7

affinity, is anti-manic in bipolar 1 (Loebel et al., 2014). Statistically significant improvement in MADRS was greater in the asenapine group at doses of 20-60mg daily and 80-120mg daily for 6 weeks demonstrated greater reductions than in the placebo group in bipolar 1 patients who experienced a depressive episode. Anxiety also improved significantly in the asenapine-treated participants compared to placebo treatment. When lurasidone was given to patients with major depressive episodes associated with bipolar 1 disorder, their mood improved significantly (Loebel et al., 2014).

The efficacy and adverse events data of SEP-4199 (subsequently named amisulpiride) were investigated in a phase 2 trial on the use of the drug in bipolar depression. A difference of MADRS scores showed a tendency (without a significant difference) towards improvement versus the placebo for amisulpride 200mg dose (Loebel et al., 2020). Recently, amisulpiride was shown to be useful in treating bipolar depression in a randomised, double-blind, placebo-controlled study (El-Mallakh et al., 2020; Loebel et al., 2022).

2.3.5 The 5-HT_7 agonists

There are contradictory findings from studies of 5-HT_7 agonists. 5-HT_7 receptor agonists have been found to affect mood and sleep function. One study found that the 5-HT_7 receptor agonist AS-19 worsened depressive symptoms in a rodent model (Li et al., 2013). At the same time, however, Adriani and colleagues found that two 5-HT_7 agonists, LP-211 and LP-378, showed more inhibitory effects in a variety of tasks, including black and white box tests, dark and light tests, and novelty seeking tests. Although the mice spent more time in the light and white boxes, a possible effect of curiosity on the results cannot be ruled out (Adriani et al., 2012). Researchers also

treated mice with agonists would spend much time in black-white box and dark-light transfer test, showing that it might have anxiolytic effects (Canale et al., 2014). Further studies will require the use of agonists, which will help to further clarify the mechanism.

2.4 Discussion

2.4.1 Administration dosage and duration

Both 5-HT$_7$ agonists and antagonists may exhibit anti-depressant and anxiolytic efficacy, and dosage and treatment duration may influence the effects. In most of the animal studies, rodent models were used to evaluate if the intervention changes animals' depressive-like or anxious-like behaviours. However, researchers also argue whether animal models are reliable, or whether they could be translated into human illness. Take FST for example, researchers saw it as an screening tool, but some parameters (e.g., depth of water, water temperatures, time between treatment, etc) have to be controlled to make the models more reliable and valid (Petit-Demouliere et al., 2005). It is important to note that animals' abnormal behaviours may not directly mirror specific features of depressive disorders in humans. Hence, researchers should be caution when interpreting results from animal models and avoid from drawing overly ambitious conclusions from them (Stanford, 2020).

In animal test, it has been shown that both 5-HT$_7$ agonists and antagonists exhibited antidepressant (Bonaventure et al., 2012b; Bonaventure et al., 2007; Canale et al., 2015; Canale, Kurczab, Partyka, SataAa, et al., 2016; Guilloux et al., 2013; Hedlund et al., 2005; Hedlund & Sutcliffe, 2007; Maxwell et al., 2019; Mnie-Filali et al., 2011b; Pytka et al., 2015a; Sarkisyan et al., 2010; Wesolowska, Nikiforuk, & Stachowicz, 2006b; Wesolowska, Nikiforuk, Stachowicz, et al., 2006b; Wesolowska et al., 2007; Zhang et

al., 2015) and anxiolytic (Guscott et al., 2005; Hedlund & Sutcliffe, 2007; Volk et al., 2008b; Volk et al., 2011; Wesolowska, Nikiforuk, & Stachowicz, 2006b; Wesolowska, Nikiforuk, Stachowicz, et al., 2006b) or having both (Latacz, Lubelska, et al., 2018; Pytka et al., 2015b; Pytka, Socala, et al., 2017; Zajdel et al., 2012b) signals of efficacy. There are also indications that compounds with 5-HT_7 receptor activity may be beneficial in older patients with recurrent Major Depressive Disorder (MDD) (Katona et al., 2012). A few studies showed no antidepressant or antianxiety efficacy (Gu et al., 2019; Maxwell et al., 2019), the dosage and treatment duration should be considered. Researchers also found the treatment duration and the assessed measures would influence the results (Baldwin, 2011; Mahableshwarkar et al., 2014). In the contradictory results of dosing vortioxetine for General Anxiety Disorder (GAD), duration of 26-54 weeks was much longer than 8 weeks, and they showed a different result, which also indicated the dosing duration might influence the effects (Baldwin & Dragheim, 2011; Rothschild et al., 2011).

2.4.2 Anti-psychotic drugs and the 5-HT_7 receptors

Some antipsychotic drugs with high affinity to the 5-HT_7 receptors, including lurasidone, amisulpiride, and asenapine, have antidepressant properties (Abbas et al., 2009; Cates et al., 2013; Delcourte et al., 2017). Considering human studies, similar effects were discovered. Vortioxetine treated MDD with proper dosage and treatment duration (Baldwin et al., 2012); JNJ-18038683 was proven to influence animal and human beings' rapid eye movement sleep and in major depressive disorder (Bonaventure et al., 2012a). Antipsychotics with high affinity for the 5-HT_7 receptor have similar effects (Clayton et al., 2018).

Most of the compounds have multiple affinities to other receptors, so the specific effects of 5-HT_7 receptors are unclear. If compounds with highly specific 5-HT_7 affinity were to be tested, research might then gain a clear understanding. Furthermore, some mental symptom domains (e.g., post-traumatic stress disorder (PTSD), insomnia, cognitive function impairment) may interact with mood disorders, however, it is not fully understood whether 5-HT_7 agents are useful to treat these disorders. Therefore, further investigation is required to clarify the relationship between 5-HT_7 agents and these related aspects of mood disorders.

2.4.3 Unclear relationship between 5-HT_7 and mania

There is limited knowledge about bipolar mania and 5-HT_7 receptors. Currently, there are few mania-related experiments identifying whether the 5-HT_7 receptor is involved with mania. Administrating lurasidone in the dosage range of 20mg-120mg significantly improved depressive symptoms in patients with bipolar 1 depression (Loebel et al., 2014). There was a statistically significant effect from the first week of vortioxetine treatment of bipolar depression (Tomassini et al., 2017) and it showed no associated increase in manic symptoms. Improvement showed when administrating the amisulpride for bipolar depression (Loebel et al., 2020 Tsai, Ozol-Godfrey, Fava & Hopkins, 2014). The efficacy of monotherapy with asenapine was significantly higher than that of placebo for Young Mania Rating Scale scores (YMRS) (Young et al., 1978; Tohen et al., 2000). However, only one open-label study tested the relations between 5-HT_7 and manic symptoms, and asenapine has a unique profile of receptor affinities and activities (Volz, 2011). It is an antagonist with strong affinity for several serotonergic (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6 und 5-HT_7), adrenergic (alpha2) and dopaminergic (e.g., D3 und D4) receptors, but has no affinity for muscarinergic

receptors; it associated with effects on several receptors. The relationship of 5-HT_7 with mania is still unclear and needs further investigation.

2.4.4 Limitations and future directions

Although we have investigated 5-HT_7 agents and mood disorders' relationships, there are some limitations in this review.

Firstly, most compounds have affinities not only with 5-HT_7 receptors but also with other 5-HT, dopamine or noradrenaline receptors. For example, amisulpiride, has affinities to 5-HT_{1A}, 5-HT_2, and Dopamine D2 receptors. Several new compounds have affinity to multiple receptors as well. Further investigation should be conducted to clarify the specific receptor locus for the effects of these medicines. Thus, it is recommended that future studies be conducted using selective 5-HT_7 compounds to further investigate the effects and mechanisms associated with this receptor.

In addition, 5-HT_7 and 5-HT_{1A} have overlapping expression in some brain areas. 5-HT_7 receptors are present in the amygdala, hippocampus, thalamus, and hypothalamus (Hedlund & Sutcliffe, 2004), and 5-HT_{1A} receptors are highly expressed in the entorhinal cortex, frontal cortex, and lateral septum, and moderately expressed in the prefrontal cortex, hippocampus, and amygdala (Beck et al., 1992; Hamon et al., 1990; Pompeiano et al., 1992). These brain areas, specifically the amygdala and hippocampus, strongly associated with mood and anxiety control: in vivo research indicated that the antidepressant and anxiolytic effects of SSRI treatment are likely facilitated by hippocampal 5-HT_{1A}/Gi2/GSK3b signalling. Similarly, SSRI-triggered GSK3b phosphorylation/inactivation in the prefrontal cortex and hippocampus is influenced by the activation of 5-HT_{1A} receptors (Albert & Vahid-Ansari, 2019; Li et al., 2004; Polter

et al., 2012). In the discussion of the following chapters, our aim is to explore the impacts of JNJ-18038683, a selective compound with high affinities to 5-HT_7 receptors, yet with affinities for 5-HT_{1A} and 5-HT_6 receptors as well. Given the shared distribution of 5-HT_7 and 5-HT_{1A} receptors in brain areas, a conservative interpretation should be preferable.

The second limitation is that other related phenomena, such as cognitive dysfunction (e.g., learning and memory) (Browning et al., 2014), circadian rhythm disturbance (Ehlen et al., 2001; Lovenberg et al., 1993; Pouzet et al., 2002), trauma (Roberts et al., 2004) and neurodegenerative disorders (e.g., Parkinson's) (Du et al., 2018; Han et al., 2016), are not included in this review. However, 5-HT_7 receptors are associated with these. The hippocampus is associated with learning and memory, and 5-HT_7 receptors are highly distributed in this area. In cognition-focused studies, both genetic and pharmacological inactivation are tested in different environments; their corresponding results are shown in several conditions, such as behavioural tests and dosing tests (Roberts & Hedlund, 2012). 5-HT_7 might be related to contextual hippocampus-dependent learning and emotional memory (Blattner et al., 2019). Trauma is strong associated with emotion (especially fear or anger) and memory, which may imply the 5-HT_7 might related to the effects of trauma (Ohmura et al., 2016). Since 5-HT_7 activation can also enhance the emotional memory (Eriksson et al., 2012), and was critical for emotional learning and memorising in animals (Takeda et al., 2017), it could be summarised that 5-HT_7 may be a target for the treatment of mental disorder involving fear memory (Ohmura et al., 2016). Also, sleep plays an important role in emotion: research showed that a lack of sleep can heighten emotional arousal and make people more sensitive to stress (Vandekerckhove & Wang, 2018). When testing 5-HT_7

agonists and antagonists, researchers discovered that sleepiness and wakefulness would be influenced (Lovenberg et al., 1993). Agonists, which increase the affinity of the receptors, induce phase-shift in sleepiness; antagonists, which block the receptor and reduce the affinity of the receptors, attenuate phase delays in sleepiness. Thus, the 5-HT_7 receptor is known for being associated with several functions, however, in order to elucidate the relation between the 5-HT_7 and mood disorders, this review only focused on specific experiments related to that topic directly.

2.5 Conclusion

5-HT_7 receptors are strongly associated with anxiety and depression. In terms of anxiety, 5-HT_7 antagonists given to rodents in an experimental setting showed anxiolytic effects resulting in a reduction of anxiety-like behaviour (Hedlund & Sutcliffe, 2007). In terms of depression, the use of 5-HT_7 antagonists in animal models has shown a reduction in immobility in tests such as the TST and the FST, suggesting a potential antidepressant effect. Furthermore, when used in combination with other drugs, 5-HT_7 antagonists showed antidepressant effects. However, the complex interactions between 5-HT_7 receptors and other 5-HT receptors are not fully understood. While some aspects of depression are associated with the 5-HT_7 receptor, its relationship with mania remains unclear. Further studies focusing on mania-related investigations are needed to investigate the specific function of the 5-HT_7 receptor here. Such results may have practical and clinical implications that may ultimately benefit patients with mood disorders. It is imperative to determine the specific effects of different drugs to ensure evidence-based treatment. In addition, future studies should

aim to employ highly selective 5-HT_7 compounds in animal and human studies to determine the specific effects of 5-HT_7 receptors.

References

Abbas, A. I., Hedlund, P. B., Huang, X.-P., Tran, T. B., Meltzer, H. Y., & Roth, B. L. (2009). Amisulpride is a potent 5-HT7 antagonist: relevance for antidepressant actions in vivo. *Psychopharmacology*, *205*(1), 119-128. https://doi.org/https://dx.doi.org/10.1007/s00213-009-1521-8

Adriani, W., Travaglini, D., Lacivita, E., Saso, L., Leopoldo, M., & Laviola, G. (2012). Modulatory effects of two novel agonists for serotonin receptor 7 on emotion, motivation and circadian rhythm profiles in mice. *Neuropharmacology*. https://doi.org/10.1016/j.neuropharm.2011.09.012

Albert, P. R., & Vahid-Ansari, F. (2019). The 5-HT1A receptor: Signaling to behavior. *Biochimie*, *161*, 34-45. https://doi.org/10.1016/j.biochi.2018.10.015

Alvarez, E., Perez, V., Dragheim, M., Loft, H., & Artigas, F. (2012). A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *The international journal of neuropsychopharmacology*, *15*(5), 589-600. https://doi.org/https://dx.doi.org/10.1017/S1461145711001027

APA. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. https://doi.org/http://dx.doi.org/10.1176/appi.books.9780890425596

Armijo-Olivo, S., Stiles, C. R., Hagen, N. A., Biondo, P. D., & Cummings, G. G. (2012). Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. *Journal of Evaluation in Clinical Practice*, *18*(1), 12-18. https://doi.org/10.1111/j.1365-2753.2010.01516.x

Balcer, O. M., Seager, M. A., Gleason, S. D., Li, X., Rasmussen, K., Maxwell, J. K., Nomikos, G., Degroot, A., & Witkin, J. M. (2019). Evaluation of 5-HT(7) receptor antagonism for the treatment of anxiety, depression, and schizophrenia through the use of receptor-deficient mice. *Behavioural Brain Research*, *360*, 270-278. https://doi.org/10.1016/j.bbr.2018.12.019

Baldwin, D., Loft, H., & Dragheim, M. . (2011). A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in MDD treatment. *European Neuropsychopharmacology*, *21*(SUPPL. 3), S390. https://doi.org/http://dx.doi.org/10.1016/S0924-977X%2811%2970627-7 (24th Congress of the European College of Neuropsychopharmacology, ECNP 2011. Paris France.

(var.pagings).)

Baldwin, D. L. H., & Dragheim, M. (2011). A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in MDD treatment. *European Neuropsychopharmacology*, *21*(SUPPL. 3), S390. https://doi.org/10.1016/S0924-977X%2811%2970627-7 (24th Congress of the European College of Neuropsychopharmacology, ECNP 2011. Paris France. (var.pagings).)

Baldwin, D. S., Hansen, T., & Florea, I. (2012). Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. *Curr Med Res Opin*, *28*(10), 1717-1724. https://doi.org/10.1185/03007995.2012.725035

Bard, J. A., Zgombick, J., Adham, N., Vaysse, P., Branchek, T. A., & Weinshank, R. L. (1993). Cloning of a novel human serotonin receptor (5-HT7) positively linked to adenylate cyclase. *The Journal of biological chemistry*, *268*(31), 23422-23426. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=8226867

Batinic, B., Djokic, V., & Ivkovic, M. (2021). Assessment of Cognitive Function, Social Disability and Basic Life Skills in Euthymic Patients with Bipolar Disorder. *Psychiatr Danub*, *33*(3), 320-327. https://doi.org/10.24869/psyd.2021.320

Beck, S. G., Choi, K. C., & List, T. J. (1992). Comparison of 5-hydroxytryptamine1A-mediated hyperpolarization in CA1 and CA3 hippocampal pyramidal cells. *The Journal of Pharmacology and Experimental Therapeutics*, *263*(1), 350-359.

Bijata, M., Bączyńska, E., Müller, F. E., Bijata, K., Masternak, J., Krzystyniak, A., Szewczyk, B., Siwiec, M., Antoniuk, S., Roszkowska, M., Figiel, I., Magnowska, M., Olszyński, K. H., Wardak, A. D., Hogendorf, A., Ruszczycki, B., Gorinski, N., Labus, J., Stępień, T., . . . Wlodarczyk, J. (2022). Activation of the 5-HT7 receptor and MMP-9 signaling module in the hippocampal CA1 region is necessary for the development of depressive-like behavior. *Cell Rep*, *38*(11), 110532. https://doi.org/10.1016/j.celrep.2022.110532

Blattner, K. M., Canney, D. J., Pippin, D. A., & Blass, B. E. (2019). Pharmacology and Therapeutic Potential of the 5-HT7 Receptor. *ACS chemical neuroscience*, *10*(1), 89-119. https://doi.org/https://dx.doi.org/10.1021/acschemneuro.8b00283

Bonaventure, P., Dugovic, C., Kramer, M., De Boer, P., Singh, J., Wilson, S., Bertelsen, K., Di, J., Shelton, J., Aluisio, L., Dvorak, L., Fraser, I., Lord, B., Nepomuceno, D., Ahnaou, A., Drinkenburg, W., Chai, W., Dvorak, C., Sands, S., . . . Lovenberg, T. W. (2012a). Translational evaluation of JNJ-18038683, a 5-hydroxytryptamine type 7 receptor

antagonist, on rapid eye movement sleep and in major depressive disorder. *Journal of Pharmacology and Experimental Therapeutics*, *342*(2), 429-440. https://doi.org/10.1124/jpet.112.193995

Bonaventure, P., Dugovic, C., Kramer, M., De Boer, P., Singh, J., Wilson, S., Bertelsen, K., Di, J., Shelton, J., Aluisio, L., Dvorak, L., Fraser, I., Lord, B., Nepomuceno, D., Ahnaou, A., Drinkenburg, W., Chai, W., Dvorak, C., Sands, S., . . . Lovenberg, T. W. (2012b). Translational evaluation of JNJ-18038683, a 5-hydroxytryptamine type 7 receptor antagonist, on rapid eye movement sleep and in major depressive disorder [Neuropsychology & Neurology 2520]. *The Journal of pharmacology and experimental therapeutics*, *342*(2), 429-440. https://doi.org/http://dx.doi.org/10.1124/jpet.112.193995 (Pharmacological Reviews)

Bonaventure, P., Kelly, L., Aluisio, L., Shelton, J., Lord, B., Galici, R., Miller, K., Atack, J., Lovenberg, T. W., & Dugovic, C. (2007). Selective blockade of 5-hydroxytryptamine (5-HT)7 receptors enhances 5-HT transmission, antidepressant-like behavior, and rapid eye movement sleep suppression induced by citalopram in rodents. *The Journal of pharmacology and experimental therapeutics*, *321*(2), 690-698. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=17314195

Browning, M., Smith, J., Conen, S., Smallman, R., Buchbjerg, J., Larsen, K. G., Olsen, C. K., Christensen, S. R., Dawson, G., Deakin, B., Morris, R., Harmer, C., & Goodwin, G. (2014). Vortioxetine reduces bold signal during performance of the N-Back task in subjects remitted from depression and healthy control participants. *Neuropsychopharmacology*, *39*(SUPPL. 1), S480. https://doi.org/10.1038/npp.2014.282 (53rd Annual Meeting of the American College of Neuropsychopharmacology, ACNP 2014. Phoenix, AZ United States. (var.pagings).)

Canale, V., Guzik, P., Kurczab, R., Verdie, P., Satala, G., Kubica, B., Pawlowski, M., Martinez, J., Subra, G., Bojarski, A. J., & Zajdel, P. (2014). Solid-supported synthesis, molecular modeling, and biological activity of long-chain arylpiperazine derivatives with cyclic amino acid amide fragments as 5-HT(7) and 5-HT(1A) receptor ligands. *European journal of medicinal chemistry*, *78*, 10-22. https://doi.org/https://dx.doi.org/10.1016/j.ejmech.2014.03.005

Canale, V., Kurczab, R., Partyka, A., Sataa, G., Ledna, T., Jastrzebska-Wiesek, M., Wesoowska, A., Bojarski, A. J., & Zajdel, P. (2016). Towards new 5-HT7 antagonists among arylsulfonamide derivatives of (aryloxy)ethyl-alkyl amines: Multiobjective

based design, synthesis, and antidepressant and anxiolytic properties. *European Journal of Medicinal Chemistry*, *108*, 334-346. https://doi.org/10.1016/j.ejmech.2015.11.040

Canale, V., Kurczab, R., Partyka, A., SataAa, G., Witek, J., Jastrzabska-Wiasek, M., Pawaowski, M., Bojarski, A. J., WesoAowska, A., & Zajdel, P. (2015). Towards novel 5-HT7 versus 5-HT1A receptor ligands among LCAPs with cyclic amino acid amide fragments: Design, synthesis, and antidepressant properties. Part II. *European Journal of Medicinal Chemistry*, *92*, 202-211. https://doi.org/10.1016/j.ejmech.2014.12.041

Canale, V., Kurczab, R., Partyka, A., SataAa, G., Witek, J., Jastrzabska-Wiasek, M., Pawaowski, M., Bojarski, A. J., WesoAowska, A., & Zajdel, P. (2016). Towards novel 5-HT7 versus 5-HT1A receptor ligands among LCAPs with cyclic amino acid amide fragments: Design, synthesis, and antidepressant properties. Part II. *European Journal of Medicinal Chemistry*, *92*, 202-211. https://doi.org/http://dx.doi.org/10.1016/j.ejmech.2014.12.041

Canale, V., Kurczab, R., Partyka, A., Satala, G., Lenda, T., Jastrzebska-Wiesek, M., Wesolowska, A., Bojarski, A. J., & Zajdel, P. (2016). Towards new 5-HT7 antagonists among arylsulfonamide derivatives of (aryloxy)ethyl-alkyl amines: Multiobjective based design, synthesis, and antidepressant and anxiolytic properties. *European journal of medicinal chemistry*, *108*, 334-346. https://doi.org/https://dx.doi.org/10.1016/j.ejmech.2015.11.040

Canale, V., Kurczab, R., Partyka, A., Satala, G., Sloczynska, K., Kos, T., Jastrzebska-Wiesek, M., Siwek, A., Pekala, E., Bojarski, A. J., Wesolowska, A., Popik, P., & Zajdel, P. (2016). N-Alkylated arylsulfonamides of (aryloxy)ethyl piperidines: 5-HT(7) receptor selectivity versus multireceptor profile. *Bioorganic & medicinal chemistry*, *24*(2), 130-139. https://doi.org/https://dx.doi.org/10.1016/j.bmc.2015.11.041

Canese, R., Zoratto, F., Altabella, L., Porcari, P., Mercurio, L., De Pasquale, F., Butti, E., Martino, G., Lacivita, E., Leopoldo, M., Laviola, G., & Adriani, W. (2015). Persistent modification of forebrain networks and metabolism in rats following adolescent exposure to a 5-HT7 receptor agonist. *Psychopharmacology*, *232*(1), 75-89. https://doi.org/10.1007/s00213-014-3639-6

Cates, L. N., Roberts, A. J., Huitron-Resendiz, S., & Hedlund, P. B. (2013). Effects of lurasidone in behavioral models of depression. Role of the 5-HT7 receptor subtype. *Neuropharmacology*, *70*, 211-217. https://doi.org/https://dx.doi.org/10.1016/j.neuropharm.2013.01.023

Clayton, A., Tsai, J., Mao, Y., & Pikalov, A. L., A. . (2018). Effect of Lurasidone on Sexual Function in Major Depressive Disorder Patients With Subthreshold Hypomanic Symptoms (Mixed Features): Results From a Placebo-Controlled. *Journal of Clinical Psychiatry*, *79*(5). https://doi.org/doi: 10.4088/JCP.18m12132

Correll, C. U., Detraux, J., De Lepeleire, J., & De Hert, M. (2015). Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry*, *14*(2), 119-136. https://doi.org/10.1002/wps.20204

Das Gupta, R., & Guest, J. F. (2002). Annual cost of bipolar disorder to UK society. *Br J Psychiatry*, *180*, 227-233. https://doi.org/10.1192/bjp.180.3.227

Delcourte, S., Abrial, E., Etievant, A., Rovera, R., Arnt, J., Didriksen, M., & Haddjeri, N. (2017). Asenapine modulates mood-related behaviors and 5-HT1A/7 receptors-mediated neurotransmission. *CNS neuroscience & therapeutics*, *23*(6), 518-525. https://doi.org/10.1111/cns.12698

Dragheim, M., Loft, H., Florea, I., & Boulenger, J. P. (2011). A double-blind, randomised, placebo-controlled, relapse-prevention study with Lu AA21004 in patients with major depressive disorder. *European Neuropsychopharmacology*, *21*(SUPPL. 3), S396-S397. https://doi.org/10.1016/S0924-977X%2811%2970638-1 (24th Congress of the European College of Neuropsychopharmacology, ECNP 2011. Paris France. (var.pagings).)

Du, C. X., Guo, Y., Zhang, Q. J., Zhang, J., Lv, S. X., & Liu, J. (2018). Involvement of prelimbic 5-HT7 receptors in the regulation of anxiety-like behaviors in hemiparkinsonian rats. *Neurological research*, *40*(10), 847-855. https://doi.org/https://dx.doi.org/10.1080/01616412.2018.1493962

Ehlen, J. C., Grossman, G. H., & Glass, J. D. (2001). In vivo resetting of the hamster circadian clock by 5-HT7 receptors in the suprachiasmatic nucleus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *21*(14), 5351-5357. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11438611

El-Mallakh, R. S., Nuss, S., Gao, D., Gao, Y., Ahmad, S. C., Schrodt, C., & Adler, C. (2020). Asenapine in the Treatment of Bipolar Depression. *Psychopharmacology bulletin*, *50*(1), 8-18. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexb&NEWS=N&AN=631350899

Eriksson, T. M., Holst, S., Stan, T. L., Hager, T., Sjogren, B., Ogren, S. O., Svenningsson, P., & Stiedl, O. (2012). 5-HT1A and 5-HT7 receptor crosstalk in the regulation of emotional memory: implications for effects of selective serotonin reuptake inhibitors. *Neuropharmacology*, *63*(6), 1150-1160. https://doi.org/https://dx.doi.org/10.1016/j.neuropharm.2012.06.061

Fagiolini, A., Forgione, R., Maccari, M., Cuomo, A., Morana, B., Dell'Osso, M. C., Pellegrini, F., & Rossi, A. (2013). Prevalence, chronicity, burden and borders of bipolar disorder. *J Affect Disord*, *148*(2-3), 161-169. https://doi.org/10.1016/j.jad.2013.02.001

Ferguson, J. M. (2001). SSRI Antidepressant Medications: Adverse Effects and Tolerability. *Primary care companion to the Journal of clinical psychiatry*, *3*(1), 22-27. https://doi.org/doi:10.4088/pcc.v03n0105

Goethe, J. W., Woolley, S. B., Cardoni, A. A., Woznicki, B. A., & Piez, D. A. (2007). Selective serotonin reuptake inhibitor discontinuation: side effects and other factors that influence medication adherence. *Journal of clinical psychopharmacology*, *27*(5), 451–458. https://doi.org/10.1097/jcp.0b013e31815152a5

Goodwin, G. M., Price, J., De Bodinat, C., & Laredo, J. (2017). Emotional blunting with antidepressant treatments: A survey among depressed patients. *Journal of affective disorders*, *221*, 31–35. https://doi.org/10.1016/j.jad.2017.05.048

Goswami, U., Sharma, A., Khastigir, U., Ferrier, I. N., Young, A. H., Gallagher, P., Thompson, J. M., & Moore, P. B. (2006). Neuropsychological dysfunction, soft neurological signs and social disability in euthymic patients with bipolar disorder. *Br J Psychiatry*, *188*, 366-373. https://doi.org/10.1192/bjp.188.4.366

Gu, Z.-S., Wang, W.-T., Qian, H., Zhou, A.-N., Sun, H.-B., Zhang, Q.-W., & Li, J.-Q. (2019). Synthesis and antidepressant effect of novel aralkyl piperazine and piperidine derivatives targeting SSRI/5-HT1A/5-HT7. *Bioorganic & Medicinal Chemistry Letters*, *29*(23), 126703. https://doi.org/10.1016/j.bmcl.2019.126703

Guilloux, J.-P., Mendez-David, I., Pehrson, A., Guiard, B. P., Reperant, C., Orvoen, S., Gardier, A. M., Hen, R., Ebert, B., Miller, S., Sanchez, C., & David, D. J. (2013). Antidepressant and anxiolytic potential of the multimodal antidepressant vortioxetine (Lu AA21004) assessed by behavioural and neurogenesis outcomes in mice. *Neuropharmacology*, *73*, 147-159. https://doi.org/10.1016/j.neuropharm.2013.05.014

Guscott, M., Bristow, L. J., Hadingham, K., Rosahl, T. W., Beer, M. S., Stanton, J. A., Bromidge, F., Owens, A. P., Huscroft, I., Myers, J., Rupniak, N. M., Patel, S., Whiting, P. J., Hutson, P. H., Fone, K. C., Biello, S. M., Kulagowski, J. J., & McAllister, G.

(2005). Genetic knockout and pharmacological blockade studies of the 5-HT7 receptor suggest therapeutic potential in depression. *Neuropharmacology*, *48*(4), 492-502. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=15755477

Hamon, M., Gozlan, H., el Mestikawy, S., Emerit, M. B., Bolaños, F., & Schechter, L. (1990). The central 5-HT1A receptors: pharmacological, biochemical, functional, and regulatory properties. *Ann N Y Acad Sci*, *600*, 114-129; discussion 129-131. https://doi.org/10.1111/j.1749-6632.1990.tb16877.x

Han, L. N., Zhang, L., Sun, Y. N., Du, C. X., Zhang, Y. M., Wang, T., Zhang, J., & Liu, J. (2016). Serotonin7 receptors in the lateral habenular nucleus regulate depressive-like behaviors in the hemiparkinsonian rats. *Brain research*, *1644*, 79-87. https://doi.org/https://dx.doi.org/10.1016/j.brainres.2016.05.016

Hedlund, P. B., Huitron-Resendiz, S., Henriksen, S. J., & Sutcliffe, J. G. (2005). 5-HT7 receptor inhibition and inactivation induce antidepressantlike behavior and sleep pattern. *Biological Psychiatry*, *58*(10), 831-837. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=16018977

Hedlund, P. B., & Sutcliffe, J. G. (2004). Functional, molecular and pharmacological advances in 5-HT7 receptor research. *Trends Pharmacol Sci*, *25*(9), 481-486. https://doi.org/10.1016/j.tips.2004.07.002

Hedlund, P. B., & Sutcliffe, J. G. (2007). The 5-HT7 receptor influences stereotypic behavior in a model of obsessive-compulsive disorder. *Neuroscience Letters*, *414*(3), 247-251. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=17267119

Henigsberg, N., Mahableshwarkar, A., Jacobsen, P., Chen, Y., & Thase, M. E. (2011). Efficacy and tolerability of multiple doses of LU AA21004 in an 8-week trial of adults with major depressive disorder. *European Neuropsychopharmacology*, *21*(SUPPL. 3), S393. https://doi.org/10.1016/S0924-977X%2811%2970632-0 (24th Congress of the European College of Neuropsychopharmacology, ECNP 2011. Paris France. (var.pagings).)

Horisawa, T., Nishikawa, H., Toma, S., Ikeda, A., Horiguchi, M., Ono, M., Ishiyama, T., & Taiji, M. (2013). The role of 5-HT7 receptor antagonism in the amelioration of MK-801-induced learning and memory deficits by the novel atypical antipsychotic drug

lurasidone. *Behavioural Brain Research*, *244*, 66-69. https://doi.org/10.1016/j.bbr.2013.01.026

Katona, C., Hansen, T., & Olsen, C. K. (2012). A randomised, double-blind, placebocontrolled, active-referenced study of the multimodal antidepressant Lu AA21004 in the treatment of elderly depressed patients. *European Neuropsychopharmacology*, *22*(SUPPL. 2), S258-S259. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=70909418 (25th European College of Neuropsychopharmacology, ECNP Congress. Vienna Australia. (var.pagings).)

Kennedy, S., Grouin, J., Cadour, S., Robert, V., & Picarel-Blanchot, F. (2016). Relative short-term efficacy and acceptability of agomelatine versus vortioxetine in adult patients suffering from major depressive disorder. *European Neuropsychopharmacology*, *26*(Supplement 2), S457-S458. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed17&NEWS=N&AN=614139003 (29th European College of Neuropsychopharmacology Congress, ECNP 2016. Austria.)

Latacz, G., Hogendorf, A. S., Hogendorf, A., Lubelska, A., Wieronska, J. M., Wozniak, M., Cieslik, P., Kiec-Kononowicz, K., Handzlik, J., & Bojarski, A. J. (2018). Search for a 5-CT alternative. In vitro and in vivo evaluation of novel pharmacological tools: 3-(1-alkyl-1H-imidazol-5-yl)-1H-indole-5-carboxamides, low-basicity 5-HT7 receptor agonists. *MedChemComm*, *9*(11), 1882-1890. https://doi.org/10.1039/c8md00313k

Latacz, G., Lubelska, A., Jastrzebska-Wiesek, M., Partyka, A., Kucwaj-Brysz, K., Wesolowska, A., Kiec-Kononowicz, K., & Handzlik, J. (2018). MF-8, a novel promising arylpiperazine-hydantoin based 5-HT7 receptor antagonist: In vitro drug-likeness studies and in vivo pharmacological evaluation. *Bioorganic and Medicinal Chemistry Letters*, *28*(5), 878-883. https://doi.org/10.1016/j.bmcl.2018.02.003

Li, X., Zhu, W., Roh, M. S., Friedman, A. B., Rosborough, K., & Jope, R. S. (2004). In vivo regulation of glycogen synthase kinase-3beta (GSK3beta) by serotonergic activity in mouse brain. *Neuropsychopharmacology*, *29*(8), 1426-1431. https://doi.org/10.1038/sj.npp.1300439

Li, Y., Raaby, K. F., Sánchez, C., & Gulinello, M. (2013). Serotonergic receptor mechanisms underlying antidepressant-like action in the progesterone withdrawal model of hormonally induced depression in rats. *Behavioural Brain Research*, *256*, 520-528. https://doi.org/10.1016/j.bbr.2013.09.002

Loebel, A., Cucchiaro, J., Silva, R., Kroger, H., Hsu, J., Sarma, K., & Sachs, G. (2014). Lurasidone Monotherapy in the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study. *American Journal of Psychiatry*, *171*(2), 160-168. https://doi.org/doi: 10.1176/appi.ajp.2013.13070984

Loebel, A., Koblan, K., Kent, J., Tsai, J., Ozol-Godfrey, A., Fava, M., & Hopkins, S. (2020). A randomized, double-blind, placebo-controlled study of SEP-4199 for the treatment of patients with bipolar depression. *Neuropsychopharmacology*, *45*, 95-96. https://doi.org/http://dx.doi.org/10.1038/s41386-020-00890-7 (59th Annual Meeting of the American College of Neuropsychopharmacology, ACNP 2020.)

Loebel, A., Koblan, K. S., Tsai, J., Deng, L., Fava, M., Kent, J., & Hopkins, S. C. (2022). A Randomized, Double-blind, Placebo-controlled Proof-of-Concept Trial to Evaluate the Efficacy and Safety of Non-racemic Amisulpride (SEP-4199) for the Treatment of Bipolar I Depression. *J Affect Disord*, *296*, 549-558. https://doi.org/10.1016/j.jad.2021.09.109

Lovenberg, T. W., Baron, B. M., de Lecea, L., Miller, J. D., Prosser, R. A., Rea, M. A., Foye, P. E., Racke, M., Slone, A. L., & Siegel, B. W. (1993). A novel adenylyl cyclase-activating serotonin receptor (5-HT7) implicated in the regulation of mammalian circadian rhythms. *Neuron*, *11*(3), 449-458. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=8398139

Mahableshwarkar, A., Jacobsen, P., Chen, Y., Serenko, M., & Palo, W. (2014). The Safety and tolerability profile of vortioxetine in the treatment of patients with major depressive disorder aged 65 years and older. *American Journal of Geriatric Psychiatry*, *22*(3 SUPPL. 1), S143-S144. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed15&NEWS=N&AN=71442072 (2014 American Association for Geriatric Psychiatry, AAGP Annual Meeting. Orlando, FL United States. (var.pagings).)

Martin-Cora, F. J., & Pazos, A. (2004). Autoradiographic distribution of 5-HT7 receptors in the human brain using [3H]mesulergine: Comparison to other mammalian species. *British Journal of Pharmacology*, *141*(1), 92-104. https://doi.org/10.1038/sj.bjp.0705576

Maxwell, J., Gleason, S. D., Falcone, J., Svensson, K., Balcer, O. M., Li, X., & Witkin, J. M. (2019). Effects of 5-HT7 receptor antagonists on behaviors of mice that detect drugs

used in the treatment of anxiety, depression, or schizophrenia. *Behavioural brain research*, *359*, 467-473. https://doi.org/https://dx.doi.org/10.1016/j.bbr.2018.11.019

McIntyre, R. S., Lophaven, S., & Olsen, C. K. (2013). Randomized, double-blind, placebo-controlled study of the efficacy of vortioxetine on cognitive dysfunction in adult patients with major depressive disorder (MDD). *Neuropsychopharmacology*, *38*(SUPPL. 2), S380-S381. https://doi.org/10.1038/npp.2013.280 (52nd Annual Meeting of the American College of Neuropsychopharmacology, ACNP 2013. Hollywood, FL United States. (var.pagings).)

Medina, R. A., Vazquez-Villa, H., Gomez-Tamayo, J. C., Benhamu, B., Martin-Fontecha, M., de la Fuente, T., Caltabiano, G., Hedlund, P. B., Pardo, L., & Lopez-Rodriguez, M. L. (2014). The extracellular entrance provides selectivity to serotonin 5-HT7 receptor antagonists with antidepressant-like behavior in vivo. *Journal of medicinal chemistry*, *57*(15), 6879-6884. https://doi.org/10.1021/jm500880c

Mnie-Filali, O., Faure, C., Lambas-Sen as, L., El Mansari, M., Belblidia, H., Gondard, E., Etievant, A., Scarna, H., Didier, A., Berod, A., Blier, P., & Haddjeri, N. (2011a). Pharmacological blockade of 5-HT7 receptors as a putative fast acting antidepressant strategy [Psychopharmacology 2580]. *Neuropsychopharmacology*, *36*(6), 1275-1288. https://doi.org/http://dx.doi.org/10.1038/npp.2011.13

Mnie-Filali, O., Faure, C., Lambas-Sen as, L., El Mansari, M., Belblidia, H., Gondard, E., Etievant, A., Scarna, H., Didier, A., Berod, A., Blier, P., & Haddjeri, N. (2011b). Pharmacological blockade of 5-HT 7 receptors as a putative fast acting antidepressant strategy. *Neuropsychopharmacology*, *36*(6), 1275-1288. https://doi.org/http://dx.doi.org/10.1038/npp.2011.13

Ohmura, Y., Yoshida, T., Konno, K., Minami, M., Watanabe, M., & Yoshioka, M. (2016). Serotonin 5-HT7 receptor in the ventral hippocampus modulates the retrieval of fear memory and stress-induced efecation. *International Journal of Neuropsychopharmacology*, *19*(6), 1-12. https://doi.org/http://dx.doi.org/10.1093/ijnp/pyv131

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews*, *5*(1), 210. https://doi.org/10.1186/s13643-016-0384-4

Petit-Demouliere, B., Chenu, F., & Bourin, M. (2005). Forced swimming test in mice: a review of antidepressant activity. *Psychopharmacology (Berl)*, *177*(3), 245-255. https://doi.org/10.1007/s00213-004-2048-7

Pithadia, A. B., & Jain, S. M. (2009). 5-Hydroxytryptamine Receptor Subtypes and their Modulators with Therapeutic Potentials. *J Clin Med Res*, *1*(2), 72-80. https://doi.org/10.4021/jocmr2009.05.1237

Polter, A. M., Yang, S., Jope, R. S., & Li, X. (2012). Functional significance of glycogen synthase kinase-3 regulation by serotonin. *Cell Signal*, *24*(1), 265-271. https://doi.org/10.1016/j.cellsig.2011.09.009

Pompeiano, M., Palacios, J. M., & Mengod, G. (1992). Distribution and cellular localization of mRNA coding for 5-HT1A receptor in the rat brain: correlation with receptor binding. *J Neurosci*, *12*(2), 440-453. https://doi.org/10.1523/jneurosci.12-02-00440.1992

Pouzet, B., Didriksen, M., & Arnt, J. (2002). Effects of the 5-HT7 receptor antagonist SB-258741 in animal models for schizophrenia. *Pharmacology Biochemistry and Behavior*, *71*(4), 655-665. https://doi.org/10.1016/S0091-3057%2801%2900744-4

Pytka, K., Gluch-Lutwin, M., Kotanska, M., Zmudzka, E., Jakubczyk, M., Waszkielewicz, A., Janiszewska, P., & Walczak, M. (2017). HBK-15 protects mice from stress-induced behavioral disturbances and changes in corticosterone, BDNF, and NGF levels. *Behavioural brain research*, *333*, 54-66. https://doi.org/https://dx.doi.org/10.1016/j.bbr.2017.06.032

Pytka, K., Partyka, A., Jastrzebska-Wiesek, M., Siwek, A., Gluch-Lutwin, M., Mordyl, B., Kazek, G., Rapacz, A., Olczyk, A., Galuszka, A., Blachuta, M., Waszkielewicz, A., Marona, H., Sapa, J., Filipek, B., & Wesolowska, A. (2015a). Antidepressant- and Anxiolytic-Like Effects of New Dual 5-HT1A and 5-HT7 Antagonists in Animal Models. *PloS one*, *10*(11), e0142499. https://doi.org/https://dx.doi.org/10.1371/journal.pone.0142499

Pytka, K., Partyka, A., Jastrzebska-Wiesek, M., Siwek, A., Gluch-Lutwin, M., Mordyl, B., Kazek, G., Rapacz, A., Olczyk, A., Galuszka, A., Blachuta, M., Waszkielewicz, A., Marona, H., Sapa, J., Filipek, B., & Wesolowska, A. (2015b). Antidepressant-new dual 5-HT1A and 5-HT7 antagonists in animal models. *PLoS ONE*, *10*(11), e0142499. https://doi.org/http://dx.doi.org/10.1371/journal.pone.0142499

Pytka, K., Socala, K., Rapacz, A., Nieoczym, D., Pierog, M., Grybos, A., Siwek, A., Waszkielewicz, A., & Wlaz, P. (2017). HBK-14 and HBK-15, triple 5-HT1A, 5-HT7 and 5-HT3 antagonists with potent antidepressant- and anxiolytic-like properties, increase seizure threshold in various seizure tests in mice. *Progress in neuro-psychopharmacology & biological psychiatry*, *79*(Pt B), 378-385. https://doi.org/https://dx.doi.org/10.1016/j.pnpbp.2017.07.013

Roberts, A. J., & Hedlund, P. B. (2012). The 5-HT7 receptor in learning and memory. *Hippocampus*. https://doi.org/10.1002/hipo.20938

Roberts, A. J., Krucker, T., Levy, C. L., Slanina, K. A., Sutcliffe, J. G., & Hedlund, P. B. (2004). Mice lacking 5-HT7 receptors show specific impairments in contextual learning. *European Journal of Neuroscience*, *19*(7), 1913-1922. https://doi.org/10.1111/j.1460-9568.2004.03288.x

Rothschild, A. J., Mahableshwarkar, A. R., Jacobsen, P., Yan, M., & Sheehan, D. V. (2011). Efficacy and tolerability of 5mg Lu AA21004 in an 8-week us trial of adults with generalized anxiety disorder. *Neuropsychopharmacology*, *36*(SUPPL. 1), S225-S226. https://doi.org/10.1038/npp.2011.292 (50th Annual Meeting of the American College of Neuropsychopharmacology, ACNP. Waikoloa, HI United States. (var.pagings).)

Ruat, M., Traiffort, E., Leurs, R., Tardivel-Lacombe, J., Diaz, J., Arrang, J. M., & Schwartz, J. C. (1993). Molecular cloning, characterization, and localization of a high-affinity serotonin receptor (5-HT7) activating cAMP formation. *Proceedings of the National Academy of Sciences of the United States of America*, *90*(18), 8547-8551. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=8397408

Sarkisyan, G., Roberts, A. J., & Hedlund, P. B. (2010). The 5-HT7 receptor as a mediator and modulator of antidepressant-like behavior. *Behavioural Brain Research*, *209*(1), 99-108. https://doi.org/10.1016/j.bbr.2010.01.022

Simon, G. E. (2003). Social and economic burden of mood disorders. *Biol Psychiatry*, *54*(3), 208-215. https://doi.org/10.1016/s0006-3223(03)00420-7

Stanford, S. C. (2020). Some Reasons Why Preclinical Studies of Psychiatric Disorders Fail to Translate: What Can Be Rescued from the Misunderstanding and Misuse of Animal 'Models'? *Altern Lab Anim*, *48*(3), 106-115. https://doi.org/10.1177/0261192920939876

Takeda, H., Tsuji, M., Ikoshi, H., Yamada, T., Masuya, J., Iimori, M., & Matsumiya, T. (2005). Effects of a 5-HT7 receptor antagonist DR4004 on the exploratory behavior in a novel environment and on brain monoamine dynamics in mice. *European journal of pharmacology*, *518*(1), 30-39. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=16002064

Takeda, K., Tsuji, M., Miyagawa, K., & Takeda, H. (2017). 5-HT7 receptor-mediated fear conditioning and possible involvement of extracellular signal-regulated kinase. *Neuroscience Letters*, *638*, 69-75. https://doi.org/10.1016/j.neulet.2016.11.065

Thase, M. E., Rush, A. J. (1995). Treatment resistant depression. In K. D. Bloom FE (Ed.), *Psychopharmacology: The Fourth Generation of Progress* (pp. 1081–1097). Raven Press Ltd.

Thomas, B. H., Ciliska, D., Dobbins, M., & Micucci, S. (2004). A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. *Worldviews on Evidence-Based Nursing*, *1*(3), 176-184. https://doi.org/10.1111/j.1524-475X.2004.04006.x

Thomas, D. R., Melotto, S., Massagrande, M., Gribble, A. D., Jeffrey, P., Stevens, A. J., Deeks, N. J., Eddershaw, P. J., Fenwick, S. H., Riley, G., Stean, T., Scott, C. M., Hill, M. J., Middlemiss, D. N., Hagan, J. J., Price, G. W., & Forbes, I. T. (2003). SB-656104-A, a novel selective 5-HT7 receptor antagonist, modulates REM sleep in rats. *British Journal of Pharmacology*, *139*(4), 705-714. https://doi.org/10.1038/sj.bjp.0705290

To, Z. P., Bonhaus, D. W., Eglen, R. M., & Jakeman, L. B. (1995). Characterization and distribution of putative 5-ht7 receptors in guinea-pig brain. *British Journal of Pharmacology*, *115*(1), 107-116. https://doi.org/https://doi.org/10.1111/j.1476-5381.1995.tb16327.x

Tomassini, L., Perrini, F., Cuomo, I., Motta, P., Amici, E., & De Filippis, S. (2017). Efficacy, safety, and tolerability of vortioxetine in the treatment of mood disorders. *European Neuropsychopharmacology*, *27*(Supplement 4), S863-S864. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed18&NEWS=N&AN=619297550 (30th European College of Neuropsychopharmacology Congress, ECNP 2017. France.)

Vandekerckhove, M., & Wang, Y. L. (2018). Emotion, emotion regulation and sleep: An intimate relationship. *AIMS Neurosci*, *5*(1), 1-17. https://doi.org/10.3934/Neuroscience.2018.1.1

Vlad, M., Raucher-Chéné, D., Henry, A., & Kaladjian, A. (2018). Functional outcome and social cognition in bipolar disorder: Is there a connection? *Eur Psychiatry*, *52*, 116-125. https://doi.org/10.1016/j.eurpsy.2018.05.002

Volk, B., Barkoczy, J., Hegedus, E., Udvari, S., Gacsalyi, I., Mezei, T., Pallagi, K., Kompagne, H., Levay, G., Egyed, A., Harsing, L. G., Jr., Spedding, M., & Simig, G. (2008a). (Phenylpiperazinyl-butyl)oxindoles as selective 5-HT7 receptor antagonists. *Journal of*

medicinal chemistry, *51*(8), 2522-2532. https://doi.org/http://dx.doi.org/10.1021/jm070279v

Volk, B., Barkoczy, J., Hegedus, E., Udvari, S., Gacsalyi, I., Mezei, T., Pallagi, K., Kompagne, H., Levay, G., Egyed, A., Harsing, L. G., Jr., Spedding, M., & Simig, G. (2008b). (Phenylpiperazinyl-butyl)oxindoles as selective 5-HT7 receptor antagonists. *Journal of medicinal chemistry*, *51*(8), 2522-2532. https://doi.org/10.1021/jm070279v

Volk, B., Gacsalyi, I., Pallagi, K., Poszavacz, L., Gyonos, I., Szabo, E., Bako, T., Spedding, M., Simig, G., & Szenasi, G. (2011). Optimization of (arylpiperazinylbutyl)oxindoles exhibiting selective 5-HT7 receptor antagonist activity. *Journal of medicinal chemistry*, *54*(19), 6657-6669. https://doi.org/10.1021/jm200547z

Volz, H. P. (2011). Asenapine. A new atypical antipsychotic for the treatment of moderate up to severe manic episodes of bipolar-I-disorder in adults. *Psychopharmakotherapie*, *18*(5), 212-219. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=362752883 (Asenapin. Ein neues atypisches Antipsychotikum zur Behandlung masiger bis schwerer manischer episoden einer bipolar-I-storung bei erwachsenen)

Wesolowska, A., Nikiforuk, A., & Stachowicz, K. (2006a). Potential anxiolytic and antidepressant effects of the selective 5-HT7 receptor antagonist SB 269970 after intrahippocampal administration to rats. *European journal of pharmacology*, *553*(1-3), 185-190. https://doi.org/http://dx.doi.org/10.1016/j.ejphar.2006.09.064

Wesolowska, A., Nikiforuk, A., & Stachowicz, K. (2006b). Potential anxiolytic and antidepressant effects of the selective 5-HT7 receptor antagonist SB 269970 after intrahippocampal administration to rats. *European Journal of Pharmacology*, *553*(1-3), 185-190. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=17097082

Wesolowska, A., Nikiforuk, A., Stachowicz, K., & Tatarczynska, E. (2006a). Effect of the selective 5-HT7 receptor antagonist SB 269970 in animal models of anxiety and depression. *Neuropharmacology*, *51*(3), 578-586. https://doi.org/http://dx.doi.org/10.1016/j.neuropharm.2006.04.017

Wesolowska, A., Nikiforuk, A., Stachowicz, K., & Tatarczynska, E. (2006b). Effect of the selective 5-HT7 receptor antagonist SB 269970 in animal models of anxiety and depression. *Neuropharmacology*, *51*(3), 578-586.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=16828124

Wesolowska, A., Tatarczynska, E., Nikiforuk, A., & Chojnacka-Wojcik, E. (2007). Enhancement of the anti-immobility action of antidepressants by a selective 5-HT7 receptor antagonist in the forced swimming test in mice. *European Journal of Pharmacology*, *555*(1), 43-47. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=17109856

Zajdel, P., Marciniec, K., Maslankiewicz, A., Satala, G., Duszynska, B., Bojarski, A. J., Partyka, A., Jastrzebska-Wiesek, M., Wrobel, D., Wesolowska, A., & Pawlowski, M. (2012a). Quinoline- and isoquinoline-sulfonamide derivatives of LCAP as potent CNS multi-receptor-5-HT1A/5-HT2A/5-HT7 and D2/D3/D4-agents: the synthesis and pharmacological evaluation. *Bioorganic & medicinal chemistry*, *20*(4), 1545-1556. https://doi.org/https://dx.doi.org/10.1016/j.bmc.2011.12.039

Zajdel, P., Marciniec, K., Maslankiewicz, A., Satala, G., Duszynska, B., Bojarski, A. J., Partyka, A., Jastrzebska-Wiesek, M., Wrobel, D., Wesolowska, A., & Pawlowski, M. (2012b). Quinoline- and isoquinoline-sulfonamide derivatives of LCAP as potent CNS multi-receptor-5-HT1A/5-HT2A/5-HT7 and D2/D3/D4-agents: The synthesis and pharmacological evaluation. *Bioorganic and Medicinal Chemistry*. https://doi.org/10.1016/j.bmc.2011.12.039

Zhang, Q. J., Du, C. X., Tan, H. H., Zhang, L., Li, L. B., Zhang, J., Niu, X. L., & Liu, J. (2015). Activation and blockade of serotonin7 receptors in the prelimbic cortex regulate depressive-like behaviors in a 6-hydroxydopamine-induced Parkinson's disease rat model. *Neuroscience*, *311*, 45-55. https://doi.org/10.1016/j.neuroscience.2015.10.016

Chapter 3 fMRI analysis – pop-faces task

3.0 Abstract

In my systematic review, I found 5-HT$_7$ to be a promising target for improving emotional functions. Emotional faces recognition paradigms were typically seen as providing insight into an essential aspect of emotional regulation functions. In this chapter, the gender discrimination emotional faces task (pop-faces paradigm) was used to test if the 5-HT$_7$ antagonist could modulate emotional regulation.

18 participants were recruited, and the analyses focused on data from 14 healthy participant. The study required four visits: the first for screening; the second to obtain a baseline of emotional and cognitive functions, and the third and fourth were for neuroimaging, in which participants took part in interviews using the International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC) cognitive function assessment, and implicit emotional processing paradigm. Participants needed to take a selective 5-HT$_7$ antagonist, JNJ-18038683 20mg daily or placebo for one week, and then to attend the visits.

The behavioural performance was assessed based on accuracy (proportion of correct responses), and speed (mean reaction time). For the fMRI data, hypothesis-led ROI-based analysis was conducted using a binarized explicit mask that included amygdala, hippocampus, thalamus, and subgenual anterior cingulate cortex (sgACC). Finally, an exploratory whole-brain analysis was conducted to explore brain activity or drug-related modulation of brain activation.

The results of the task behaviour analysis showed participants made slower gender-discrimination decisions for fearful faces. In neuroimaging analysis, there was no significant

task activation within the pre-defined region of interest – the amygdala, thalamus, hippocampus and sgACC. Furthermore, the whole-brain mapping found fusiform gyrus was activated in flexible factorial design in the main effect on emotion, but no significant differences due to the drug.

Generally, no significant drug-related changes were found in behavioural performance and brain activation. However, there were some limitations, including the sufficiency of the paradigm to elicit activation with brain areas responsive to emotional faces (the robustness of response), gender discrimination within the task due to the gender bias, and the limited drug administration dosage and duration, which could explain the paucity of significant findings in this study. Further investigations should be conducted using a larger dose or treatment duration of JNJ-18038683 and perhaps different fMRI paradigm.

3.1 Introduction

3.1.1 Emotional regulation and 5-HT$_7$

The 5-HT$_7$ receptor is a serotonin G-protein-coupled receptor (GPCR) that was identified in 1993 (Bard et al., 1993; Cisler & Koster, 2010; Lovenberg et al., 1993; Ruat et al., 1993). Recently researchers have reported that 5-HT$_7$ function was associated with several essential processes, including maintaining the circadian rhythm (Adriani et al., 2012; Ehlen et al., 2001; Shelton et al., 2014; Sprouse et al., 2004), thermoregulation (Hagan et al., 2000; Thomas et al., 2003), learning and memory (Leopoldo et al., 2011; Meneses, 2004). It is also associated with several psychiatric disorders, including depression (Kennedy et al., 2016; Mahableshwarkar et al., 2014; McIntyre et al., 2013; Tomassini et al., 2017), anxiety (Baldwin, 2011), and others (e.g., schizophrenia, substance abuse) (Blattner et al., 2019; East et al., 2002; Hauser et al., 2014). In the previous chapter, the systematic review, there is evidence for 5-HT$_7$ regulating multiple processes from animal studies including emotional processes (Abbas et al., 2009; Andressen et al., 2015; Canale et al., 2016; Canale et al., 2017; Cates et al., 2013; Delcourte et al., 2017; Jankowska et al., 2020; Kennedy et al., 2016; Mahableshwarkar et al., 2014; McIntyre et al., 2013, 2014; Tomassini et al., 2017). Indeed, the systematic review demonstrated how 5-HT$_7$ antagonism produces effects which improve function in classic depression and anxiety models in rodents, but classic models have been questioned for their construct validity and their translational predictive value (Stanford, 2020). It is not clear from the studies in animals if 5-HT$_7$ antagonism alone could produce such effect, for example, a selective 5-HT$_7$ antagonist, SB-269970, was found to reduce rodents' immobility when combined with other drugs, such as citalopram (a selective serotonin reuptake inhibitor, SSRI), imipramine

(a tricyclic antidepressant, TCA), desipramine (a tricyclic antidepressant, TCA), and moclobemide (monoamine oxidase, MAO, inhibitor), suggesting it might have antidepressant effects over other antidepressant drugs (Wesolowska et al., 2007). The specific effects of SB-269970 alone were not clear, since the SB-269970 worked well mainly when combined with other antidepressant drugs.

The effects of 5-HT_7 antagonists on human remains unclear as well, because the evidence came from antipsychotics or antidepressant, not selective compounds. Antipsychotics with high affinity for 5-HT_7, including lurasidone, amisulpiride and asenapine (Abbas et al., 2009; Cates et al., 2013; Delcourte et al., 2017), clozapine and olanzapine (Andressen et al., 2015), have antidepressant properties. Vortioxetine, an antidepressant with high affinity for 5-HT_7 receptors, and acts as a receptor antagonist, also enhances mood in patients with depression (Kennedy et al., 2016; Mahableshwarkar et al., 2014; McIntyre et al., 2013; Tomassini et al., 2017). As yet, there is limited evidence in humans with selective compounds, since the compounds used have affinities to other receptors.

From these results and others reviewed in chapter 2, it is reasonable to suggest that 5-HT_7 antagonists showed antidepressant-like properties, and may also prove anxiolytic, but no selective compounds have been tested on emotional processing in humans. Taken together, these findings suggest that 5-HT_7 receptors might be associated with emotion, and the 5-HT_7 agonists or antagonists may be potential treatments for mood disorders.

Thus, in this chapter, I tested a selective 5-HT_7 antagonist, JNJ-18038683, to see if it could improve or modulate emotional functions in healthy human volunteers. I report

the results of a behavioural and neuroimaging investigation of changes in emotional function following one week of treatment with a daily dose of 20mg of JNJ-18038683.

JNJ-18038683 is an antagonist of the 5-HT_7 receptor (Shelton et al., 2014). It was developed by Janssen Research & Development, LLC, and is now in the phase 2 stage of development:

(https://clinicaltrials.gov/ct2/show/NCT02466685,
https://clinicaltrials.gov/study/NCT00566202,
https://clinicaltrials.gov/ct2/show/NCT02466685).

To explore the effects on emotional processing, the gender discrimination emotional faces task (i.e., the pop-faces task) was used (Passamonti et al., 2010).

3.1.2 Emotional processing and pop-faces task

The gender discrimination emotional faces task was originally developed using physical photographs showing faces expressing emotions, including fear, happiness and a neutral expression. However, computer-based versions of this paradigm now exist that can present faces expressing a wider range of emotions. Though the other similar paradigms are capable of presenting additional emotions, my investigation was limited to examining brain activity related to these three particular emotional expressions during gender discrimination. Such tasks are typically also seen as providing insight into an essential aspect of social cognition (Ekman, 1992a, 1992b, 1993; Montagne et al., 2007). There is growing evidence that social cognitive functions are related to social perception, social understanding, and social decision-making (Arioli et al., 2018; Lieberman, 2007). In addition, depression is characterised by negative emotional biases, which antidepressants can normalise by increasing positive emotional processing.

Imaging studies allow researchers to observe how antidepressants alter emotional biases and modulate activity in emotion processing tasks. Detecting these effects on emotional processing and brain activity can reveal a compound's potential antidepressant properties even before changes in mood occur. Therefore, imaging emotional processing in response to novel compounds provides an early indicator of their ability to rebalance emotional biases and engage brain networks underlying these changes, establishing their promise as antidepressant treatments (Harmer et al., 2009).

Several emotional faces recognition tasks have been used to identify brain regions related to emotional processing (Montagne et al., 2007; Ruffman et al., 2008; Sprengelmeyer et al., 1998), for example, processing emotional faces activated visual, limbic, temporoparietal and prefrontal regions, plus the putamen and cerebellum, while the amygdala responded selectively to happy, fearful and sad expressions, with greatest sensitivity to fear (Fusar-Poli et al., 2009), another study revealed that the ventral visual pathway, particularly the left fusiform face area was more responsive to facial expressions (Liu et al., 2021). However, there was also a paper questioned the reliability of these tasks (Nord et al., 2017). The researchers concluded that the reliability of some neural responses to emotional faces measured in healthy controls was unstable: activation in specific brain areas, such as amygdala or sgACC, was rarely reliable over time.

Nord and her colleagues analysed the young healthy controls, which was similar to our participants demographic features (please see 3.3.1) (Nord et al., 2017); in addition, despite the growing interest in 5-HT_7 agonists and antagonists, the effects of JNJ-18038683 remain unclear. To date, no investigation using fMRI has explored the impact of JNJ-18038683 on the neural correlates of emotional functions. Therefore, in this

chapter I report the findings of my study using a gender discrimination emotional faces task (i.e., the pop-faces task) for pharmacological fMRI to test the following hypotheses.

3.1.3 Hypotheses

- Hypothesis 1. The drug JNJ-18038683 has the potential to induce alterations in behavioural performance during an gender discrimonation emotional facial processing task, leading to notable variations in response accuracy proportions and decreased reaction times.
- Hypothesis 2. Activity in brain areas related to emotional functions, including the areas listed below, would be modulated by JNJ-18038683 treatment in healthy controls performing the same emotional processing task.
    - Subgenual cingulate cortex (sgACC) (Drevets et al., 2008; Kühn et al., 2012).
    - Thalamus, amygdala, hippocampus – these areas were based on the density of 5-HT_7 receptors (Hedlund & Sutcliffe, 2004).
- Hypothesis 3. There will be correlations with change in performance and BOLD responses in the pre-specified ROIs (i.e., amygdala, hippocampus, thalamus, and sgACC).

3.2 Methods

3.2.1 Participants

The study was approved by the London Camberwell St Giles Research Ethics Committee (Reference Number: 18/LO/0762) and was conducted between August 2018 and September 2022. A total of 18 participants completed the study, including 4 bipolar patients and 14 healthy controls.

3.2.1.1 Inclusion criteria.

We recruited male and female patients with a current diagnosis of bipolar disorder and healthy volunteers as participants (further information is shown in the protocol) (Young et al., 2018). Participants were included in the study if they were healthy, right-handed, and aged between 18 and 60 years. Clinical laboratory test results must be within the reference range during the index screening visit. Female volunteers will be asked to confirm a negative pregnancy test at screening and to provide consent and acceptance of medical contraception. Male volunteers must also provide consent to use contraception throughout the study. In addition, all participants must meet the criteria for a safe MRI scan to ensure no contraindications.

Other inclusion criteria for the healthy controls included the following:

1. Evidence of a personally signed and dated informed consent document indicating that the subject had been informed of all pertinent aspects of the trial.
2. Right-handed participants between the ages of 18 and 60 years.
3. The participant was able to understand written and verbal instructions in English.
4. The participant was willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.
5. The participant had clinical laboratory test values within the reference ranges based on the blood and urine samples taken at the index screening visit. Borderline value parameters needed to be accepted if they are, in the opinion of the investigator, clinically insignificant.
6. The participant had a resting pulse ≥ 51bpm and ≤ 100bpm.
7. The participant had a resting systolic blood pressure ≥ 91mmHg and ≤ 140mmHg and a resting diastolic blood pressure ≥ 51mmHg and ≤ 95mmHg at

the screening visit. An out-of-range resting systolic blood pressure needed to be repeated if a medically valid reason is present, for example, the subject suffers from white-coat hypertension (i.e., felling anxious in clinical environment) or experienced stress (e.g., late arrival). The medically valid reason must be documented and signed by the investigator.

8. Women of childbearing potential must have a negative pregnancy test at screening and at baseline visits and must agree to use a medically accepted method of contraception throughout the study.
9. Women of childbearing potential must agree to use one of the following contraception methods throughout the study: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success, sexual abstinence: potential participant must guarantee that she will be abstinent for the duration of the study and the entire washout period.
10. Fertile men must agree to use one of the following contraception methods: for the duration of the study, men should use condoms during intercourse, and their partner should be using effective contraception or sexual abstinence: potential participant must guarantee that he will be abstinent for the duration of the study and the entire washout period.

3.2.1.2 Exclusion criteria.

In the general criteria, we excluded participants who had experienced clinically significant haematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, neurologic, allergic diseases, or any primary psychiatric diagnosis other than bipolar disorder from this study.

1. The following physical health issues were reasons for exclusion from the study: abnormal electrocardiogram (ECG) and abnormal blood test results during the screen visits. Additionally, a history or evidence of clinically significant haematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, neurologic, allergic disease. Individuals with any primary psychiatric diagnosis other than bipolar disorder will be excluded from the study.
2. Herbal supplements were discontinued 28 days prior to the first dose of JNJ-18038683 or placebo.

Healthy control participants were recruited through public advertising, online and social media, and through National Institute for Health and Care Research Mental Health Clinical Research Network (NIHR CRN), advertisement within King's College London newsletter, in the local press, online, and through contacting participants from previous studies who have expressed an interest in further research participation. Patients were recruited through South London and Maudsley NHS Foundation Trust clinical services, with other trusts potentially contributing to recruitment (however, in this chapter, we only analysed healthy controls' data).

In this study, 97 participants were screened for inclusion. Sixty-one were excluded due to screen failures or lost follow up. Thirty-six participants entered randomisation, eleven were lost at follow-up, two due to noncompliance, four due to Principal

Investigator's decision, one due to pregnancy. All participants provided written informed consent. Finally, a total of 18 participants completed the study, including four bipolar patients and 14 healthy controls. However, even though both patients and healthy controls completed the study, due to the small sample size of patient group and data quality, we focused on analysing the data from 14 healthy controls.

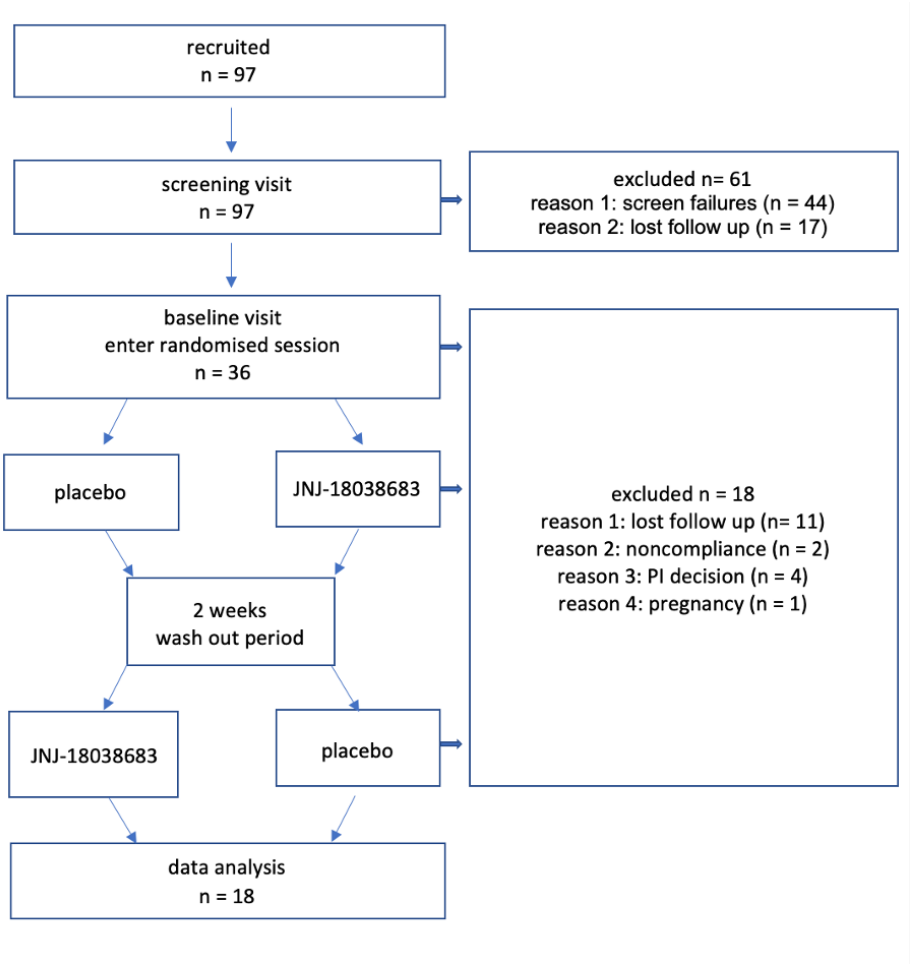

Figure 3-1

Trial flow diagram.

3.2.2 Study design and procedure

3.2.2.1 Medicine information and instruction

JNJ-18038683 is a 5-HT_7 antagonist. The drug is a strong inhibitor of cytochrome P450 2D6, so participants who use the CYP2D6 substrates will be an exclusion. JNJ-18038683 is also a moderate inhibitor of cytochrome P450 2C19, so participants use of the following CYP2C19 substrates will be an exclusion.

The above was checked in the index screening visit (visit 1); and interviews during visit 2, 3, and 4, was used to collect responses to baseline questionnaires, emotional scales and measures of cognitive function. Prior the visits 3 and 4, participants were randomised to take JNJ-18038683 20mg or a placebo once daily for one week. JNJ-18038683 and matching placebos will be provided by Janssen Research and Development, LLC, the manufacturer of JNJ-18038683.

3.2.2.2 Study design.

This was a randomised, double-blind, placebo-controlled, cross-over, pharmacological functional MRI (phfMRI) design study, aiming to examine the neural and behavioural effects of one week's treatment with the 5-HT_7 antagonist, JNJ-18038683, and placebo. Each participant attended the study four times, including an index screening visit (visit 1), a baseline visit (visit 2), and two neuroimaging visits (visit 3 & 4). During the neuroimaging visits, structural data, arterial spin labelling (ASL) perfusion images, resting state and task-based functional MRI was collected. The tasks used during fMRI scans included a gender discrimination emotional faces task (called the pop-faces task). In addition, a working memory task (N-back) was included which will be the subject of the next chapter, and a paired associated visuospatial learning task (vPAL) which is

not included in this thesis. In this chapter, I focused on analysing the emotional pop-faces data.

3.2.2.3 Study procedure.

In visit 1, participants were invited to join an index screening assessment, in which an examination of their physical health, including blood test, electrocardiogram (ECG) and urine drug screen (UDS) was conducted. Participants' diagnosis was assessed by Mini International Neuropsychiatric Interview (M.I.N.I. 6.0) (Sheehan et al., 1998). Their mood status and symptoms were assessed by Hamilton Depression Rating Scale (also named Hamilton Rating Scale for Depression, HAM-D) (Hamilton, 1960, 1980), Young Mania Rating Scale (YMRS) (Young et al., 1978), Altman Self-Rating Mania Scale (ASRM) (Altman et al., 1997), Quick Inventory of Depression Symptomatology (QIDS-C16) (Rush et al., 2003), Columbia-Suicide Severity Rating (C-SSRS) (available at www.cssrs.columbia.edu) (Oquendo et al., 2003) and Hamilton Anxiety Rating Scale (also named Hamilton Rating Scale for Anxiety, HAM-A) (Hamilton, 1959; Thompson, 2015). Moreover, Cannabis experiences (CEQ3) (Birnbaum et al., 2019), Fagerstrom smoking (Fagerstrom Test for Nicotine Dependence, FND) (Heatherton et al., 1991) and Alcohol use disorders identification Test (AUDIT) (Reinert & Allen, 2002) questionnaires were also employed to determine if they used these substances.

Table 3-1

Study procedure.

	Screening visit (Visit 1)	Baseline visit (Visit 2, Day 1)	Imaging visit 1 (Visit 3, Day 7)	Imaging visit 2 (Visit 4, Day 28)
Informed consent	✓			
Physical examination	✓	✓	✓	✓
Laboratory tests	✓	✓	✓	✓
Mood assessment	✓	✓	✓	✓
Cognitive assessment		✓	✓	✓
AE assessment			✓	✓
MRI			✓	✓
Drug blood sample			✓	✓

AE: Adverse Event. MRI: Magnetic Resonance Imaging.

Eligible participants were invited to join visits 2, 3, and 4. In addition to a healthy physical examination, participants also took part in cognitive functions assessments with a neuropsychological battery, the International Society for Bipolar Disorders – Battery for Assessment of Neurocognition (ISBD-BANC) (Yatham et al., 2010). In the ISBD-BANC, speed of processing was evaluated with symbol coding, animal naming category fluency and Trial Making Test – Part A; attention was evaluated with continuous performance test (CPT) – identical pairs; working memory was evaluated with Wechsler Memory Scale letter-number sequencing and spatial span (in visit 3 and 4, participants also conducted N-back working memory task, which was one of the fMRI paradigms), verbal learning and memory was evaluated with Hopkin's Verbal learning test-revised, visual learning using the brief visuospatial memory test; executive function was evaluated with Stroop Test, Trial Making Test – Part B and Wisconsin

Card Sorting test (WCST) (Barceló & Knight, 2002). Cognitive impairment was evaluated with Perceived Deficits Questionnaire (PDQ) (Strober et al., 2016); psychosocial function was evaluated with the Functional Assessment Short Test (FAST) (Siegel-Ramsay et al., 2023); sleep quality was evaluated with the Pittsburgh Sleep Quality Index *(*PSQI) (Buysse et al., 1989).

Randomisation was conducted by computer-generated, pseudo-random code based on stacks of William's Squares, ensuring an equal distribution of each treatment across each study period. A blinded randomisation list and master list were provided by the pharmacist and delegated to the investigator. Participants took JNJ-18038683 20mg daily for one week and switched to placebo for one week, or vice versa, after a two-week wash-out period. Investigators maintained contact with participants via phone, reaching out 24 hours after the start and end of each treatment period to assess the safety and tolerability of the assigned treatment. On the seventh day of each treatment period, participants were scanned at the neuroimaging centre.

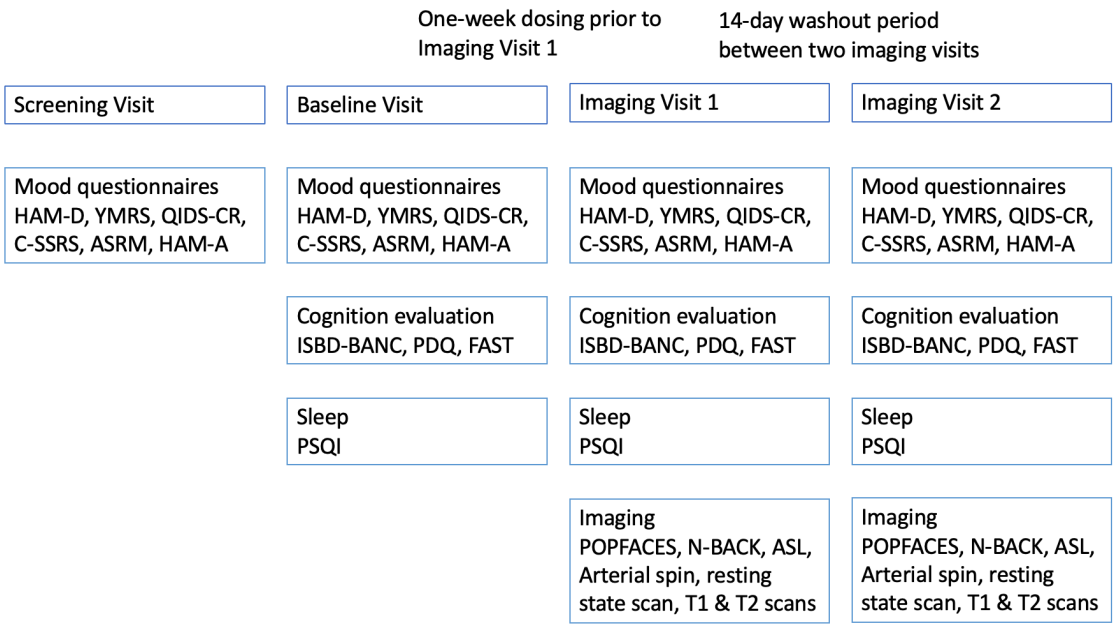

Figure 3-2

Study measures.

3.2.3 fMRI tasks

3.2.3.1 Gender discrimination emotional faces task (pop-faces task)

The pop-faces task is a gender discrimination emotional faces task paradigm. Participants were asked to identify the gender of the faces shown in grey-scale photographs (50% female) presented on the screen. Emotion processing is understood as an ability to identify, facilitate, regulate, understand, and manage emotions (Mayer et al., 2001; Monferrer et al., 2023). This task used faces expressing one of three emotions: neutral, fearful, and happy, and the stimuli were presented in a pseudo-random pattern. Each block had a series of ten emotional faces, and the faces, all drawn from the same emotional grouping, and were presented on the screen for 1000ms. Each block also included 5 null fixation cross cues, presented for 750ms, distributed amongst the 10 face stimuli. The null condition was 1750ms with the same fixation cross. Twelve emotional blocks (four for each of neutral, fearful, and happy) were presented. The images of faces used in the paradigm were taken from the NimStim dataset with the appropriate permissions. The dataset includes 672 photographs taken by 43 professional actors, including 18 females and 25 males, whose ages ranged from 21 to 30 years old (Tottenham et al., 2009). The scan lasted for 10 minutes 30 seconds.

Participants responded using a two-button button box; they needed to press left if the perceived stimulus type of the face was female, and to press right if the perceived stimulus type of the face was male. The accuracy, speed, and brain activations were recorded.

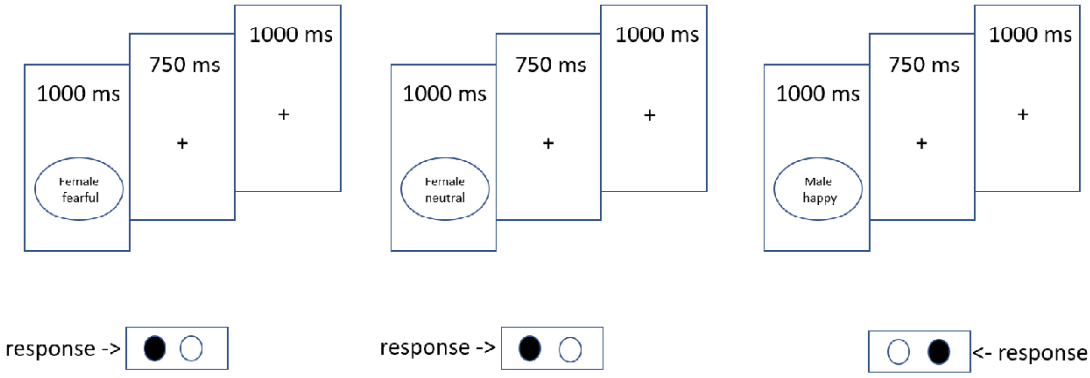

Figure 3-3

Illustration of pop-faces gender discrimination emotional faces paradigm. Adapted from Passamonti et al. (2010).

3.2.3.2 Statistical analysis of behavioural performance

The demographic and behavioural variables were analysed by using SPSS 28 (https://www.ibm.com/analytics/spss-statistics-software). The mean and standard deviation were calculated for demographic and emotional questionnaires and scales (please see Table 3-2). For behavioural performance data a two-way repeated measures analysis of variance (rmANOVA) was also used to show the differences in accuracy (i.e., proportion of correct trials) and speed (i.e., mean reaction time) between drug and placebo across three facial emotions. When the assumption of sphericity was violated, the Greenhouse-Geisser was applied.

3.2.4 fMRI acquisition and preprocessing

In this study, MRI scans were acquired on 3 Tesla MR scanner (General Electric MR750) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology

and Neuroscience, King's College London. The T1-weighted structural MRI scans were using a magnetisation-prepared rapid gradient echo sequence (Repetition Time (TR): 7.31ms, Echo Time (TE): 3.02ms; flip angle (FA): 11°; matrix size: 256 × 256mm^2; FOV: 270mm; slice thickness: 1.2mm).

T2*-weighted images were acquired by using gradient-echo planar imaging sequence (TR: 2000ms, TE: 30ms, FA: 75°, slice thickness: 3mm, FoV: 240mm, and matrix size: 64 × 64mm^2, slice gap: 3.3mm, 41 slices). The gender discrimination emotional faces task lasted 630 seconds.

When conducting pre-processing, Statistical Parametric Mapping Software 12 (SPM12) (http://fil.ion.ucl.ac.uk/spm/), a neuroimaging software suite that runs within Matlab (R2018b), was used. I converted raw Digital Imaging and Communications in Medicine (DICOM) images to Neuroimaging Informatics Technology Initiative (NIFTI) format. Secondly, the origins (coordinate [0 0 0]) of the functional timeseries and the structural scan were adjusted to lie on the anterior commissure, parallel to the AC-PC line. Thirdly, realignment of the functional timeseries was carried out to correct for volume-to-volume head displacement. The realigned fMRI data was then co-registered to bring it into alignment with the T1 weighted image. The deformation fields encoding the transformations required to take the data from native to standard Montreal Neurological Institute and Hospital coordinate system (i.e., MNI template space), were generated by unified segmentation of the T1 weighted structural image. These warping parameters were then applied to the functional timeseries that were previously registered to the T1 image. Lastly, the spatially normalised scans were smoothed with Gaussian smoothing kernels specified as 8 mm Full-Width-at-Half-Maximum height (FWHM) (Pera-Guardiola et al., 2016). After these steps, the movement parameters were visually

inspected, and data containing movement over the run of greater than 1 voxel (~3.3mm) was considered unsuitable for analysis and discarded. Additionally, the volume-to-volume framewise displacement was calculated based on the movement parameters. Volumes with framewise displacements of more than 0.5mm were subsequently modelled during first-level fMRI analysis by means of separate scan-nulling regressors.

3.2.4.1 First-level fMRI analysis

In the subject-specific first-level fMRI analysis, the Blood Oxygen Level Dependent (BOLD) response during the gender discrimination emotional faces task was modelled using 6 regressors encoding the predicted BOLD in response to trials of the following types: neutral, happy, fearful, incorrect response, missed, and false positive. All first-level models included regressors encoding the six realignment parameters (translations in the x, y, and z axes, and rotation around them), and additional scan-nulling regressors as nuisance regressors. A high-pass filter with a 128s cut was applied, and temporal autocorrelation was modelled using a first-order autoregressive function (AR(1)).

Following parameter estimation, contrasts of parameter estimates were generated for all emotional faces vs fixation (i.e., all-faces > fixation), and each emotionally expressive face (i.e. happy or fearful) condition compared to the response to neutral trials (i.e., happy > neutral, fearful > neutral, and fearful > happy). I chose an all-faces > fixation contrasting condition because comparing all emotional faces to a baseline of fixation enables better detection of the regions implicated in face processing.

3.2.4.2 Second-level fMRI analysis

For each task, subject-specific contrasts of parameter estimated for each of the primary contrast of interest were taken forward to group-level random effects analyses.

The primary contrast of interest was all-faces vs fixation. To identify task-related activation, I first carried out one-sample t-tests using the all-faces > fixation contrasts on drug and placebo sessions, respectively. Here, I would like to see what brain regions are activated in response to the working memory challenge compared to a low-level control condition.

Subsequently, to explore the changes in brain activity, I examined contrasts for each of the three emotional faces (neutral, fearful, and happy) condition into a one-way ANOVA.

To explore the effects of treatment on task activity, a paired sample t-test (placebo vs drug sessions) was carried out using the all-faces > fixation first-level contrasts as a model input.

Lastly, I implemented a repeated measures ANOVA (implemented with a Flexible Factorial model in SPM) to explore the main effect of emotions, the main effect of drug, and the load-by-treatment interactions.

For the hypothesis-led analysis of the pop-faces, ROIs were generated in WFU atlas: amygdala (right, left), hippocampus (right, left), thalamus (left, right) (Hedlund & Sutcliffe, 2004), were generated by automated anatomical atlas (AAL) (Tzourio-Mazoyer et al., 2002) and the sgACC (bilateral) (Drevets et al., 2008; Kühn et al., 2012) was generated in and combined into a single mask with WFU Pick Atlas (Maldjian et al., 2003). The mask was exported from WFU Pick Atlas and used in the ROIs analysis with SPM12.

The mask was used for small-volume correction to control for type 1 errors in the ROIs analysis at the second-level (i.e., group-level).

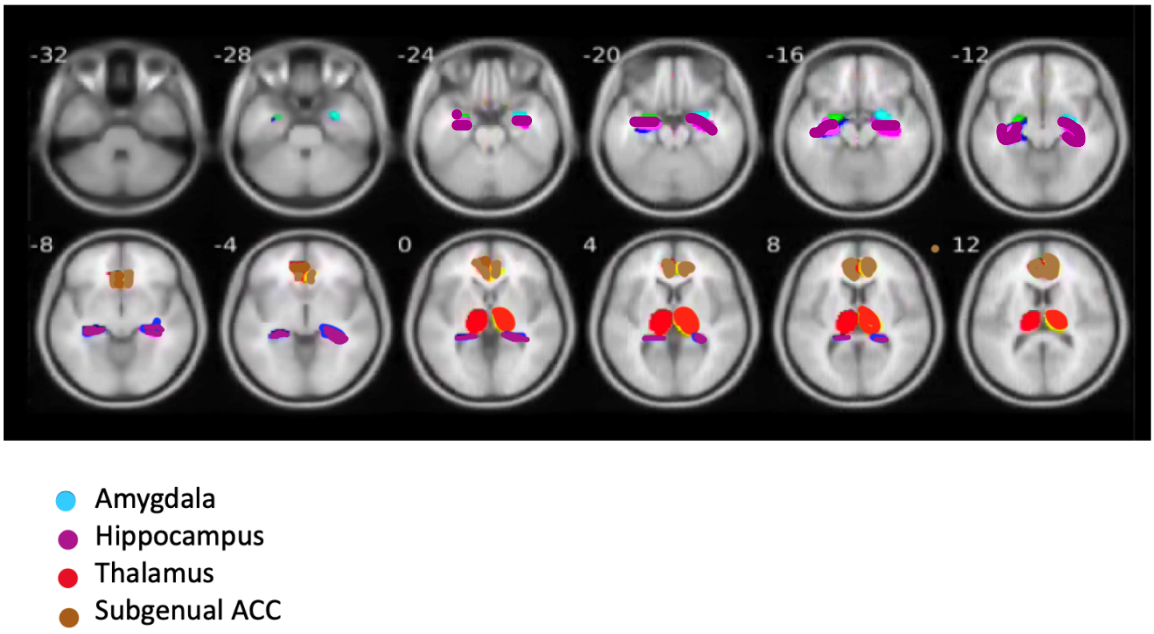

Figure 3-4

ROIs used in the analysis of the neuroimaging data collected during the performance of the pop-faces task: amygdala, hippocampus, thalamus, and sgACC.

For the exploratory whole-brain analysis, a result was considered significant if it survived whole-brain family-wise error (pFWE < .05) based on cluster extent, using an initial uncorrected cluster-forming threshold of p < .001.

3.3 Results

3.3.1 Demographic sample characteristics

Healthy control participants' mean age was 30.29 (SD = 9.94). The results of the clinical measures are shown in Table 3-2 are not in the ranges expected in patients.

Table 3-2

Descriptive statistics of mood questionnaires of healthy control participants.

	Male (n = 6)	Female (n = 8)	Total
Age (mean (SD))	32.17 (13.21)	28.88 (7.32)	30.29 (9.94)
ASRMS	.83 (1.17)	.88 (1.73)	.85 (1.46)
HAM-A	1.83 (3.13)	.38 (.74)	1.00 (2.15)
HAM-D	1.50 (2.35)	.63 (.92)	1.00 (1.66)
PDQ	9.60 (8.56)	9.50 (9.58)	9.54 (8.86)
QIDS-C16	1.67 (2.25)	.86 (1.57)	1.23 (1.88)
YMRS	.50 (1.00)	.25 (.71)	.33 (.78)

ASRMS: Altman Self-Rating Mania Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; PDQ: Perceived Deficits Questionnaire; QIDS: Quick Inventory of Depression Symptomatology; YMRS: Young Mania Rating Scale.

3.3.2 Pop-faces behavioural performance results

A two-way repeated measures ANOVA was conducted to explore the effect of two treatments (drug and placebo) on the same participants' performance, i.e., the proportion of correct trials, when conducting a gender discrimination task, across three emotions. The main effect of treatment was not significant, F (1, 13) = 1.10, p = .31, partial eta squared = .08. The main effect of emotion was significant F (1.80, 23.35) = 6.65, p = .006, partial eta squared = .34. The interaction between treatment and emotion was not significant F (2, 17.69) = 2.20, p = .13, partial eta squared = .15. The results showed that no difference in accuracy between drug and placebo, as shown in Figure 3-5.

Post-hoc comparisons using the t-test with Bonferroni correction indicated that the proportion of correct score for the happy faces (M = .95, SD = .01) was significantly

different than the neutral faces (M = .92, SD = .11) and fearful faces (M = .91, SD = .016), which means participants had more correct responses in happy faces.

Figure 3-5

Proportion of correct in responding to three emotional faces in the pop-faces task.

A two-way repeated measures ANOVA was conducted to explore the effect of two treatments (drug and placebo) on the same participants' performance, i.e., the mean reaction time, when performing the gender discrimination task, across three emotions. The main effect of treatment was not significant, F (1, 13) = 2.20, p = .16, partial eta squared = .14. The main effect of emotion was significant F (1.85, 24.10) = 26.77, p < .001, partial eta squared = .67. The interaction between treatment and emotion was not significant F (1.69, 21.98) = .35, p = .68, partial eta squared = .03. The results

showed that no difference in accuracy between drug and placebo, as shown in Figure 3-6.

Post-hoc comparisons using the t-test with Bonferroni correction indicated that the proportion of correct responses for the happy faces (M = .78, SD = .02) was significantly different than the neutral faces (M = .76, SD = .02) and fearful faces (M = .74, SD = .02), which means participants had respond slower in fearful faces than neutral and happy faces.

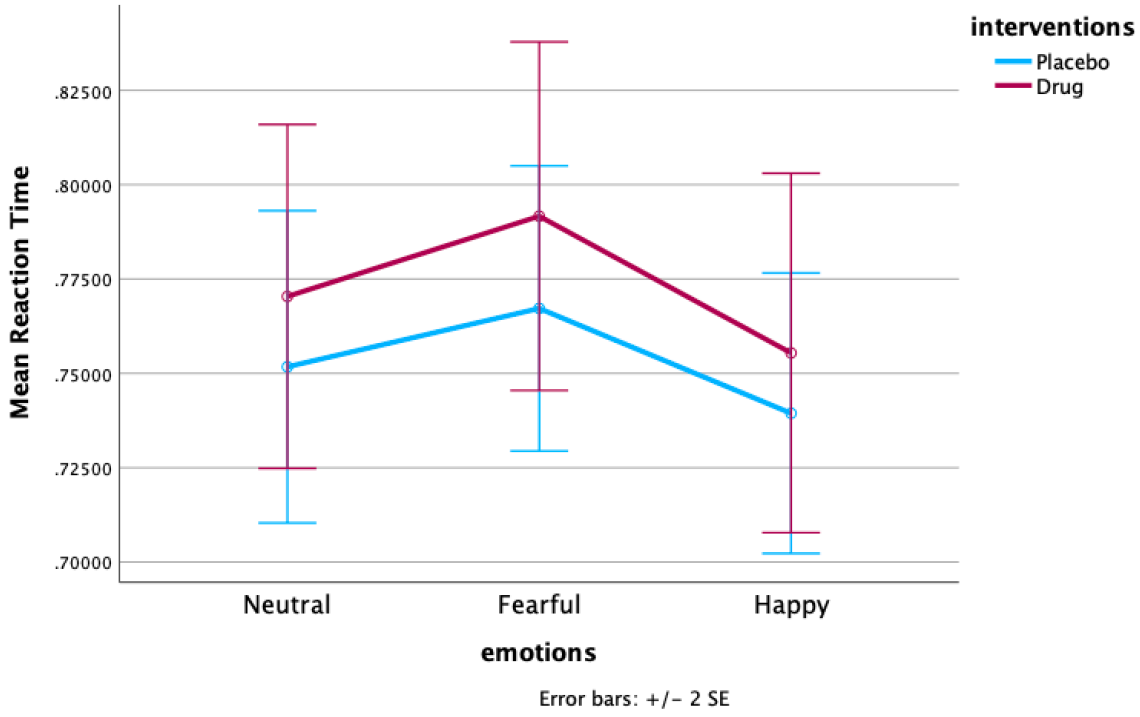

Figure 3-6

Mean reaction time in responding to three emotional faces in the pop-faces task.

3.3.3 fMRI results

3.3.3.1 ROIs analysis

In this study, a combined mask based on the pre-defined ROIs of the amygdala, hippocampus, sgACC and thalamus was used for small-volume correction in the second-level analysis. There was no significant activation in any ROIs. There was no suprathreshold cluster or significant difference in one-sample t-test, paired t-test, and no ROIs in the flexible factorial design in the main effect on emotion, main effect on drug, and task-by-drug interaction.

3.3.3.2 Whole brain exploration

The contrast of interest for the pop-faces was all-faces > fixation. To identify task-related activation, I first carried out two one-sample t-tests using the all-faces > fixation contrasts from drug and placebo sessions, respectively. The fusiform gyrus and postcentral gyrus in one-sample t-test of all-faces > fixation contrasts following the drug administration.

To explore the effects of drug on task activity, a paired sample t-test (placebo vs drug sessions) was carried out using the all-faces > fixation first-level contrasts as a model input. There was no suprathreshold clusters and no significant activation.

To examine the drug's effects on task-related brain activity, I implemented a repeated measures ANOVA (implemented with a Flexible Factorial model in SPM). There were no suprathreshold cluster or no significant main effects of drug or task-by-drug interactions were identified in any brain region. When using a more liberal cluster-forming threshold, bilateral fusiform activity was seen, but only the responses in the

right fusiform gyrus survived cluster-wise correction for multiple comparisons. The details are shown in Table 3-3 and Figure 3-7.

Table 3-3

Repeated-measures ANOVA on main effect across three emotion conditions, p = .001.

Coordinates			Cluster *p*(FWE-corr)	Peak *Z*	No. of above-threshold voxels	Brain label
x	y	z				
						fusiform gyrus
36	-48	-18	* .042	14.07	319	(right)
36	-62	-14		11.67		
26	-76	-8		8.45		
						fusiform gyrus
-38	-54	-18	.292	13.33	132	(left)

* $p < .05$ after family-wise error correction

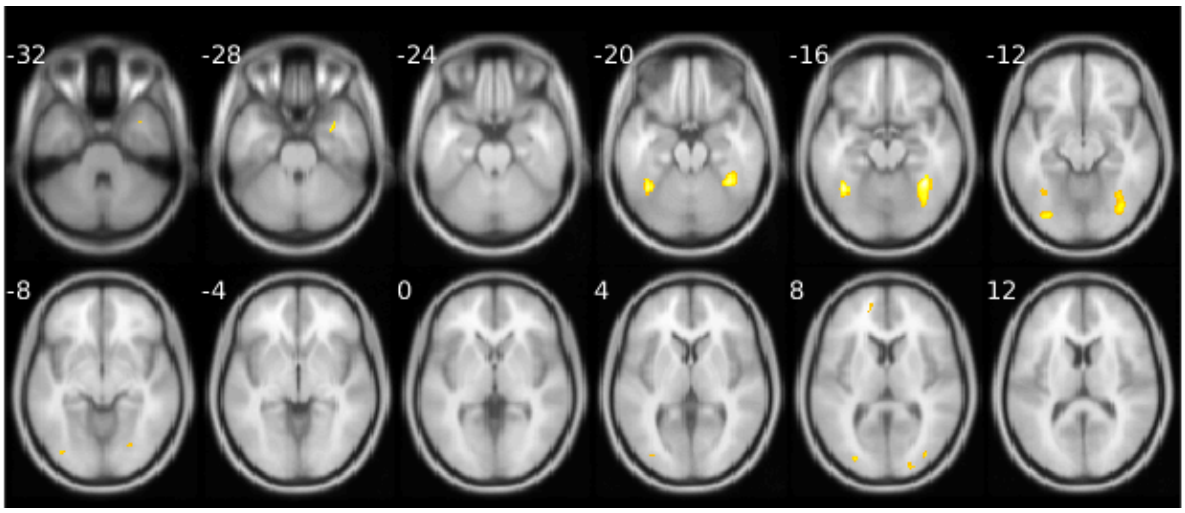

Figure 3-7

The activation in the fusiform gyrus for the main effect of task level. Results displayed using an uncorrected height threshold of p < .001 overlaid on the MNI152 template image provided with the xjview in SPM. Numbers show the z coordinate of each transracial slice. Only the right survived correction for multiple comparisons.

3.4 Discussion

In this study, I tested whether the 5-HT_7 antagonist, JNJ-18038683, could modulate the processing of faces expressing emotions using the pop-faces task.

3.4.1 Behavioural performance

Behaviourally, I used the two-way repeated measures ANOVA to test if there was significant difference between taking either one week of JNJ-18038683 or placebo. The results showed that there was no significant difference found in the accuracy and speed after taking 20mg JNJ-18038683 daily for one week. However, in the main effect of emotion analysis, I found that there were significant differences in accuracy and speed. In accuracy post-hoc analysis, participants had more corrects in responding happy faces; in speed post-hoc analysis, participants were slower in responding to fearful faces.

An a priori power analysis was conducted using G*Power 3.1 (Faul et al., 2007) to determine the required total sample size for a paired-samples t-test of the drug effect, with input parameters of $d = 0.70$, $\alpha = 0.05$, power = 0.80, and a two-tailed hypothesis. The analysis indicated a required total sample size of $n = 19$ to detect an effect of this magnitude or larger. The sample size of $n = 19$ should provide sufficient statistical sensitivity to test the hypothesis regarding whether JNJ-18038683 can modulate brain activity, but in this study $n = 14$. Post-hoc power analyses were conducted based on the effects observed in this study. For the comparison of accuracy and speed between the drug and placebo, with a sample size of 14 participants, a two-tailed dependent t-test, and the effect size found in our sample $d = 0.7$, $\alpha = 0.05$, the achieved power was 0.68. A higher proportion of correct gender discriminations in responding to happy faces and slower in fearful faces may be caused by several reasons. First, there is evidence that 'positive bias' in cognition, whereby people tend to pay more attention to positive

stimuli, which may lead to more accurate recognition of happy faces. When participants saw happy faces, they might unconsciously recognise happiness more quickly, which may improve their ability to recognise and respond to this positive emotion accurately (Tae et al., 2022). In addition, participants spend more time on responding to fearful faces, which might be related to cognitive resources. Evidence indicated that fearful faces can attract spatial attention only when they are consciously perceived and when there are sufficient attentional resources available (Qiu et al., 2023). Recently, researchers also found that responses were fastest and most accurate for happy expressions, but slowest and least accurate for fearful expressions (Barros et al., 2023).

3.4.2 Neuroimaging analysis

3.4.2.1 ROIs analysis

It was hoped to see whether the task activated the areas of ROIs and further whether activity in these regions was modulated by JNJ-18038683, but in the neuroimaging analysis, no areas were activated in the ROIs. In the whole brain mapping, the fusiform gyrus was activated at the task level, indicating the task was effective for this region. We failed to detect any observable effect of the drug, JNJ-18038683 using the gender discrimination emotional faces task.

In the hypothesis-led ROIs analyses of the fMRI data (using a mask including amygdala, hippocampus, thalamus, and sgACC), I found that no areas that were differentially activated across the three emotional conditions (i.e., neutral, fearful and happy) or modulated by the drug. This may be caused by several reasons. First, the ROIs being chosen due to the density of 5-HT_7 receptors in those regions (Fan et al., 2016; Hedlund & Sutcliffe, 2004), and excluding some regions linked to the performance of the

emotional task itself. This may also explain the lack of sgACC activation for the emotional task (Drevets et al., 2008; Kühn et al., 2012).

The previous studies showed amygdala and sgACC could be activated in face recognition tasks. There is some evidence that the amygdala activity may strongly connect with fearful faces perception (Adolphs, 2008; Breiter et al., 1996; Costafreda et al., 2008; Morris et al., 1998; Ruffman et al., 2008); a meta-analysis further identified that amygdala activation would be increased when responding fearful faces (Fusar-Poli et al., 2009). However, the amygdala is difficult to reliably find activity for (Costafreda et al., 2008). Some studies showed that hippocampus habituation to fearful faces in healthy control subjects (Holt et al., 2005), but we did not find a similar result. This may be due to the amygdala and the sgACC exhibited limited reliability across time, and the reliability of the more anterior areas (as opposed to the fusiform gyrus) appears to be only moderate to low consistent (Nord et al., 2017). The potential impact of this on task activations remains uncertain, and it is needed to have larger studies for a clearer understanding.

In addition, in the original paradigm, the participants were adolescents (Passamonti et al., 2010). Due to the task's inherent nature, the brief intervals between stimuli in contrast with fixation might have impacted its sensitivity. There was evidence showed that an interaction effect emerged between age and neuroticism may influence the results of emotional faces recognition task, and the study also suggested that high levels of neuroticism posed a disadvantage for younger adults, but not for older adults, in terms of their performance in emotion recognition tasks that aim to enhance arousal (Svärd et al., 2012). Since our study was conducted by healthy control adults rather than adolescents, the sensitivity of the paradigm might be influenced.

To our knowledge, most SSRIs need to be administered for more than two weeks, before the clinical benefits are detectable (Machado-Vieira et al., 2010; Taylor et al., 2006), and this might imply the duration of administering in serotonin-related compounds influenced the outcome. In human studies, the effects of antidepressants with 5-HT_7 affinity, like vortioxetine (which acts as an antagonist of 5-HT_3, 5-HT_{1D}, and 5-HT_7 receptors), were evaluated (Chen et al., 2018). Short-term and long-term clinical trials demonstrated the clinical efficacy of vortioxetine in treating depressive symptoms and cognitive deficits in major depressive disorder patients, and taking 10-20mg vortioxetine for 8 weeks could significantly enhance mood (Jacobsen et al., 2015; Mahableshwarkar et al., 2015; McIntyre et al., 2014). Therefore, future studies should be planned to test more robustly whether 20mg daily of JNJ-18038683 for one week, can modulate affect emotional performance and neural responses.

3.4.2.2 Whole-brain exploration

In the whole-brain exploration, we found activation in the fusiform gyrus varied as a function of the facial emotions (i.e., their valence). However, this differential sensitivity to emotional faces was not influenced by the administration of the drug. The fusiform gyrus is a large region in the inferior temporal cortex that plays a central role in object recognition, face perception, and reading (Weiner & Zilles, 2016); researchers have investigated its function in mental disorder studies (Jung et al., 2021; Ma et al., 2020). The fusiform gyrus is also strongly associated with the face recognition task (Sprengelmeyer et al., 1998; Surguladze et al., 2005). Consequently, the observed activation in this area is unsurprising (Guyer et al., 2008; Weiner & Zilles, 2016).

3.4.3 Limitations and future directions

This is a randomised, placebo-controlled, cross-over, double-blinded drug administration study which could improve the accuracy of the outcomes due to each participant acting as his or her own control, but there were still some limitations in the study.

1. The sufficiency of the paradigm: even though the emotional faces recognition task is a popular paradigm for evaluating emotional processing function, the issue of efficacy is still argued. Facial expressions can be classified to basic emotions (e.g. anger, disgust, fear, joy, sadness, and surprise) (Du et al., 2014), and may prove useful in the identification of individuals with psychotic or depression, at least to some extent (Monferrer et al., 2023). However, the efficacy of this was challenged: when assessing the reliability of neural responses to emotional faces in a sample of healthy controls, researchers found the experiment revealed that activation patterns within specific brain regions, such as the amygdala or sgACC, demonstrated limited reliability (Nord et al., 2017). Furthermore, neutral faces are not common in society, since the neutral faces is not common, the definition of 'neutral' should also be re-considered (Albohn & Adams, 2021). Lastly, as mentioned above, the original paradigm was designed for adolescents rather than adults. These raised concerns regarding the efficacy of the paradigm used. Given the findings, it is necessary to re-evaluate the effectiveness and to interpret the results conservatively.
2. Gender discrimination: the gender stereotype was an issue which has been raised by researchers (Adams et al., 2012; García-Gutiérrez et al., 2017; Hess et al., 2004). In a study, it showed that females showed more happiness and

fear expressions, and males showed more anger expressions (Hess et al., 2009). Since gender discrimination is at the heart of the task, it likely influenced the outcome of behavioural performance and neuroimaging analysis.

3. Limited drug administrating dosage and duration: the fact that the drug did not show any significant effects may be caused by the short duration and low dosage drug administrating of drug. Compared to other serotonergic drugs which need two weeks to work, one week duration is short (Machado-Vieira et al., 2010). In addition, in another study that tested JNJ-18038683, researchers used 20mg JNJ-18038683 from 20 days to 7 weeks. Additionally, there was a possibility that participants may not have been fully compliant in taking the drug; in our study, participants took the drugs home and completed a diary in the documents, but we did not check drug levels in the blood due to high costs. Further studies to clarify the issues would be helpful to clarify more details of drug onset, effective duration and dosage.
4. A small sample size: as pointed out above, we have a relatively small sample size, and we only analysed healthy controls' data (n = 14), compared to the typical sample size (n = 20 to n = 30) for fMRI research (Grady et al., 2021).

3.4.4 Conclusion

In this chapter, I aimed to test whether the 5-HT_7 antagonist, JNJ-18038683, could improve participants' performances or modulate their brain activations in the gender discrimination emotional faces processing task. Participants were asked to complete the pop-face task after being administered either the drug or placebo for one week. Results showed no significant differences after the one-week drug treatment compared to placebo, indicating that JNJ-18038683 may not modulate emotional processing in

healthy volunteers, or that this study was not sensitive to any modulation as described in the limitations. In the behavioural analysis, participants responded more corrects to happy faces, and responded to fearful faces more slowly. Some factors may have contributed to this unexpected finding, including positivity bias and facial features. The fMRI data analysis did not show any differential activation of regions in the three emotional conditions, and the amygdala, hippocampus, thalamus, and sgACC were not differentially activated in response to fearful faces. Some limitations, such as efficacy of the paradigm (i.e., that participants we focused on gender discrimination rather than the emotions expressed by the faces), the drug dosage being too low or administration duration being too short, could not be avoided or mitigated in this study, but should be considered when planning future investigations.

References

Abbas, A. I., Hedlund, P. B., Huang, X.-P., Tran, T. B., Meltzer, H. Y., & Roth, B. L. (2009). Amisulpride is a potent 5-HT7 antagonist: relevance for antidepressant actions in vivo. *Psychopharmacology*, *205*(1), 119-128. https://doi.org/https://dx.doi.org/10.1007/s00213-009-1521-8

Adams, R. B., Jr., Nelson, A. J., Soto, J. A., Hess, U., & Kleck, R. E. (2012). Emotion in the neutral face: a mechanism for impression formation? *Cogn Emot*, *26*(3), 431-441. https://doi.org/10.1080/02699931.2012.666502

Adolphs, R. (2008). Fear, faces, and the human amygdala. *Curr Opin Neurobiol*, *18*(2), 166-172. https://doi.org/10.1016/j.conb.2008.06.006

Adriani, W., Travaglini, D., Lacivita, E., Saso, L., Leopoldo, M., & Laviola, G. (2012). Modulatory effects of two novel agonists for serotonin receptor 7 on emotion, motivation and circadian rhythm profiles in mice. *Neuropharmacology*, *62*(2), 833-842. https://doi.org/10.1016/j.neuropharm.2011.09.012

Albohn, D. N., & Adams, R. B. (2021). Emotion Residue in Neutral Faces: Implications for Impression Formation. *Social Psychological and Personality Science*, *12*(4), 479-486. https://doi.org/10.1177/1948550620923229

Altman, E. G., Hedeker, D., Peterson, J. L., & Davis, J. M. (1997). The Altman Self-Rating Mania Scale. *Biol Psychiatry*, *42*(10), 948-955. https://doi.org/10.1016/s0006-3223(96)00548-3

Andressen, K. W., Manfra, O., Brevik, C. H., Ulsund, A. H., Vanhoenacker, P., Levy, F. O., & Krobert, K. A. (2015). The atypical antipsychotics clozapine and olanzapine promote down-regulation and display functional selectivity at human 5-HT7 receptors. *Br J Pharmacol*, *172*(15), 3846-3860. https://doi.org/10.1111/bph.13169

Arioli, M., Crespi, C., & Canessa, N. (2018). Social Cognition through the Lens of Cognitive and Clinical Neuroscience. *Biomed Res Int*, *2018*, 4283427. https://doi.org/10.1155/2018/4283427

Baldwin, D., Loft, H., & Dragheim, M. . (2011). A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in MDD treatment. *European Neuropsychopharmacology*, *21*(SUPPL. 3), S390. https://doi.org/http://dx.doi.org/10.1016/S0924-977X%2811%2970627-7 (24th Congress of the European College of Neuropsychopharmacology, ECNP 2011. Paris France.

Barceló, F., & Knight, R. T. (2002). Both random and perseverative errors underlie WCST deficits in prefrontal patients. *Neuropsychologia*, *40*(3), 349-356. https://doi.org/10.1016/s0028-3932(01)00110-5

Bard, J. A., Zgombick, J., Adham, N., Vaysse, P., Branchek, T. A., & Weinshank, R. L. (1993). Cloning of a novel human serotonin receptor (5-HT7) positively linked to adenylate cyclase. *J Biol Chem*, *268*(31), 23422-23426.

Barros, F., Soares, S. C., Rocha, M., Bem-Haja, P., Silva, S., & Lundqvist, D. (2023). The angry versus happy recognition advantage: the role of emotional and physical properties. *Psychol Res*, *87*(1), 108-123. https://doi.org/10.1007/s00426-022-01648-0

Birnbaum, M. L., Cleary, S. D., Ramsay Wan, C., Pauselli, L., & Compton, M. T. (2019). Factor structure of the Cannabis Experiences Questionnaire in a first-episode psychosis sample. *Early Interv Psychiatry*, *13*(3), 495-501. https://doi.org/10.1111/eip.12509

Blattner, K. M., Canney, D. J., Pippin, D. A., & Blass, B. E. (2019). Pharmacology and Therapeutic Potential of the 5-HT(7) Receptor. *ACS Chem Neurosci*, *10*(1), 89-119. https://doi.org/10.1021/acschemneuro.8b00283

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., Strauss, M. M., Hyman, S. E., & Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*, *17*(5), 875-887. https://doi.org/10.1016/s0896-6273(00)80219-6

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*, *28*(2), 193-213. https://doi.org/10.1016/0165-1781(89)90047-4

Canale, V., Kurczab, R., Partyka, A., Satała, G., Lenda, T., Jastrzębska-Więsek, M., Wesołowska, A., Bojarski, A. J., & Zajdel, P. (2016). Towards new 5-HT7 antagonists among arylsulfonamide derivatives of (aryloxy)ethyl-alkyl amines: Multiobjective based design, synthesis, and antidepressant and anxiolytic properties. *Eur J Med Chem*, *108*, 334-346. https://doi.org/10.1016/j.ejmech.2015.11.040

Canale, V., Partyka, A., Kurczab, R., Krawczyk, M., Kos, T., Satała, G., Kubica, B., Jastrzębska-Więsek, M., Wesołowska, A., Bojarski, A. J., Popik, P., & Zajdel, P. (2017). Novel 5-HT(7)R antagonists, arylsulfonamide derivatives of (aryloxy)propyl piperidines: Add-on effect to the antidepressant activity of SSRI and DRI, and pro-cognitive profile. *Bioorg Med Chem*, *25*(10), 2789-2799. https://doi.org/10.1016/j.bmc.2017.03.057

Cates, L. N., Roberts, A. J., Huitron-Resendiz, S., & Hedlund, P. B. (2013). Effects of lurasidone in behavioral models of depression. Role of the 5-HT7 receptor subtype. *Neuropharmacology*, *70*, 211-217. https://doi.org/https://dx.doi.org/10.1016/j.neuropharm.2013.01.023

Chen, C., Hu, C. H., & Cheng, Y. (2017). Mismatch negativity (MMN) stands at the crossroads between explicit and implicit emotional processing. *Hum Brain Mapp*, *38*(1), 140-150. https://doi.org/10.1002/hbm.23349

Chen, G., Højer, A. M., Areberg, J., & Nomikos, G. (2018). Vortioxetine: Clinical Pharmacokinetics and Drug Interactions. *Clin Pharmacokinet*, *57*(6), 673-686. https://doi.org/10.1007/s40262-017-0612-7

Cisler, J. M., & Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clin Psychol Rev*, *30*(2), 203-216. https://doi.org/10.1016/j.cpr.2009.11.003

Costafreda, S. G., Brammer, M. J., David, A. S., & Fu, C. H. (2008). Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. *Brain Res Rev*, *58*(1), 57-70. https://doi.org/10.1016/j.brainresrev.2007.10.012

Delcourte, S., Abrial, E., Etievant, A., Rovera, R., Arnt, J., Didriksen, M., & Haddjeri, N. (2017). Asenapine modulates mood-related behaviors and 5-HT1A/7 receptors-mediated neurotransmission. *CNS neuroscience & therapeutics*, *23*(6), 518-525. https://doi.org/10.1111/cns.12698

Drevets, W. C., Savitz, J., & Trimble, M. (2008). The subgenual anterior cingulate cortex in mood disorders. *CNS Spectr*, *13*(8), 663-681. https://doi.org/10.1017/s1092852900013754

Du, S., Tao, Y., & Martinez, A. M. (2014). Compound facial expressions of emotion. *Proc Natl Acad Sci U S A*, *111*(15), E1454-1462. https://doi.org/10.1073/pnas.1322355111

East, S. Z., Burnet, P. W., Kerwin, R. W., & Harrison, P. J. (2002). An RT-PCR study of 5-HT(6) and 5-HT(7) receptor mRNAs in the hippocampal formation and prefrontal cortex in schizophrenia. *Schizophr Res*, *57*(1), 15-26. https://doi.org/10.1016/s0920-9964(01)00323-1

Ehlen, J. C., Grossman, G. H., & Glass, J. D. (2001). In vivo resetting of the hamster circadian clock by 5-HT7 receptors in the suprachiasmatic nucleus. *J Neurosci*, *21*(14), 5351-5357. https://doi.org/10.1523/jneurosci.21-14-05351.2001

Ekman, P. (1992a). Are there basic emotions? *Psychol Rev*, *99*(3), 550-553. https://doi.org/10.1037/0033-295x.99.3.550

Ekman, P. (1992b). Facial expressions of emotion: an old controversy and new findings. *Philos Trans R Soc Lond B Biol Sci*, *335*(1273), 63-69. https://doi.org/10.1098/rstb.1992.0008

Ekman, P. (1993). Facial expression and emotion. *Am Psychol*, *48*(4), 384-392. https://doi.org/10.1037//0003-066x.48.4.384

Etkin, A., Klemenhagen, K. C., Dudman, J. T., Rogan, M. T., Hen, R., Kandel, E. R., & Hirsch, J. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron*, *44*(6), 1043-1055. https://doi.org/10.1016/j.neuron.2004.12.006

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A. R., Fox, P. T., Eickhoff, S. B., Yu, C., & Jiang, T. (2016). The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture. *Cereb Cortex*, *26*(8), 3508-3526. https://doi.org/10.1093/cercor/bhw157

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*, *39*(2), 175-191. https://doi.org/10.3758/bf03193146

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., Benedetti, F., Abbamonte, M., Gasparotti, R., Barale, F., Perez, J., McGuire, P., & Politi, P. (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *J Psychiatry Neurosci*, *34*(6), 418-432.

García-Gutiérrez, A., Aguado, L., Romero-Ferreiro, V., & Pérez-Moreno, E. (2017). Discrimination of face gender and expression under dual-task conditions. *Atten Percept Psychophys*, *79*(2), 614-627. https://doi.org/10.3758/s13414-016-1236-y

Grady, C. L., Rieck, J. R., Nichol, D., Rodrigue, K. M., & Kennedy, K. M. (2021). Influence of sample size and analytic approach on stability and interpretation of brain-behavior correlations in task-related fMRI data. *Hum Brain Mapp*, *42*(1), 204-219. https://doi.org/10.1002/hbm.25217

Guyer, A. E., Monk, C. S., McClure-Tone, E. B., Nelson, E. E., Roberson-Nay, R., Adler, A. D., Fromm, S. J., Leibenluft, E., Pine, D. S., & Ernst, M. (2008). A developmental examination of amygdala response to facial expressions. *J Cogn Neurosci*, *20*(9), 1565-1582. https://doi.org/10.1162/jocn.2008.20114

Hagan, J. J., Price, G. W., Jeffrey, P., Deeks, N. J., Stean, T., Piper, D., Smith, M. I., Upton, N., Medhurst, A. D., Middlemiss, D. N., Riley, G. J., Lovell, P. J., Bromidge, S. M., &

Thomas, D. R. (2000). Characterization of SB-269970-A, a selective 5-HT(7) receptor antagonist. *Br J Pharmacol*, *130*(3), 539-548. https://doi.org/10.1038/sj.bjp.0703357

Hamilton, M. (1959). The assessment of anxiety states by rating. *Br J Med Psychol*, *32*(1), 50-55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x

Hamilton, M. (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry*, *23*(1), 56-62. https://doi.org/10.1136/jnnp.23.1.56

Hamilton, M. (1980). Rating depressive patients. *J Clin Psychiatry*, *41*(12 Pt 2), 21-24.

Harmer, C. J., Goodwin, G. M., & Cowen, P. J. (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *Br J Psychiatry*, *195*(2), 102-108. https://doi.org/10.1192/bjp.bp.108.051193

Hauser, S. R., Hedlund, P. B., Roberts, A. J., Sari, Y., Bell, R. L., & Engleman, E. A. (2014). The 5-HT7 receptor as a potential target for treating drug and alcohol abuse. *Front Neurosci*, *8*, 448. https://doi.org/10.3389/fnins.2014.00448

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerström, K. O. (1991). The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict*, *86*(9), 1119-1127. https://doi.org/10.1111/j.1360-0443.1991.tb01879.x

Hedlund, P. B., & Sutcliffe, J. G. (2004). Functional, molecular and pharmacological advances in 5-HT7 receptor research. *Trends Pharmacol Sci*, *25*(9), 481-486. https://doi.org/10.1016/j.tips.2004.07.002

Hess, U., Adams, R. B., Jr., Grammer, K., & Kleck, R. E. (2009). Face gender and emotion expression: are angry women more like men? *J Vis*, *9*(12), 19.11-18. https://doi.org/10.1167/9.12.19

Hess, U., Adams, R. B., Jr., & Kleck, R. E. (2004). Facial appearance, gender, and emotion expression. *Emotion*, *4*(4), 378-388. https://doi.org/10.1037/1528-3542.4.4.378

Holt, D. J., Weiss, A. P., Rauch, S. L., Wright, C. I., Zalesak, M., Goff, D. C., Ditman, T., Welsh, R. C., & Heckers, S. (2005). Sustained activation of the hippocampus in response to fearful faces in schizophrenia. *Biol Psychiatry*, *57*(9), 1011-1019. https://doi.org/10.1016/j.biopsych.2005.01.033

Jacobsen, P. L., Mahableshwarkar, A. R., Serenko, M., Chan, S., & Trivedi, M. H. (2015). A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. *J Clin Psychiatry*, *76*(5), 575-582. https://doi.org/10.4088/JCP.14m09335

Jankowska, A., Satała, G., Kołaczkowski, M., Bucki, A., Głuch-Lutwin, M., Świerczek, A., Pociecha, K., Partyka, A., Jastrzębska-Więsek, M., Lubelska, A., Latacz, G., Gawalska, A., Bojarski, A. J., Wyska, E., & Chłoń-Rzepa, G. (2020). Novel anilide and benzylamide derivatives of arylpiperazinylalkanoic acids as 5-HT(1A)/5-HT(7) receptor antagonists and phosphodiesterase 4/7 inhibitors with procognitive and antidepressant activity. *Eur J Med Chem*, *201*, 112437. https://doi.org/10.1016/j.ejmech.2020.112437

Jung, S., Kim, J. H., Kang, N. O., Sung, G., Ko, Y. G., Bang, M., Park, C. I., & Lee, S. H. (2021). Fusiform gyrus volume reduction associated with impaired facial expressed emotion recognition and emotional intensity recognition in patients with schizophrenia spectrum psychosis. *Psychiatry Res Neuroimaging*, *307*, 111226. https://doi.org/10.1016/j.pscychresns.2020.111226

Kalhan, S., McFadyen, J., Tsuchiya, N., & Garrido, M. I. (2022). Neural and computational processes of accelerated perceptual awareness and decisions: A 7T fMRI study. *Hum Brain Mapp*, *43*(12), 3873-3886. https://doi.org/10.1002/hbm.25889

Kennedy, S., Grouin, J., Cadour, S., Robert, V., & Picarel-Blanchot, F. (2016). Relative short-term efficacy and acceptability of agomelatine versus vortioxetine in adult patients suffering from major depressive disorder. *European Neuropsychopharmacology*, *26*(Supplement 2), S457-S458. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed17&NEWS=N&AN=614139003 (29th European College of Neuropsychopharmacology Congress, ECNP 2016. Austria.)

Kühn, S., Vanderhasselt, M. A., De Raedt, R., & Gallinat, J. (2012). Why ruminators won't stop: the structural and resting state correlates of rumination and its relation to depression. *J Affect Disord*, *141*(2-3), 352-360. https://doi.org/10.1016/j.jad.2012.03.024

Leopoldo, M., Lacivita, E., Berardi, F., Perrone, R., & Hedlund, P. B. (2011). Serotonin 5-HT7 receptor agents: Structure-activity relationships and potential therapeutic applications in central nervous system disorders. *Pharmacol Ther*, *129*(2), 120-148. https://doi.org/10.1016/j.pharmthera.2010.08.013

Lieberman, M. D. (2007). Social cognitive neuroscience: a review of core processes. *Annu Rev Psychol*, *58*, 259-289. https://doi.org/10.1146/annurev.psych.58.110405.085654

Liu, M., Liu, C. H., Zheng, S., Zhao, K., & Fu, X. (2021). Reexamining the neural network involved in perception of facial expression: A meta-analysis. *Neurosci Biobehav Rev*, *131*, 179-191. https://doi.org/10.1016/j.neubiorev.2021.09.024

Lovenberg, T. W., Baron, B. M., de Lecea, L., Miller, J. D., Prosser, R. A., Rea, M. A., Foye, P. E., Racke, M., Slone, A. L., Siegel, B. W., & et al. (1993). A novel adenylyl cyclase-activating serotonin receptor (5-HT7) implicated in the regulation of mammalian circadian rhythms. *Neuron*, *11*(3), 449-458. https://doi.org/10.1016/0896-6273(93)90149-l

Ma, D., Fetahu, I. S., Wang, M., Fang, R., Li, J., Liu, H., Gramyk, T., Iwanicki, I., Gu, S., Xu, W., Tan, L., Wu, F., & Shi, Y. G. (2020). The fusiform gyrus exhibits an epigenetic signature for Alzheimer's disease. *Clin Epigenetics*, *12*(1), 129. https://doi.org/10.1186/s13148-020-00916-3

Machado-Vieira, R., Baumann, J., Wheeler-Castillo, C., Latov, D., Henter, I. D., Salvadore, G., & Zarate, C. A. (2010). The Timing of Antidepressant Effects: A Comparison of Diverse Pharmacological and Somatic Treatments. *Pharmaceuticals (Basel)*, *3*(1), 19-41. https://doi.org/10.3390/ph3010019

Mahableshwarkar, A., Jacobsen, P., Chen, Y., Serenko, M., & Palo, W. (2014). The Safety and tolerability profile of vortioxetine in the treatment of patients with major depressive disorder aged 65 years and older. *American Journal of Geriatric Psychiatry*, *22*(3 SUPPL. 1), S143-S144. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed15&NEWS=N&AN=71442072 (2014 American Association for Geriatric Psychiatry, AAGP Annual Meeting. Orlando, FL United States. (var.pagings).)

Mahableshwarkar, A. R., Zajecka, J., Jacobson, W., Chen, Y., & Keefe, R. S. (2015). A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder. *Neuropsychopharmacology*, *40*(8), 2025-2037. https://doi.org/10.1038/npp.2015.52

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*, *19*(3), 1233-1239. https://doi.org/10.1016/s1053-8119(03)00169-1

Mayer, J. D., Salovey, P., Caruso, D. R., & Sitarenios, G. (2001). Emotional intelligence as a standard intelligence. *Emotion*, *1*(3), 232-242.

McIntyre, R. S., Lophaven, S., & Olsen, C. K. (2013). Randomized, double-blind, placebo-controlled study of the efficacy of vortioxetine on cognitive dysfunction in adult patients with major depressive disorder (MDD). *Neuropsychopharmacology*, *38*(SUPPL. 2), S380-S381. https://doi.org/10.1038/npp.2013.280 (52nd Annual Meeting of the American College of Neuropsychopharmacology, ACNP 2013. Hollywood, FL United States. (var.pagings).)

McIntyre, R. S., Lophaven, S., & Olsen, C. K. (2014). A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*, *17*(10), 1557-1567. https://doi.org/10.1017/s1461145714000546

Meneses, A. (2004). Effects of the 5-HT7 receptor antagonists SB-269970 and DR 4004 in autoshaping Pavlovian/instrumental learning task. *Behav Brain Res*, *155*(2), 275-282. https://doi.org/10.1016/j.bbr.2004.04.026

Monferrer, M., García, A. S., Ricarte, J. J., Montes, M. J., Fernández-Caballero, A., & Fernández-Sotos, P. (2023). Facial emotion recognition in patients with depression compared to healthy controls when using human avatars. *Sci Rep*, *13*(1), 6007. https://doi.org/10.1038/s41598-023-31277-5

Montagne, B., Kessels, R. P., De Haan, E. H., & Perrett, D. I. (2007). The Emotion Recognition Task: a paradigm to measure the perception of facial emotional expressions at different intensities. *Percept Mot Skills*, *104*(2), 589-598. https://doi.org/10.2466/pms.104.2.589-598

Morris, J. S., Friston, K. J., Büchel, C., Frith, C. D., Young, A. W., Calder, A. J., & Dolan, R. J. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain*, *121 (Pt 1)*, 47-57. https://doi.org/10.1093/brain/121.1.47

Nord, C. L., Gray, A., Charpentier, C. J., Robinson, O. J., & Roiser, J. P. (2017). Unreliability of putative fMRI biomarkers during emotional face processing. *Neuroimage*, *156*, 119-127. https://doi.org/10.1016/j.neuroimage.2017.05.024

Passamonti, L., Fairchild, G., Goodyer, I. M., Hurford, G., Hagan, C. C., Rowe, J. B., & Calder, A. J. (2010). Neural abnormalities in early-onset and adolescence-onset conduct disorder. *Arch Gen Psychiatry*, *67*(7), 729-738. https://doi.org/10.1001/archgenpsychiatry.2010.75

Pera-Guardiola, V., Contreras-Rodríguez, O., Batalla, I., Kosson, D., Menchón, J. M., Pifarré, J., Bosque, J., Cardoner, N., & Soriano-Mas, C. (2016). Brain Structural Correlates of

Emotion Recognition in Psychopaths. *PLoS One*, *11*(5), e0149807. https://doi.org/10.1371/journal.pone.0149807

Qiu, Z., Jiang, J., Becker, S. I., & Pegna, A. J. (2023). Attentional capture by fearful faces requires consciousness and is modulated by task-relevancy: A dot-probe EEG study. *Front Neurosci*, *17*, 1152220. https://doi.org/10.3389/fnins.2023.1152220

Reinert, D. F., & Allen, J. P. (2002). The Alcohol Use Disorders Identification Test (AUDIT): a review of recent research. *Alcohol Clin Exp Res*, *26*(2), 272-279.

Riedel, P., Jacob, M. J., Müller, D. K., Vetter, N. C., Smolka, M. N., & Marxen, M. (2016). Amygdala fMRI Signal as a Predictor of Reaction Time. *Front Hum Neurosci*, *10*, 516. https://doi.org/10.3389/fnhum.2016.00516

Ruat, M., Traiffort, E., Leurs, R., Tardivel-Lacombe, J., Diaz, J., Arrang, J. M., & Schwartz, J. C. (1993). Molecular cloning, characterization, and localization of a high-affinity serotonin receptor (5-HT7) activating cAMP formation. *Proc Natl Acad Sci U S A*, *90*(18), 8547-8551. https://doi.org/10.1073/pnas.90.18.8547

Ruffman, T., Henry, J. D., Livingstone, V., & Phillips, L. H. (2008). A meta-analytic review of emotion recognition and aging: implications for neuropsychological models of aging. *Neurosci Biobehav Rev*, *32*(4), 863-881. https://doi.org/10.1016/j.neubiorev.2008.01.001

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., Markowitz, J. C., Ninan, P. T., Kornstein, S., Manber, R., Thase, M. E., Kocsis, J. H., & Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*, *54*(5), 573-583. https://doi.org/10.1016/s0006-3223(02)01866-8

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*, *59 Suppl 20*, 22-33;quiz 34-57.

Shelton, J., Yun, S., Losee Olson, S., Turek, F., Bonaventure, P., Dvorak, C., Lovenberg, T., & Dugovic, C. (2014). Selective pharmacological blockade of the 5-HT7 receptor attenuates light and 8-OH-DPAT induced phase shifts of mouse circadian wheel running activity. *Front Behav Neurosci*, *8*, 453. https://doi.org/10.3389/fnbeh.2014.00453

Siegel-Ramsay, J. E., Wu, B., Kapczinski, F., Lanza di Scalea, T., David, S., Frey, B. N., Strakowski, S. M., & Almeida, J. R. C. (2023). Functional assessment short test (FAST): Self-administration in outpatient mental health settings. *J Psychiatr Res*, *160*, 258-262. https://doi.org/10.1016/j.jpsychires.2023.02.029

Sprengelmeyer, R., Rausch, M., Eysel, U. T., & Przuntek, H. (1998). Neural structures associated with recognition of facial expressions of basic emotions. *Proc Biol Sci*, *265*(1409), 1927-1931. https://doi.org/10.1098/rspb.1998.0522

Sprouse, J., Reynolds, L., Li, X., Braselton, J., & Schmidt, A. (2004). 8-OH-DPAT as a 5-HT7 agonist: phase shifts of the circadian biological clock through increases in cAMP production. *Neuropharmacology*, *46*(1), 52-62. https://doi.org/10.1016/j.neuropharm.2003.08.007

Stanford, S. C. (2020). Some Reasons Why Preclinical Studies of Psychiatric Disorders Fail to Translate: What Can Be Rescued from the Misunderstanding and Misuse of Animal 'Models'? *Altern Lab Anim*, *48*(3), 106-115. https://doi.org/10.1177/0261192920939876

Strober, L. B., Binder, A., Nikelshpur, O. M., Chiaravalloti, N., & DeLuca, J. (2016). The Perceived Deficits Questionnaire: Perception, Deficit, or Distress? *Int J MS Care*, *18*(4), 183-190. https://doi.org/10.7224/1537-2073.2015-028

Surguladze, S., Brammer, M. J., Keedwell, P., Giampietro, V., Young, A. W., Travis, M. J., Williams, S. C., & Phillips, M. L. (2005). A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biol Psychiatry*, *57*(3), 201-209. https://doi.org/10.1016/j.biopsych.2004.10.028

Svärd, J., Wiens, S., & Fischer, H. (2012). Superior recognition performance for happy masked and unmasked faces in both younger and older adults. *Front Psychol*, *3*, 520. https://doi.org/10.3389/fpsyg.2012.00520

Tae, J., Weldon, R. B., Almasi, R. C., An, C., Lee, Y., & Sohn, M. H. (2022). Stimuli with a positive valence can facilitate cognitive control. *Mem Cognit*, *50*(5), 911-924. https://doi.org/10.3758/s13421-021-01257-z

Taylor, M. J., Freemantle, N., Geddes, J. R., & Bhagwagar, Z. (2006). Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry*, *63*(11), 1217-1223. https://doi.org/10.1001/archpsyc.63.11.1217

Thomas, D. R., Melotto, S., Massagrande, M., Gribble, A. D., Jeffrey, P., Stevens, A. J., Deeks, N. J., Eddershaw, P. J., Fenwick, S. H., Riley, G., Stean, T., Scott, C. M., Hill, M. J., Middlemiss, D. N., Hagan, J. J., Price, G. W., & Forbes, I. T. (2003). SB-656104-A, a

novel selective 5-HT7 receptor antagonist, modulates REM sleep in rats. *Br J Pharmacol*, *139*(4), 705-714. https://doi.org/10.1038/sj.bjp.0705290

Thompson, E. (2015). Hamilton Rating Scale for Anxiety (HAM-A). *Occup Med (Lond)*, *65*(7), 601. https://doi.org/10.1093/occmed/kqv054

Tomassini, L., Perrini, F., Cuomo, I., Motta, P., Amici, E., & De Filippis, S. (2017). Efficacy, safety, and tolerability of vortioxetine in the treatment of mood disorders. *European Neuropsychopharmacology*, *27*(Supplement 4), S863-S864. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed18&NEWS=N&AN=619297550 (30th European College of Neuropsychopharmacology Congress, ECNP 2017. France.)

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., Marcus, D. J., Westerlund, A., Casey, B. J., & Nelson, C. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res*, *168*(3), 242-249. https://doi.org/10.1016/j.psychres.2008.05.006

Vergallito, A., Mattavelli, G., Gerfo, E. L., Anzani, S., Rovagnati, V., Speciale, M., Vinai, P., Vinai, P., Vinai, L., & Lauro, L. J. R. (2020). Explicit and Implicit Responses of Seeing Own vs. Others' Emotions: An Electromyographic Study on the Neurophysiological and Cognitive Basis of the Self-Mirroring Technique. *Front Psychol*, *11*, 433. https://doi.org/10.3389/fpsyg.2020.00433

Weiner, K. S., & Zilles, K. (2016). The anatomical and functional specialization of the fusiform gyrus. *Neuropsychologia*, *83*, 48-62. https://doi.org/10.1016/j.neuropsychologia.2015.06.033

Wesolowska, A., Tatarczynska, E., Nikiforuk, A., & Chojnacka-Wojcik, E. (2007). Enhancement of the anti-immobility action of antidepressants by a selective 5-HT7 receptor antagonist in the forced swimming test in mice. *European Journal of Pharmacology*, *555*(1), 43-47. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=17109856

Xiao, R., Li, X., Li, L., & Wang, Y. (2016). Can We Distinguish Emotions from Faces? Investigation of Implicit and Explicit Processes of Peak Facial Expressions. *Front Psychol*, *7*, 1330. https://doi.org/10.3389/fpsyg.2016.01330

Yatham, L. N., Torres, I. J., Malhi, G. S., Frangou, S., Glahn, D. C., Bearden, C. E., Burdick, K. E., Martínez-Arán, A., Dittmann, S., Goldberg, J. F., Ozerdem, A., Aydemir, O., & Chengappa, K. N. (2010). The International Society for Bipolar Disorders-Battery for

Assessment of Neurocognition (ISBD-BANC). *Bipolar Disord*, *12*(4), 351-363. https://doi.org/10.1111/j.1399-5618.2010.00830.x

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*, *133*, 429-435. https://doi.org/10.1192/bjp.133.5.429

Chapter 4 fMRI – N-back working memory task

4.0 Abstract

In the systematic review, it was clear that 5-HT_7 receptor antagonists are a promising target for improving cognitive functions. The N-back task has been widely used to evaluate working memory in neuroimaging studies. In this chapter, the N-back working memory paradigm was used to test if the 5-HT_7 antagonist could modulate participants' working memory function.

18 participants were recruited, with data from 14 healthy participants included in the analysis. The study required four visits: the first for screening, the second to obtain a baseline of emotional and cognitive functions, and the third and fourth were for neuroimaging, in which participants undertook the gender discrimination emotional faces task, N-back working memory paradigm and performed tasks using the International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC) cognitive function assessment. Participants took a selective 5-HT_7 antagonist, JNJ-18038683 20mg or placebo daily for one week prior to the third and fourth visits within a double-blind, placebo-controlled, randomised cross-over study design.

In addition to the fMRI analysis, the behavioural performance, including accuracy (proportion of correct responses) and speed (mean reaction time), was analysed. To confirm the task activated expected regions and assess potential drug effects in these a priori defined regions, ROI analysis of the fMRI data was then conducted within the cognitive control network (i.e., the postcentral gyrus, praecuneus, angular gyrus, anterior and posterior divisions of the supramarginal gyrus, parietal operculum cortex, superior parietal lobule, superior and the middle frontal gyri). Lastly, whole-brain mapping was conducted to explore brain activations and drug-induced changes in brain activation.

In behavioural analysis, participants showed no difference between the drug and placebo visit. In neuroimaging analysis, significant task-related activation was found in the inferior parietal lobule, middle frontal gyrus and postcentral gyrus. In whole-brain mapping, the caudate was the centre of a cluster defined by a significant load-by-treatment interaction.

The 5-HT_7 antagonist, JNJ-18038683, could be a promising drug for modulating brain activation for working memory. However, there were some limitations, including small sample size and bias in participant selection (i.e., only analysed healthy controls' data). Future studies should be conducted with a larger sample size and expand on the findings by including individuals with bipolar disorder.

4.1 Introduction

4.1.1 Cognitive functions and 5-HT$_7$

In chapter 3, I explored whether the 5-HT$_7$ antagonist, JNJ-18038683, could modulate emotional processing function with pop-faces fMRI paradigm. In this chapter, I focused on JNJ-18038683's effects on cognitive function, specifically working memory, with the N-back fMRI paradigm. In the previous systematic review, we found cognitive improvement both in animal and human studies. The improvements were present in pharmacologically impaired and non-impaired animals using selective 5-HT$_7$ antagonists and compounds with 5-HT$_7$ antagonist activity. In humans, the evidence was limited to non-selective compounds with 5-HT$_7$ activity.

Research has shown that individuals with bipolar disorder often have difficulties with their cognitive functions. These challenges can affect various aspects of cognition: between 9.6% and 51.9% of people with bipolar disorder may experience problems with working memory and attention, and 12% to 40% of them may have some level of cognitive impairment, which can affect areas such as verbal memory, working memory, and executive functions (Burdick et al., 2014; Solé et al., 2017). This impairment, however, may be improved by compounds with 5-HT$_7$ affinities.

In animal studies, several studies, showed that 5-HT$_7$ compounds were associated with improved memory: a 5-HT$_7$ antagonist, compound 25, showed improved performance on novel object recognition task, interpreted as episodic memory improvements (Canale et al., 2017); other 5-HT$_7$ antagonists, namely compound 31 & compound 33, ameliorated phencyclidine-induced memory deficits in rats (Canale, Kurczab, Partyka, Satała, Słoczyńska, et al., 2016); the other weak 5-HT$_7$ antagonist, compound 22,

significantly reversed MK-801-induced episodic memory deficits (Jankowska et al., 2020). In a mouse model, 5-HT_7 receptor knock-out mice have been used in various experiments to demonstrate the involvement of 5-HT_7 receptors in regulating mood, memory processing, and cognition (Costa et al., 2012; Żmudzka et al., 2018).

In human studies, people with major depressive disorder reported improved subjective and objective measures of cognitive functions in neuropsychological tests after 8 weeks vortioxetine (an antidepressant with 5-HT_7 affinity) administration (McIntyre et al., 2014). A study found vortioxetine appeared to have greater improvement in cognitive and physical functioning questionnaire (CPFQ) scores compared to placebo, but this difference did not reach the level of statistical significance. Despite this, such findings suggest that the potential benefits of such drugs should be further investigated (Mahableshwarkar et al., 2015). The human studies were consistent with the animal studies, providing a promising target outcome for pharmacological treatments. However, despite some indirect evidence to support 5-HT_7 being associated cognitive modulation via drugs with 5-HT_7 affinity (Okada et al., 2021; Westrich et al., 2015), there is a lack data with selective 5-HT_7 modulation. The studies to date suggest 5-HT_7 antagonists could be candidates for improving bipolar disorder patients' cognitive impairments. Thus, I investigated the effect of a selective 5-HT_7 antagonist on working memory performance and task-related brain activity.

Among the compounds with 5-HT_7 affinity, JNJ-18038683 is a compound that acts as an antagonist of the 5-HT_7 receptor (Bonaventure et al., 2012; Shelton et al., 2014). It was developed by Janssen Research & Development, LLC, and is now at the phase 2 stage. In a study, administration of JNJ-18038683 was found to increase the latency of

rapid eye movement (REM) sleep in rats and reduce the amount of REM sleep; JNJ-18038683 was also found to potentiate the effects of citalopram on REM sleep latency and REM sleep reduction in rats. In the same article, researchers also found JNJ-18038683 improved people's emotion (Bonaventure et al., 2012).

In this chapter, I reported the results of a behavioural and neuroimaging investigation of the effects of a one-week course of 20mg daily of JNJ-18038683 on the N-back working memory task.

4.1.2 Working memory and N-back paradigm

Working memory is the ability to maintain and manipulate information in mind (Diamond, 2013). In order to achieve this, successful working memory can be considered a compound process that incorporates aspects of inhibitory and executive control; furthermore, manipulation, and utilisation, requiring the integration of multiple cognitive functions (Kane & Engle, 2002).

The N-back task is a working memory test, which was first introduced by Wayne Kirchner (Kirchner, 1958). The task requires several cognition processes, including encoding the stimulus, storage of the stimulus, renewing the stimulus, inhibiting the non-presented stimulus, and abandoning non-presented stimulus from memory (Rac-Lubashevsky & Kessler, 2016). After several decades of development, the usage of N-back has expanded from use in cognitive assessment to brain measurement with (electroencephalogram) EEG (Cutillo and Gevins 1993) and fMRI (Owen et al. 2005) and also in cognitive training (Jaeggi et al., 2010; Lawlor-Savage & Goghari, 2016; Soveri et al., 2017). This task is widely used in evaluating working memory (Cremaschi et al., 2013; Jaeggi et al., 2010; Kane et al., 2007; Karlsgodt et al., 2011); it is also

intensively used in fMRI studies because combining the N-back task with fMRI helps researchers to examine the neural mechanisms of working memory and cognitive control (Yaple & Arsalidou, 2018; Yaple et al., 2019).

The performance of the N-back task involves executive functioning, attention, verbal learning, and working memory (MacQueen et al., 2005; Thompson et al., 2007). Individuals with damage to the dorsolateral prefrontal cortex (DLPFC) have impairments in tasks using attention, memory, and reasoning (Barceló & Knight, 2002; Bidet-Caulet et al., 2015; Chao & Knight, 1998; Manes et al., 2002; Owen et al., 1990). Researchers have reported decreased neural activity in patients with DLPFC impairment during selective auditory attention, which can result in distractibility (Chao & Knight, 1998; Woods & Knight, 1986). Those with DLPFC damage have been found to struggle with higher-level cognitive tasks, including learning and task-switching, as evidenced by poor performance in tests such as the Wisconsin Card Sorting Task (a cognitive assessment of executive function and inhibition ability) (Barceló & Knight, 2002).

Neuroimaging studies show the DLPFC activates when healthy individuals perform complex decision-making tasks like the Tower of London (Unterrainer & Owen, 2006), This indicates the DLPFC's role in higher cognitive functions such as decision-making (Manes et al., 2002; Owen et al., 1990). In addition to the DLPFC, frontal-parietal cortices, the left middle frontal gyrus, and left inferior frontal gyrus activate during the N-back task (Van Snellenberg et al., 2015; Wang et al., 2019).

For the N-back task performance is typically measured using the accuracy (number of correct) and response speed (reaction time), although false positives can also be considered. In terms of reaction time some studies have shown that participants had

faster responding with better performance accuracy (G. Li et al., 2021) and they could also slow down their speed to maintain accuracy (Meule, 2017). Such performance measures, including accuracy and speed, are known to be correlated with task-related activation of some brain areas. In the early work, it was found that bilateral premotor or lateral prefrontal cortex was associated with performance on the N-back task (Cole et al., 2012; Nagel et al., 2011). Furthermore, recent studies have identified other brain areas associated with task performance, including the supplementary premotor area, bilateral frontal cortex, right anterior insula and dorsal anterior cingulate cortex (G. Li et al., 2021). From meta-analysis findings, cortical regions were activated robustly, including lateral premotor cortex, dorsal cingulate and medial premotor cortex, dorsolateral and ventrolateral prefrontal cortex, frontal poles, and medial and lateral posterior parietal cortex (Owen et al., 2005); another paper reported that bilateral middle frontal gyrus (BA 10), bilateral inferior parietal lobule (BA 40), bilateral precuneus (BA 7); left superior frontal gyrus (BA 6), left anterior insula (BA 13), bilateral thalamus were activated by N-back task (Wang et al., 2019). In addition, N-back is sensitive in bipolar disorder, which is a target group for this study of 5-HT_7 (Cremaschi et al., 2013; Verdolini et al., 2023). Despite growing interest in the effects of 5-HT_7 agonists and antagonists, the effects of JNJ-18038683 remain unclear. The effects of JNJ-18038683 on the neural correlates of cognitive function has not been investigated using fMRI. Thus, I planned to test if the 5-HT_7 antagonist could modulate working memory with N-back task, and defined some regions that were activated by N-back (Owen et al., 2005; Wang et al., 2019) and overlap with high 5-HT_7 (Hedlund & Sutcliffe, 2004) density as regions of interest (ROIs) in the following hypothesis.

4.1.3 Hypotheses

- Hypothesis 1. The JNJ-18038683 will change behavioural performance during N-back working memory task, leading to variations in response accuracy. There was no prediction on the direction of effect in healthy volunteers. For reaction time would be reduced when task becomes difficult.
- Hypothesis 2. In neuroimaging analysis, N-Back working memory-related Blood Oxygen Level Dependent (BOLD) responses in the core brain regions linked to working memory performance, see list below, will be modulated by JNJ-18038683 treatment in healthy controls during task performance.
    - Activation in the cognitive control network (CCN), including the postcentral gyrus, praecuneus, angular gyrus, anterior and posterior divisions of the supramarginal gyrus, parietal operculum cortex, superior parietal lobule, superior and middle frontal gyri, would be found (Macoveanu et al., 2021; Miskowiak & Petersen, 2019).
    - Activations in the amygdala, thalamus, and hippocampus: these areas were based on the density of 5-HT_7 receptors (Hedlund & Sutcliffe, 2004), which the CCN covered.
- Hypothesis 3. There will be a significant correlation between changes in performance and changes in brain activities within the ROIs.

4.2 Methods

In chapter 3, fMRI analysis of findings from the pop-face paradigm were reported, I have introduced the participants, including inclusion and exclusion criteria, study design and study procedure. In the following, I will introduce the N-back working memory paradigm with brief descriptions of the essential information.

4.2.1 Participants

The study was approved by the London Camberwell St Giles Research Ethics Committee (Reference Number: 18/LO/0762) and was conducted between August 2018 and September 2022. We recruited 4 bipolar patients and 14 healthy controls aged between 18 to 60 years. Whilst the larger study aimed to compare the effects of this drug on bipolar patients and healthy controls, here I focused on analysing the healthy controls data due to the pandemic impact on recruitment and data quality.

4.2.2 Study design and procedure

This was a randomised, double-blind, placebo-controlled, cross-over design, pharmacological functional MRI (phfMRI) study, aiming to examine the neural and behavioural effects of one week's dosing with the 5-HT_7 antagonist, JNJ-18038683, and placebo. In this chapter, I focused on the N-back datasets.

4.2.3 N-back fMRI tasks

Each participant completed three fMRI tasks, including N-back (working memory task), vPal (visual-spatial memory task), and pop-faces (gender discrimination emotional faces task). This chapter will focus on the analysis of the neuroimaging data acquired during N-back working memory task.

The N-back is a task, in which we tested participants' working memory (Gevins & Cutillo, 1993) by asking them to identify if a specific letter has been previously presented within a series of letters. This study had four working memory load condition levels: 0-back, 1-back, 2-back, and 3-back; stimuli were presented in a pseudo-random order. Each block has a series of fourteen different letters, and the letters were presented in the middle of the screen for 1000ms, and then a blank screen for 1000ms.

When starting the block, instruction was provided to ensure the participants knew how to respond correctly during each task block. Participants used a two-button button box and held it in the right hand; they needed to press the left button when they saw a non-target letter, and to press right if the presented letter stimulus was a target letter. The task is separated into blocks. During the 0-back condition, the target letter was simply the letter 'X'. During 1-back trials, the target letter was one that repeated the letter immediately preceding it. In the 2-back condition a presented letter was a target if it matched the stimulus presented two stimuli earlier, and for the 3-back the stimulus was a target if it was the same letter as was presented three cues earlier. Consequently, increasing task load reflected and increased amount of information that was to be held and updated from trial to trial. The accuracy (number of correct, number of incorrect, and number of false positives), speed (reaction time), and brain activations were recorded. The task ran for a total of 456 seconds (7 minutes 46 seconds).

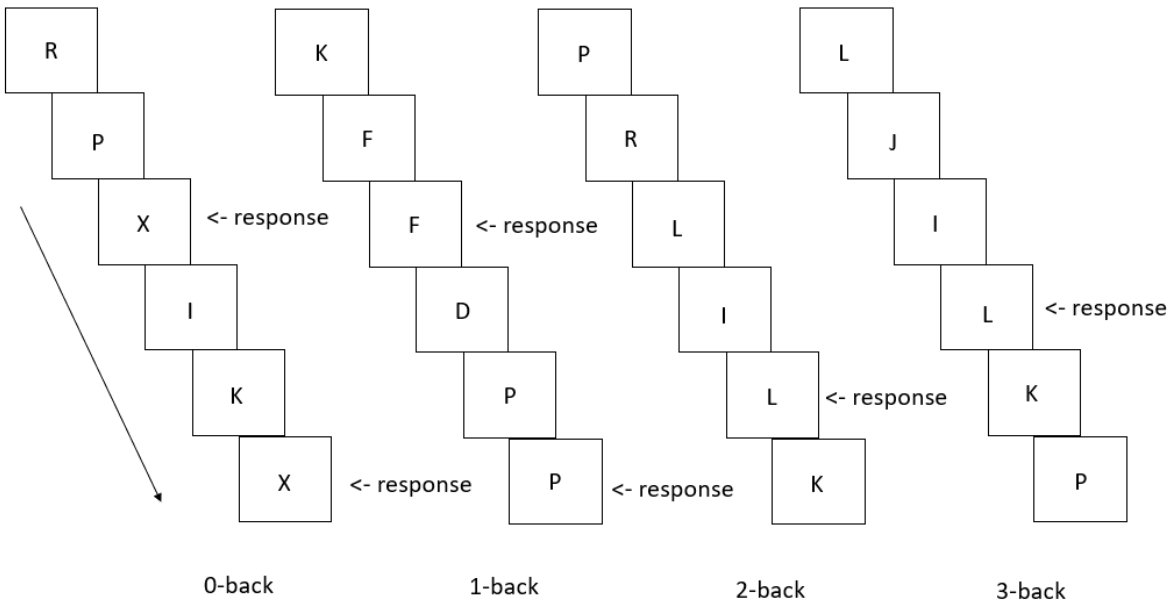

Figure 4-1

Illustration of the N-back task. Adapted from Yalin et al. (2021).

4.2.4 Statistical analysis of behavioural performance

Regarding the statistical analysis, the demographic and behavioural variables were analysed by using SPSS 28 (https://www.ibm.com/analytics/spss-statistics-software). I calculated the mean and standard deviation for demographic and clinical data and presented the data with table. For behavioural performance data, I plotted the accuracy and speed across four difficulty levels (0-back, 1-back, 2-back, 3-back). I also used two-way repeated-measures analysis of variance (rmANOVA) to test for differences between drug and placebo across different levels of difficulty in N-back task.

4.2.5 fMRI acquisition and preprocessing

In this study, MRI scans were acquired on 3 Tesla MR scanner (General Electric MR750) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London. The T1-weighted structural MRI scans were using a magnetisation-prepared rapid gradient echo sequence (Repetition Time (TR): 7.31ms, Echo Time (TE): 3.02ms; flip angle (FA): 11°; martix size: 256 × 256mm^2; FOV: 270mm; slice thickness: 1.2mm).

T2*-weighted images were acquired by using gradient-echo planar imaging sequence (TR: 2000ms, TE: 30ms, FA: 75°, slice thickness: 3mm, FoV: 240mm, and matrix size: 64 × 64mm^2, slice gap: 3.3mm, 41 slices). The N-back task lasted for 456 seconds (228 volumes were acquire).

When conducting pre-processing, the Statistical Parametric Mapping Software 12 (SPM12) (http://fil.ion.ucl.ac.uk/spm/), running in Matlab (R2018b), was used. I converted raw Digital Imaging and Communications in Medicine (DICOM) images to

Neuroimaging Informatics Technology Initiative (NIFTI) format. Secondly, the origins (coordinate [0 0 0]) of the functional timeseries and the structural scan were adjusted to lie on the anterior commissure, parallel to the AC-PC line. Thirdly, realignment of the functional timeseries was carried out to correct for volume-to-volume head displacement. The realigned fMRI data was then co-registered to bring it into alignment with the T1 weighted image. The deformation fields encoding the transformations required to take the data from native to standard Montreal Neurological Institute and Hospital coordinate system (i.e., MNI template space), were generated by unified segmentation of the T1 weighted structural image. These warping parameters were then applied to the functional timeseries that were previously registered to the T1 image. Lastly, the spatially normalised scans were smoothed with Gaussian smoothing kernels specified as 8 mm full-width-half-maximum height (FWHM) (Worsley, 2005). After these steps, the movement was visually inspected, and data containing movement over the run of greater than 1 voxel (~3.3mm) was considered unsuitable for analysis and discarded. Additionally, the volume-to-volume framewise displacement was calculated based on the movement parameters. Volumes with framewise displacements of more than 0.5mm were subsequently modelled during first-level fMRI analysis by means of separate scan-nulling regressors.

4.2.6 First-level fMRI analysis

In the first level fMRI analysis, the BOLD signal was modelled with 12 regressors in N-back, including 6 experimental factors (essential regressors) and 6 realignment parameters (nuisances regressors).

Subject-specific parameter estimates were generated under a random-effects framework. Following model fitting, for the N-back task, generated the following beta-

maps/parameter-estimate maps: instruction, 0-back, 1-back, 2-back, 3-back, false positives (no target but pressed the button) and misses (should have pressed the button but did not). The contrasts of parameter estimates were generated for all-back > 0-back, 1-back > 0-back, 2-back > 0-back, 3-back > 0-back, 2-back > 1-back, 3-back > 1-back, and 3-back > 2-back. These contrasts were taken forward to the group-level analysis to permit population-level inference.

All first-level models included regressors encoding the six realignment parameters (translations in the x, y, and z axes and rotation around those axes) and additional scan-nulling regressors as nuisance variables. The remaining variables were set at the default values in SPM12, including 128s cut-off temporal high-pass filter, a 0.8 masking threshold, and temporal autocorrelation was modelled using a first-order autoregressive function (AR (1)).

4.2.7 Second-level fMRI analysis

For each participant, subject-specific contrasts of parameter estimates for each of the primary contrasts of interest were taken forward to group-level random effects analyses.

The contrast of interest in the N-back was all-back (combined 0-back, 1-back, 2-back and 3-back) > 0-back (baseline). The contrast of interests in the N-back was all-back > 0-back. Using all-back > 0-back could highlight brain activity that is specifically associated with the cognitive load of working memory with multiple trials. To identify task-related activation, we first carried out one-sample t-tests using the all-back > 0-back contrasts. Here, I would like to see what brain regions show a generalised response to a working memory challenge compared to the low-level 0-back control condition.

To explore the effects of treatment on task activity, a paired sample t-test (placebo vs drug sessions) was carried out using the all-back > 0-back first-level contrasts as a model input.

To examine drug and the working memory load-dependent brain activity, I implemented a repeated measures ANOVA (implemented with a Flexible Factorial model in SPM). Here I explored the main effect of task level (working memory load), the main effect of drug, and the load-by-drug interactions.

For the hypothesis-led analysis of the N-Back, regions of interest (ROIs) were defined with cognitive control network (CCN) mask (Macoveanu et al., 2021; Miskowiak & Petersen, 2019). The CCN is closely related to executive function and includes working memory and cognitive control processes. The N-back task relies heavily on working memory and involves cognitive control to manage the updating and manipulation of information, the selection of ROIs within the cognitive control network is consistent with the theoretical framework in which these regions may be involved in the task. I constructed the mask on the MNI template using FSLeyes (part of the FMRIB's Software Library (FSL)) (Smith et al., 2004). The following bilateral cortical structures were included, taken from the probabilistic Harvard-Oxford Cortical Structural Atlas: the postcentral gyrus, praecuneus, angular gyrus, anterior and posterior divisions of the supramarginal gyrus, parietal operculum cortex, superior parietal lobule, superior and the middle frontal gyri. All structures were added together to form the final mask. The mask was exported from FSL, and used for small volume correction in the second level analysis with SPM12.

For the exploratory whole-brain analysis, a result was considered significant if it survived whole-brain family-wise error (pFWE < .05) on the basis of cluster extent, using a cluster-forming threshold of $p < .001$.

4.3 Results

4.3.1 Demographic details

Participants' mean age was 30.92 (SD = 10.05). The scores on the different rating scales in Table 4-1 are not in the ranges expected in patients.

Table 4-1

Descriptive statistics of the scores of questionnaires and scales.

	Male (n = 6)	Female (n = 7)	Total
Age (mean (SD))	32.17 (13.21)	29.86 (7.30)	30.92 (10.05)
ASRMS	.83 (1.17)	.86 (1.86)	0.85 (1.52)
HAM-A	1.83 (3.13)	.43 (.79)	1.08 (2.22)
HAM-D	1.50 (2.35)	.71 (.95)	1.08 (1.71)
PDQ	9.60 (8.56)	9.57 (10.34)	11.67 (14.41)
QIDS-C16	1.67 (2.25)	1.00 (1.67)	1.33 (1.92)
YMRS	.50 (1.00)	.29 (.76)	.36 (.81)

ASRMS: Altman Self-Rating Mania Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; PDQ: Perceived Deficits Questionnaire; QIDS: Quick Inventory of Depression Symptomatology; YMRS: Young Mania Rating Scale.

4.3.2 N-back Behavioural performance results

The analysis of behavioural performance, including accuracy (proportion of correct response in each level of difficulty) and speed (mean reaction time in responding each level of difficulties) showed the following results.

A two-way repeated measures ANOVA was conducted to explore the effect of two interventions (drug and placebo) on the same participants' performance, i.e., the proportion of correct trials, when conducting the N-back task, across four difficulties. The main effect of intervention was significant, F (1, 12) = 6.02, p = .03, partial eta squared = .33. The main effect of difficulty was significant F (3, 36) = 11.50, p < .001, partial eta squared = .49. The interaction between intervention and difficulty was not significant F (3, 36) = .26, p = .85, partial eta squared = .02. The results showed that no difference in accuracy between drug and placebo across four difficulties, as shown in Figure 4-2.

Post-hoc comparisons using the t-test with Bonferroni correction indicated that the proportion of correct trials for drug (M = .78, SD = .05) was significantly different than the placebo (M = .87, SD = .02), which means participants had more correct responses in drug visit. In addition, the proportion of correct trials for 0-back (M = .88, SD = .04) and for 1-back (M = .90, SD = .03) were significantly different than the 3-back (M = .71, SD = .04); 1-back was significantly different than 2-back (M = .81, SD = .04).

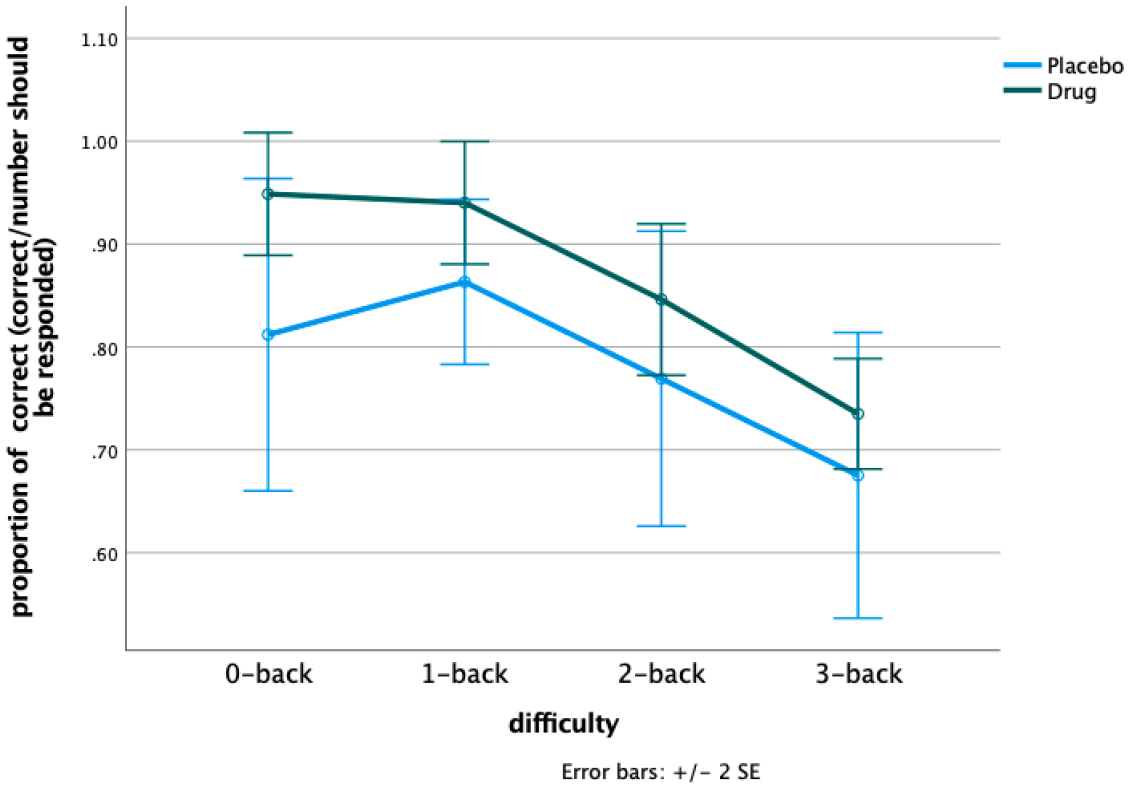

Figure 4-2

Proportion of correct across four levels of difficulty on drug/placebo for N-back task, suggesting there was difference in the effectiveness of the drug.

A two-way repeated measures ANOVA was conducted to explore the effect of two interventions (drug and placebo) on the same participants' performance, i.e., the reaction time, when conducting the N-back task, across four difficulties. The main effect of intervention was not significant, F (1, 12) = .04, p = .84, partial eta squared = .003. The main effect of emotion was significant F (3, 36) = 11.37, p < .001, partial eta squared = .49. The interaction between intervention and difficulty was not significant F (3, 36) = .06, p = .98, partial eta squared = .005. The results showed that no difference in speed between drug and placebo, as shown in Figure 4-3.

Post-hoc comparisons using the t-test with Bonferroni correction indicated that the reaction time for the 0-back (M = .53, SD = .02) was significantly different than the 2-back (M = .60, SD = .03) and 3-back (M = .66, SD = .04), which means participants spent more time (slower) on 2-back and 3-back.

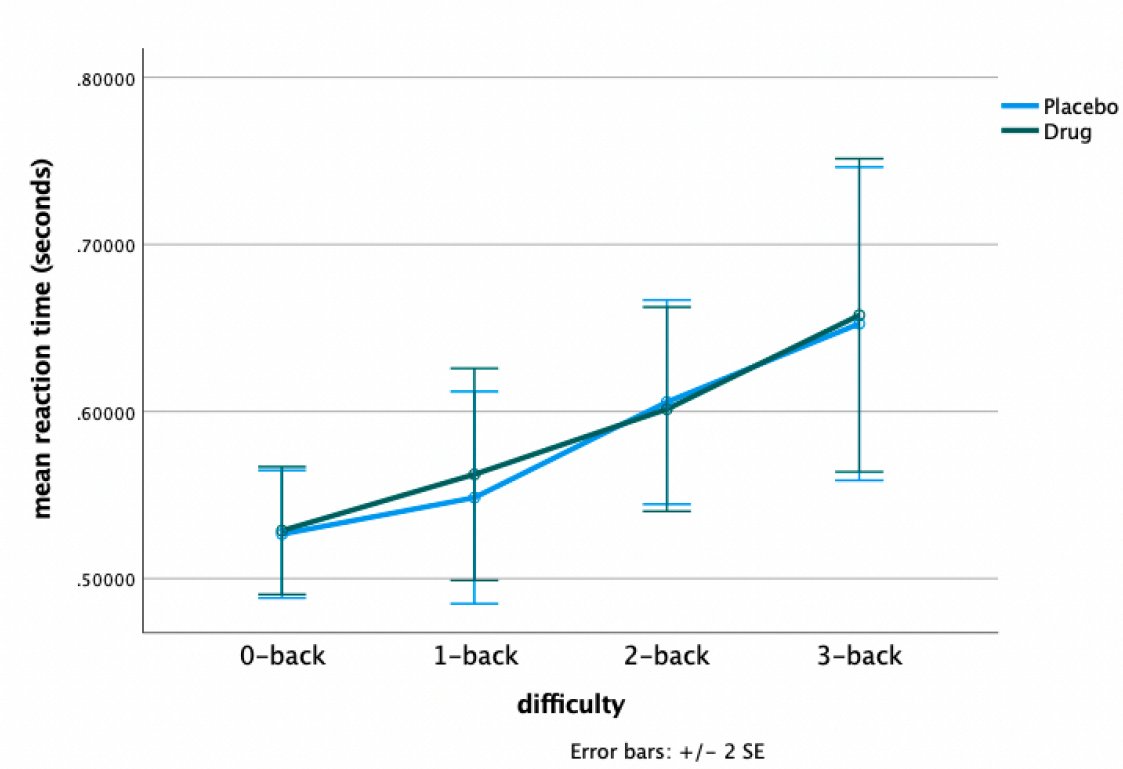

Figure 4-3

Mean reaction time (speed) across four levels of difficulty on drug/placebo for N-back task, suggesting no difference in the effectiveness of the drug.

In the results of accuracy and speed, the difference did not reach statistical significance. The effect of the drug across four difficulty levels for improving cognitive function was not different from the placebo significantly.

4.3.3 fMRI results

4.3.3.1 ROIs analysis

In the ROIs analysis, I made one mask based on all the ROIs (i.e., Cognitive Control Network, CCN) with FSL and used it for small volume correction in the second-level analysis with SPM12.

First, one-sample t-test for the contrast of all-back > 0-back (drug and placebo) was conducted, and the middle frontal gyrus was activated in drug visit. In paired t-test of all-back > 0-back, there was no significant difference between drug and placebo visits. In the repeated-measures ANOVA analysis, activities in the parietal lobe, middle frontal gyrus, medial frontal gyrus, postcentral gyrus were found for the main effect of task level, but no significant for the main effect of drug; paracentral lobule was modulated for the load-by-drug interactions.

4.3.3.2 Whole brain exploratory analyses

I first present the task related activation for all-back > 0-back from one-sample t-tests on drug and placebo. Next, I used paired t-test to see if there is an effect of drug to alter working memory. Third, I conducted a repeated measures ANOVA including the different levels of working memory load. Here the main effect of task level was clear with the middle frontal gyrus, parietal lobe, medial frontal gyrus, inferior frontal gyrus, inferior parietal lobule and cingulate gyrus showing effects. For the main effect of drug and for the load-by-drug interaction, the caudate was modulated. The details were shown in Table 4-2, and the activated area was shown in Figure 4-4.

Table 4-2

Repeated-measures ANOVA main effect of task level: the medial frontal gyrus, postcentral gyrus, inferior parietal lobule, fusiform gyrus, cingulate gyrus, were modulated.

Coordinates			Cluster *p*(FWE-corr)	Peak *Z*	No. of above-threshold voxels	Brain label
x	y	z				
44	30	32	*. 017	14.51	462	middle frontal gyrus
-30	6	56	**< .001	13.72	1228	middle frontal gyrus
-32	-52	42	* .001	13.38	946	parietal lobe
26	10	50	* .004	13.35	664	middle frontal gyrus
-8	18	48	* .019	12.37	452	medial frontal gyrus
36	-46	36	** .001	11.8	849	parietal lobe
52	-14	56	.104	11.44	248	postcentral gyrus
-46	14	28	* .006	10.46	604	inferior frontal gyrus
50	-26	24	* .002	10.19	792	inferior parietal lobule
-4	-50	28	* .007	9.92	566	cingulate gyrus

*$p < .05$ after family-wise error correction.

**$p < .001$ after family-wise error correction.

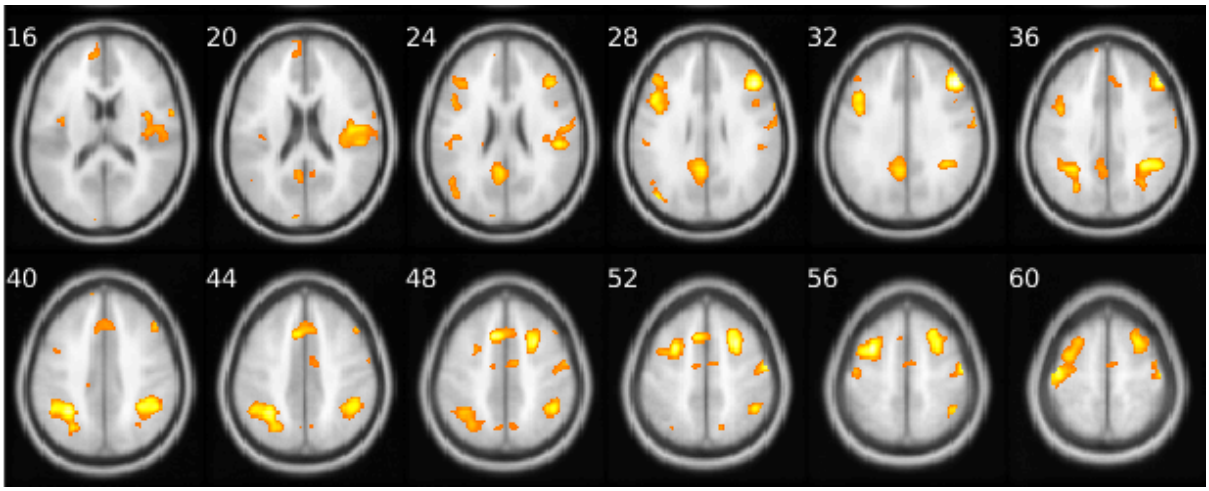

Figure 4-4

The activation in the middle frontal gyrus, inferior parietal lobule, postcentral gyrus, fusiform gyrus, cingulate gyrus, medial frontal gyrus for the main effect of task level. Results displayed using an uncorrected height threshold of $p < .001$ overlaid on the MNI152 template image provided with SPM. Numbers show the z coordinate of each transracial slice.

In the repeated-measure ANOVA main effect of drug, using cluster-forming threshold of $p < .001$ (uncorrected), the caudate was modulated; for the main effect of drug the there was an increase in activity on drug in two clusters with peaks in the caudate nucleus. The details were shown in Table 4-3 and the activated area was shown in Figure 4-5.

Table 4-3

Repeated-measures ANOVA main effect of drug, the caudate was activated (note, the clusters clearly include the caudate, but the peaks are in white matter).

Coordinates	Cluster *p*(FWE-corr)	Peak Z	No. of above-threshold voxels	Brain label

x	y	z				
16	14	22	** < .001	31.11	1310	caudate
24	10	22		26.79		
34	-8	24		23.87		
-16	-4	24	* .046	21.45	401	caudate
-18	-20	26				
-18	12	24				

*$p < .05$ after family-wise error correction.

**$p < .001$ after family-wise error correction.

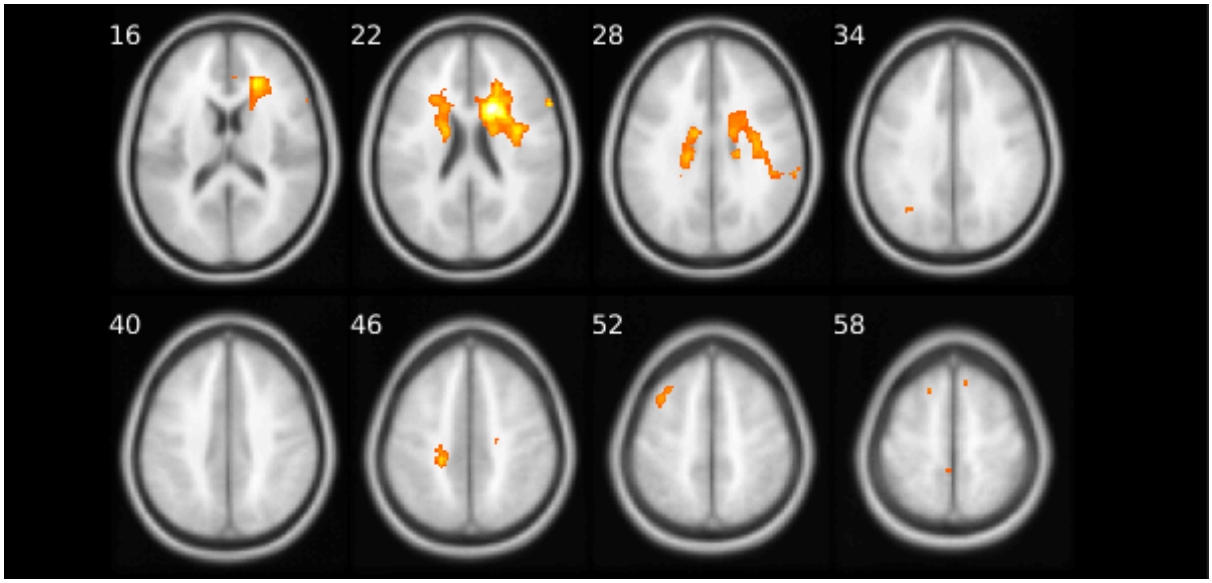

Figure 4-5

The activation in the caudate for the main effect of drug. Results displayed using an uncorrected height threshold of p < .001 overlaid on the MNI152 template image provided with SPM. Numbers show the z coordinate of each transracial slice.

In the repeated-measures ANOVA there was a load-by-drug interaction, using cluster-forming threshold of $p < .001$ (uncorrected) in a cluster overlapping the caudate nucleus. The details were shown as Table 4-6 and the activated area was shown in Figure 4-8.

Table 4-4

Repeated-measures ANOVA load-by-drug interaction: the caudate was activated (note, the clusters clearly include the caudate, but the peaks are in white matter).

Coordinates			Cluster *p*(FWE-corr)	Peak Z	No. of above-threshold voxels	Brain label
x	y	z				
16	12	24	** < .001	16.91	2160	caudate
38	-4	24		12.99		
22	34	18		11.01		
-16	-4	24	* .002	9.6	742	caudate
-46	22	20		9.04		
-20	-22	26		8.46		

*$p < .05$ after family-wise error correction.

**$p < .001$ after family-wise error correction.

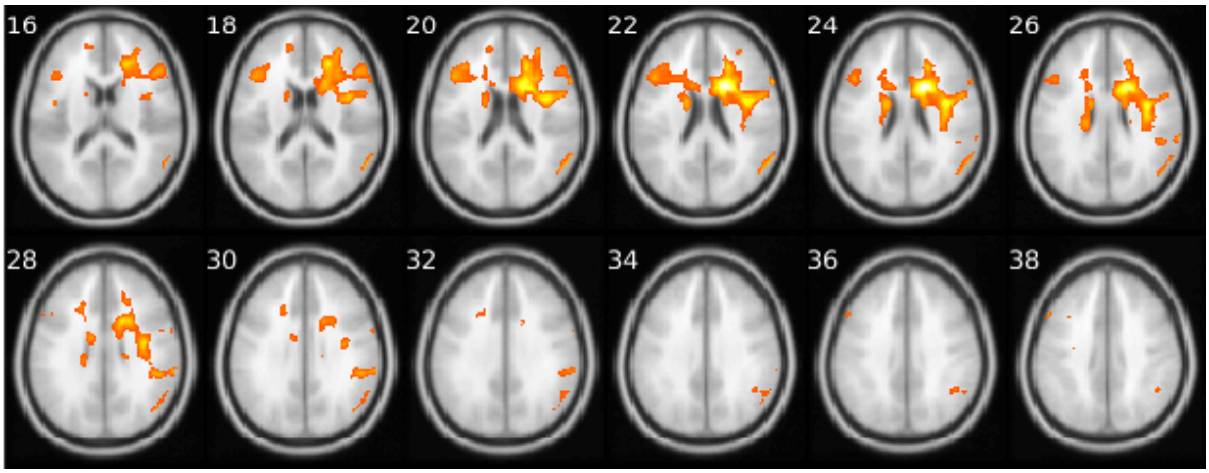

Figure 4-6

The activation in the caudate for the interaction between the task and drug. Results displayed using an uncorrected height threshold of $p < .001$ overlaid on the MNI152 template image provided with SPM. Numbers show the z coordinate of each transracial slice.

4.4 Discussion

In this study, I tested whether the 5-HT_7 antagonist, JNJ-18038683, could change the behavioural performances or modulate brain activation, using the N-back working memory task.

4.4.1 Behavioural performance

Behaviourally, there were no significant differences in either accuracy or reaction time between taking one week of JNJ-18038683 or a placebo. In the analysis of the behavioural performance data, there was no significant difference between drug and placebo sessions, which indicated that the behavioural performances, including accuracy and speed, were not improved by JNJ-18038683. Generally, participants did worsen in 3-back, better in 2-back, and then 1-back and similarly 0-back. The mean reaction time increased linearly from 0-back to 3-back. This results accords to existing studies, in which have shown that when the levels of difficulty increases, the accuracy decreases (having less correct) and the reaction time increases (becoming slower) (Carlson et al., 1998; Jonides et al., 1997; Perlstein et al., 2003; Schmidt et al., 2009).

4.4.2 Neuroimaging analysis

In the neuroimaging analysis, the parietal lobe, middle frontal gyrus, medial frontal gyrus, postcentral gyrus, were activated in the ROIs. In the whole brain mapping, the middle frontal gyrus, parietal lobe, medial frontal gyrus, inferior frontal gyrus, inferior parietal lobule and cingulate gyrus, were modulated at the task level, indicating the task

was effective. The activity of the caudate was modulated by the drug, and also displayed a load-by-drug interaction, suggesting a mechanism by which JNJ-18038683 could modulate working memory system.

4.4.2.1 ROIs analysis

In the hypothesis, I predicted that the CCN would be activated in N-back working memory task (Macoveanu et al., 2021). Two analyses were conducted: one where the a priori defined ROIs were combined into a mask and only these areas were examined and another where the whole brain was included. Both analyses showed fronto-parietal regions activated by the task, similar to what was expected based on earlier meta-analyses (Owen et al., 2005; Wang et al., 2019). The CCN, which including DLPFC and medial PFC (Miskowiak & Petersen, 2019) regions, were activated in N-back working memory task and this activation was modulated by JNJ-18038683. The DLPFC is a key functional structure strongly associated with higher cognitive functions like executive functions, working memory, and selective attention (Barbey et al., 2013; Curtis & D'Esposito, 2004). When conducting the N-back working memory task, participants need to engage several cognitive abilities that were associated with the DLPFC, including working memory to retain the target letters, attentional control to stay focused on the task, inhibition to avoid responding to non-targets, and executive functions to coordinate these processes. The DLPFC is a covered by the broader CCN, which encompasses the DLPFC and interconnected prefrontal regions. Activation of this network is critical for effective cognition. In this study, we found the CCN was engaged across multiple levels of task difficulty, aligning with previous evidence. These findings provide evidence that 5-HT_7 antagonist can modulate activity in brain regions like the CCN, which cover DLPFC, that support higher-level cognition. Further

research is needed to better characterise the neurochemical drivers of the CCN and associated executive functions.

4.4.2.2 Whole brain exploration

In the whole brain mapping, the middle frontal gyrus, parietal lobe, medial frontal gyrus, postcentral gyrus, inferior frontal gyrus, inferior parietal gyrus, cingulate gyrus, were activated at the main effect of task level, indicating the task was effective. In addition, caudate were activated in repeated-measure ANOVA displayed a significant in main effect of drug and load-by-drug interaction.

The CCN plays a role in executive functions including working memory, cognitive control, and also specific attentional processes like attentional disengagement (Aumont et al., 2019). Our study aligns with several studies that highlight the involvement of the caudate. The caudate is associated with working memory, alongside other regions within the basal ganglia and the prefrontal cortex (Levy et al., 1997; Postle & D'Esposito, 1999; Provost et al., 2010). The caudate activation observed suggests this brain region may have a role in both emotional and higher cognitive functions.

The caudate is linked to executive functions, particularly those related to goal-directed actions and planning, learning, memory, reward, motivation, emotion (Driscoll et al., 2023; Grahn et al., 2008). The caudate and frontal lobe are known as responsible for generating and monitoring strategies and interactions between decision making and performance monitoring within prefrontal cortex (Dahmani & Bohbot, 2015). Executive functions play an essential role when conducting N-back (MacQueen et al., 2005; Thompson et al., 2007), suggesting the caudate could be influenced by the demands of N-back task. Even though the caudate region of the brain doesn't have a particularly high density of 5-HT_7 receptors, JNJ-18038683 does have affinities for 5-

HT_{1A} and 5-HT_6 receptors. These receptors are strongly linked to executive function (Baba et al., 2015; Lane et al., 2008). The importance of executive function in N-back and indicates that the effects of JNJ-18038683 on 5-HT_{1A} and 5-HT_6 receptors may have implications for cognitive functions that are closely linked to executive control. Additionally, cognitive modulation may be via attentional modulation (Gazzaley, 2011), which could be the reason why we see in the main effect of task and the load-by-drug interaction. The evidence showed attention affects working memory at multiple stages of processing, including cognitive load, task practice, perceptual training, and ageing. These showed the dynamic relationship between perception, attention and memory and support the findings of activations.

For emotion, in the chapter 3, the fusiform gyrus activation was seen in main effect of task level, and the fusiform gyrus is associate with face perception and object recognition (Weiner & Zilles, 2016). For cognition, in this chapter, the CCN activation was seen, and the CCN is associated with high level cognitive functions (Macoveanu et al., 2021). Accumulating of these, which further supported the hypothesis of 5-HT_7 antagonist might be associated with both emotion and cognition (Abbas et al., 2009; Andressen et al., 2015; Canale, Kurczab, Partyka, Satała, Lenda, et al., 2016; Canale et al., 2017; Cates et al., 2013; Delcourte et al., 2017; Jankowska et al., 2020; Kennedy et al., 2016; Mahableshwarkar et al., 2014; McIntyre et al., 2013, 2014; Tomassini et al., 2017), but the intricate relationship should be further investigated.

Additionally, there was no improvement in behavioural performances, but some brain areas did be activated or modulated by JNJ-18038683. There are two possibilities that lead to these results. First, the healthy participants have no cognitive impairment, so they did not be benefit from the drug. Studies suggest that modulation of serotonergic

neurotransmission may influence performance and activation during the N-back task in healthy women (Jonassen et al., 2012). However, it has been observed that antidepressants do not significantly affect cognitive function in non-depressed individuals (Prado et al., 2018). Second, it is notable that there were no performance changes but there were brain activations in the ROIs analysis and whole brain mapping. However, evidence showed that the changes of neuroimaging measures could be identified earlier than mood changes (Harmer et al., 2009).

Finally, in the whole-brain mapping, I found that there was an extensive white matter contribution to the cluster. It has been shown that neural activities are encoded in white matter circuits similarly to cortical responses (Ding et al., 2018). Recent studies have shown that BOLD signals can be reliably detected in white matter in the resting state and various task states (Courtemanche et al., 2018; Ding et al., 2018; Gawryluk et al., 2014; Gore et al., 2019; M. Li et al., 2021; Li et al., 2019). Moreover, white matter signals are heterogeneous in nature and depend on local structural-vascular-functional associations (M. Li et al., 2021). Another study pointed out that functional connectivity (FC) can be detected in white matter using BOLD signals in fMRI, and the result showed that white matter FC is associated with structural connectivity (Huang et al., 2023). To deal with this, Courtemanche and his colleague suggested that some optimisation factors, such as the hemodynamic response function (HRF) model, were essential to enhance the characterisation of white matter activity seen with fMRI (Courtemanche et al., 2018). Other researchers have also emphasised the importance of making significant changes to the current standard models for accurately characterising the HRFs for adapting the typical methods used to analyse functional imaging data (Li et al., 2019).

4.4.3 Limitations and future directions

This is a randomised, placebo-controlled, cross-over, double-blinded drug administration study which could modulate brain activation, but there were some limitations in the study.

1. A small sample size: in the analysis, we included 13 healthy control participants. In the initial recruitment, a total 14 participants healthy control participants were included. However, to ensure the data with good quality, I excluded one participant because the button out of work when the subject conducting the N-back task in visit 3 (i.e., the 1st neuroimaging visit). The exclusion of one participant due to technical issues resulted in a small sample size, which may have reduced the statistical power of the study. Potentially, with a small sample size, it may be difficult to detect significant effects or to generalise the findings to a larger population.

   In a previous study by Miskowiak and her colleague (Miskowiak et al., 2016) observed an effect size of Cohen's d = 0.7 for the right superior frontal gyrus during an N-back working memory task following erythropoietin treatment in people with bipolar disorder with cognitive impairment. Thus, to determine the required sample size for the current study to achieve adequate statistical power to detect a similar effect, an a priori power analysis was conducted using G*Power 3.1 (Faul et al., 2007). Specifically, a paired-samples t-test was selected, with input parameters of d = 0.70, $\alpha = 0.05$, power = 0.80, and a two-tailed hypothesis. The analysis indicated a required total sample size of n = 19 to detect an effect of this magnitude at the defined statistical significance and power criteria. The sample n =19 size should

provide sufficient statistical sensitivity to test the hypothesis regarding whether JNJ-18038683 can modulate brain activity.

Post-hoc power analyses were conducted based on the effects observed in this study. For the comparison of reaction times between the drug and placebo, with a sample size of 13 participants per group, a two-tailed dependent t-test, and the effect size found in our sample ($d = 0.7$), $\alpha = 0.05$, the achieved power was 0.64. We analysed 13 participants from a dataset with a total of 14 participants, and a larger sample size study should be considered in the future.

2. Bias in participant selection: The study included only healthy controls, which may limit the generalisation of the findings to clinical populations (i.e., bipolar patients). In addition, the mean age of the healthy controls was young ($M = 30.92$, $SD = 10.05$), which may have introduced an age-related bias in the analysis.

4.4.4 Conclusion

In this chapter, I aimed to tested if one week's design with a 5-HT_7 antagonist, JNJ-18038683, could improve participants' behavioural performances or modulate their brain activations during the N-back verbal working memory task. In the behavioural performances, participants did not show significant improvement in accuracy and speed. In ROI analysis, the inferior parietal lobule, middle frontal gyrus, medial frontal gyrus, postcentral gyrus, were activated by task. The CCN and caudate are believed to contribute to working memory, and incorporate aspects of inhibitory and executive control; furthermore, the manipulation, and utilisation of information stored in working

memory requires the integration of multiple cognitive functions linked to these structures (Driscoll et al., 2023; Kane & Engle, 2002).

The involvement of the serotonergic system in cognitive processes is well-established, and modulation of this system may affect cognitive function. Nonetheless, it's important to note that the impact of antidepressants on cognitive function in individuals who are not experiencing depression may be minimal. Additionally, the use of serotonergic medications for managing bipolar disorder should be approached cautiously, as there is a risk of triggering manic episodes. Future studies should focus on the 5-HT_7 antagonist in a large sample size with longitudinal data collection, but should be cautious regarding possibility of inducing mania with the serotonergic compounds.

References

Abbas, A. I., Hedlund, P. B., Huang, X.-P., Tran, T. B., Meltzer, H. Y., & Roth, B. L. (2009). Amisulpride is a potent 5-HT7 antagonist: relevance for antidepressant actions in vivo. *Psychopharmacology*, *205*(1), 119-128. https://doi.org/https://dx.doi.org/10.1007/s00213-009-1521-8

Andressen, K. W., Manfra, O., Brevik, C. H., Ulsund, A. H., Vanhoenacker, P., Levy, F. O., & Krobert, K. A. (2015). The atypical antipsychotics clozapine and olanzapine promote down-regulation and display functional selectivity at human 5-HT7 receptors. *Br J Pharmacol*, *172*(15), 3846-3860. https://doi.org/10.1111/bph.13169

Aumont, É., Arguin, M., Bohbot, V., & West, G. L. (2019). Increased flanker task and forward digit span performance in caudate-nucleus-dependent response strategies. *Brain Cogn*, *135*, 103576. https://doi.org/10.1016/j.bandc.2019.05.014

Baba, S., Murai, T., Nakako, T., Enomoto, T., Ono, M., Shimizu, I., & Ikeda, K. (2015). The serotonin 5-HT$_1$A receptor agonist tandospirone improves executive function in common marmosets. *Behav Brain Res*, *287*, 120-126. https://doi.org/10.1016/j.bbr.2015.03.025

Barbey, A. K., Koenigs, M., & Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. *Cortex*, *49*(5), 1195-1205. https://doi.org/10.1016/j.cortex.2012.05.022

Barceló, F., & Knight, R. T. (2002). Both random and perseverative errors underlie WCST deficits in prefrontal patients. *Neuropsychologia*, *40*(3), 349-356. https://doi.org/10.1016/s0028-3932(01)00110-5

Bidet-Caulet, A., Buchanan, K. G., Viswanath, H., Black, J., Scabini, D., Bonnet-Brilhault, F., & Knight, R. T. (2015). Impaired Facilitatory Mechanisms of Auditory Attention After Damage of the Lateral Prefrontal Cortex. *Cereb Cortex*, *25*(11), 4126-4134. https://doi.org/10.1093/cercor/bhu131

Bonaventure, P., Dugovic, C., Kramer, M., De Boer, P., Singh, J., Wilson, S., Bertelsen, K., Di, J., Shelton, J., Aluisio, L., Dvorak, L., Fraser, I., Lord, B., Nepomuceno, D., Ahnaou, A., Drinkenburg, W., Chai, W., Dvorak, C., Sands, S., . . . Lovenberg, T. W. (2012). Translational evaluation of JNJ-18038683, a 5-hydroxytryptamine type 7 receptor antagonist, on rapid eye movement sleep and in major depressive disorder. *J Pharmacol Exp Ther*, *342*(2), 429-440. https://doi.org/10.1124/jpet.112.193995

Burdick, K. E., Russo, M., Frangou, S., Mahon, K., Braga, R. J., Shanahan, M., & Malhotra, A. K. (2014). Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. *Psychol Med*, *44*(14), 3083-3096. https://doi.org/10.1017/s0033291714000439

Canale, V., Kurczab, R., Partyka, A., Satała, G., Lenda, T., Jastrzębska-Więsek, M., Wesołowska, A., Bojarski, A. J., & Zajdel, P. (2016). Towards new 5-HT7 antagonists among arylsulfonamide derivatives of (aryloxy)ethyl-alkyl amines: Multiobjective based design, synthesis, and antidepressant and anxiolytic properties. *Eur J Med Chem*, *108*, 334-346. https://doi.org/10.1016/j.ejmech.2015.11.040

Canale, V., Kurczab, R., Partyka, A., Satała, G., Słoczyńska, K., Kos, T., Jastrzębska-Więsek, M., Siwek, A., Pękala, E., Bojarski, A. J., Wesołowska, A., Popik, P., & Zajdel, P. (2016). N-Alkylated arylsulfonamides of (aryloxy)ethyl piperidines: 5-HT(7) receptor selectivity versus multireceptor profile. *Bioorg Med Chem*, *24*(2), 130-139. https://doi.org/10.1016/j.bmc.2015.11.041

Canale, V., Partyka, A., Kurczab, R., Krawczyk, M., Kos, T., Satała, G., Kubica, B., Jastrzębska-Więsek, M., Wesołowska, A., Bojarski, A. J., Popik, P., & Zajdel, P. (2017). Novel 5-HT(7)R antagonists, arylsulfonamide derivatives of (aryloxy)propyl piperidines: Add-on effect to the antidepressant activity of SSRI and DRI, and pro-cognitive profile. *Bioorg Med Chem*, *25*(10), 2789-2799. https://doi.org/10.1016/j.bmc.2017.03.057

Carlson, S., Martinkauppi, S., Rämä, P., Salli, E., Korvenoja, A., & Aronen, H. J. (1998). Distribution of cortical activation during visuospatial n-back tasks as revealed by functional magnetic resonance imaging. *Cereb Cortex*, *8*(8), 743-752. https://doi.org/10.1093/cercor/8.8.743

Cates, L. N., Roberts, A. J., Huitron-Resendiz, S., & Hedlund, P. B. (2013). Effects of lurasidone in behavioral models of depression. Role of the 5-HT7 receptor subtype. *Neuropharmacology*, *70*, 211-217. https://doi.org/https://dx.doi.org/10.1016/j.neuropharm.2013.01.023

Chao, L. L., & Knight, R. T. (1998). Contribution of human prefrontal cortex to delay performance. *J Cogn Neurosci*, *10*(2), 167-177. https://doi.org/10.1162/089892998562636

Cole, M. W., Yarkoni, T., Repovs, G., Anticevic, A., & Braver, T. S. (2012). Global connectivity of prefrontal cortex predicts cognitive control and intelligence. *J Neurosci*, *32*(26), 8988-8999. https://doi.org/10.1523/jneurosci.0536-12.2012

Costa, L., Spatuzza, M., D'Antoni, S., Bonaccorso, C. M., Trovato, C., Musumeci, S. A., Leopoldo, M., Lacivita, E., Catania, M. V., & Ciranna, L. (2012). Activation of 5-HT7 serotonin receptors reverses metabotropic glutamate receptor-mediated synaptic plasticity in wild-type and Fmr1 knockout mice, a model of Fragile X syndrome. *Biol Psychiatry*, *72*(11), 924-933. https://doi.org/10.1016/j.biopsych.2012.06.008

Courtemanche, M. J., Sparrey, C. J., Song, X., MacKay, A., & D'Arcy, R. C. N. (2018). Detecting white matter activity using conventional 3 Tesla fMRI: An evaluation of standard field strength and hemodynamic response function. *Neuroimage*, *169*, 145-150. https://doi.org/10.1016/j.neuroimage.2017.12.008

Cremaschi, L., Penzo, B., Palazzo, M., Dobrea, C., Cristoffanini, M., Dell'Osso, B., & Altamura, A. C. (2013). Assessing working memory via N-back task in euthymic bipolar I disorder patients: a review of functional magnetic resonance imaging studies. *Neuropsychobiology*, *68*(2), 63-70. https://doi.org/10.1159/000352011

Curtis, C. E., & D'Esposito, M. (2004). The effects of prefrontal lesions on working memory performance and theory. *Cogn Affect Behav Neurosci*, *4*(4), 528-539. https://doi.org/10.3758/cabn.4.4.528

Dahmani, L., & Bohbot, V. D. (2015). Dissociable contributions of the prefrontal cortex to hippocampus- and caudate nucleus-dependent virtual navigation strategies. *Neurobiol Learn Mem*, *117*, 42-50. https://doi.org/10.1016/j.nlm.2014.07.002

Delcourte, S., Abrial, E., Etievant, A., Rovera, R., Arnt, J., Didriksen, M., & Haddjeri, N. (2017). Asenapine modulates mood-related behaviors and 5-HT1A/7 receptors-mediated neurotransmission. *CNS neuroscience & therapeutics*, *23*(6), 518-525. https://doi.org/10.1111/cns.12698

Diamond, A. (2013). Executive functions. *Annu Rev Psychol*, *64*, 135-168. https://doi.org/10.1146/annurev-psych-113011-143750

Ding, Z., Huang, Y., Bailey, S. K., Gao, Y., Cutting, L. E., Rogers, B. P., Newton, A. T., & Gore, J. C. (2018). Detection of synchronous brain activity in white matter tracts at rest and under functional loading. *Proc Natl Acad Sci U S A*, *115*(3), 595-600. https://doi.org/10.1073/pnas.1711567115

Driscoll, M. E., Bollu, P. C., & Tadi, P. (2023). Neuroanatomy, Nucleus Caudate. In *StatPearls*. StatPearls Publishing

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*, *39*(2), 175-191. https://doi.org/10.3758/bf03193146

Gawryluk, J. R., Mazerolle, E. L., & D'Arcy, R. C. (2014). Does functional MRI detect activation in white matter? A review of emerging evidence, issues, and future directions. *Front Neurosci*, *8*, 239. https://doi.org/10.3389/fnins.2014.00239

Gazzaley, A. (2011). Influence of early attentional modulation on working memory. *Neuropsychologia*, *49*(6), 1410-1424. https://doi.org/10.1016/j.neuropsychologia.2010.12.022

Gevins, A., & Cutillo, B. (1993). Spatiotemporal dynamics of component processes in human working memory. *Electroencephalogr Clin Neurophysiol*, *87*(3), 128-143. https://doi.org/10.1016/0013-4694(93)90119-g

Gore, J. C., Li, M., Gao, Y., Wu, T. L., Schilling, K. G., Huang, Y., Mishra, A., Newton, A. T., Rogers, B. P., Chen, L. M., Anderson, A. W., & Ding, Z. (2019). Functional MRI and resting state connectivity in white matter - a mini-review. *Magn Reson Imaging*, *63*, 1-11. https://doi.org/10.1016/j.mri.2019.07.017

Grahn, J. A., Parkinson, J. A., & Owen, A. M. (2008). The cognitive functions of the caudate nucleus. *Prog Neurobiol*, *86*(3), 141-155. https://doi.org/10.1016/j.pneurobio.2008.09.004

Harmer, C. J., Goodwin, G. M., & Cowen, P. J. (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *Br J Psychiatry*, *195*(2), 102-108. https://doi.org/10.1192/bjp.bp.108.051193

Hedlund, P. B., & Sutcliffe, J. G. (2004). Functional, molecular and pharmacological advances in 5-HT7 receptor research. *Trends Pharmacol Sci*, *25*(9), 481-486. https://doi.org/10.1016/j.tips.2004.07.002

Huang, Y., Wei, P. H., Xu, L., Chen, D., Yang, Y., Song, W., Yi, Y., Jia, X., Wu, G., Fan, Q., Cui, Z., & Zhao, G. (2023). Intracranial electrophysiological and structural basis of BOLD functional connectivity in human brain white matter. *Nat Commun*, *14*(1), 3414. https://doi.org/10.1038/s41467-023-39067-3

Jaeggi, S. M., Buschkuehl, M., Perrig, W. J., & Meier, B. (2010). The concurrent validity of the N-back task as a working memory measure. *Memory*, *18*(4), 394-412. https://doi.org/10.1080/09658211003702171

Jankowska, A., Satała, G., Kołaczkowski, M., Bucki, A., Głuch-Lutwin, M., Świerczek, A., Pociecha, K., Partyka, A., Jastrzębska-Więsek, M., Lubelska, A., Latacz, G., Gawalska,

A., Bojarski, A. J., Wyska, E., & Chłoń-Rzepa, G. (2020). Novel anilide and benzylamide derivatives of arylpiperazinylalkanoic acids as 5-HT(1A)/5-HT(7) receptor antagonists and phosphodiesterase 4/7 inhibitors with procognitive and antidepressant activity. *Eur J Med Chem*, *201*, 112437. https://doi.org/10.1016/j.ejmech.2020.112437

Jonassen, R., Endestad, T., Neumeister, A., Foss Haug, K. B., Berg, J. P., & Landrø, N. I. (2012). Serotonin transporter polymorphism modulates N-back task performance and fMRI BOLD signal intensity in healthy women. *PLoS One*, *7*(1), e30564. https://doi.org/10.1371/journal.pone.0030564

Jonides, J., Schumacher, E. H., Smith, E. E., Lauber, E. J., Awh, E., Minoshima, S., & Koeppe, R. A. (1997). Verbal Working Memory Load Affects Regional Brain Activation as Measured by PET. *J Cogn Neurosci*, *9*(4), 462-475. https://doi.org/10.1162/jocn.1997.9.4.462

Kane, M. J., Conway, A. R. A., Miura, T. K., & Colflesh, G. J. H. (2007). Working memory, attention control, and the N-back task: a question of construct validity. *J Exp Psychol Learn Mem Cogn*, *33*(3), 615-622. https://doi.org/10.1037/0278-7393.33.3.615

Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. *Psychon Bull Rev*, *9*(4), 637-671. https://doi.org/10.3758/bf03196323

Karlsgodt, K. H., Bachman, P., Winkler, A. M., Bearden, C. E., & Glahn, D. C. (2011). Genetic influence on the working memory circuitry: behavior, structure, function and extensions to illness. *Behav Brain Res*, *225*(2), 610-622. https://doi.org/10.1016/j.bbr.2011.08.016

Kennedy, S., Grouin, J., Cadour, S., Robert, V., & Picarel-Blanchot, F. (2016). Relative short-term efficacy and acceptability of agomelatine versus vortioxetine in adult patients suffering from major depressive disorder. *European Neuropsychopharmacology*, *26*(Supplement 2), S457-S458. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed17&NEWS=N&AN=614139003 (29th European College of Neuropsychopharmacology Congress, ECNP 2016. Austria.)

Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *J Exp Psychol*, *55*(4), 352-358. https://doi.org/10.1037/h0043688

Lane, H. Y., Liu, Y. C., Huang, C. L., Hsieh, C. L., Chang, Y. L., Chang, L., Chang, Y. C., & Chang, W. H. (2008). Prefrontal executive function and D1, D3, 5-HT2A and 5-HT6 receptor gene variations in healthy adults. *J Psychiatry Neurosci*, *33*(1), 47-53.

Lawlor-Savage, L., & Goghari, V. M. (2016). Dual N-Back Working Memory Training in Healthy Adults: A Randomized Comparison to Processing Speed Training. *PLoS One*, *11*(4), e0151817. https://doi.org/10.1371/journal.pone.0151817

Levy, R., Friedman, H. R., Davachi, L., & Goldman-Rakic, P. S. (1997). Differential activation of the caudate nucleus in primates performing spatial and nonspatial working memory tasks. *J Neurosci*, *17*(10), 3870-3882. https://doi.org/10.1523/jneurosci.17-10-03870.1997

Li, G., Chen, Y., Le, T. M., Wang, W., Tang, X., & Li, C. R. (2021). Neural correlates of individual variation in two-back working memory and the relationship with fluid intelligence. *Sci Rep*, *11*(1), 9980. https://doi.org/10.1038/s41598-021-89433-8

Li, M., Gao, Y., Ding, Z., & Gore, J. C. (2021). Power spectra reveal distinct BOLD resting-state time courses in white matter. *Proc Natl Acad Sci U S A*, *118*(44). https://doi.org/10.1073/pnas.2103104118

Li, M., Newton, A. T., Anderson, A. W., Ding, Z., & Gore, J. C. (2019). Characterization of the hemodynamic response function in white matter tracts for event-related fMRI. *Nat Commun*, *10*(1), 1140. https://doi.org/10.1038/s41467-019-09076-2

Macoveanu, J., Kjærstad, H. L., Vinberg, M., Harmer, C., Fisher, P. M., Knudsen, G. M., Kessing, L. V., & Miskowiak, K. W. (2021). Affective episodes in recently diagnosed patients with bipolar disorder associated with altered working memory-related prefrontal cortex activity: A longitudinal fMRI study. *J Affect Disord*, *295*, 647-656. https://doi.org/10.1016/j.jad.2021.08.110

MacQueen, G. M., Hajek, T., & Alda, M. (2005). The phenotypes of bipolar disorder: relevance for genetic investigations. *Mol Psychiatry*, *10*(9), 811-826. https://doi.org/10.1038/sj.mp.4001701

Mahableshwarkar, A., Jacobsen, P., Chen, Y., Serenko, M., & Palo, W. (2014). The Safety and tolerability profile of vortioxetine in the treatment of patients with major depressive disorder aged 65 years and older. *American Journal of Geriatric Psychiatry*, *22*(3 SUPPL. 1), S143-S144. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed15&NEWS=N&AN=71442072 (2014 American Association for Geriatric Psychiatry, AAGP Annual Meeting. Orlando, FL United States. (var.pagings).)

Mahableshwarkar, A. R., Zajecka, J., Jacobson, W., Chen, Y., & Keefe, R. S. (2015). A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder. *Neuropsychopharmacology*, *40*(8), 2025-2037. https://doi.org/10.1038/npp.2015.52

Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., & Robbins, T. (2002). Decision-making processes following damage to the prefrontal cortex. *Brain*, *125*(Pt 3), 624-639. https://doi.org/10.1093/brain/awf049

McIntyre, R. S., Lophaven, S., & Olsen, C. K. (2013). Randomized, double-blind, placebo-controlled study of the efficacy of vortioxetine on cognitive dysfunction in adult patients with major depressive disorder (MDD). *Neuropsychopharmacology*, *38*(SUPPL. 2), S380-S381. https://doi.org/10.1038/npp.2013.280 (52nd Annual Meeting of the American College of Neuropsychopharmacology, ACNP 2013. Hollywood, FL United States. (var.pagings).)

McIntyre, R. S., Lophaven, S., & Olsen, C. K. (2014). A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*, *17*(10), 1557-1567. https://doi.org/10.1017/s1461145714000546

Meule, A. (2017). Reporting and Interpreting Working Memory Performance in n-back Tasks. *Front Psychol*, *8*, 352. https://doi.org/10.3389/fpsyg.2017.00352

Miskowiak, K. W., & Petersen, C. S. (2019). Neuronal underpinnings of cognitive impairment and - improvement in mood disorders. *CNS Spectr*, *24*(1), 30-53. https://doi.org/10.1017/s1092852918001062

Miskowiak, K. W., Vinberg, M., Glerup, L., Paulson, O. B., Knudsen, G. M., Ehrenreich, H., Harmer, C. J., Kessing, L. V., Siebner, H. R., & Macoveanu, J. (2016). Neural correlates of improved executive function following erythropoietin treatment in mood disorders. *Psychol Med*, *46*(8), 1679-1691. https://doi.org/10.1017/s0033291716000209

Nagel, I. E., Preuschhof, C., Li, S. C., Nyberg, L., Bäckman, L., Lindenberger, U., & Heekeren, H. R. (2011). Load modulation of BOLD response and connectivity predicts working memory performance in younger and older adults. *J Cogn Neurosci*, *23*(8), 2030-2045. https://doi.org/10.1162/jocn.2010.21560

Okada, M., Matsumoto, R., Yamamoto, Y., & Fukuyama, K. (2021). Effects of Subchronic Administrations of Vortioxetine, Lurasidone, and Escitalopram on Thalamocortical

Glutamatergic Transmission Associated with Serotonin 5-HT7 Receptor. *Int J Mol Sci*, *22*(3). https://doi.org/10.3390/ijms22031351

Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*, *28*(10), 1021-1034. https://doi.org/10.1016/0028-3932(90)90137-d

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp*, *25*(1), 46-59. https://doi.org/10.1002/hbm.20131

Perlstein, W. M., Dixit, N. K., Carter, C. S., Noll, D. C., & Cohen, J. D. (2003). Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. *Biol Psychiatry*, *53*(1), 25-38. https://doi.org/10.1016/s0006-3223(02)01675-x

Postle, B. R., & D'Esposito, M. (1999). Dissociation of human caudate nucleus activity in spatial and nonspatial working memory: an event-related fMRI study. *Brain Res Cogn Brain Res*, *8*(2), 107-115. https://doi.org/10.1016/s0926-6410(99)00010-5

Prado, C. E., Watt, S., & Crowe, S. F. (2018). A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. *Neuropsychol Rev*, *28*(1), 32-72. https://doi.org/10.1007/s11065-018-9369-5

Provost, J. S., Petrides, M., & Monchi, O. (2010). Dissociating the role of the caudate nucleus and dorsolateral prefrontal cortex in the monitoring of events within human working memory. *Eur J Neurosci*, *32*(5), 873-880. https://doi.org/10.1111/j.1460-9568.2010.07333.x

Rac-Lubashevsky, R., & Kessler, Y. (2016). Dissociating working memory updating and automatic updating: The reference-back paradigm. *J Exp Psychol Learn Mem Cogn*, *42*(6), 951-969. https://doi.org/10.1037/xlm0000219

Schmidt, H., Jogia, J., Fast, K., Christodoulou, T., Haldane, M., Kumari, V., & Frangou, S. (2009). No gender differences in brain activation during the N-back task: an fMRI study in healthy individuals. *Hum Brain Mapp*, *30*(11), 3609-3615. https://doi.org/10.1002/hbm.20783

Shelton, J., Yun, S., Losee Olson, S., Turek, F., Bonaventure, P., Dvorak, C., Lovenberg, T., & Dugovic, C. (2014). Selective pharmacological blockade of the 5-HT7 receptor attenuates light and 8-OH-DPAT induced phase shifts of mouse circadian wheel running activity. *Front Behav Neurosci*, *8*, 453. https://doi.org/10.3389/fnbeh.2014.00453

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, *23 Suppl 1*, S208-219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Solé, B., Jiménez, E., Torrent, C., Reinares, M., Bonnin, C. D. M., Torres, I., Varo, C., Grande, I., Valls, E., Salagre, E., Sanchez-Moreno, J., Martinez-Aran, A., Carvalho, A. F., & Vieta, E. (2017). Cognitive Impairment in Bipolar Disorder: Treatment and Prevention Strategies. *Int J Neuropsychopharmacol*, *20*(8), 670-680. https://doi.org/10.1093/ijnp/pyx032

Soveri, A., Antfolk, J., Karlsson, L., Salo, B., & Laine, M. (2017). Working memory training revisited: A multi-level meta-analysis of n-back training studies. *Psychon Bull Rev*, *24*(4), 1077-1096. https://doi.org/10.3758/s13423-016-1217-0

Thompson, J. M., Gray, J. M., Hughes, J. H., Watson, S., Young, A. H., & Ferrier, I. N. (2007). Impaired working memory monitoring in euthymic bipolar patients. *Bipolar Disord*, *9*(5), 478-489. https://doi.org/10.1111/j.1399-5618.2007.00470.x

Tomassini, L., Perrini, F., Cuomo, I., Motta, P., Amici, E., & De Filippis, S. (2017). Efficacy, safety, and tolerability of vortioxetine in the treatment of mood disorders. *European Neuropsychopharmacology*, *27*(Supplement 4), S863-S864. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed18&NEWS=N&AN=619297550 (30th European College of Neuropsychopharmacology Congress, ECNP 2017. France.)

Unterrainer, J. M., & Owen, A. M. (2006). Planning and problem solving: from neuropsychology to functional neuroimaging. *J Physiol Paris*, *99*(4-6), 308-317. https://doi.org/10.1016/j.jphysparis.2006.03.014

Van Snellenberg, J. X., Slifstein, M., Read, C., Weber, J., Thompson, J. L., Wager, T. D., Shohamy, D., Abi-Dargham, A., & Smith, E. E. (2015). Dynamic shifts in brain network activation during supracapacity working memory task performance. *Hum Brain Mapp*, *36*(4), 1245-1264. https://doi.org/10.1002/hbm.22699

Verdolini, N., Alonso-Lana, S., Salgado-Pineda, P., Sarró, S., Salvador, R., Maristany, T., Goikolea, J. M., Bonnin, C. M., Martín, I., Saló, L., Romaguera, A., Rodriguez-Cano, E., Rosa, A. R., Vieta, E., & Pomarol-Clotet, E. (2023). The relationship between cognition and functioning in Bipolar Disorder: An investigation using functional

imaging during working memory performance. *Psychiatry Res*, *319*, 114981. https://doi.org/10.1016/j.psychres.2022.114981

Wang, H., He, W., Wu, J., Zhang, J., Jin, Z., & Li, L. (2019). A coordinate-based meta-analysis of the n-back working memory paradigm using activation likelihood estimation. *Brain Cogn*, *132*, 1-12. https://doi.org/10.1016/j.bandc.2019.01.002

Weiner, K. S., & Zilles, K. (2016). The anatomical and functional specialization of the fusiform gyrus. *Neuropsychologia*, *83*, 48-62. https://doi.org/10.1016/j.neuropsychologia.2015.06.033

Westrich, L., Haddjeri, N., Dkhissi-Benyahya, O., & Sánchez, C. (2015). Involvement of 5-HT_7 receptors in vortioxetine's modulation of circadian rhythms and episodic memory in rodents. *Neuropharmacology*, *89*, 382-390. https://doi.org/10.1016/j.neuropharm.2014.10.015

Woods, D. L., & Knight, R. T. (1986). Electrophysiologic evidence of increased distractibility after dorsolateral prefrontal lesions. *Neurology*, *36*(2), 212-216. https://doi.org/10.1212/wnl.36.2.212

Worsley, K. J. (2005). An improved theoretical P value for SPMs based on discrete local maxima. *Neuroimage*, *28*(4), 1056-1062. https://doi.org/10.1016/j.neuroimage.2005.06.053

Yaple, Z., & Arsalidou, M. (2018). N-back Working Memory Task: Meta-analysis of Normative fMRI Studies With Children. *Child Dev*, *89*(6), 2010-2022. https://doi.org/10.1111/cdev.13080

Yaple, Z. A., Stevens, W. D., & Arsalidou, M. (2019). Meta-analyses of the n-back working memory task: fMRI evidence of age-related changes in prefrontal cortex involvement across the adult lifespan. *Neuroimage*, *196*, 16-31. https://doi.org/10.1016/j.neuroimage.2019.03.074

Żmudzka, E., Sałaciak, K., Sapa, J., & Pytka, K. (2018). Serotonin receptors in depression and anxiety: Insights from animal studies. *Life Sci*, *210*, 106-124. https://doi.org/10.1016/j.lfs.2018.08.050

Chapter 5 Neuroimaging brain age

5.0 Abstract

Human brains change in structure and function with age. Researchers have developed a programme brainageR to evaluate people's biological age. Compared to chronological age, brain age provides a biological age of brain, which may detect brain atrophy and its functional deterioration. Here, we calculated people's brain age and tested if the brain age of people with bipolar disorder is older than healthy controls. Also, we investigated if some cognitive functions, including IQ, attention, and memory, are associated with the gap between brain age and chronological age.

The programme brainageR was used to calculate 147 participants' brain ages from 4 data sets: a total of 147 participants' brain age were evaluated. Linear regression was used to see if brain ages differed between BD and HC. T-tests were used to assess if there is a difference between the gap of brain age and scan age in people with bipolar disorders and healthy control (HC) groups. One-way ANOVA was used to evaluate if there is a difference between the gap of brain age and scan age in bipolar disorder patients (BD), bipolar disorder patients taking lithium (BDL), and HC groups. Linear regression was used with predictors including intelligence quotient (IQ), attention, and processing speed.

Bipolar patients' brain age is older than healthy controls. The gap between brain age and scan age is larger for bipolar patients than for healthy controls, but there was no significant difference between the three groups (BD, BDL, HC). Cognitive functions, including IQ, processing speed, and short-term memory, were associated with the gap between brain age and chronological age.

Our findings showed a significant difference in the gap between brain age and chronological age between the BD and HC groups, which means individuals with bipolar disorder may have more brain atrophy than healthy people. The gap between brain age and chronological age is no difference between the three groups (BD, BDL, HC). Cognitive functions, including IQ, processing speed, and short-term memory, could predict brain age. Further studies can focus on identifying the brain age of specific areas or the relationship between brain age and cognitive functions.

5.1 Introduction

5.1.1 Brain age as a new biomarker

Bipolar disorder is a common, complex and challenging neuropsychiatric disorder. The condition affects men and women equally in bipolar 1 and there is a predominance of women in bipolar 2; it has a prevalence of approximately 1-4% (Loftus et al., 2020; Merikangas et al., 2011; Vieta et al., 2018). Episodes are associated not only with mood changes but also with changes in cognitive function; notably cognitive impairments and brain structure abnormalities are also found in people with bipolar disorder. Furthermore, 40-60% of bipolar disorder patients showed psychosocial difficulties even in euthymic status (Van Rheenen et al., 2020).

As for cognitive function, a large body of evidence supports a strong association between ageing and both changes in function, and decrements in cognitive function, and brain structure (Binder et al., 2009; Dubois et al., 2021; Hoffman & Morcom, 2018; Peters, 2006). Executive function was associated with cortical thickness in the medial prefrontal cortex, lateral prefrontal and occipital regions in bipolar 2 patients (Abé et al., 2018). (Hoffman & Morcom, 2018). In recent years, meta-analyses, which combine collaborative data, have further clarified the evidence in support of structural brain changes associated with bipolar disorder. Researchers reported amygdala, hippocampus, and thalamus volumes (Hajek et al., 2012; Hibar et al., 2016) and cortical regions (Ganzola & Duchesne, 2017; Hajek et al., 2012) changed in this group of patients compared with healthy control subjects. Some studies also showed lower cortical thickness, subcortical volume and disrupted white matter integrity were associated with bipolar disorder, with body mass index (BMI), and with familial risk, which explained the differences between individuals (Abramovic et al., 2018; Ching et

al., 2022; Zhu et al., 2022). White matter and grey matter density or volume changes in people with bipolar disorder were found in some studies (Barysheva et al., 2013; Clark & Sahakian, 2008; Lyoo et al., 2004; Masuda et al., 2020; Xu et al., 2020). To be specific, loss of grey matter in the left pars opercularis, left fusiform gyrus, left rostral middle frontal cortex, and the hippocampus, has been observed as well (Cao et al., 2016; Hibar et al., 2016; Vieta et al., 2018). In a meta-analysis, individuals with bipolar disorders have faster enlargement of ventricular volumes and slower thinning of the fusiform and parahippocampal cortex (Abé et al., 2022). In a meta-analysis, it has been shown that psychiatric disorders and neurological diseases are associated with earlier brain ageing (Wrigglesworth et al., 2021). Studies demonstrated that older people showed less activation in the typical left-hemisphere semantic network, and more activation in right frontal and parietal regions.

Individuals with bipolar disorder are also recognised to have an increased risk of developing dementia (Diniz et al., 2017; Kessing et al., 2008). Lithium, however, has neuroprotective effects (Diniz et al., 2013; Puglisi-Allegra et al., 2021; Won & Kim, 2017), which could be a promising treatment for neurodegenerative disorders, including Alzheimer's disease and related neurodegenerative disorders, and schizophrenia (Forlenza et al., 2014; Puglisi-Allegra et al., 2021; Ryskalin et al., 2018). Since lithium may reduce the risk of Alzheimer's disease in elderly patients with bipolar disorder (Kessing et al., 2008), prescribing long-term lithium treatment may reduce the risk of dementia, and also preserve the hippocampus volume (Hajek et al., 2019; Haukvik et al., 2022; Hibar et al., 2018; Nunes et al., 2007). Lithium currently is still a recommended first-line prescription for treatment and maintenance of bipolar disorder (Fountoulakis et al., 2022). Following the development of machine learning methods for neuroimaging analyses, a novel index of brain age has been developed. It has been

proposed that the gap between biological age, here indexed with brain age, and chronological age, may be an informative marker of alterations in brain structure and function in psychiatric disorders (Gaser et al., 2013; Löwe et al., 2016; Varikuti et al., 2018). Changes in brain structure and functions with age are established with changes in overall volume, cortical thickness, subcortical volumes, and in the white matter (Raz et al., 2010; Salat et al., 2005; Storsve et al., 2014). Using the programme 'brainageR' or BrainAGE to evaluate the brain biological age, the brain may be classified as having more ageing or less ageing (James H. Cole, Tiina Annus, et al., 2017; Cole & Franke, 2017; Cole et al., 2015; James H. Cole, Jonathan Underwood, et al., 2017; Franke et al., 2013; Franke et al., 2018; Gaser et al., 2013; Koutsouleris et al., 2014; Nenadić et al., 2017; Pardoe et al., 2017).

In terms of brain age calculation, we highlight two influential software packages here. In Germany, Franke et al used individual structural images and a machine learning system to develop Brain Age Gap Estimation (BrainAGE), in which T1-weighted MRI scans of 650 health subjects (aged 19-86 years) were utilised (Franke & Gaser, 2019; Franke et al., 2010). In the UK, Cole and colleagues used 3377 healthy participants' T1-weighted MRI scans from seven open datasets (mean age = 40.6 years, SD = 21.4, aged 18-92 years) and a machine learning model to develop the package brainageR (J. H. Cole et al., 2017; Cole et al., 2018). Using neuroimaging, a model has been developed to predict brain age from machine-learning algorithms. This artificial intelligence technique and statistical analysis have been used to analyse the structure or the functions of neuroimaging data (Cole & Franke, 2017), and to obtain the baseline of healthy people's brain age (Dosenbach et al., 2010; Franke et al., 2010) from brain scans.

5.1.2 Brain age and brain disorders

The concept of brain age has been developed as a biomarker with advanced software and some further details, such as the predicted whole-brain age, the anatomical images of grey matter (GM) and white matter (WM). Many psychiatric disorders have been investigated by means of this biomarker, including Alzheimer's disease (AD) (which can start off as mild cognitive impairment), psychosis (e.g., schizophrenia), mood disorders (e.g., bipolar disorder, major depressive disorder), personality disorders (e.g., borderline personality disorder), and alcohol dependence disorder (Franke et al., 2013; Franke et al., 2010; Guggenmos et al., 2017; Löwe et al., 2016; Nenadić et al., 2017). Brain age might predict individual deterioration from mild cognitive impairment to AD, a common form of dementia. A positive brain age gap indicates accelerated atrophy, and the brain age gap of people with AD is between 5.8 and 10 years older than healthy control (Franke et al., 2013; Franke et al., 2010; Gaser et al., 2013; Li et al., 2017; Löwe et al., 2016; Varikuti et al., 2018).

Currently, for progression to AD, the maximum sensitivity range is around from 70% to 90%, but the specificity range is around 40% to 70% (Beach et al., 2012; Syaifullah et al., 2020). Some researchers defined clinical utility as greater than 80% (Duara et al., 2008; McKeith et al., 2007). Finding a new approach to detect early signs is essential work at this stage.

As noted above, researchers have gained insight into how psychiatric disorders, brain abnormalities, and cognitive impairments, are strongly associated with each other (Abé et al., 2022; Ching et al., 2022; Douglas et al., 2018; Haukvik et al., 2022; Solé et al., 2017; Van Rheenen et al., 2020; Xu et al., 2020). When focusing on brain abnormalities, a study focusing on four disorders showed that people with schizophrenia have a greater

gap between brain age and chronological age than healthy controls (5.5 years older) (Koutsouleris et al., 2014). In the same study, the gap for patients with major depressive disorder (MDD) was 4.0 years older, and the gap for those with borderline personality disorder (BPD) was 3.1 years older. It was also found that early onset of MDD and BPD have more significant brain atrophy (Koutsouleris et al., 2014). In the case of schizophrenia, the brain age gap was between 2.6 and 5.5 years older, as shown in Table 5-1 (Koutsouleris et al., 2014; Nenadić et al., 2017; Schnack et al., 2016). These results have shown that brain age could become a sensitive biomarker to detect early signs of psychiatric disorders, which could potentially be useful in predicting progression.

While most diagnoses discussed thus far have an older brain age gap, a study by Nenadić et al. suggested there was no significant difference between individuals with bipolar disorder and healthy controls. The study included schizophrenia, bipolar disorder, and healthy control groups, and showed that the brains of those in the schizophrenia group appeared, on average, to be 2.56 years older than their biological age, but the bipolar disorder group's brains appeared to be approximately 1.25 years younger than their actual age, whilst the heathy control's brains were suggested to be 0.22 years younger based on the estimated BrainAGE score. It found that the difference between bipolar disorder group and healthy controls group did not reach statistical significance. Since there is only one study showing this, further research should aim for replication. Even though biomarkers of brain age have been used in some clinical research such as the above, it is not clear how to apply it to practical fields. In addition, lithium was proven to have neuroprotective effects (Diniz et al., 2013; Puglisi-Allegra et al., 2021; Won & Kim, 2017) but researchers have not yet examined if the effects could be evaluated by brain age, or the relationship between either brain age and lithium

or brain age and cognitive function. Therefore, these are essential questions we tried to answer in this chapter.

Table 5-1

Brain diseases and gap of brain age.

Brain Diseases & Psychiatric Disorders	Difference between chronological and neuroimaging marker brain age (years)		
Cognitive impairment			
Alzheimer disease	(Franke et al., 2010)	AD=102 HC=232	10 years older $p < .001$
	(Löwe et al., 2016)	sMCI=36 pMCI=112 AD=150	0.88 years younger to 0.09 years older 5.83 to 5.54 years older 5.76 to 6.20 years older $p < .001$
	(Li et al., 2017)	AD=411 MCI=411 HC=411	AD 5.1 years younger to 7.0 years older $p = .03, .03$ MCI 3.9 years younger to .07 years older $p = .03, .07$

	(Varikuti et al., 2018)	MCI=64 AD=163 HC=244	MCI=5.4 to 6.2 older AD=8.5 to 10.7 years older *p* value: n/a
Mild cognitive impairment	(Gaser et al., 2013)	pMCI_early= 58 pMCI_late=75 sMCI = 62	pMCI_early 8.73 years older pMCI_late 5.62 years older sMCI 0.75 *p* < .001
	(Löwe et al., 2016)	sMCI=36 pMCI=112	sMCI 0.9 years younger pMCI 5.8 years older *p* < .001
	(Varikuti et al., 2018)	MCI=64 AD=163 HC=244	MCI 5.4 to 6.2 older AD 8.5 to 10.7 years older *p* value: n/a
Psychosis			
High psychosis risk	(Koutsouleris et al., 2014)	SZ= 141 MDD=104 BPD=57 ARMS= 89	SZ 5.5 years older MDD 4.0 years older BPD 3.1 years older ARMS 1.7 years older *p* < .001

Psychosis	(Kolenic et al., 2018)	SZ=120 HC=114	2.64 years older $p < .001$
schizophrenia	(Koutsouleris et al., 2014)	SZ=141 MDD=104 BPD=57 ARMS=89	5.5 years older $p < .001$ Between-group differences were found in SZ vs BPD ($p < .007$) SZ vs ARMS ($p < .001$) MD vs ARMS ($p < .005$).
	(Schnack et al., 2016)	SZ=192	3.48 years older $p < .001$
	(Nenadić et al., 2017)	SZ=45 HC=70 BD=22	2.6 years older
Mood disorders			
bipolar disorder	(Nenadić et al., 2017)	SZ=45 HC=70 BD=22	HC vs BD $p = .34$
major depressive disorder	(Koutsouleris et al., 2014)	SZ=141 MDD=104 BPD=57 ARMS=89	4.0 years older $p < .001$

Personality disorders				
borderline disorder	personality	(Koutsouleris et al., 2014)	SZ=141 MDD=104 BPD=57 ARMS=89	3.1 years older $p < .001$
Others				
alcohol disorder	dependence	(Guggenmos et al., 2017)	HC=97 ADD=119	4.0 years older $p < .001$

AD: Alzheimer's disorder; sMCI: BD: bipolar disorder; sMCI: stable mind cognitive impairment; pMCI: progressive mild cognitive impairment; HC: healthy controls; SZ: schizophrenia; MDD: major depressive disorder; BPD: bordenline personality disorder; ARMS: at-risk mental states for psycholsis; ADE: Alcohol dependence disorder.

5.1.3 Knowledge gap and research questions

We aimed advance the bipolar disorders related studies by brain age analysis and apply the outcomes to practical fields. Even if we might not achieve this goal at this stage, we still could gain more knowledge in this study area, especially in using the brain age predictive skills to improve peoples' health (Cole & Franke, 2017). Since researchers found that individuals with bipolar disorder have brain abnormalities, cognitive impairment problems, and a potentially increased risk of dementia, identifying brain age may detect early signs of these disorders (Abé et al., 2022; Ching et al., 2022; Douglas et al., 2018; Haukvik et al., 2022; Solé et al., 2017; Van Rheenen et al., 2020; Xu et al., 2020). Several papers claim that brain age is closely related to neuropsychiatric disorders, but uncertainties remain concerning bipolar disorder in current studies. Here, we tried to answer three essential

questions regarding brain structural atrophy and functional impairment in people with bipolar disorders. Thus, the questions are:

- Is there a significant difference between bipolar disorder and healthy controls in terms of the degree to which their estimated brain age is lower or higher (i.e., apparently different brain age) than their chronological age?
- Is exposure to lithium associated with a younger estimated brain age, likely related to reduced brain atrophy-related processes normally seen with ageing?
- What kinds of cognitive functions are associated with the differences between estimated brain age and the brain's chronological age?

Based on prior research (Nenadić et al., 2017), our first research question attempted to replicate the finding that people with bipolar disorders have an estimated brain age similar to healthy controls (i.e., their brain age appears to be no difference between individuals with bipolar disorder and healthy controls). The second aim was to compare bipolar patients who take lithium as long-term treatment (BDL) for brain age compared with bipolar disorder lithium naïve (BD) and healthy controls (HC). The third aim was to explore which types of cognitive functions are associated with brain age estimates, or more specifically the disparity between estimated and actual brain age. A link between brain abnormalities and cognitive dysfunctions is commonly observed in people with bipolar disorder (Abé et al., 2022; Ching et al., 2022; Douglas et al., 2018; Haukvik et al., 2022; Solé et al., 2017; Van Rheenen et al., 2020; Xu et al., 2020), but these studies typically use mass-univariate analyses and voxel-wise measures rather than a global metric like brain age, to which the same abnormalities likely contribute.

5.2 Method

5.2.1 Study design

This study analyses four data sets: from the Translational Validation of 5-HT_7 Antagonists as a treatment for cognitive impairment in bipolar disorder, a proof of principle neuroimaging study (SIMBA); the Cognitive Remediation in Bipolar (CRiB) study (Strawbridge et al., 2016; Strawbridge et al., 2020); the Biomedical Research Centre Functional Magnetic Resonance Spectroscopy (BRCFMRS) (Jelen et al., 2022); and the Bipolar Lithium Imaging and Spectroscopy Study (BLISS) (Necus et al., 2019). The study proposal was reviewed and approved by the London Camberwell St Giles Research Ethics Committee (Reference Number: 18/LO/0762), the City Road & Hampstead NHS Research Ethics Committee (reference 15/LO/1557) and the North East - Newcastle and North Tyneside 1 National Research Ethics Service Committee respectively.

5.2.2 Study participants

Participants were enrolled from SIMBA, CRiB and BRCFMRS projects at the Department of Psychological Medicine, King's College London, and BLISS project from the Newcastle Magnetic Resonance Centre, Newcastle University.

The SIMBA project included 1 outpatient with a DSM-5 diagnosis of bipolar disorder (BD) patients and 14 healthy subjects that were recruited from the community via online advertisements and through mental health organisations. All participants were aged between 18 and 60 years. Mini International Neuropsychiatric Interview (M.I.N.I.) 6.0 (Sheehan et al., 1998) was used to confirm mood states. At the time of scanning, participants' mood and anxiety states were defined as ≤ 8 on the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) and Young Mania Rating Scale (YMRS) (Young et al., 1978). People with serious medical or neurological conditions, a history

of major psychiatric disorder, such as autism or attention deficit-hyperactivity disorder were excluded.

The CRiB project included 26 outpatients (a subgroup of the main study who underwent neuroimaging) with a DSM-5 diagnosis of BD recruited from the community and primary/secondary care services. All participants were fluent in English and aged between 18 and 65 years. M.I.N.I. was used to confirm the BD subtype. Participants had been free of acute mood symptoms for ≥ 1 month prior to inclusion, with euthymia defined as scoring ≤ 7 on the HAM-D and YMRS and were screened over the 1-month period. Participants with a neurological disorder, personality disorder diagnosis, abuse or dependence on alcohol or illicit substances over the past six months were excluded.

The BLISS project enrolled 68 patients with a DSM-5 diagnosis of bipolar disorder and 25 healthy subjects recruited from North East primary and secondary care settings and established research volunteer databases. All participants were aged 18-65. The patients with BD were specifically recruited as two groups: those taking lithium as a long-term treatment (Bipolar Disorder Lithium, BDL n = 41) and those taking other maintenance treatments but naïve to lithium (Bipolar Disorder Control, BD n = 27). The healthy control subjects (HC) had no history of psychiatric illness and were not taking any psychotropic medications. Subjects attended a screening visit to confirm eligibility and underwent a structured clinical interview using the Net Structured Clinical Interview Version for DSM (NetSCID) diagnostic tool. Interviews and observer ratings of mood were conducted by a trained clinical research assistant and discussed with a senior psychiatrist, and subjects returned subjective mood rating scales (BDI and ASRM). All participants were deemed to be euthymic at enrolment, defined as < 7 on both the HAM-D and the YMRS.

The BRCFMRS project recruited participants right-handed and aged between 22 and 57 years. M.I.N.I. was used to confirm the diagnosis. Fifteen bipolar 2 participants from the Improving Access to Psychological Therapies services. Fourteen healthy controls were recruited from local and online advertisements, and all were medication naïve.

5.2.3. Data analysis

5.2.3.1 MRI acquisition

In SIMBA, CRiB and BRCFMRS projects, high-resolution T1-weighted structural MRI scans were acquired on a MR750 3.0T MR scanner using a magnetisation-prepared rapid gradient echo sequence (TR: 7.31ms, TE: 3.02ms; flip angle: 11°; martix: 256 × 256mm^2; FOV: 270mm; slice thickness: 1.2mm).

In BLISS, a 3D T1-weighted image of brain anatomy was acquired using Philips 8-channel SENSE head coil with a 1H gradient echo sequence (TR: 9.6ms, TE: 4.6ms, FOV: 240 x 240 x 180mm^3, acquisition matrix: 240 × 208 × 180mm^3 with acquisition voxel size: 1 x 1.15 x 1, reconstructed into a matrix size of 256 × 256 × 180mm^3 on average).

5.2.3.2 Software for evaluating brain age

BrainageR can be used to calculate a person's brain age (Cole et al., 2015) using T1-weighted scans combined with a database evaluated with machine learning (Cole et al., 2015). The brainageR was developed with a four-step procedure, including acquisition parameters, image preprocessing, machine learning prediction of age, and model validation. The updated 2.1 version was trained on 3377 healthy individuals (mean age = 40.6 years, SD = 21.4, age range 18-92 years) from seven publicly available datasets and tested on n = 857 (mean age = 40.1 years, SD = 21.8, age range 18-90 years) (Cole

et al., 2018). The brain age of all subjects in the four datasets were calculated using brainageR version 2.1.

5.2.3.3 Statistical Analysis

All analyses were conducted using SPSS (version 28; IBM, New York).

Based on our research questions, the first aim is to investigate, using all datasets, if people with bipolar disorders have younger estimated than chronological brain age. We also calculated the gap between brain age and chronological age. To calculate the gap, we used brain age minus chronological age; therefore, the positive age gap means more brain maturity or atrophy, and vice versa. In addition, while the bipolar disorder participants were chronologically older on average than the HC group, the statistical significance of this difference was formally tested in a two-tailed t-test. Second, to investigate if there are differences in the gap of brain age and chronological age between people with bipolar disorder taking lithium (BDL), bipolar disorder lithium-naïve (non-lithium) (BD), and healthy controls (HC) groups, a one-way ANOVA was used. Thirdly, to explore which types of cognitive functions were significantly related to the disparity between estimated brain age and chronological brain age, a linear regression was used. Significance was defined at $p < .05$.

5.2.3.4 Analysis methods for each study

To reach the three aims, the analysis methods were designed as follows.

- To see if people with bipolar disorders have younger brain age than healthy controls, linear regression was used between HC and BD. The age at scan (chronological age) was controlled.
- To see if there are differences between the three groups (HC, BD, and BDL) in the gap between brain age and chronological age, one-way ANOVA was used. When it comes to two groups (HC and BD), a t-test ($p < .05$, two-tailed) was used.

- To see the association between the gap of brain age, chronological age, and cognitive function, regression was used with predictors including intelligence quotient (IQ), processing speed (PS, tested with Trial Making Test, TMT), and short-term memory (STM, tested with Verbal Fluency Test, VFT).

5.3 Result

Table 5-2

Description of studies.

	BLISS N=79	KCL N=74		
Demographic Details	N Age Gender (F/M)	N Age Gender (F/M)	Brain age	Age gap
HC	23 49.39 (10.85) 10/13	29 32.31(10.30) 16/13	37.86 (12.70)	-1.62 (6.64)
BD	26 41.12 (11.99) 19/7	45 39.18 (11.84) 28/17	40.49 (15.03)	.60 (6.65)
BDL	30 49.63 (11.51) 18/12	- - -	51.71 (12.87)	2.08 (7.28)

BD: Bipolar Disorder; BDL: Bipolar Disorder taking Lithium; HC: Healthy Controls; Age gap: the gap between brain age and chronological age.

For hypothesis 1, to test the difference in brain-age between BP groups and HC, we conducted a linear regression with all the data sets. After accounting age of the scan, no significant group difference between BD and HC was observed. The results of the regression indicated that the model explained 72.6% of the variance in brain-age, F (2, 76) = 100.68, $p < .001$. It too showed bipolar patients' estimated brain ages do not significantly differ from those of healthy controls.

Table 5-3

Difference in brain age between BD and HC (reference group).

Dependent variable:		Standardised		
Brain age	Coefficients	Coefficients	95% CI LB	95% CI UB
(Constant)	1.95		-5.15	9.05
Age at scan **	.936	.86	.81	1.07
Bipolar Disorder	3.40	.12	-0.6	6.8

* $p < 0.05$; ** $p < 0.001$

95% confidence intervals (CI) upper (UB) and lower (LB) bounds

We conducted an independent-sample t-test to compare this gap between BD and HC groups using all data sets. The group difference in scores for BD (M = 2.42, SD = 0.92) and HC (M = -1.21, SD = 7.02); t (77) = -2.12, p =. 037 groups was significant, which showed the gap between estimated brain age and age at scan (chronological age) is larger for bipolar patients than for healthy controls.

To determine whether lithium was associated with a larger disparity between estimated and chronological brain age, specifically reflective of slower aging, we used one-way ANOVA to compare the age gap between brain age and chronological age for the BD, BDL, and HC groups using the BLISS data set. There was no significant difference at the $p < .05$ level in age gaps for the three age groups: F (2, 76) = 2.3, p = .12. post-hoc comparisons using the Tukey HSD test indicated that the mean score for HC (M = -1.21, SD = 7.02) was not significantly different from BD (M = 2.82, SD = 6.53) and BDL (M = 2.07, SD = 7.28). The result showed no significant difference between the three groups.

Testing of hypothesis 3, the relationship between brain age disparity and cognitive function assessments, was restricted to the participants drawn from the BLISS data set. We used to explore the relationships between the gap between estimated brain age and chronological age, and the following parameters: year of education, IQ, working memory (VFT), and processing speed (TMT). The result indicated a significant positive relationship between working memory (r = - .24, n = 76, $p < .05$). The results indicated that the larger the gap between brain age and chronological age showed poorer working memory. To investigate the relationship between the age gap and cognitive functions, we used a regression model to explore further details with the BLISS dataset. In BLISS dataset, the sample size is 79, mean education years (n = 69) is 14.94 (SD = 3.64), Full-scale IQ (n = 74) is 109.85 (SD = 7.95), Processing speed (TMT score) (n = 76) is 30.16 (SD = 11.93), and Short-term memory (VFT score) (n = 76) is 22.49 (SD = 6.09).

Table 5-4

Pearson's r correlation of cognitive functions in BLISS.

Correlations		age gap	education (year)	Full scale IQ	Short term memory (VFT)	Processing speed (TMT)
age gap	Correlation	1	0.020	0.194	-.239*	0.222
	Sig		0.867	0.098	0.037	0.054
	N	79	69	74	76	76
education (year)	Correlation	0.020	1	.551**	.270*	-0.225
	Sig	0.867		0.000	0.027	0.068
	N	69	69	65	67	67
	Correlation	0.194	.551**	1	.238*	-0.140

Full scale IQ	Sig	0.098	0.000		0.043	0.237
	N	74	65	74	73	73
Short term memory (VFT)	Correlation	-.239*	.270*	.238*	1	-.300**
	Sig	0.037	0.027	0.043		0.008
	N	76	67	73	76	76
Processing speed (TMT)	Correlation	0.222	-0.225	-0.140	-.300**	1
	Sig	0.054	0.068	0.237	0.008	
	N	76	67	73	76	76

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

The regression model explained 26.1% of the variance, F (5, 58) = 4.104, $p < .05$. It showed that larger gap between brain age and chronological age was strongly associated with younger chronological age (beta = .36, $p < .05$). This would be logical because people with younger chronological age leads larger age gap when calculating scan age (chronological age) minus brain age; when one year age gap increased, .216 younger scan age was detected. After accounting for it, we also found that some cognitive functions, including IQ, processing speed, and short-term memory could predict brain age. Higher full-scale IQ was associated with larger brain age gap (beta = .39, $p < .05$); slower processing speed was associated with older brain age (beta = .26, $p < .05$); but poorer short-term memory is associated with older brain age (beta = -.30, $p < .05$). Compared to chronological age, the associations between age gap and the cognitive function variables are relatively weak.

Table 5-5

The relationships between gap between brain age and chronological age and cognitive functions.

Dependent variable: age gap	Coefficients	Standardised coefficients	95% CI LB	95% CI UB
Constant	-24.43		-50.08	1.21
BD	2.71	.19	-1.62	7.04
BDL	3.17	.20	-1.00	7.33
Age at scan *	-.19	-.31	-.35	-.02
Education (years)	-.22	-.11	-.83	.39
Full scale IQ *	.35	.37	.08	.61
Processing speed (TMT) *	.15	.25	.01	.30
Short-term memory (VFT) *	-.30	-.26	-.57	-.02

* $p < 0.05$; ** $p < 0.001$

95% confidence intervals (CI) upper (UB) and lower (LB) bounds. TMT: Trail Making Test. VFT: Verbal Fluency (Animal Naming) Test.

5.4 Discussion

The results in the present study show that, over all datasets, there is a significant difference between the two main groups (BD and HC) in the disparity between age gap between brain age and chronological age (BD and HC). Within the BLISS data we found no evidence to support suggestions that lithium protects against ageing-related atrophic processes. Finally, estimated brain age was significantly associated with several measures linked to cognitive functioning, including IQ, processing speed, and short-term memory.

The absence of significant differences between the BD and HC groups in our study contrasts with prior findings (Hajek et al., 2019; Nenadić et al., 2017), where no statistical difference was shown between the two groups. However, our study revealed that individuals with bipolar disorder appear to exhibit signs of higher brain age compared to the HC, potentially indicating accelerated age-related atrophic processes. This observation aligns with previous research indicating alterations in white matter and grey matter density or volume in individuals with BD, as noted in studies (Barysheva et al., 2013; Clark & Sahakian, 2008; Lyoo et al., 2004; Masuda et al., 2020; Xu et al., 2020). The brainageR programme, which assesses grey matter volume, produced results that are consistent with studies pointing to brain abnormalities, specifically loss of grey matter, in individuals with bipolar disorder. The contradictory findings of these two studies may be for the reason that differences in the data contributing to the training of the models used by the two programmes (i.e., BrainAGE and brainageR).

The absence of evidence to support suggestions that lithium slows disease-related atrophy is surprising. However, it should be noted that the BLISS dataset, with a total of 79 participants' T1-weighted MRI scans, is a relatively small sample. This is particularly the case as the BD with and without lithium groups were 30 (BDL) and 26 (BD), respectively. Consequently, the study may have been insufficiently powered to detect such an effect.

The potential protective effects of lithium, which we hoped to index as using the brain age estimation process, is an important consideration for patients prescribed lithium (Ochoa, 2022; Shulman, 2010). Taking lithium may impair renal function (Gupta & Khastgir, 2017; Van Alphen et al., 2021), but this might be weighed against evidence

that it may slow brain ageing (Ochoa, 2022; Van Gestel et al., 2019) and reduces cognitive and functional decline in bipolar disorder patients with mild cognitive impairment (Cousins et al., 2020; Van Gestel et al., 2019), i.e., if the brain could be protected by lithium taking (Díaz Ortiz et al., 2021; Diniz et al., 2013; Puglisi-Allegra et al., 2021; Won & Kim, 2017). We tested whether BDL's brain age is younger than BD, and the result showed that there is no difference between the three groups (BD, BDL, HC). The outcome may be because we have not calculated the lithium dosage and duration yet. In addition, some researchers raised the issue that the variation of people with bipolar disorder, such as different age groups (i.e., young-age, middle-age, or older-age), or onset age (i.e., early-onset or late-onset), should be considered separately (Lepkifker et al., 2007; Villa et al., 2022). Further research should investigate these.

Previous studies have shown that many bipolar disorder patients suffer from cognitive decline, and this phenomenon may correlate with the cognitive ageing (Bourne et al., 2013; Douglas et al., 2018; Solé et al., 2017). In the brain age analysis, we found that attention function and brain age were strongly associated, which may be relevant to clinical practice. Therapies focussed on improving cognitive function, especially attention and memory training, may be valuable adjunct treatments that boost the efficacy of psychotherapy. However, this suggestion requires further investigation.

There are some counter intuitive results in our findings. Generally, people with brain atrophy tend to have a lower IQ (Kubota et al., 2015; Ohi et al., 2021), and poor processing speed performance (Benedict et al., 2010; Doi et al., 2014). The counter intuitive results, including higher IQ and faster processing speed, were associated with larger gap between brain age and chronological age and may be due to the limitations

of brainageR. In brainageR, people's grey matter & white matter volume images are calculated (Cole et al., 2015), but it's not possible to identify the specific areas where partial atrophy, that is contributing to an individual's estimated brain age, is located. Prior findings indicate changes in the hippocampus and temporal lobe (Hajek et al., 2019; Hartberg et al., 2015) and the reduction of grey volume in areas such as the left fusiform gyrus, the right rostral dorsolateral prefrontal cortex, and the left inferior frontal gyrus (Ekman et al., 2017) are all linked to ageing. Moreover, the multivariate estimation of brain age is a relatively new technique, so the biological parameters informing the model are not currently fully elucidated or understood.

Even with this research, further analysis should be considered, specifically the association between brain atrophy, the protective effects of lithium, and cognitive training. A limitation of this study is regarding the data collection. Using three data sets means the data we have collected may not have the same information, which leads to utility being limited. The neuroimaging brain age may be able to predict people's potential illness and ageing-related brain disease and psychiatric disorders, this application may potentially contribute to both neuroscience and clinical practice.

References

Abé, C., Ching, C. R. K., Liberg, B., Lebedev, A. V., Agartz, I., Akudjedu, T. N., Alda, M., Alnæs, D., Alonso-Lana, S., Benedetti, F., Berk, M., Bøen, E., Bonnin, C. D. M., Breuer, F., Brosch, K., Brouwer, R. M., Canales-Rodríguez, E. J., Cannon, D. M., Chye, Y., . . . Landén, M. (2022). Longitudinal Structural Brain Changes in Bipolar Disorder: A Multicenter Neuroimaging Study of 1232 Individuals by the ENIGMA Bipolar Disorder Working Group. *Biol Psychiatry*, *91*(6), 582-592. https://doi.org/10.1016/j.biopsych.2021.09.008

Abé, C., Rolstad, S., Petrovic, P., Ekman, C. J., Sparding, T., Ingvar, M., & Landén, M. (2018). Bipolar disorder type I and II show distinct relationships between cortical thickness and executive function. *Acta psychiatrica Scandinavica*, *138*(4), 325-335. https://doi.org/10.1111/acps.12922

Abramovic, L., Boks, M. P. M., Vreeker, A., Verkooijen, S., van Bergen, A. H., Ophoff, R. A., Kahn, R. S., & van Haren, N. E. M. (2018). White matter disruptions in patients with bipolar disorder. *Eur Neuropsychopharmacol*, *28*(6), 743-751. https://doi.org/10.1016/j.euroneuro.2018.01.001

Barysheva, M., Jahanshad, N., Foland-Ross, L., Altshuler, L. L., & Thompson, P. M. (2013). White matter microstructural abnormalities in bipolar disorder: A whole brain diffusion tensor imaging study. *Neuroimage Clin*, *2*, 558-568. https://doi.org/10.1016/j.nicl.2013.03.016

Beach, T. G., Monsell, S. E., Phillips, L. E., & Kukull, W. (2012). Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. *J Neuropathol Exp Neurol*, *71*(4), 266-273. https://doi.org/10.1097/NEN.0b013e31824b211b

Benedict, R. H., Morrow, S. A., Weinstock Guttman, B., Cookfair, D., & Schretlen, D. J. (2010). Cognitive reserve moderates decline in information processing speed in multiple sclerosis patients. *J Int Neuropsychol Soc*, *16*(5), 829-835. https://doi.org/10.1017/s1355617710000688

Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex*, *19*(12), 2767-2796. https://doi.org/10.1093/cercor/bhp055

Bourne, C., Aydemir, O., Balanzá-Martínez, V., Bora, E., Brissos, S., Cavanagh, J. T. O., Clark, L., Cubukcuoglu, Z., Dias, V. V., Dittmann, S., Ferrier, I. N., Fleck, D. E., Frangou, S., Gallagher, P., Jones, L., Kieseppä, T., Martínez-Aran, A., Melle, I., Moore, P. B., . . .

Goodwin, G. M. (2013). Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: An individual patient data meta-analysis. *Acta Psychiatrica Scandinavica*, *128*(3), 149-162. https://doi.org/10.1111/acps.12133

Cao, B., Passos, I. C., Mwangi, B., Bauer, I. E., Zunta-Soares, G. B., Kapczinski, F., & Soares, J. C. (2016). Hippocampal volume and verbal memory performance in late-stage bipolar disorder. *Journal of psychiatric research*, *73*, 102-107. https://doi.org/10.1016/j.jpsychires.2015.12.012

Ching, C. R. K., Hibar, D. P., Gurholt, T. P., Nunes, A., Thomopoulos, S. I., Abé, C., Agartz, I., Brouwer, R. M., Cannon, D. M., de Zwarte, S. M. C., Eyler, L. T., Favre, P., Hajek, T., Haukvik, U. K., Houenou, J., Landén, M., Lett, T. A., McDonald, C., Nabulsi, L., . . . Andreassen, O. A. (2022). What we learn about bipolar disorder from large-scale neuroimaging: Findings and future directions from the ENIGMA Bipolar Disorder Working Group. *Hum Brain Mapp*, *43*(1), 56-82. https://doi.org/10.1002/hbm.25098

Clark, L., & Sahakian, B. J. (2008). Cognitive neuroscience and brain imaging in bipolar disorder. *Dialogues Clin Neurosci*, *10*(2), 153-163. https://doi.org/10.31887/DCNS.2008.10.2/lclark

Cole, J. H., Annus, T., Wilson, L. R., Remtulla, R., Hong, Y. T., Fryer, T. D., Acosta-Cabronero, J., Cardenas-Blanco, A., Smith, R., Menon, D. K., Zaman, S. H., Nestor, P. J., & Holland, A. J. (2017). Brain-predicted age in Down syndrome is associated with beta amyloid deposition and cognitive decline. *Neurobiology of aging*, *56*, 41-49. https://doi.org/10.1016/j.neurobiolaging.2017.04.006

Cole, J. H., & Franke, K. (2017). Predicting Age Using Neuroimaging: Innovative Brain Ageing Biomarkers. *Trends in neurosciences*, *40*(12), 681-690. https://doi.org/10.1016/j.tins.2017.10.001

Cole, J. H., Leech, R., & Sharp, D. J. (2015). Prediction of brain age suggests accelerated atrophy after traumatic brain injury. *Annals of neurology*, *77*(4), 571-581. https://doi.org/10.1002/ana.24367

Cole, J. H., Poudel, R. P. K., Tsagkrasoulis, D., Caan, M. W. A., Steves, C., Spector, T. D., & Montana, G. (2017). Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. *NeuroImage*, *163*, 115-124. https://doi.org/10.1016/j.neuroimage.2017.07.059

Cole, J. H., Ritchie, S. J., Bastin, M. E., Valdés Hernández, M. C., Muñoz Maniega, S., Royle, N., Corley, J., Pattie, A., Harris, S. E., Zhang, Q., Wray, N. R., Redmond, P., Marioni, R. E., Starr, J. M., Cox, S. R., Wardlaw, J. M., Sharp, D. J., & Deary, I. J. (2018). Brain

age predicts mortality. *Molecular psychiatry*, *23*(5), 1385-1392. https://doi.org/10.1038/mp.2017.62

Cole, J. H., Underwood, J., Caan, M. W. A., De Francesco, D., van Zoest, R. A., Leech, R., Wit, F. W. N. M., Portegies, P., Geurtsen, G. J., Schmand, B. A., Schim van der Loeff, M. F., Franceschi, C., Sabin, C. A., Majoie, C. B. L. M., Winston, A., Reiss, P., & Sharp, D. J. (2017). Increased brain-predicted aging in treated HIV disease. *Neurology*, *88*(14), 1349-1357. https://doi.org/10.1212/WNL.0000000000003790

Cousins, D. A., Squarcina, L., Boumezbeur, F., Young, A. H., & Bellivier, F. (2020). Lithium: past, present, and future. *Lancet Psychiatry*, *7*(3), 222-224. https://doi.org/10.1016/s2215-0366(19)30365-7

Díaz Ortiz, A. C., Upeguí, C. V., Ospina, J. P. Z., Acevedo, D. C. A., Pineda Zapata, J. A., & Jaramillo, C. A. L. (2021). Correlation Between Cognitive Performance and Structural Neuroanatomy in Patients with Type I Bipolar Affective Disorder Treated with and Without Lithium. *Rev Colomb Psiquiatr (Engl Ed)*. https://doi.org/10.1016/j.rcp.2020.10.003 (Correlación entre el desempeño cognitivo y la neuroanatomía estructural en pacientes con trastorno afectivo bipolar tipo I tratados con y sin litio.)

Diniz, B. S., Machado-Vieira, R., & Forlenza, O. V. (2013). Lithium and neuroprotection: translational evidence and implications for the treatment of neuropsychiatric disorders. *Neuropsychiatr Dis Treat*, *9*, 493-500. https://doi.org/10.2147/ndt.S33086

Diniz, B. S., Teixeira, A. L., Cao, F., Gildengers, A., Soares, J. C., Butters, M. A., & Reynolds, C. F., 3rd. (2017). History of Bipolar Disorder and the Risk of Dementia: A Systematic Review and Meta-Analysis. *Am J Geriatr Psychiatry*, *25*(4), 357-362. https://doi.org/10.1016/j.jagp.2016.11.014

Doi, T., Shimada, H., Makizako, H., Tsutsumimoto, K., Uemura, K., Anan, Y., & Suzuki, T. (2014). Cognitive function and gait speed under normal and dual-task walking among older adults with mild cognitive impairment. *BMC Neurol*, *14*, 67. https://doi.org/10.1186/1471-2377-14-67

Dosenbach, N. U. F., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., Nelson, S. M., Wig, G. S., Vogel, A. C., Lessov-Schlaggar, C. N., Barnes, K. A., Dubis, J. W., Feczko, E., Coalson, R. S., Pruett, J. R., Jr., Barch, D. M., Petersen, S. E., & Schlaggar, B. L. (2010). Prediction of individual brain maturity using fMRI. *Science (New York, N.Y.)*, *329*(5997), 1358-1361. https://doi.org/10.1126/science.1194144

Douglas, K. M., Gallagher, P., Robinson, L. J., Carter, J. D., McIntosh, V. V., Frampton, C. M., Watson, S., Young, A. H., Ferrier, I. N., & Porter, R. J. (2018). Prevalence of cognitive impairment in major depression and bipolar disorder. *Bipolar Disord*, *20*(3), 260-274. https://doi.org/10.1111/bdi.12602

Duara, R., Loewenstein, D. A., Potter, E., Appel, J., Greig, M. T., Urs, R., Shen, Q., Raj, A., Small, B., Barker, W., Schofield, E., Wu, Y., & Potter, H. (2008). Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. *Neurology*, *71*(24), 1986-1992. https://doi.org/10.1212/01.wnl.0000336925.79704.9f

Dubois, B., Villain, N., Frisoni, G. B., Rabinovici, G. D., Sabbagh, M., Cappa, S., Bejanin, A., Bombois, S., Epelbaum, S., Teichmann, M., Habert, M. O., Nordberg, A., Blennow, K., Galasko, D., Stern, Y., Rowe, C. C., Salloway, S., Schneider, L. S., Cummings, J. L., & Feldman, H. H. (2021). Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol*, *20*(6), 484-496. https://doi.org/10.1016/s1474-4422(21)00066-1

Ekman, C. J., Petrovic, P., Johansson, A. G. M., Sellgren, C., Ingvar, M., & Landén, M. (2017). A History of Psychosis in Bipolar Disorder is Associated With Gray Matter Volume Reduction. *Schizophrenia bulletin*, *43*(1), 99-107. https://doi.org/10.1093/schbul/sbw080

Forlenza, O. V., De-Paula, V. J., & Diniz, B. S. (2014). Neuroprotective effects of lithium: implications for the treatment of Alzheimer's disease and related neurodegenerative disorders. *ACS Chem Neurosci*, *5*(6), 443-450. https://doi.org/10.1021/cn5000309

Fountoulakis, K. N., Tohen, M., & Zarate, C. A., Jr. (2022). Lithium treatment of Bipolar disorder in adults: A systematic review of randomized trials and meta-analyses. *Eur Neuropsychopharmacol*, *54*, 100-115. https://doi.org/10.1016/j.euroneuro.2021.10.003

Franke, K., & Gaser, C. (2019). Ten Years of BrainAGE as a Neuroimaging Biomarker of Brain Aging: What Insights Have We Gained? *Frontiers in neurology*, *10*, 789. https://doi.org/10.3389/fneur.2019.00789

Franke, K., Gaser, C., Manor, B., & Novak, V. (2013). Advanced BrainAGE in older adults with type 2 diabetes mellitus. *Frontiers in aging neuroscience*, *5*, 90. https://doi.org/10.3389/fnagi.2013.00090

Franke, K., Gaser, C., Roseboom, T. J., Schwab, M., & de Rooij, S. R. (2018). Premature brain aging in humans exposed to maternal nutrient restriction during early gestation. *NeuroImage*, *173*, 460-471. https://doi.org/10.1016/j.neuroimage.2017.10.047

Franke, K., Ziegler, G., Klöppel, S., & Gaser, C. (2010). Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: exploring the influence of various parameters. *NeuroImage*, *50*(3), 883-892. https://doi.org/10.1016/j.neuroimage.2010.01.005

Ganzola, R., & Duchesne, S. (2017). Voxel-based morphometry meta-analysis of gray and white matter finds significant areas of differences in bipolar patients from healthy controls. *Bipolar Disord*, *19*(2), 74-83. https://doi.org/10.1111/bdi.12488

Gaser, C., Franke, K., Klöppel, S., Koutsouleris, N., & Sauer, H. (2013). BrainAGE in Mild Cognitive Impaired Patients: Predicting the Conversion to Alzheimer's Disease. *PloS one*, *8*(6), e67346. https://doi.org/10.1371/journal.pone.0067346

Guggenmos, M., Schmack, K., Sekutowicz, M., Garbusow, M., Sebold, M., Sommer, C., Smolka, M. N., Wittchen, H.-U., Zimmermann, U. S., Heinz, A., & Sterzer, P. (2017). Quantitative neurobiological evidence for accelerated brain aging in alcohol dependence. *Translational psychiatry*, *7*(12), 1279. https://doi.org/10.1038/s41398-017-0037-y

Gupta, S., & Khastgir, U. (2017). Drug information update. Lithium and chronic kidney disease: debates and dilemmas. *BJPsych Bull*, *41*(4), 216-220. https://doi.org/10.1192/pb.bp.116.054031

Hajek, T., Franke, K., Kolenic, M., Capkova, J., Matejka, M., Propper, L., Uher, R., Stopkova, P., Novak, T., Paus, T., Kopecek, M., Spaniel, F., & Alda, M. (2019). Brain Age in Early Stages of Bipolar Disorders or Schizophrenia. *Schizophrenia bulletin*, *45*(1), 190-198. https://doi.org/10.1093/schbul/sbx172

Hajek, T., Kopecek, M., Höschl, C., & Alda, M. (2012). Smaller hippocampal volumes in patients with bipolar disorder are masked by exposure to lithium: a meta-analysis. *J Psychiatry Neurosci*, *37*(5), 333-343. https://doi.org/10.1503/jpn.110143

Hamilton, M. (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry*, *23*(1), 56-62. https://doi.org/10.1136/jnnp.23.1.56

Hartberg, C. B., Jørgensen, K. N., Haukvik, U. K., Westlye, L. T., Melle, I., Andreassen, O. A., & Agartz, I. (2015). Lithium treatment and hippocampal subfields and amygdala volumes in bipolar disorder. *Bipolar Disord*, *17*(5), 496-506. https://doi.org/10.1111/bdi.12295

Haukvik, U. K., Gurholt, T. P., Nerland, S., Elvsåshagen, T., Akudjedu, T. N., Alda, M., Alnaes, D., Alonso-Lana, S., Bauer, J., Baune, B. T., Benedetti, F., Berk, M., Bettella, F., Bøen, E., Bonnín, C. M., Brambilla, P., Canales-Rodríguez, E. J., Cannon, D. M., Caseras,

X., . . . Agartz, I. (2022). In vivo hippocampal subfield volumes in bipolar disorder-A mega-analysis from The Enhancing Neuro Imaging Genetics through Meta-Analysis Bipolar Disorder Working Group. *Hum Brain Mapp*, *43*(1), 385-398. https://doi.org/10.1002/hbm.25249

Hibar, D. P., Westlye, L. T., Doan, N. T., Jahanshad, N., Cheung, J. W., Ching, C. R. K., Versace, A., Bilderbeck, A. C., Uhlmann, A., Mwangi, B., Krämer, B., Overs, B., Hartberg, C. B., Abé, C., Dima, D., Grotegerd, D., Sprooten, E., Bøen, E., Jimenez, E., . . . Andreassen, O. A. (2018). Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. *Molecular psychiatry*, *23*(4), 932-942. https://doi.org/10.1038/mp.2017.73

Hibar, D. P., Westlye, L. T., van Erp, T. G., Rasmussen, J., Leonardo, C. D., Faskowitz, J., Haukvik, U. K., Hartberg, C. B., Doan, N. T., Agartz, I., Dale, A. M., Gruber, O., Krämer, B., Trost, S., Liberg, B., Abé, C., Ekman, C. J., Ingvar, M., Landén, M., . . . Andreassen, O. A. (2016). Subcortical volumetric abnormalities in bipolar disorder. *Molecular psychiatry*, *21*(12), 1710-1716. https://doi.org/10.1038/mp.2015.227

Hoffman, P., & Morcom, A. M. (2018). Age-related changes in the neural networks supporting semantic cognition: A meta-analysis of 47 functional neuroimaging studies. *Neurosci Biobehav Rev*, *84*, 134-150. https://doi.org/10.1016/j.neubiorev.2017.11.010

Jelen, L. A., Green, M. S., King, S., Morris, A. G., Zhang, X., Lythgoe, D. J., Young, A. H., De Belleroche, J., & Stone, J. M. (2022). Variants in the zinc transporter-3 encoding gene (SLC30A3) in schizophrenia and bipolar disorder: Effects on brain glutamate-A pilot study. *Front Psychiatry*, *13*, 929306. https://doi.org/10.3389/fpsyt.2022.929306

Kessing, L. V., Søndergård, L., Forman, J. L., & Andersen, P. K. (2008). Lithium treatment and risk of dementia. *Arch Gen Psychiatry*, *65*(11), 1331-1335. https://doi.org/10.1001/archpsyc.65.11.1331

Kolenic, M., Franke, K., Hlinka, J., Matejka, M., Capkova, J., Pausova, Z., Uher, R., Alda, M., Spaniel, F., & Hajek, T. (2018). Obesity, dyslipidemia and brain age in first-episode psychosis. *Journal of psychiatric research*, *99*, 151-158. https://doi.org/10.1016/j.jpsychires.2018.02.012

Koutsouleris, N., Davatzikos, C., Borgwardt, S., Gaser, C., Bottlender, R., Frodl, T., Falkai, P., Riecher-Rössler, A., Möller, H.-J., Reiser, M., Pantelis, C., & Meisenzahl, E. (2014). Accelerated brain aging in schizophrenia and beyond: a neuroanatomical marker of psychiatric disorders. *Schizophrenia bulletin*, *40*(5), 1140-1153. https://doi.org/10.1093/schbul/sbt142

Kubota, M., van Haren, N. E. M., Haijma, S. V., Schnack, H. G., Cahn, W., Hulshoff Pol, H. E., & Kahn, R. S. (2015). Association of IQ Changes and Progressive Brain Changes in Patients With Schizophrenia. *JAMA psychiatry*, *72*(8), 803-812. https://doi.org/10.1001/jamapsychiatry.2015.0712

Lepkifker, E., Iancu, I., Horesh, N., Strous, R. D., & Kotler, M. (2007). Lithium therapy for unipolar and bipolar depression among the middle-aged and older adult patient subpopulation. *Depress Anxiety*, *24*(8), 571-576. https://doi.org/10.1002/da.20273

Li, Y., Liu, Y., Wang, P., Wang, J., Xu, S., & Qiu, M. (2017). Dependency criterion based brain pathological age estimation of Alzheimer's disease patients with MR scans. *Biomedical engineering online*, *16*(1), 50. https://doi.org/10.1186/s12938-017-0342-y

Loftus, J., Scott, J., Vorspan, F., Icick, R., Henry, C., Gard, S., Kahn, J. P., Leboyer, M., Bellivier, F., & Etain, B. (2020). Psychiatric comorbidities in bipolar disorders: An examination of the prevalence and chronology of onset according to sex and bipolar subtype. *Journal of affective disorders*, *267*, 258-263. https://doi.org/10.1016/j.jad.2020.02.035

Löwe, L. C., Gaser, C., & Franke, K. (2016). The Effect of the APOE Genotype on Individual BrainAGE in Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease. *PloS one*, *11*(7), e0157514. https://doi.org/10.1371/journal.pone.0157514

Lyoo, I. K., Kim, M. J., Stoll, A. L., Demopulos, C. M., Parow, A. M., Dager, S. R., Friedman, S. D., Dunner, D. L., & Renshaw, P. F. (2004). Frontal lobe gray matter density decreases in bipolar I disorder. *Biol Psychiatry*, *55*(6), 648-651. https://doi.org/10.1016/j.biopsych.2003.10.017

Masuda, Y., Okada, G., Takamura, M., Shibasaki, C., Yoshino, A., Yokoyama, S., Ichikawa, N., Okuhata, S., Kobayashi, T., Yamawaki, S., & Okamoto, Y. (2020). White matter abnormalities and cognitive function in euthymic patients with bipolar disorder and major depressive disorder. *Brain Behav*, *10*(12), e01868. https://doi.org/10.1002/brb3.1868

McKeith, I., O'Brien, J., Walker, Z., Tatsch, K., Booij, J., Darcourt, J., Padovani, A., Giubbini, R., Bonuccelli, U., Volterrani, D., Holmes, C., Kemp, P., Tabet, N., Meyer, I., & Reininger, C. (2007). Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. *Lancet Neurol*, *6*(4), 305-313. https://doi.org/10.1016/s1474-4422(07)70057-1

Merikangas, K. R., Jin, R., He, J. P., Kessler, R. C., Lee, S., Sampson, N. A., Viana, M. C., Andrade, L. H., Hu, C., Karam, E. G., Ladea, M., Medina-Mora, M. E., Ono, Y.,

Posada-Villa, J., Sagar, R., Wells, J. E., & Zarkov, Z. (2011). Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry*, *68*(3), 241-251. https://doi.org/10.1001/archgenpsychiatry.2011.12

Necus, J., Sinha, N., Smith, F. E., Thelwall, P. E., Flowers, C. J., Taylor, P. N., Blamire, A. M., Cousins, D. A., & Wang, Y. (2019). White matter microstructural properties in bipolar disorder in relationship to the spatial distribution of lithium in the brain. *Journal of affective disorders*, *253*, 224-231. https://doi.org/10.1016/j.jad.2019.04.075

Nenadić, I., Dietzek, M., Langbein, K., Sauer, H., & Gaser, C. (2017). BrainAGE score indicates accelerated brain aging in schizophrenia, but not bipolar disorder. *Psychiatry research. Neuroimaging*, *266*, 86-89. https://doi.org/10.1016/j.pscychresns.2017.05.006

Nunes, P. V., Forlenza, O. V., & Gattaz, W. F. (2007). Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. *Br J Psychiatry*, *190*, 359-360. https://doi.org/10.1192/bjp.bp.106.029868

Ochoa, E. L. M. (2022). Lithium as a Neuroprotective Agent for Bipolar Disorder: An Overview. *Cell Mol Neurobiol*, *42*(1), 85-97. https://doi.org/10.1007/s10571-021-01129-9

Ohi, K., Takai, K., Sugiyama, S., Kitagawa, H., Kataoka, Y., Soda, M., Kitaichi, K., Kawasaki, Y., Ito, M., & Shioiri, T. (2021). Intelligence decline across major depressive disorder, bipolar disorder, and schizophrenia. *CNS spectrums*, 1-7. https://doi.org/10.1017/S1092852921000298

Pardoe, H. R., Cole, J. H., Blackmon, K., Thesen, T., & Kuzniecky, R. (2017). Structural brain changes in medically refractory focal epilepsy resemble premature brain aging. *Epilepsy research*, *133*, 28-32. https://doi.org/10.1016/j.eplepsyres.2017.03.007

Peters, R. (2006). Ageing and the brain. *Postgrad Med J*, *82*(964), 84-88. https://doi.org/10.1136/pgmj.2005.036665

Puglisi-Allegra, S., Ruggieri, S., & Fornai, F. (2021). Translational evidence for lithium-induced brain plasticity and neuroprotection in the treatment of neuropsychiatric disorders. *Translational psychiatry*, *11*(1), 366. https://doi.org/10.1038/s41398-021-01492-7

Raz, N., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Lindenberger, U. (2010). Trajectories of brain aging in middle-aged and older adults: regional and individual differences. *NeuroImage*, *51*(2), 501-511. https://doi.org/10.1016/j.neuroimage.2010.03.020

Ryskalin, L., Limanaqi, F., Frati, A., Busceti, C. L., & Fornai, F. (2018). mTOR-Related Brain Dysfunctions in Neuropsychiatric Disorders. *Int J Mol Sci*, *19*(8). https://doi.org/10.3390/ijms19082226

Salat, D. H., Tuch, D. S., Greve, D. N., van der Kouwe, A. J. W., Hevelone, N. D., Zaleta, A. K., Rosen, B. R., Fischl, B., Corkin, S., Rosas, H. D., & Dale, A. M. (2005). Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiology of aging*, *26*(8), 1215-1227. https://doi.org/10.1016/j.neurobiolaging.2004.09.017

Schnack, H. G., van Haren, N. E. M., Nieuwenhuis, M., Hulshoff Pol, H. E., Cahn, W., & Kahn, R. S. (2016). Accelerated Brain Aging in Schizophrenia: A Longitudinal Pattern Recognition Study. *The American journal of psychiatry*, *173*(6), 607-616. https://doi.org/10.1176/appi.ajp.2015.15070922

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*, *59 Suppl 20*, 22-33;quiz 34-57.

Shulman, K. I. (2010). Lithium for older adults with bipolar disorder: Should it still be considered a first-line agent? *Drugs Aging*, *27*(8), 607-615. https://doi.org/10.2165/11537700-000000000-00000

Solé, B., Jiménez, E., Torrent, C., Reinares, M., Bonnin, C. D. M., Torres, I., Varo, C., Grande, I., Valls, E., Salagre, E., Sanchez-Moreno, J., Martinez-Aran, A., Carvalho, A. F., & Vieta, E. (2017). Cognitive Impairment in Bipolar Disorder: Treatment and Prevention Strategies. *Int J Neuropsychopharmacol*, *20*(8), 670-680. https://doi.org/10.1093/ijnp/pyx032

Storsve, A. B., Fjell, A. M., Tamnes, C. K., Westlye, L. T., Overbye, K., Aasland, H. W., & Walhovd, K. B. (2014). Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: regions of accelerating and decelerating change. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *34*(25), 8488-8498. https://doi.org/10.1523/JNEUROSCI.0391-14.2014

Syaifullah, A. H., Shiino, A., Kitahara, H., Ito, R., Ishida, M., & Tanigaki, K. (2020). Machine Learning for Diagnosis of AD and Prediction of MCI Progression From Brain MRI Using Brain Anatomical Analysis Using Diffeomorphic Deformation. *Frontiers in neurology*, *11*, 576029. https://doi.org/10.3389/fneur.2020.576029

Van Alphen, A. M., Bosch, T. M., Kupka, R. W., & Hoekstra, R. (2021). Chronic kidney disease in lithium-treated patients, incidence and rate of decline. *International journal of bipolar disorders*, *9*(1), 1. https://doi.org/10.1186/s40345-020-00204-2

Van Gestel, H., Franke, K., Petite, J., Slaney, C., Garnham, J., Helmick, C., Johnson, K., Uher, R., Alda, M., & Hajek, T. (2019). Brain age in bipolar disorders: Effects of lithium treatment. *The Australian and New Zealand journal of psychiatry*, *53*(12), 1179-1188. https://doi.org/10.1177/0004867419857814

Van Rheenen, T. E., Lewandowski, K. E., Bauer, I. E., Kapczinski, F., Miskowiak, K., Burdick, K. E., & Balanzá-Martínez, V. (2020). Current understandings of the trajectory and emerging correlates of cognitive impairment in bipolar disorder: An overview of evidence. *Bipolar Disord*, *22*(1), 13-27. https://doi.org/10.1111/bdi.12821

Varikuti, D. P., Genon, S., Sotiras, A., Schwender, H., Hoffstaedter, F., Patil, K. R., Jockwitz, C., Caspers, S., Moebus, S., Amunts, K., Davatzikos, C., & Eickhoff, S. B. (2018). Evaluation of non-negative matrix factorization of grey matter in age prediction. *NeuroImage*, *173*, 394-410. https://doi.org/10.1016/j.neuroimage.2018.03.007

Vieta, E., Berk, M., Schulze, T. G., Carvalho, A. F., Suppes, T., Calabrese, J. R., Gao, K., Miskowiak, K. W., & Grande, I. (2018). Bipolar disorders. *Nat Rev Dis Primers*, *4*, 18008. https://doi.org/10.1038/nrdp.2018.8

Villa, L. M., Colic, L., Kim, J. A., Sankar, A., Goldman, D. A., Lessing, B., Pittman, B., Alexopoulos, G. S., van Dyck, C. H., & Blumberg, H. P. (2022). Aging of the brain in bipolar disorder: Illness- and onset-related effects in cortical thickness and subcortical gray matter volume. *Journal of affective disorders*, *323*, 875-883. https://doi.org/10.1016/j.jad.2022.12.026

Won, E., & Kim, Y. K. (2017). An Oldie but Goodie: Lithium in the Treatment of Bipolar Disorder through Neuroprotective and Neurotrophic Mechanisms. *Int J Mol Sci*, *18*(12). https://doi.org/10.3390/ijms18122679

Wrigglesworth, J., Ward, P., Harding, I. H., Nilaweera, D., Wu, Z., Woods, R. L., & Ryan, J. (2021). Factors associated with brain ageing - a systematic review. *BMC Neurol*, *21*(1), 312. https://doi.org/10.1186/s12883-021-02331-4

Xu, N., Huggon, B., & Saunders, K. E. A. (2020). Cognitive Impairment in Patients with Bipolar Disorder: Impact of Pharmacological Treatment. *CNS drugs*, *34*(1), 29-46. https://doi.org/10.1007/s40263-019-00688-2

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*, *133*, 429-435. https://doi.org/10.1192/bjp.133.5.429

Zhu, Z., Zhao, Y., Wen, K., Li, Q., Pan, N., Fu, S., Li, F., Radua, J., Vieta, E., Kemp, G. J., Biswa, B. B., & Gong, Q. (2022). Cortical thickness abnormalities in patients with bipolar disorder: A systematic review and meta-analysis. *Journal of affective disorders*, *300*, 209-218. https://doi.org/10.1016/j.jad.2021.12.080

Chapter 6 General Discussion

6.1 Summary of the findings

In this thesis, I started with a literature review, which indicated that emotion and cognition were strongly associated with 5-HT_7 receptor functions. In the systematic review, I investigated the relationships between 5-HT_7 and mood disorders. The first finding, mainly from research in experimental animals was that 5-HT_7 has a role in anxiety and depression, such that antagonists could be beneficial, although effects in mania were unclear. The second finding was that sleep and memory were associated with 5-HT_7. However, none of the human studies have been able to test these ideas because of a lack of any 5-HT_7 ligand for emission tomography and no studies using a drug selective for the 5-HT_7 receptor. Thus, there are two major contributions of this thesis: (i) we used a selective 5-HT_7 receptor antagonist, and (ii) I combined this with behavioural and imaging assessments of cognition. This is the first attempt to use neuroimaging combined with the selective 5-HT_7 antagonist JNJ-18038683. Two previously used paradigms for fMRI analysis, pop-faces and N-back working memory were used. The pop-faces paradigm allowed us to examine the neural circuits involved in emotion processing, while the N-back task allowed us to examine working memory and cognitive control, as well as activity in the cognitive control network (CCN). These paradigms are well-specified for measuring different cognitive domains and allow us to better understand the effects of JNJ-18038683 on emotional and cognitive processes (Owen et al., 2005; Townsend & Altshuler, 2012). In the final experimental chapter, I reported the findings from my exploration of brain age, cognitive functions and brain atrophy. I follow these chapters, with this general discussion where I attempt to synthesise my findings across chapters and draw some conclusions for the field.

In the chapter 3, the fMRI analysis for emotional functions, I found there was no significant difference between interventions (drug or placebo) both in behavioural performances, and brain activations. The whole-brain exploratory analysis revealed that the fusiform gyrus was activated when participants were engaged in the task, which was expected given the face-processing demand within the task. The drug did not affect emotional processing related behaviour. For brain activation, there was no simple main effect across the three emotions, and no emotion-by-drug interaction were observed. Since no emotion-by-drug interaction were observed, the drug administering dosage and duration (20mg daily for one week, a relative low dosage and short duration) should be considered. The observed dose and timing of administration showed effects on cognitive tests, but not on emotional processing.

In the chapter 4, cognitive function analysis, activity of the CCN was modulated by drug in ROIs analysis, and caudate activation reflected an in interaction between task level and drug in the whole brain exploration. However, a small sample size and bias of participants selection should be considered. It showed that the brain areas were modulated by drug in cognitive domain but not emotional domain; however, some area, such as changes in amygdala, is difficult to detected (Costafreda et al., 2008). The cognitive paradigm (N-back task) is commonly used in adults, compared to the gender discrimination emotional faces task (pop-faces) was used in adolescents (Passamonti et al., 2010). These contradict findings indicated that the underlying mechanisms of the drug were intricate and multifaceted.

After two fMRI chapters, I further used the programming 'brainageR' to explore the relationships between the chronological age (age at scan) and predicted biological brain age (brain age). In the findings, larger gap between chronological age and brain age

was found in individuals with bipolar disorder. In addition, the relations between brain age and cognitive functions, including IQ, working memory, and processing speed, were investigated: higher IQ, higher processing speed, and lower memory, were associated a larger gap between chronological age and brain age. Some outcomes are counter intuitive, but considering brainageR only evaluates whole grey matter volume, the interpretation should be relatively conservative.

6.2 Overall discussion

6.2.1 BD and 5-HT$_7$

In the conclusion of the first chapter, I noted how 5-HT$_7$ receptors are highly expressed in brain areas abnormal in bipolar disorder, including abnormalities in amygdala, hippocampus, and thalamus were found (Hajek et al., 2012; Hibar et al., 2016); as well as lower volume thickness and surface in frontal brain regions were found in both bipolar 1 and bipolar 2; reduced grey matter volumes in fusiform gyrus and hippocampus were found in bipolar patients (Cao et al., 2016; Hibar et al., 2016; Vieta et al., 2018). This was shown for not only structural measures but also functional for fMRI. Both behavioural performance and brain abnormalities were found in individuals with bipolar disorder. Individuals with bipolar disorder were found significantly lower difficulty-related activation differences in the left lateral occipital and right cortices compared to healthy controls and patients with monosyndromic disorder. Greater difficulty-related slowing of reaction time was associated with changes in activity in several brain regions, including prefrontal, frontal, parietal, posterior parietal and lateral occipital cortices (Manelis et al., 2022). In my findings, there was no significant activation in emotional recognition task, while CCN were found to be associated with working memory task. The findings indicated that the 5-HT$_7$ antagonist, JNJ-18038683,

may be a promising drug for modulating brain activation for enhancing cognitive functions, supporting the conclusions of the systematic review.

5-HT_7 receptors are highly expressed in amygdala, hippocampus, and thalamus (Hedlund & Sutcliffe, 2004). Thus, we expected the 5-HT_7 antagonist, JNJ-18038683, would modulate the brain activation in these areas. From the findings from fMRI chapters, the fusiform gyrus was activated in the main effect of task level. The fusiform gyrus is an area involved in visual processing, face perception, and object recognition (Jung et al., 2021; Palejwala et al., 2020; Weiner & Zilles, 2016), and the activation of the fusiform gyrus meant that the task and drug may modulate the aspect of facial recognition or emotional processing (Jung et al., 2021; Kawasaki et al., 2012). I explored whether the drug modulated brain activation, and the result indicated that the drug did not influence the neural activity associated with the emotion task. This could potentially mean that the drug did not affect the processing of faces underlying the gender discrimination emotional faces task, and suggested that the drug might have limited effects on emotional processing. Individuals with bipolar disorder showed lower grey matter in the fusiform gyrus, and our finding was that activity within the fusiform gyrus would be modulated by the drug. Even though the drug could alter the BOLD activation, whether 5-HT_7 has an effect on emotion regulation or other emotion processing functions is still unclear (Penton-Voak et al., 2021).

5-HT is associated with emotion, and most of the anti-depressants, SSRIs or SNRIs, modulate serotonergic signalling (Jauhar et al., 2023; Kraus et al., 2017; Meneses & Liy-Salmeron, 2012). In addition to emotion, researchers further investigated the relationships between 5-HT and cognitive functions. The findings suggested that decreased serotonin neurotransmission has a detrimental impact on cognition,

especially learning and memory (Harvey, 2003; Meneses & Liy-Salmeron, 2012): the prefrontal cortex serotonin is involved in working memory, attention, decision-making and reversal learning (Clark et al., 2004; Ogren et al., 2008; Perez-Garcia & Meneses, 2008; Robbins, 2000), the hippocampus 5-HT is involved in memory processing and decision-making (Lisman et al., 2017; Sekeres et al., 2018; Teixeira et al., 2018), and the amygdala 5-HT is involved in fear and anxiety responses (Christianson et al., 2010; Johnson et al., 2015; Sengupta et al., 2017). Indeed, some researchers have proposed that reduced 5-HT could be a characteristic trait marker for bipolar disorder (Mahmood & Silverstone, 2001). While direct in vivo evidence supporting this claim is currently lacking, it is established that restoring serotonin activity to normal levels can have positive effects, emphasising the potential of targeting 5-HT and its receptors as pharmacological interventions to enhance cognitive performance in neuropsychiatric disorders (Švob Štrac et al., 2016). Further research has indicated that a lower level of 5-HT_{2A} was associated with mania (Yatham et al., 2010) and that there were significantly decreased brain levels of 5-HT (Young et al., 1994). These findings provide evidence for a significant relationship between 5-HT and bipolar disorder.

The objective of the pop-faces chapter was to examine the potential emotional benefits of JNJ-18038683 and elucidate its neural mechanisms through whole-brain mapping. However, there was no significant positive effect on emotional regulation, either on behavioural performance or on brain activation.

The aim of the N-back working memory chapter was to investigate the potential cognitive benefits of JNJ-18038683 and to explore the neural mechanism with whole-brain mapping. Our results showed the drug improved participants' behavioural performance, and the CCN, which includes the DLPFC, was activated during the N-

back following treatment. It may indicate that 5-HT$_7$ improves working memory through modulating DLPFC. These brain areas have previously been shown to be involved in working memory and executive function, and these findings with JNJ-18038683 highlighted the potential for developing more effective treatments for cognitive impairments in the future. A growing body of literature confirms the relationship between the DLPFC and working memory (Mencarelli et al., 2019; Owen et al., 2005). The current study tried to test whether JNJ-18038683 can modulate the CCN areas, such as DLPFC, and thus influence working memory. Although the study focused on healthy controls, it is important to note that the drug has the potential to modulate brain function, particularly cognitive functions. Therefore, if used in individuals with bipolar disorder, JNJ-18038683 improved working memory by modulating the CCN.

The 5-HT$_7$ antagonist, JNJ-18038683, is a serotonergic drug. It should be noted that certain antidepressants, especially the serotonergic drugs have been known to induce mania, which is a significant concern (Patel et al., 2015). While it is possible to treat bipolar depression with antidepressants, the risk of inducing mania is greater in bipolar 1 as compared to bipolar 2. Moreover, treatment with Tricyclic antidepressants and venlafaxine also carries a risk of inducing mania (Antosik-Wójcińska et al., 2015). Therefore, using serotonergic drugs to treat bipolar disorder should be done with caution.

6.2.2 Administrating dosage and duration of 5-HT$_7$

5-HT$_7$ antagonist may not help improve performances in all cognitive tasks, however, the effect of dosage and duration should be considered with respect to our findings. In our study, JNJ-18038683 20mg daily was administrated for one week, but the dosage

and duration were low and short, compared to the previous 5-HT_7 antagonists effective dosage and duration (Bonaventure et al., 2012). If compared to LU AA21004 (vortioxetine), one of the common drugs with 5-HT_7 affinity, our dosage and duration was single repeated dose. Researchers have tried to use the dosage from 1mg, 2.5mg, 5mg, 10mg, 15mg, 20mg vortioxetine for 6 to 8 weeks (Alvarez et al., 2012; Baldwin et al., 2012; Henigsberg et al., 2012; Mahableshwarkar et al., 2013; McIntyre et al., 2014), and one of the longest studies used LU AA21004 with open-label 20 weeks plus double-blinded period 24-56 weeks for 5 mg or 10mg daily (Baldwin et al., 2012), due to uncertainty about the appropriate dosage and treatment duration for mood disorders using 5-HT_7 antagonists. Therefore, they tested the efficacy of several combinations of dose and duration in an attempt to determine the optimal regimen such as improving in the emotional scales in Hamilton Anxiety (HAM-A) or Hamilton Depression Scale (HAM-D) (Baldwin et al., 2012; Mahableshwarkar et al., 2013). As to JNJ-18038683, in a paper published in 2012, the researchers used (i) 100mg JNJ-18038683 for the 1st day and 20mg for the 2nd and 3rd day; (ii) 20mg JNJ-18038683 for 17 days. (iii) 20mg JNJ-18038683 for 7 weeks. Studies (ii) and (iii), were considerably longer than our study, and the dosage is larger in study (i) (Bonaventure et al., 2012). Generally, SSRIs are viewed as requiring two weeks or more of dosing for the clinical benefits to manifest (Taylor et al., 2006), including antidepressants with greater potency at 5-HT_7 receptors, the JNJ-18038683 duration of administering could be an issue that needed to be considered. Integrating the previous studies and our findings, people who were administrated with JNJ-18038683 likely should take it more than 20mg dosage, for more than one weeks duration, to benefit from it. And this may also explain the lack of significant results in the emotional faces task.

In our investigation, we did not undertake a clinical trial to assess efficacy in patients, given the presence of unknown variables, including the optimal dosage, dosing timing, and duration. Instead, our focus centred on a comprehensive study of whether the drug, JNJ-18038683, effectively modulates brain functions. By establishing evidence for the systems and processes likely influenced by the drug, we contributed valuable insights into its potential therapeutic impact. Recognising that alterations in brain function may precede observable changes in behaviour, we chose neuroimaging as a suitable method for detecting the modulatory effects of the drug. This approach allows for a exploration of how the drug interacts with neural processes, to develop the comprehensive understanding of its potential applications and implications.

Lastly, investigating the effects of compounds with 5-HT_7 affinity in clinical populations, there are several additional conditions that should be considered, including the types of bipolar disorder (e.g., bipolar 1, bipolar 2, or rapid cyclothymic), courses of disease (mania or depression), or phases (e.g., acute or chronical status). Further investigation should consider two factors: multiple combinations of dosage and a range of treatment duration could be considered, in order to gain more insights and knowledge of this drug.

6.2.3 Implications and future studies

In chapter 5, brain age analysis, we combined four datasets, increasing sample size to improve sensitivity. A larger sample size increased statistical power and improved the generalisability of findings. In addition, it could reduce measurement error by averaging out differences in measurement between studies. We gained novel insights from datasets combination, and there could be potential methods to facilitate study design for more accurate results. In this chapter, the brain age reflected people's brain

biological condition (grey matter volume) and it may also be applied to some types of studies, such as ageing or neurodegenerative diseases. In some studies, researchers assigned participants to different age groups to present their demographic and biological features (e.g., young, middle, or older age). For example, in a study for bipolar disorder, researchers divided participants in to three age group to present young (M = 23.57, SD = 5.63), middle age (M = 38.13, SD = 5.63), and older (M = 66.86, SD = 5.70) features (Yaple et al., 2019). However, depending on biological age may be reflect participants' brain structure and brain functions appropriately. In this condition, using brain age, which represents the predicted neurological brain age, could be one potential solution. Researchers could consider stratifying the population based on the deviation between their age and the predicted brain age. Individuals with the greatest brain age and chronological age gap may need treatment the most, and they may be more willing to accept the associated side effects and to benefit from some potential treatments. In addition, the observed effect size is relatively small, and the association with cognition showed some paradoxical patterns. Certain outcomes were counter intuitive. To elucidate the relationships and underlying mechanisms, further investigation could make efforts on using larger sample sizes and conducting longitudinal follow-up studies.

6.3 Strengths and limitations

6.3.1 Strengths

There are several salient strengths in this study.

1. JNJ-18038683 is a selective compound: The drug we used was a compound with a high affinity for the 5-HT_7 receptor and is relatively selective compared to other compounds with an affinity for 5-HT_7 such as lurasidone

or vortioxetine. These antipsychotics or antidepressants that also have affinity for other receptors have been used in human studies, but it was difficult to isolate the effects of 5-HT_7. In this study, we used JNJ-18038683, a compound with high selectivity for the 5-HT_7 receptor, allowing us to more clearly determine its efficacy. This result suggested that JNJ-18038683 may have a promising effect on cognitive processes, with perhaps less efficacy in the emotional domain, and the high selectivity of JNJ-18038683 makes it a promising candidate for future studies, which may further investigate its mechanism of action and potential therapeutic applications.

2. This study design minimised the potential influence of several biases: a randomised, double-blind, cross-over study could reduce experimenter biases; moreover, every participant acts as his or her own control, which made the result highly reliable (Misra, 2012; Wellek & Blettner, 2012). Our recruitment included 1:1.3 (M:F), in which male (n = 6) and female (n = 8); This close ratio helped minimise gender bias in our study.

6.3.2 Limitations and future directions

There are some limitations in this study.

1. Small sample size: we had a small sample size, and I only analysed healthy controls' data (n = 14 in pop-faces task and n = 13 in N-back task), but the ultimate expectation is to use JNJ-18038683 to improve bipolar patients' cognitive and emotional functions. Pharmacological fMRI studies conducted with a small number of participants, and this may limit the generalisability of the findings and reduce the statistical power of the study. Generally, in fMRI study, the common number of participants is between 20 to 30, but this

is unlikely to be sufficient for acquiring reproducible brain-behavioural correlations (Grady et al., 2021). However, even though we tried to remove the issues of high costs of imaging and the need for specific expertise (e.g., doctor to prescribe the drug, or blood laboratory test), it was also difficult to recruit participants. During the screening visit, forty-four people were excluded from the study due to various reasons such as abnormal ECG or blood test results, almost fainting during blood tests, presence of other psychiatric or physical conditions, and non-compliance. The COVID-19 pandemic further hindered the recruitment process, resulting in a two-year delay in participant recruitment. Despite these challenges, the study aimed to maintain high standards of data quality, which led to the exclusion of a significant amount of data from bipolar patients. Because this is originally designed as a proof of concept (POC) study, applying the outcome to people with bipolar disorder and developing an effective treatment is essential and ultimate concern in the future. A larger sample size studies should be conducted in the future.

2. Low dosage and short duration*:* since we administrated JNJ-18038683 20mg da*ily* for one week, an effective usage of dosage (more than 20mg) and duration (two weeks to six weeks), which was based on the previous studies (Bonaventure et al., 2012; Taylor et al., 2006). However, as an experimental drug test instead of a clinical trial, we could only provide a comprehensive study to establish the drug's modulation of some key brain functions, using neuroimaging to detect potential drug effects on neural processes preceding behavioural changes. Studies on optimal dosage and duration could be further investigated.

3. Homogenous groups: our participants had similar demographic features. We included 14 healthy control participants and 4 bipolar patients in this study; for the healthy control participants, their mean age is young 32.17 (SD = 13.21); for bipolar patients, we recruited individuals in euthymic status. Due to the feature of the participants, they may not reflect the real-world situations. The drug may have different effects on the brain function of young healthy controls compared to its actions in bipolar patients who have emotional and cognitive impairment. In work exploring the use of ketamine as a novel antidepressant, similar differential effects were seemed between healthy controls and patients. Ketamine has been found to induce perceptual distortion, affective flatting and alogia (Pomarol-Clotet et al., 2006), and it has shown promising treatment effects in individuals with depression (Jelen & Stone, 2021; McIntyre et al., 2021; Rosenblat et al., 2019), However, a study has found distinct electrophysiological and behavioural effects of ketamine in depressed and healthy subjects (Nugent et al., 2019). These differential effects between healthy controls and patients highlight a potential issue with study JNJ-18038683 in healthy controls. Thus, the findings in our study may not accurately reflect how the JNJ-18038683 will behave in individuals with bipolar, and caution should be taken when extrapolating these results. Further research is needed to fully understand the effects of JNJ-18038683 in individuals with bipolar and how these may differ from its effects in healthy controls. I analysed the healthy controls' data, but in the future, studies could recruit individuals with bipolar disorder and ultimately develop an evidence-based effective treatment.

4. Potential side effects of drug: studies have revealed the relationships between 5-HT_7 and the respiratory (Ayaz et al., 2017; Cadirci et al., 2013) and cardiovascular systems (Damaso et al., 2007; Ramage & Villalón, 2008), highlighting 5-HT_7 receptors' role in these bodily functions. The presence of 5-HT_7 receptors in multiple systems in the body has raised some concerns about possible bias in BOLD signalling assays (Carmichael et al., 2018). The use of 5-HT_7 antagonists may affect participants' respiratory and cardiovascular systems, leading to potential changes in their BOLD signalling during the study. By considering these factors, researchers can minimise potential bias and accurately interpret their findings.

6.4 Research conclusion

From systematic review, we gained the insight that 5-HT_7 may be a promising target for mood disorders. I then summarised that 5-HT_7 was associated with emotion and cognition and further investigated the emotional functions with fMRI and emotional faces recognition paradigm in the chapter 3 and explored the cognitive functions with fMRI and N-back working memory paradigm in chapter 4. The two fMRI chapters analysis based on the tasks worked so that the drug effects could be evaluated accurately. When trying to apply these findings to clinical field, I focused on the effects of bipolar disorder.

Individuals diagnosed with bipolar disorder typically demonstrate cognitive deficits in multiple domains, including executive functioning, attention, verbal learning, processing speed and working memory. These deficits have been well documented in the literature in early stage (MacQueen et al., 2005; Thompson et al., 2007). More recently, several studies have found that these cognitive deficits may persist even in

remission (Beshkov et al., 2018; Bora et al., 2009; Cremaschi et al., 2013; Lage et al., 2013; Lee et al., 2014; Solé et al., 2017; Soraggi-Frez et al., 2017; Tsapekos et al., 2021), suggesting that they may act as potential biomarkers of bipolar disorder (Cremaschi et al., 2013; Gruber et al., 2010), rather than merely being a state-dependent manifestation of the condition. This finding has important implications for the diagnosis and treatment of bipolar disorder, as it highlights the need for ongoing cognitive monitoring and potential interventions.

Given the high priority of developing effective treatments for bipolar disorder, including pharmacological interventions, we sought to investigate the potential of 5-HT_7 antagonists in healthy controls. The results of this study suggested that JNJ-18038683 has potential effects to enhance cognitive functions, specifically working memory. It indicated that 5-HT_7 antagonists could improve cognitive functions in healthy controls, and this might apply to individuals with bipolar disorder. However, 5-HT is frequently targeted in therapeutic approaches for depression, but it is not as effective for bipolar disorder, which might raise the likelihood of experiencing manic episodes (Goldberg et al., 2021; Goldberg & Truman, 2003; Patel et al., 2015; Tondo et al., 2010). Future studies can investigate the efficacy of this drug in individuals with bipolar disorder and explore the extent to which it can modulate the CCN to improve working memory. Furthermore, brain age analysis revealed an accelerated brain ageing process in individuals with bipolar disorder compared to healthy controls, suggesting more pronounced brain atrophy in this population. Factors such as participant bias, a small sample size, dosage and duration, and limitations associated with the combined datasets, should be considered when investigating reasons for conflicting results with previous studies. It is also important to integrate the results of previous studies to develop effective interventions, such as the 5-HT_7 antagonist explored in this study,

offering optimistic prospects for enhancing the cognitive functions and improving the lives of individuals with bipolar disorder.

References

Alvarez, E., Perez, V., Dragheim, M., Loft, H., & Artigas, F. (2012). A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol*, *15*(5), 589-600. https://doi.org/10.1017/s1461145711001027

Antosik-Wójcińska, A. Z., Stefanowski, B., & Święcicki, Ł. (2015). Efficacy and safety of antidepressant's use in the treatment of depressive episodes in bipolar disorder - review of research. *Psychiatr Pol*, *49*(6), 1223-1239. https://doi.org/10.12740/pp/37914

Ayaz, G., Halici, Z., Albayrak, A., Karakus, E., & Cadirci, E. (2017). Evaluation of 5-HT7 Receptor Trafficking on In Vivo and In Vitro Model of Lipopolysaccharide (LPS)-Induced Inflammatory Cell Injury in Rats and LPS-Treated A549 Cells. *Biochem Genet*, *55*(1), 34-47. https://doi.org/10.1007/s10528-016-9769-2

Baldwin, D. S., Loft, H., & Florea, I. (2012). Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder. *Int Clin Psychopharmacol*, *27*(4), 197-207. https://doi.org/10.1097/YIC.0b013e3283530ad7

Beshkov, A., Topolov, M., Ahmed-Popova, F., & Sivkov, S. (2018). A Review of Neuroimaging Studies on Working Memory Paradigms in Patients with Bipolar Disorder. *Curr Top Med Chem*, *18*(21), 1883-1892. https://doi.org/10.2174/1568026619666181130135703

Bonaventure, P., Dugovic, C., Kramer, M., De Boer, P., Singh, J., Wilson, S., Bertelsen, K., Di, J., Shelton, J., Aluisio, L., Dvorak, L., Fraser, I., Lord, B., Nepomuceno, D., Ahnaou, A., Drinkenburg, W., Chai, W., Dvorak, C., Sands, S., . . . Lovenberg, T. W. (2012). Translational evaluation of JNJ-18038683, a 5-hydroxytryptamine type 7 receptor antagonist, on rapid eye movement sleep and in major depressive disorder. *J Pharmacol Exp Ther*, *342*(2), 429-440. https://doi.org/10.1124/jpet.112.193995

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord*, *113*(1-2), 1-20. https://doi.org/10.1016/j.jad.2008.06.009

Brunoni, A. R., Moffa, A. H., Sampaio-Júnior, B., Gálvez, V., & Loo, C. K. (2017). Treatment-emergent mania/hypomania during antidepressant treatment with transcranial direct current stimulation (tDCS): A systematic review and meta-analysis. *Brain Stimul*, *10*(2), 260-262. https://doi.org/10.1016/j.brs.2016.11.005

Cadirci, E., Halici, Z., Bayir, Y., Albayrak, A., Karakus, E., Polat, B., Unal, D., Atamanalp, S. S., Aksak, S., & Gundogdu, C. (2013). Peripheral 5-HT7 receptors as a new target for prevention of lung injury and mortality in septic rats. *Immunobiology*, *218*(10), 1271-1283. https://doi.org/10.1016/j.imbio.2013.04.012

Cao, B., Passos, I. C., Mwangi, B., Bauer, I. E., Zunta-Soares, G. B., Kapczinski, F., & Soares, J. C. (2016). Hippocampal volume and verbal memory performance in late-stage bipolar disorder. *J Psychiatr Res*, *73*, 102-107. https://doi.org/10.1016/j.jpsychires.2015.12.012

Carmichael, O., Schwarz, A. J., Chatham, C. H., Scott, D., Turner, J. A., Upadhyay, J., Coimbra, A., Goodman, J. A., Baumgartner, R., English, B. A., Apolzan, J. W., Shankapal, P., & Hawkins, K. R. (2018). The role of fMRI in drug development. *Drug Discov Today*, *23*(2), 333-348. https://doi.org/10.1016/j.drudis.2017.11.012

Christianson, J. P., Ragole, T., Amat, J., Greenwood, B. N., Strong, P. V., Paul, E. D., Fleshner, M., Watkins, L. R., & Maier, S. F. (2010). 5-hydroxytryptamine 2C receptors in the basolateral amygdala are involved in the expression of anxiety after uncontrollable traumatic stress. *Biol Psychiatry*, *67*(4), 339-345. https://doi.org/10.1016/j.biopsych.2009.09.011

Clark, L., Cools, R., & Robbins, T. W. (2004). The neuropsychology of ventral prefrontal cortex: decision-making and reversal learning. *Brain Cogn*, *55*(1), 41-53. https://doi.org/10.1016/s0278-2626(03)00284-7

Cremaschi, L., Penzo, B., Palazzo, M., Dobrea, C., Cristoffanini, M., Dell'Osso, B., & Altamura, A. C. (2013). Assessing working memory via N-back task in euthymic bipolar I disorder patients: a review of functional magnetic resonance imaging studies. *Neuropsychobiology*, *68*(2), 63-70. https://doi.org/10.1159/000352011

Costafreda, S. G., Brammer, M. J., David, A. S., & Fu, C. H. (2008). Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. *Brain Res Rev*, *58*(1), 57-70. https://doi.org/10.1016/j.brainresrev.2007.10.012

Damaso, E. L., Bonagamba, L. G., Kellett, D. O., Jordan, D., Ramage, A. G., & Machado, B. H. (2007). Involvement of central 5-HT7 receptors in modulation of cardiovascular reflexes in awake rats. *Brain Res*, *1144*, 82-90. https://doi.org/10.1016/j.brainres.2007.01.088

Goldberg, J. F., Nierenberg, A. A., & Iosifescu, D. V. (2021). Wrestling With Antidepressant Use in Bipolar Disorder: The Ongoing Debate. *J Clin Psychiatry*, *82*(1). https://doi.org/10.4088/JCP.19ac13181

Goldberg, J. F., & Truman, C. J. (2003). Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord*, *5*(6), 407-420. https://doi.org/10.1046/j.1399-5618.2003.00067.x

Grady, C. L., Rieck, J. R., Nichol, D., Rodrigue, K. M., & Kennedy, K. M. (2021). Influence of sample size and analytic approach on stability and interpretation of brain-behavior correlations in task-related fMRI data. *Hum Brain Mapp*, *42*(1), 204-219. https://doi.org/10.1002/hbm.25217

Gruber, O., Tost, H., Henseler, I., Schmael, C., Scherk, H., Ende, G., Ruf, M., Falkai, P., & Rietschel, M. (2010). Pathological amygdala activation during working memory performance: Evidence for a pathophysiological trait marker in bipolar affective disorder. *Hum Brain Mapp*, *31*(1), 115-125. https://doi.org/10.1002/hbm.20849

Hajek, T., Kopecek, M., Höschl, C., & Alda, M. (2012). Smaller hippocampal volumes in patients with bipolar disorder are masked by exposure to lithium: a meta-analysis. *J Psychiatry Neurosci*, *37*(5), 333-343. https://doi.org/10.1503/jpn.110143

Harvey, J. A. (2003). Role of the serotonin 5-HT(2A) receptor in learning. *Learn Mem*, *10*(5), 355-362. https://doi.org/10.1101/lm.60803

Hedlund, P. B., & Sutcliffe, J. G. (2004). Functional, molecular and pharmacological advances in 5-HT7 receptor research. *Trends Pharmacol Sci*, *25*(9), 481-486. https://doi.org/10.1016/j.tips.2004.07.002

Henigsberg, N., Mahableshwarkar, A. R., Jacobsen, P., Chen, Y., & Thase, M. E. (2012). A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry*, *73*(7), 953-959. https://doi.org/10.4088/JCP.11m07470

Hibar, D. P., Westlye, L. T., van Erp, T. G., Rasmussen, J., Leonardo, C. D., Faskowitz, J., Haukvik, U. K., Hartberg, C. B., Doan, N. T., Agartz, I., Dale, A. M., Gruber, O., Krämer, B., Trost, S., Liberg, B., Abé, C., Ekman, C. J., Ingvar, M., Landén, M., . . . Andreassen, O. A. (2016). Subcortical volumetric abnormalities in bipolar disorder. *Mol Psychiatry*, *21*(12), 1710-1716. https://doi.org/10.1038/mp.2015.227

Jauhar, S., Cowen, P. J., & Browning, M. (2023). Fifty years on: Serotonin and depression. *J Psychopharmacol*, *37*(3), 237-241. https://doi.org/10.1177/02698811231161813

Jelen, L. A., & Stone, J. M. (2021). Ketamine for depression. *Int Rev Psychiatry*, *33*(3), 207-228. https://doi.org/10.1080/09540261.2020.1854194

Johnson, P. L., Molosh, A., Fitz, S. D., Arendt, D., Deehan, G. A., Federici, L. M., Bernabe, C., Engleman, E. A., Rodd, Z. A., Lowry, C. A., & Shekhar, A. (2015). Pharmacological depletion of serotonin in the basolateral amygdala complex reduces anxiety and disrupts fear conditioning. *Pharmacol Biochem Behav*, *138*, 174-179. https://doi.org/10.1016/j.pbb.2015.09.021

Jung, S., Kim, J. H., Kang, N. O., Sung, G., Ko, Y. G., Bang, M., Park, C. I., & Lee, S. H. (2021). Fusiform gyrus volume reduction associated with impaired facial expressed emotion recognition and emotional intensity recognition in patients with schizophrenia spectrum psychosis. *Psychiatry Res Neuroimaging*, *307*, 111226. https://doi.org/10.1016/j.pscychresns.2020.111226

Kawasaki, H., Tsuchiya, N., Kovach, C. K., Nourski, K. V., Oya, H., Howard, M. A., & Adolphs, R. (2012). Processing of facial emotion in the human fusiform gyrus. *J Cogn Neurosci*, *24*(6), 1358-1370. https://doi.org/10.1162/jocn_a_00175

Kraus, C., Castrén, E., Kasper, S., & Lanzenberger, R. (2017). Serotonin and neuroplasticity - Links between molecular, functional and structural pathophysiology in depression. *Neurosci Biobehav Rev*, *77*, 317-326. https://doi.org/10.1016/j.neubiorev.2017.03.007

Lage, G. M., Malloy-Diniz, L. F., Neves, F. S., Gallo, L. G., Valentini, A. S., & Corrêa, H. (2013). A kinematic analysis of manual aiming control on euthymic bipolar disorder. *Psychiatry Res*, *208*(2), 140-144. https://doi.org/10.1016/j.psychres.2012.09.046

Lee, R. S., Hermens, D. F., Scott, J., Redoblado-Hodge, M. A., Naismith, S. L., Lagopoulos, J., Griffiths, K. R., Porter, M. A., & Hickie, I. B. (2014). A meta-analysis of neuropsychological functioning in first-episode bipolar disorders. *J Psychiatr Res*, *57*, 1-11. https://doi.org/10.1016/j.jpsychires.2014.06.019

Lisman, J., Buzsáki, G., Eichenbaum, H., Nadel, L., Ranganath, C., & Redish, A. D. (2017). Viewpoints: how the hippocampus contributes to memory, navigation and cognition. *Nat Neurosci*, *20*(11), 1434-1447. https://doi.org/10.1038/nn.4661

MacQueen, G. M., Hajek, T., & Alda, M. (2005). The phenotypes of bipolar disorder: relevance for genetic investigations. *Mol Psychiatry*, *10*(9), 811-826. https://doi.org/10.1038/sj.mp.4001701

Mahableshwarkar, A. R., Jacobsen, P. L., & Chen, Y. (2013). A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. *Curr Med Res Opin*, *29*(3), 217-226. https://doi.org/10.1185/03007995.2012.761600

Mahmood, T., & Silverstone, T. (2001). Serotonin and bipolar disorder. *J Affect Disord*, *66*(1), 1-11. https://doi.org/10.1016/s0165-0327(00)00226-3

Manelis, A., Halchenko, Y. O., Bonar, L., Stiffler, R. S., Satz, S., Miceli, R., Ladouceur, C. D., Bebko, G., Iyengar, S., Swartz, H. A., & Phillips, M. L. (2022). Working memory updating in individuals with bipolar and unipolar depression: fMRI study. *Transl Psychiatry*, *12*(1), 441. https://doi.org/10.1038/s41398-022-02211-6

McIntyre, R. S., Lophaven, S., & Olsen, C. K. (2014). A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J*

Neuropsychopharmacol, *17*(10), 1557-1567. https://doi.org/10.1017/s1461145714000546

McIntyre, R. S., Rosenblat, J. D., Nemeroff, C. B., Sanacora, G., Murrough, J. W., Berk, M., Brietzke, E., Dodd, S., Gorwood, P., Ho, R., Iosifescu, D. V., Lopez Jaramillo, C., Kasper, S., Kratiuk, K., Lee, J. G., Lee, Y., Lui, L. M. W., Mansur, R. B., Papakostas, G. I., . . . Stahl, S. (2021). Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. *Am J Psychiatry*, *178*(5), 383-399. https://doi.org/10.1176/appi.ajp.2020.20081251

Mencarelli, L., Neri, F., Momi, D., Menardi, A., Rossi, S., Rossi, A., & Santarnecchi, E. (2019). Stimuli, presentation modality, and load-specific brain activity patterns during n-back task. *Hum Brain Mapp*, *40*(13), 3810-3831. https://doi.org/10.1002/hbm.24633

Meneses, A., & Liy-Salmeron, G. (2012). Serotonin and emotion, learning and memory. *Rev Neurosci*, *23*(5-6), 543-553. https://doi.org/10.1515/revneuro-2012-0060

Misra, S. (2012). Randomized double blind placebo control studies, the "Gold Standard" in intervention based studies. *Indian J Sex Transm Dis AIDS*, *33*(2), 131-134. https://doi.org/10.4103/0253-7184.102130

Nugent, A. C., Ballard, E. D., Gould, T. D., Park, L. T., Moaddel, R., Brutsche, N. E., & Zarate, C. A., Jr. (2019). Ketamine has distinct electrophysiological and behavioral effects in depressed and healthy subjects. *Mol Psychiatry*, *24*(7), 1040-1052. https://doi.org/10.1038/s41380-018-0028-2

Ogren, S. O., Eriksson, T. M., Elvander-Tottie, E., D'Addario, C., Ekström, J. C., Svenningsson, P., Meister, B., Kehr, J., & Stiedl, O. (2008). The role of 5-HT(1A) receptors in learning and memory. *Behav Brain Res*, *195*(1), 54-77. https://doi.org/10.1016/j.bbr.2008.02.023

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp*, *25*(1), 46-59. https://doi.org/10.1002/hbm.20131

Palejwala, A. H., O'Connor, K. P., Milton, C. K., Anderson, C., Pelargos, P., Briggs, R. G., Conner, A. K., O'Donoghue, D. L., Glenn, C. A., & Sughrue, M. E. (2020). Anatomy and white matter connections of the fusiform gyrus. *Sci Rep*, *10*(1), 13489. https://doi.org/10.1038/s41598-020-70410-6

Patel, R., Reiss, P., Shetty, H., Broadbent, M., Stewart, R., McGuire, P., & Taylor, M. (2015). Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study. *BMJ Open*, *5*(12), e008341. https://doi.org/10.1136/bmjopen-2015-008341

Passamonti, L., Fairchild, G., Goodyer, I. M., Hurford, G., Hagan, C. C., Rowe, J. B., & Calder, A. J. (2010). Neural abnormalities in early-onset and adolescence-onset conduct disorder. *Arch Gen Psychiatry*, *67*(7), 729-738. https://doi.org/10.1001/archgenpsychiatry.2010.75

Pearce, E. F., & Murphy, J. A. (2014). Vortioxetine for the treatment of depression. *Ann Pharmacother*, *48*(6), 758-765. https://doi.org/10.1177/1060028014528305

Penton-Voak, I. S., Adams, S., Button, K. S., Fluharty, M., Dalili, M., Browning, M., Holmes, E. A., Harmer, C. J., & Munafò, M. R. (2021). Emotional recognition training modifies neural response to emotional faces but does not improve mood in healthy volunteers with high levels of depressive symptoms. *Psychol Med*, *51*(7), 1211-1219. https://doi.org/10.1017/s0033291719004124

Perez-Garcia, G., & Meneses, A. (2008). Memory formation, amnesia, improved memory and reversed amnesia: 5-HT role. *Behav Brain Res*, *195*(1), 17-29. https://doi.org/10.1016/j.bbr.2007.11.027

Pomarol-Clotet, E., Honey, G. D., Murray, G. K., Corlett, P. R., Absalom, A. R., Lee, M., McKenna, P. J., Bullmore, E. T., & Fletcher, P. C. (2006). Psychological effects of ketamine in healthy volunteers. Phenomenological study. *Br J Psychiatry*, *189*, 173-179. https://doi.org/10.1192/bjp.bp.105.015263

Ramage, A. G., & Villalón, C. M. (2008). 5-hydroxytryptamine and cardiovascular regulation. *Trends Pharmacol Sci*, *29*(9), 472-481. https://doi.org/10.1016/j.tips.2008.06.009

Robbins, T. W. (2000). From arousal to cognition: the integrative position of the prefrontal cortex. *Prog Brain Res*, *126*, 469-483. https://doi.org/10.1016/s0079-6123(00)26030-5

Rosenblat, J. D., Carvalho, A. F., Li, M., Lee, Y., Subramanieapillai, M., & McIntyre, R. S. (2019). Oral Ketamine for Depression: A Systematic Review. *J Clin Psychiatry*, *80*(3). https://doi.org/10.4088/JCP.18r12475

Sekeres, M. J., Winocur, G., & Moscovitch, M. (2018). The hippocampus and related neocortical structures in memory transformation. *Neurosci Lett*, *680*, 39-53. https://doi.org/10.1016/j.neulet.2018.05.006

Sengupta, A., Bocchio, M., Bannerman, D. M., Sharp, T., & Capogna, M. (2017). Control of Amygdala Circuits by 5-HT Neurons via 5-HT and Glutamate Cotransmission. *J Neurosci*, *37*(7), 1785-1796. https://doi.org/10.1523/jneurosci.2238-16.2016

Solé, B., Jiménez, E., Torrent, C., Reinares, M., Bonnin, C. D. M., Torres, I., Varo, C., Grande, I., Valls, E., Salagre, E., Sanchez-Moreno, J., Martinez-Aran, A., Carvalho, A. F., & Vieta, E. (2017). Cognitive Impairment in Bipolar Disorder: Treatment and Prevention Strategies. *Int J Neuropsychopharmacol*, *20*(8), 670-680. https://doi.org/10.1093/ijnp/pyx032

Soraggi-Frez, C., Santos, F. H., Albuquerque, P. B., & Malloy-Diniz, L. F. (2017). Disentangling Working Memory Functioning in Mood States of Bipolar Disorder: A Systematic Review. *Front Psychol*, *8*, 574. https://doi.org/10.3389/fpsyg.2017.00574

Švob Štrac, D., Pivac, N., & Mück-Šeler, D. (2016). The serotonergic system and cognitive function. *Transl Neurosci*, *7*(1), 35-49. https://doi.org/10.1515/tnsci-2016-0007

Taylor, M. J., Freemantle, N., Geddes, J. R., & Bhagwagar, Z. (2006). Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry*, *63*(11), 1217-1223. https://doi.org/10.1001/archpsyc.63.11.1217

Teixeira, C. M., Rosen, Z. B., Suri, D., Sun, Q., Hersh, M., Sargin, D., Dincheva, I., Morgan, A. A., Spivack, S., Krok, A. C., Hirschfeld-Stoler, T., Lambe, E. K., Siegelbaum, S. A., & Ansorge, M. S. (2018). Hippocampal 5-HT Input Regulates Memory Formation and

Schaffer Collateral Excitation. *Neuron*, *98*(5), 992-1004.e1004. https://doi.org/10.1016/j.neuron.2018.04.030

Thompson, J. M., Gray, J. M., Hughes, J. H., Watson, S., Young, A. H., & Ferrier, I. N. (2007). Impaired working memory monitoring in euthymic bipolar patients. *Bipolar Disord*, *9*(5), 478-489. https://doi.org/10.1111/j.1399-5618.2007.00470.x

Tondo, L., Vázquez, G., & Baldessarini, R. J. (2010). Mania associated with antidepressant treatment: comprehensive meta-analytic review. *Acta Psychiatr Scand*, *121*(6), 404-414. https://doi.org/10.1111/j.1600-0447.2009.01514.x

Townsend, J., & Altshuler, L. L. (2012). Emotion processing and regulation in bipolar disorder: a review. *Bipolar Disord*, *14*(4), 326-339. https://doi.org/10.1111/j.1399-5618.2012.01021.x

Tsapekos, D., Strawbridge, R., Cella, M., Wykes, T., & Young, A. H. (2021). Cognitive impairment in euthymic patients with bipolar disorder: Prevalence estimation and model selection for predictors of cognitive performance. *J Affect Disord*, *294*, 497-504. https://doi.org/10.1016/j.jad.2021.07.036

Vieta, E., Berk, M., Schulze, T. G., Carvalho, A. F., Suppes, T., Calabrese, J. R., Gao, K., Miskowiak, K. W., & Grande, I. (2018). Bipolar disorders. *Nat Rev Dis Primers*, *4*, 18008. https://doi.org/10.1038/nrdp.2018.8

Weiner, K. S., & Zilles, K. (2016). The anatomical and functional specialization of the fusiform gyrus. *Neuropsychologia*, *83*, 48-62. https://doi.org/10.1016/j.neuropsychologia.2015.06.033

Wellek, S., & Blettner, M. (2012). On the proper use of the crossover design in clinical trials: part 18 of a series on evaluation of scientific publications. *Dtsch Arztebl Int*, *109*(15), 276-281. https://doi.org/10.3238/arztebl.2012.0276

Yaple, Z. A., Stevens, W. D., & Arsalidou, M. (2019). Meta-analyses of the n-back working memory task: fMRI evidence of age-related changes in prefrontal cortex involvement across the adult lifespan. *Neuroimage*, *196*, 16-31. https://doi.org/10.1016/j.neuroimage.2019.03.074

Yatham, L. N., Liddle, P. F., Erez, J., Kauer-Sant'Anna, M., Lam, R. W., Imperial, M., Sossi, V., & Ruth, T. J. (2010). Brain serotonin-2 receptors in acute mania. *Br J Psychiatry*, *196*(1), 47-51. https://doi.org/10.1192/bjp.bp.108.057919

Young, L. T., Warsh, J. J., Kish, S. J., Shannak, K., & Hornykeiwicz, O. (1994). Reduced brain 5-HT and elevated NE turnover and metabolites in bipolar affective disorder. *Biol Psychiatry*, *35*(2), 121-127. https://doi.org/10.1016/0006-3223(94)91201-7

Appendices for Chapter 2

Common animal behavioural tests

Anxiety

1. Four-Plate Test

The four-Plate Test (FPT) is an anxiety test, which based on mice's spontaneous response. Mice will be exposed to a novel environment of mild electric foot shocks, and can only escape from the aversive condition by maintaining motionless (Aron et al, 1971). In many four-plate tests, anti-anxiolytic drugs, benzodiazepines (BZDs) induce an anti-punishment result, which indicates they have the ability to resist their own anxious feelings (Martine Hascoët & Michel Bourin, 2011).

2. Elevated Plus-Maze Test

Interpreted by researcher (Wesolowska, 2006), the elevated plus maze test is an experimental test using a cross where the animals run to examine mice's anxious behaviours. In general, mice will try to run the wall-closed roads faster than opened roads. However, when anti-anxiolytic medicines were used, they will run faster in opened roads than usual.

3. Marble Burying Test

Anxiety and obsessive-compulsive disorder behaviour will be detected in the marble burying test. Mice or rats will bury harmful or harmless objects in their bedding. However, whether the experiment can detect anxiolytic behaviour in the open field is controversial (Albelda, 2012).

4. Open Field Test

The open field test is to exam the locomotor activity levels, anxiety, and willingness to explore in mice and rats' behaviours (Aulieh ,1976). Rodents demonstrate an aversion to brightly open areas. Anxiety will induce less locomotion and preference to stay close to the wall of the field (Mucignat-Caretta et al, 2006).

5. Sources Preference Test

In this test, animals' anhedonia will be measured (Sclafani and Ackroff, 2003). Animals, especially rats, are allowed to access to multiple environments differing in one or more ways. This test can exam different types of animals' behaviours, such as duration of time spent, range of activities observed, and motion detected. Rodents' anxiety will be detected in the preference test. Animals' anhedonia will be checked in this test (Fox, 2011).

6. Vogel Conflict Drinking Test

The vogel conflict test is used to determine anxiolytic properties of medicine. General anxiety disorder and acute anxiety status will be checked (Witkin, 2011). There is a conflict situation which rodents will be punished by electrical shocks when they try to get food. The number of times of animal searches for food will be decreased in this condition. However, when dosing anxiolytic medicine, the number of times will increase.

Depression

1. Forced Swimming test

The forced swimming test is used as a preclinical test for detecting antidepressant-like activity, which based on rats' response to the threat of drowning (Borsini and Meli, 1988; Porsolt et al., 1977). It also runs well in mouse model (Cryan et al., 2002). Mice will be separated into two groups as trial and control groups. The duration of keeping their heads

above will be recorded, which assesses predictive validity for using antidepressants in acute condition.

2. Head-Twitch Response

Originally, the head-twitch response was designed to test the movement that occurs in mice or rats after 5HT2A receptors have been activated. However, here, it was used to measure the $5HT_7$ properties. By side-to-side head movement, animals' depressive behaviours may be tested.

3. Tail Suspension Test

When running the test, mice's depressive-related behaviours can be detected (Steru et al., 1985). To examine whether the medicine is a potential antidepressant drugs, mice's tail will be taped to the top of the box, and the time spent will be recorded. When the mouse tries to move, it can assess the validity for antidepressant. Tail suspension test requires only a single acute treatment for positive effects. On the opposite side, chronic test of antidepressant usage is not suitable to this test (Fox, 2011).

4. Novelty-Supressed Feeding Test

Mice which be exposure to a novel environment that suppresses feeding behaviour, has been used to assess behaviour in animals for 70 years. Novelty-suppressed feeding test is sensitive to chronic, but not acute, antidepressant treatment, and it can be applied to human patients for antidepressant response (Fox, 2011).

References

Albelda, Noa; Joel, Daphna (2012). "Animal models of obsessive-compulsive disorder: Exploring pharmacology and neural substrates". *Neuroscience and Biobehavioral Reviews*. **36** (1): 47–63

Aullch, D. (1976). Escape versus explorators actlvlty: an mterpretatron of rats' behaviour In the open field and a light-dark preference *test. Behav Processes,* **1:**153-164.

Blasco-Serra, A., González-Soler, E. M., Cervera-Ferri, A., Teruel-Martí, V., & Valverde-Navarro, A. A. (2017). A standardization of the Novelty-Suppressed Feeding Test protocol in rats. *Neuroscience Letters, 658*, 73-78.

Cryan JF, Markou A, Lucki I (2002): Assessing antidepressant activity in rodents: Recent developments and future needs. *Trends Pharmacol Sci* 23:238 –245.

Diagnostic and statistical manual of mental disorders. (2013). London: American Psychiatric Association.

File SE (1990) "One-trial tolerance to the anxiolytic effects of chlordiazepoxide in the plus-maze." Psychopharmacology (Berl) 100:281–282

Gould, T. D. (2011). *Mood and anxiety related phenotypes in mice*. New York, NY: Humana Press.

Grant A. Fox, Eugene Torigoe, Greg Q. Butcher (2018). Constructing an Inexpensive Elevated Plus Maze. *J Undergrad Neurosci Educ*. 2018 Spring; 16(2): R44–R47.

Hall, CS; Ballachey EL (1932).A study of the rat's behaviour in a field- a contribution to method in comparative pshcology. *University of California Publications in Psychology*. **6**:1-12.

Liu, H., Irving, H. R., & Coupar, I. M. (2001). Expression patterns of 5-HT7 receptor isoforms in the rat digestive tract. *Life Sciences,69*(21), 2467-2475.

Mucignat-Caretta C, Bondi M, Caretta A (2006) Time course of alterations after olfactory bulbectomy in mice. Physiol Behav 89(5): 637–643

Steru L, Chermat R, Thierry B, Simon P (1985): The tail suspension test: A new method for screening antidepressants in mice. *Psychopharmacology(Berl)* 85:367–370.

Witkin, Jeffrey (2011). "A Vogel Conflict Test Using Food Reinforcement in Mice". *Mood and Anxiety Related Phenotypes in Mice*. **63**: 159–169

Animal studies of the effects of 5-HT$_7$ compounds for anxiety, depression, and mania.

Authorship	Animal/ intervention/ evaluation	Primary outcome	Secondary outcome	Conclusion		
				Potential anxiolytic effects	Potential anti-depressant effects	Potential anti-manic effects
Guscott et al., 2005	Mouse/ SB-258719 and KO mice/ 5-HT$_7$ receptor antagonist/ FST EMT	KC and WT had no difference in time spent in EMT. KO displayed reduction in immobility compared to WT in FST. SB-258719, produced a small but non-significant decrease in immobility in WT.	SB-258719 only had potential antidepressant effect in dark, which suggested the rhythm circadian may also affected on mood status.		✓	
Hedlund et al., 2005	Mouse/ SB-269970, 5-HT$_7$ KO/ 5-HT$_7$ receptor antagonist/ FST	5-HT$_7$-/- mice showed decreased immobility in both tests, consistent with an antidepressant like behaviour. The selective 5-HT$_7$ receptor	The 5-HT$_7$ receptor might have a role in mood disorders and antagonists might have therapeutic value as antidepressants.		✓	

	TST	antagonist SB-269970 also decreased immobility. Secondary outcome (Sleep): KO mice spent less time in and had less frequent episodes of REM sleep (consistent with antidepressant like state)			
Takeda et al., 2005	Mouse/ DR-4004/ 5-HT_7 antagonist/ HBT	DR4004 (2.5 – 10 mg/kg, i.p.) treated mice showed a dose-dependent decrease in locomotor activity.	DR-4004 had potential antidepressant effect.		✓
Wesolowska, A.; Nikiforuk, A.; Stachowicz, K., 2006b	Rat/ SB-269970/ selective 5-HT_7 receptor antagonist/ VCT FST	SB-269970 showed an anti-conflict effect which was weaker than that of diazepam (40 mug), whereas SB 269970 had marked anti-immobility action comparable to that of imipramine.		✓	✓

Wesolowska, A.; Nikiforuk, A.; Stachowicz, K.; Tatarczynska, E., 2006a	Rat & Mouse/ SB-269970 (0.25-20 mg/kg)/ selective 5-HT_7 receptor antagonist/ VCT, EMT (rats) / FPT, FST, TST (mice)	SB-269970 exerted a specific antianxiety-like effect in the VCT in rats, in EMT in rats and in the four-plate test in mice.			✓
Hedlund & Sutcliffe, 2007	Mouse/ SB-269970, KO/ 5-HT_7 receptor antagonist/ Marble Burying Test	Both inactivation (SB-269910) and blockade (KO) of the 5-HT_7 receptor reduced stereotypic behaviour in that the number of marbles buried decreased.	5-HT_7 receptor is a candidate target for the treatment of obsessive-compulsive disorder.	✓	
Bonaventure, et al., 2007	Mouse/ SB-269970/ 5-HT_7 receptor antagonist/ TST	SB-269970 administration decreased immobility time in TST compared to vehicle only treated mice. Citalopram also decreased immobility	Selective blockade of 5-HT_7 receptors may enhance the antidepressant efficacy of citalopram and may provide a novel		✓

		time; addition of SB-269970 significantly enhanced, also influenced sleep REM.	therapy to alleviate sleep disturbances associated with depression.		
Volk et al., 2008	Rat (conflict drinking) & Mouse (light dark)/ (Phenylpiperazinyl-butyl)oxindoles/ 5-HT_7 receptor antagonist/ VCT L/D	Minimal effective doses were achieved for both - therefore there is an amount that has clinical effect.		✓	
Abbas, Atheir I.; Hedlund, Peter B.; Huang, Xi-Ping; Tran, Thuy	Mouse/ Amisulpiride; used in both $5HT_7$ KO mice and WT/ 5-HT_7 receptor antagonist/ TST FST	Amisulpiride significantly reduced immobility time in both TST and FST, in WT mice			✓

B.; Meltzer, Herbert Y.; Roth, Bryan L., 2009				
Mnie-Filali et al., 2011	Rat/ SB-269970/ 5-HT_7 receptor antagonist/ Open-field test FST	No significant change in behaviour for OFT (anxiety) compared to vehicle. Reduction in immobility during FST (anxiety), but did not increase locomotor activity.		✓
Volk et al., 2011	Mouse (FST) (light dark) & Rat (conflict drinking)/ (Arylpiperazinylbutyl) oxindoles/5-HT_7 receptor antagonist/ FST VCT L/D	none of the compounds produced an antidepressant-like action in the forced swimming test in mice despite sufficiently high brain concentrations.	✓	

Zajdel et al., 2011	Mouse/ Compound 54/ Potent 5-HT_7 antagonist with good selectivity over 5-HT1A, 5-HT2A, 5-HT6 receptors/ FST	Reduced immobility in FST similar to SB-269970		✓
Bonaventure et al., 2012	Mouse (TST and locomotor test) & Rat (telemetry study)/ JNJ-18038683/ 5-HT_7 receptor antagonist/ TST	JNJ-18038683 decreased immobility time compared to vehicle in TST, but did not change locomotor. Secondary outcome (Sleep): Increased latency to REM sleep and decreased REM duration.		✓
Mork et al., 2012	Rat (FRL and FSL types - FSL rat has lower density of 5-	FRL rats did not show increased immobility during FST, unlike FSL rats.	✓	✓

	HT_{1A} receptors but a higher density of 5-HT_{1B} receptors in several brain regions compared with those of the FRL rat)/ Lu AA21004/ 5-HT_7-receptor antagonist (5-HT3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter)/ FST condition fear-induced vocalisation			
Zajdel et al., 2012	Mouse (FST) & Rat (PMT)/	Compound 36 reduced immobility in FST in mice	Compound 36 had antidepressant effect in	✓

	compound 36/ 5-HT_7 receptor antagonist (antagonistic activity at 5-HT_7, 5-HT_{2A}, D2 postsynaptic sites)/ FST EMT	high dose but not in the lower or middle doses.	mice and anxiolytic effect in rats, without decrease in overall locomotor activity.	
Cates, L. N.; Roberts, A. J.; Huitron-Resendiz, S.; Hedlund, P. B., 2013	Mouse/ Lurasidone/ 5-HT_7 receptor antagonist/ TST FST Open-space swim test L/D Marble burying test	Lurasidone decreased immobility in TST and FST. Change absent in mice lacking receptor, but they were already significantly lower in immobile time.	Antidepressant effects (both acute and chronic models of depression) but not anxiolytic effects.	✓

Chlon-Rzepa et al., 2013	Mouse/ compounds 21 and 42/ Mixed 5-HT_{1A}/5-HT_{2A}/5-HT_7 receptor ligand (compounds 21), mixed 5-HT_{1A}/5-HT_7 ligand (compounds 42)/ FST FPT	Compounds 21 produced an antidepressant-like effect in FST and exerted anxiolytic-like activity in FPT. Compounds 42 produced slightly, (non-significant) attenuated immobility time of mice in FST and was devoid of activity in FPT.	✓	✓
Guilloux et al., 2013	Mouse/ Vortioxetine/ 5-HT_7 receptor antagonist (5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and	Acute (OFT and FST) and repeated (NSF) dosing of Vortioxetine produced more pronounced anxiolytic (NSF) and antidepressant-like activities (OFT and FST).	✓	✓

	inhibitor of the 5-HT transporter)/ Open-field test FST Novelty-suppressed feeding paradigm		
Li, Y.; Raaby, K. F.; Sanchez, C.; Gulinello, M., 2013	Rat/ Vortioxetine, SB-269970 & AS-19/ 5-HT_7 receptor antagonist (5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter) / 5-HT_7 receptor agonist/ FST	Vortioxetine reduced immobility time in female rats with progesterone withdrawal induced depression. SB-269970 did not decrease immobility time compared to vehicle. However, agonist AS-19 did increase immobility time.	Vortioxetine ✓ SB-269970× AS-19×

Canale, et al., 2015	Mouse/ compound 32, a novel series of long-chain arylpiperazines (5-HT_7 antagonist)/ 5-HT_7 receptor antagonist/ FST	Compound 32 reduced immobility in a manner similar to the selective 5-HT7 antagonist SB-269970.		✓
Pytka et al., 2015	Rat (FST and EMT) and Mouse (FST and FPT)/ HBK-14, HBK-15/ 5-HT_7 and 5-HT_{1A} receptor antagonists/ FST FPT EMT	HBK-14 and HBK-15 both showed decreased immobility time in FST (mice). Both showed decreased immobility and increased swim time in FST (rats). HBK-14 and HBK-15 both showed anxiolytic effects in mice and rats.	✓	✓

Waszkielewicz et al., 2015	Mouse/ 1-[(2-chloro-6-methylphenoxy)ethoxyethyl]-4-(2-methoxyphenyl)piperazine hydrochloride ; derivative of N-(2-methoxyphenyl)piperazine/ TST Locomotor activity test Motor co-ordination test	1-[(2-chloro-6-methylphenoxy)ethoxyethyl]-4-(2-methoxyphenyl)piperazine hydrochloride, exhibiting affinity toward receptors 5-HT_{1A} and 5-HT_7			✓
Zagorska et al., 2015	Mouse/ selected derivatives of 1,3-dimethyl-(1H,8H)-imidazo[2,1-f]purine-2,4-dione (Compounds 8, 9)/	Compound 8 had slightly higher inhibition of control agonist response in 5-HT1A, 5-HT_7 and D2 than compound 9.	Compound 8 & 9 worked on multiple receptor subtypes.	✓	✓

	mixed 5-HT1A/5-HT$_7$ (8, 9) receptor ligands with d2 affinity/ FPT FST			
Canale et al., 2016	Mouse (FST) & Rats (NOR)/ Compound 31 (potent and selective 5-HT$_7$ receptor antagonist) & compound 33 (multimodal 5-HT/dopamine receptor ligand/ 5-HT$_7$ receptor antagonist/ FST NOR	All showed reduced immobility (all compounds and SB-269970) with compounds 31 and 33 being most stable with similar potency to SB-269970.	Both compounds found to dose-dependently ameliorate PCP-induced memory deficits in rats. SB-269970 had pro-cognitive effect in rats.	✓

Canale, et al., 2016b	Mouse/ PZ-1417 & PZ-1150/ 5-HT_7 receptor antagonist/ FST TST FPT	Both compounds showed antidepressant and anxiolytic properties in FST, TST, and FPT.	✓	✓
Kim et al., 2016	Mouse/ compound 28/ 5-HT_7 receptor antagonist/ FST	Compound 28 showed reduced immobility time in FST.		✓
Zagórska et al., 2016	Mouse/ Compound 9 (8-(5-(4-(2-fluorophenyl)piperazin-1-yl)pentyl)-1,3,7-trimethyl-1H-	Compound 9 as well as comparator citalopram showed antidepressant like properties (at middle doses - showing U shaped response curve).	✓	

	imidazo[2,1-f]purine-2,4(3H,8H)-dione)/ High 5-HT_7 and very high 5-HT_{1A} receptor antagonists/ FST FPT			
Canale, et al., 2017	Mouse (FST, TST) & Rat (NOR)/ Compound 25 (3-chloro-N-{1-[3-(1,1-biphenyl-2- yloxy)2-hydroxypropyl]piperidin-4-yl}benzenesulfonamide)/ 5-HT_7 receptor antagonist/ FST TST	Compound 25 demonstrated significant antidepressant-like activity in the FST.	Compound 25 reversed (in a dose-dependent manner) natural forgetting impairment in rats (similar effects in SB-269970).	✓

	NOR				
Delcourte et al., 2017	Rat/ asenapine/ 5-HT_7 receptor antagonist/ FST	Behavioural experiments showed that asenapine had no significant effect on immobility time in the FST in control rats. Decreased hyper-locomotion in manic rats.	asenapine displays robust anti-manic property and effective in vivo antagonistic activity at 5-$HT_{1A/7}$ receptors.		✓
Gu et al., 2017	Rat/ Compound 8j/ 5-HT_7 receptor antagonist (also high affinity for 5-HT_{1A} and 5-HT reuptake inhibitor)/ FST	Compound 8j showed a marked antidepressant-like activity in the FST model.	Compound 8j showed antidepressant effect; however, it worked on multiple receptor types.	✓	
Partyka et al., 2017	Mouse/ compound 16, 21/ D2, 5-HT_{1A} and 5-HT_7 receptor antagonist/	Compound 16 and 21 displayed antidepressant-like effect in FST.		✓	

	FST				
Pytka et al., 2017	Mouse/ HBK-14 & HBK-15/ 5-HT_7 and 5-HT_{1A} receptor antagonists/ FST Step-Through passive avoidance task	Chronic HBK-14 and HBK-15 treatment (21 days consecutively) reduced immobility during FST, but did not decrease overall locomotor activity. Secondary outcome (Sleep): In retention trial, HBK-15 (but not HBK-14 or fluoxetine) increased latency time.	HBK-15 shows potential for cognitive enhancing features.		✓
Pytka et al,.2017	Mouse (subjected to chronic mild stress - behavioural)/ HBK-15/ 5-HT_7 and 5-HT_{1A} receptor antagonists/	Chronically stressed mice displayed significantly less sugar intake (SPT), increased mobility time (FST) and decrease exploratory activity	HBK-15 had potential antidepression, and anxiolytic effect in corticosterone treated mice. However, these changes were not	✓	✓

	Sucrose Consumption/Preference Test (SPT) FST EMT	(EPM) compared to control mice.	explained by overall decrease in locomotor activity.		
Gu et al., 2018	Mouse/ Compound 21n/ Serotonin reuptake inhibitor, and high 5-HT_{1A} and 5-HT_7 receptor affinities/ FST TST	Compound 21n significantly reduced immobility time in FST and TST.	Compound 21n had potential antidepressant effect; however, it worked on multiple receptor types (5-HT_{1A} and reuptake).		✓
Kucwaj-Brysz et al., 2018	Mouse/ Compounds (5-8)/ 5-HT_7 receptor antagonist/ FST FPT	New compounds (5-8) displayed potent affinity and selectivity for 5-HT7 in (over $5HT_{1A}$ and D2). Immobility significantly decreased in FST for higher doses (10 and	Compounds (5-8) had antidepressant effect, and trend towards anxiolytic effect.	✓	✓

		20 mg/kg). Tendency to increase measure in FPT but did not reach significance (i.e., not anxiolytic). No changes to spontaneous locomotor activity.		
Latacz et al., 2018	Mouse & Rat/ MF-8/ 5-HT_7 receptor antagonist/ FST FPT	MF-8 showed decreased immobility time in both rats and mice (higher dose of 5 mg/kg) but not lower doses.	✓	✓
Lax et al., 2018	Mouse/ DUQ0002I, KO and WT mice/ 5-HT_7 receptor antagonist/ EOM LDP	DUQ0002I administration on WT showed lower immobile time in FST compared to controls, no change in TST, greater time in open arm of EOM, more overall time in	✓	✓

	TST FST MST	light for LDP test, no changes in overall locomotor activity.			
Pytka et al., 2018	Mouse (cortisone induced depression)/ HBK-15/ 5-HT_7 and 5-HT_{1A} receptor antagonists/ SPT FST EMT	Corticosterone treated mice displayed significantly less sugar intake (SPT), increased mobility time (FST) and decrease exploratory activity (EPM) compared to control mice injected with saline.	HBK-15 had potential antidepression, and anxiolytic effect in corticosterone treated mice.	✓	✓
Balcer et al., 2019	Mouse/ WT or KO/ 5-HT_7 receptor antagonist/ FST SIH FC	Behaviours of 5-HT_7 WT and 5-HT_7 KO mice were compared across 10 different assays (7 for anxiety, 1 for depression, 2 for psychosis) to identify differences that could indicate clinical		✓	✓

	Shock-probe burying NSF Punishment responding Punishment memory EMT	potential for 5-HT_7 receptor antagonism. FC, NSF & FST showed a decrease in anxiety/depressant like responses in KO mice. SIH, punished responding, and EMT did not show a difference between KO and WT. Shock-probe burying saw more anxious behaviours in KO mice.	
Gu et al., 2019	Mouse/novel aralkyl piperazine and piperidine derivatives & compound 19a/ 5-HT_{1A} and 5-HT_7 antagonist and potent	Compound 19a significantly reduced immobility time in FST and TST.	Compound 19a had potential antidepressant effect; however, it worked on multiple receptor types (1A and reuptake).

	serotonin reuptake inhibitor/ FST TST			
Maxwell et al., 2019	Mouse/ DR-4004 and SB-269970/ selective 5-HT_7 receptor antagonist/ EMT VCT TST	No significant antidepressant activity seen in TST or anxiolytic activity in EMT and VCT.	DR-4004 and SB-269970 seemed have no potential antidepressant activity in TST or anxiolytic activity in EMT and VCT.	
Partyka et al., 2019	Rat/ PZ-1433 & ADN-1184/ Preferential 5-HT_7 antagonist / monoaminergic ligand	PZ-1433 AND ADN-1184 showed reduced immobility time at medium dose.	PZ-1433 AND ADN-1184 had potential antidepressant activity in FST but with no decrease in locomotor activity.	✓

	with potent 5-$HT_{6/7}$ antagonist properties/ FST open field test			
Wang et al., 2019	Mouse/ Compound 7a & 15g/ Serotonin reuptake inhibitor, and high 5-HT_{1A} and 5-HT_7 receptor affinities/ FST TST	Both Compound 7a & 15g showed decrease in immobility time in mice FST.	Compound 7a & 15g had potential antidepressant effect, however the compounds worked on multiple receptor types.	✓
Wrobel et al., 2019	Mouse/ 3-(1H-indol-3-yl)pyrrolidine-2,5-dione = CompoundMW005 (4A, 4J)/ FST	MW005 (agonist of the pre- and postsynaptic 5-HT1a receptor) exhibited promising affinities for the 5-HT_{1A}/SERT/D2/5-HT_6/5-HT_7 receptors and showed	MW005 did not produce differences in immobility time (i.e., no antidepressant effect when adding 5-HT_7 affinity.)	

		antidepressant-like activity in the FST model.		
Jankowska et al., 2020	Rat/ Compound 22/ Weak 5-HT_7 receptor antagonist (and potent 5-HT_{1A} receptor antagonist)/ FST NOR	Compound 22 significantly reversed MK-801 induced episodic memory deficits in the NOR, also reduced the immobility time of animals in FST.	Reversed MK-801 induced memory impairment.	✓

KO: receptor knockout, WT: wild-type, BWB: Black/White Boxes, D/L: Dark/Light test, N-S: Novelty-seeking test, FST: Force swimming test, TST: Tail suspension test, EMT: Elevated maze test; OFT: Open-field test; SPT: Sucrose consumption test; VCT: Vogel conflict test; NSF: Novelty-suppressed feeding; FC: Fear conditioning; SIH: Stress-induced hyperthermia; HBT: Hole-board test; EOM: Elevated zero maze; LDP: Light/dark preference

Human studies of the effects of 5-HT$_7$ compounds for anxiety, depression, and mania.

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
Mahableshwarkar et al., 2015	RCT/ 8 weeks/ MDD/ 10 or 15 mg Vortioxetine vs placebo	45.1±12.4/ 70.15%/ 434 (149 Placebo, 143 Vortioxetine 10mg, 142 Vortioxetine 15mg)	**PBO** = 27 – 6 AE, 4 LoE, 17 other **VOR10** = 26 – 8 AE, 2 LoE, 16 other **VOR15** = 31 – 12 AE, 0 LoE, 19 other	MADRS/ **PBO** = -12.87 **VOR10** = -13.66 **VOR15** = -13.36	Differences from placebo in primary endpoint (change in MADRS score) were not statistically significant for either 10 or 15 mg Vortioxetine. **Secondary Outcome (cognition):** Both Vortioxetine doses showed numerically greater improvement in CPFQ (cognitive and physical functioning questionnaire) scores compared to placebo, but neither were statistically significant.

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
McIntyre, Lophaven & Olsen, 2014	RCT/ 8 weeks/ MDD/ 10 or 20 mg Vortioxetine vs placebo	45.7±12.0/ 66.22%/ 598 (196 placebo, 195 VOR 10 mg, 207 VOR 20mg)	N/R	MADRS/ **PBO** = -10.9±0.6 **VOR10** = -15.6±0.6 **VOR20** = -17.6±0.6 (MMRM)	Patients in both Vortioxetine groups separated from placebo in depressive symptom and CGI variables. Patients also reported objective and subjective measures of cognitive function independent of its effect on improving depression symptoms. **Secondary Outcome (cognition):** In the pre-defined primary efficacy analysis, both doses of Vortioxetine were significantly better than placebo.

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
Alvarez, Perez, Dr agheim, Loft & Artigas, 2011	RCT/ 6 weeks/ MDD/ 5 or 10mg Lu AA21004 vs 225mg venlafaxine XR or placebo	43.3±11.5 62.70% 360 (87 placebo, 93 Venlafaxine XR, 98 LU AA21004 5mg, 82 LU AA21004 10mg)	**PBO = 18** – 4 AEs, 6 LoE, 8 other **VEN = 20** – 16 AEs, 2 LoE, 2 other **LUA5 = 10** – 3 AEs, 6 LoE, 1 other **LUA10 = 18** –	MADRS/ **PBO** = -16.6±1.0 **VEN** = -24.2±0.9 **LUA5** = -22.3±0.9 **LUA10** = -23.4±1.0 (OC)	Lu AA21004 was statistically significantly superior to PBO in mean change from baseline in MADRS total score at week 6.

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
			7AEs, 3 LoE, 8 other		
Mahableshwarkar et al., 2013	RCT/ 8 weeks/ MDD/ 2.5 or 5 mg Vortioxetine vs 60mg duloxetine or placebo	N/R N/R 611 randomised	N/R	HAM-D24/ *(mean and SE)* **PBO** = -10.5±0.76 **VOR2.5** = -12.04±0.74 **VOR5** = -11.08±0.74 **DUL** = -13.47±0.75	Vortioxetine doses were associated with declines in HAM-D24 total scores compared to placebo but were not statistically significant.

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
Henigsberg et al., 2012	RCT/ 8 weeks/ MDD/ 1, 5, or 10 mg Lu AA21004 vs placebo	46.4±12.1 62.60% 505 total (127 placebo, 127 LUA 1mg, 129 LUA 5mg, 122 LUA 10mg	**PBO = 13** – 2 AES, 8 LoE, 3 other **LUA1 = 13** – 3 AEs, 4 LoE, 6 other **LUA5 = 11** – 1 AE, 2 LoE, 8 other **LUA10 = 18** –	HDRS-24/ **PBO** = -10.1±0.7 **LUA1** = -14.82±0.7. **LUA5** = -15.42±0.7 **LUA10** = -16.23±0.8 (MMRM	Lu AA21004 10 mg there was a significant reduction in HDRS-24 total score compared with placebo in adults with MDD.

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
			5 AEs, 3 LoE, 10 other		
El-Mallakh et al., 2020	RCT (subset of larger study) 8 weeks Bipolar depression 5-20mg Asenapine vs placebo	(18-55) N/R 9 (4 asenapine, 5 placebo)	N/R	MADRS PBO = -3.80±9.01 ASE= -19.80±8.59	Improvement in MADRS was statistically significantly greater in the Asenapine group than the placebo group measured as changes from baseline to week 8.
Baldwin, Loft &	Open-label + double-blinded	43.3±13.3 63.20%	N/R	HAM-A // time to relapse	The result of the primary efficacy analysis showed a statistically significant effect of

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
Florea, 2012	period (20 weeks plus 24-56 weeks) GAD (DSM-IV-TR) 5 or 10mg LU AA21004 (as decided in open label period) vs placebo	278 (121 placebo, 157 Lu AA21004)			Lu AA21004 relative to placebo on the time to relapse in the double-blind period.
Loebel, Cucchiaro	RCT 6 weeks	N/A 56.90%	**PBO = 43** –	MADRS	Lurasidone treatment significantly reduced mean MADRS total scores at week 6 for

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
, Silva, Kroger, Hsu & Sarma, 2014	20-60mg or 80-120mg Lurasidone daily vs placebo	374 (127 placebo, 123 Lur20-60, 124 Lur80-120)	11 AEs, 13 LoE, 19 other **Lur20-60 =** 43 – 11 AEs, 12 LoE, 20 other **Lur80-120 = 45** – 10 AEs, 5 LoE, 30 other	**PBO =** -10.7 **Lur20-60 =** -15.4 **Lur80-120 =** -15.4	both the 20–60 mg/day group and the 80–120 mg/day group.
Bonaventure et al., 2012	RCT 7 weeks	N/A	N/A	MADRS	Neither JNJ-18038683 nor escitalopram demonstrated a significant improvement from baseline to week 7 in MADRS score.

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
	Moderate to Severe MDD 20mg JNJ-18038683 vs 20mg citalopram or placebo	218 total (71 placebo, 72 JNJ, 75 escitalopram)		**PBO** = -13.8 **JNJ** = -15.2 **ESC** = -13.5	**Secondary outcome (sleep)**: JNJ-18038683 prolonged REM latency and reduced REM sleep duration in healthy controls.
Rothschild, Mahableshwarkar, Jacobsen,	RCT 8 weeks GAD (DSM-IV-TR) 5mg Vortioxetine	41.2±13.4 65.80% 239 total (125 Vortioxetine, 114 placebo)	**PBO = 37** – 4 AEs, 3 LoE, 30 other **VOR5 = 27** –	HAMA **PBO** = -13.16±0.655 **VOR5** = -12.57±0.646	There was no significant difference between change in HAM-A scores between Vortioxetine and placebo.

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
Yan & Sheehan, 2012			3 AEs, 1 LoE, 23 other		
Jacobsen et al., 2015	RCT 8 weeks MDD 10 or 20 mg Vortioxetine vs placebo	42.8±12.2 72.51% 457 (155 placebo, 154 Vortioxetine 10mg, 148 Vortioxetine 20mg)	**PBO =** 18 -2 AE, 1 LoE, 15 other **VOR10 =** 31 – 9 AE, 3 LoE, 19 other **VOR20 =** 28 – 7 AE, 1 LoE, 20 other	MADRS **PBO =** -10.8±0.81 **VOR10 =** -13.0±0.83 **VOR20 =** -14.4±0.85	Vortioxetine at 20 mg showed significant improvement in MADRS score at 8 weeks compared to placebo. The difference between placebo and 10 mg Vortioxetine did not reach significance.

Author ship	Study Design/ Study Length / Diagnoses/ Drug/ Comparator/	Age of participants (mean±SD)/ Gender (M:F or F%)/ Total number of participants who completed treatment	Drop-outs (including AEs and LOC, not including not randomised / not treated) *	Outcome (Mood) Measure / Change Pre vs Post Treatment Score (mean and SD) (stat method)	Clinical outcome (CGI)/ Secondary Outcome (sleep or cognition)
Suppes T et al., 2016	RCT 6 weeks MDD with 2-3 manic/hypomanic symptoms 20-60g Lurasidone vs placebo	44.9±12.1 69.38% 189 (102 Lurasidone, 87 placebo)	**PBO = 15** – 5 AE, 4 LoE, 6 other **LUR = 7** - 3 AE, 2 LoE, 2 other	MADRS **PBO** = - 13.0 ±1.0 **LUR** = -20.5±1.0	Lurasidone significantly improved depressive symptoms and overall illness severity assessed by least squares mean change at week 6 in MADRS and CGI-S. Significant improvement in manic symptoms assess by YMRS was also observed.

Results of Quality Assessment

Authorship	selective bias	study design	confounders	blinding	data collect	withdrawal	intervention integrity	analysis	Global rating	GLOBAL RATING
Alvarez, Perez, Dragheim, Loft & Artigas, 2011	1	1	1	1	1	1	1,1,2	Y	1	STRONG
Baldwin, Loft & Dragheim, 2011	1	1	1	1	1	2	1,1,2	Y	1	STRONG
Mahableshwarkar et al., 2013	1	1	1	1	1	1	1,3,3	Y	1	STRONG
Henigsberg et al., 2012	2	1	1	1	1	1	1,3,2	Y	1	STRONG
McIntyre, Lophaven & Olsen, 2014	1	1	1	1	1	1	1,1,2	Y	1	STRONG
El-Mallakh et al., 2020	2	1	1	2	1	1	1,1,2	Y	1	STRONG
Baldwin, Loft & Florea, 2012	1	1	1	2	1	2	1,1,3	Y	1	STRONG
Loebel, Cucchiaro, Silva, Kroger, Hsu & Sarma, 2014	1	1	1	2	1	1	1,1,2	Y	1	STRONG
Bonaventure et al., 2012	1	1	1	2	1	1	1,1,2	Y	1	STRONG

Rothschild, Mahableshwarkar, Jacobsen, Yan & Sheehan, 2012	1	1	1	2	1	1	1,3,3	Y	1	STRONG
Mahableshwarkar et al., 2015	1	1	1	2	1	1	1,1,2	Y	1	STRONG
Jacobsen, Mahableshwarkar, Serenko, Chan & Trivedi, 2014	1	1	1	1	1	1	1,1,2	Y	1	STRONG
Suppes, Silva, Cucchiaro, Mao, Targum, Streicher, Pikalov & Loebel, 2016	1	1	1	1	1	1	1,1,2	Y	1	STRONG

Appendices for Chapter 3

Pop-faces paradigm

MATLAB script for fMRI preprocessing

```
clear all; clc
root = '/data/project/SIMBAphd/COPY/'; % define filepath and filename of the data
cd(root)
folders = dir('SIMBA*');

for i =  1:length (folders) % loop, to use the batch to do preprocessing in the same way
repeatedly
    tic
   cd([root folders(i).name '/NIFTI/data/MPRAGE/'])

   % map, choose the structral data T1 images
   T1 = spm_select('FPList', pwd, '^00*.*_MPRAGE*.*_reo.nii')

   % map, choose the functional data POPFACE scans
      cd([root folders(i).name '/NIFTI/data/FACES/'])
   func = spm_select('EXTFPList', pwd,'^00*.*_fMRI_POPFACES_*.*_reo.nii');

   % read in the header information for the file
   fmri = spm_vol(func);

   % number of slices 3D dimentions
   nslices = fmri(1).dim(3);

   clear matlabbatch
    matlabbatch{1}.spm.spatial.preproc.channel.vols = cellstr(T1)
    matlabbatch{1}.spm.spatial.preproc.channel.biasreg = 0.001;
    matlabbatch{1}.spm.spatial.preproc.channel.biasfwhm = 60;
    matlabbatch{1}.spm.spatial.preproc.channel.write = [0 1];
    matlabbatch{1}.spm.spatial.preproc.tissue(1).tpm =
{'/nan/ceph/network/system/el7/spm/spm-12-20181114/tpm/TPM.nii,1'};
    matlabbatch{1}.spm.spatial.preproc.tissue(1).ngaus = 1;
    matlabbatch{1}.spm.spatial.preproc.tissue(1).native = [1 0];
    matlabbatch{1}.spm.spatial.preproc.tissue(1).warped = [0 0];
    matlabbatch{1}.spm.spatial.preproc.tissue(2).tpm =
{'/nan/ceph/network/system/el7/spm/spm-12-20181114/tpm/TPM.nii,2'};
    matlabbatch{1}.spm.spatial.preproc.tissue(2).ngaus = 1;
    matlabbatch{1}.spm.spatial.preproc.tissue(2).native = [1 0];
    matlabbatch{1}.spm.spatial.preproc.tissue(2).warped = [0 0];
    matlabbatch{1}.spm.spatial.preproc.tissue(3).tpm =
{'/nan/ceph/network/system/el7/spm/spm-12-20181114/tpm/TPM.nii,3'};
    matlabbatch{1}.spm.spatial.preproc.tissue(3).ngaus = 2;
    matlabbatch{1}.spm.spatial.preproc.tissue(3).native = [1 0];
    matlabbatch{1}.spm.spatial.preproc.tissue(3).warped = [0 0];
```

```
   matlabbatch{1}.spm.spatial.preproc.tissue(4).tpm =
{'/nan/ceph/network/system/el7/spm/spm-12-20181114/tpm/TPM.nii,4'};
   matlabbatch{1}.spm.spatial.preproc.tissue(4).ngaus = 3;
   matlabbatch{1}.spm.spatial.preproc.tissue(4).native = [1 0];
   matlabbatch{1}.spm.spatial.preproc.tissue(4).warped = [0 0];
   matlabbatch{1}.spm.spatial.preproc.tissue(5).tpm =
{'/nan/ceph/network/system/el7/spm/spm-12-20181114/tpm/TPM.nii,5'};
   matlabbatch{1}.spm.spatial.preproc.tissue(5).ngaus = 4;
   matlabbatch{1}.spm.spatial.preproc.tissue(5).native = [1 0];
   matlabbatch{1}.spm.spatial.preproc.tissue(5).warped = [0 0];
   matlabbatch{1}.spm.spatial.preproc.tissue(6).tpm =
{'/nan/ceph/network/system/el7/spm/spm-12-20181114/tpm/TPM.nii,6'};
   matlabbatch{1}.spm.spatial.preproc.tissue(6).ngaus = 2;
   matlabbatch{1}.spm.spatial.preproc.tissue(6).native = [0 0];
   matlabbatch{1}.spm.spatial.preproc.tissue(6).warped = [0 0];
   matlabbatch{1}.spm.spatial.preproc.warp.mrf = 1;
   matlabbatch{1}.spm.spatial.preproc.warp.cleanup = 1;
   matlabbatch{1}.spm.spatial.preproc.warp.reg = [0 0.001 0.5 0.05 0.2];
   matlabbatch{1}.spm.spatial.preproc.warp.affreg = 'mni';
   matlabbatch{1}.spm.spatial.preproc.warp.fwhm = 0;
   matlabbatch{1}.spm.spatial.preproc.warp.samp = 3;
   matlabbatch{1}.spm.spatial.preproc.warp.write = [1 1];
   matlabbatch{2}.spm.spatial.realign.estwrite.data{1} = cellstr(func);
   matlabbatch{2}.spm.spatial.realign.estwrite.eoptions.quality = 0.9;
   matlabbatch{2}.spm.spatial.realign.estwrite.eoptions.sep = 4;
   matlabbatch{2}.spm.spatial.realign.estwrite.eoptions.fwhm = 5;
   matlabbatch{2}.spm.spatial.realign.estwrite.eoptions.rtm = 1;
   matlabbatch{2}.spm.spatial.realign.estwrite.eoptions.interp = 2;
   matlabbatch{2}.spm.spatial.realign.estwrite.eoptions.wrap = [0 0 0];
   matlabbatch{2}.spm.spatial.realign.estwrite.eoptions.weight = '';
   matlabbatch{2}.spm.spatial.realign.estwrite.roptions.which = [0 1];
   matlabbatch{2}.spm.spatial.realign.estwrite.roptions.interp = 4;
   matlabbatch{2}.spm.spatial.realign.estwrite.roptions.wrap = [0 0 0];
   matlabbatch{2}.spm.spatial.realign.estwrite.roptions.mask = 1;
   matlabbatch{2}.spm.spatial.realign.estwrite.roptions.prefix = 'r';
   matlabbatch{3}.spm.temporal.st.scans{1}(1) = cfg_dep('Realign: Estimate & Reslice:
Realigned Images (Sess 1)', substruct('.','val', '{}',{2}, '.','val', '{}',{1}, '.','val', '{}',{1}, '.','val',
'{}',{1}), substruct('.','sess', '()',{1}, '.','cfiles'));
   matlabbatch{3}.spm.temporal.st.nslices = nslices;
   matlabbatch{3}.spm.temporal.st.tr = 2;
   matlabbatch{3}.spm.temporal.st.ta = 2 - (2/nslices);
   matlabbatch{3}.spm.temporal.st.so = nslices:-1:1;
   matlabbatch{3}.spm.temporal.st.refslice = ceil(nslices/2);
   matlabbatch{3}.spm.temporal.st.prefix = 'a';
   matlabbatch{4}.spm.spatial.coreg.estimate.ref(1) = cfg_dep('Segment: Bias Corrected (1)',
substruct('.','val', '{}',{1}, '.','val', '{}',{1}, '.','val', '{}',{1}), substruct('.','channel', '()',{1},
'.','biascorr', '()',{':'}));
   matlabbatch{4}.spm.spatial.coreg.estimate.source(1) = cfg_dep('Realign: Estimate &
Reslice: Mean Image', substruct('.','val', '{}',{2}, '.','val', '{}',{1}, '.','val', '{}',{1}, '.','val',
'{}',{1}), substruct('.','rmean'));
```

```
   matlabbatch{4}.spm.spatial.coreg.estimate.other(1) = cfg_dep('Slice Timing: Slice Timing
Corr. Images (Sess 1)', substruct('.','val', '{}',{3}, '.','val', '{}',{1}, '.','val', '{}',{1}),
substruct('()',{1}, '.','files'));
   matlabbatch{4}.spm.spatial.coreg.estimate.eoptions.cost_fun = 'nmi';
   matlabbatch{4}.spm.spatial.coreg.estimate.eoptions.sep = [4 2];
   matlabbatch{4}.spm.spatial.coreg.estimate.eoptions.tol = [0.02 0.02 0.02 0.001 0.001
0.001 0.01 0.01 0.01 0.001 0.001 0.001];
   matlabbatch{4}.spm.spatial.coreg.estimate.eoptions.fwhm = [7 7];
   matlabbatch{5}.spm.spatial.normalise.write.subj.def(1) = cfg_dep('Segment: Forward
Deformations', substruct('.','val', '{}',{1}, '.','val', '{}',{1}, '.','val', '{}',{1}),
substruct('.','fordef', '()',{':'}));
   matlabbatch{5}.spm.spatial.normalise.write.subj.resample(1) = cfg_dep('Coregister:
Estimate: Coregistered Images', substruct('.','val', '{}',{4}, '.','val', '{}',{1}, '.','val', '{}',{1},
'.','val', '{}',{1}), substruct('.','cfiles'));
   matlabbatch{5}.spm.spatial.normalise.write.woptions.bb = [-78 -112 -70
                                                             78 76 85];
   matlabbatch{5}.spm.spatial.normalise.write.woptions.vox = [2 2 2];
   matlabbatch{5}.spm.spatial.normalise.write.woptions.interp = 4;
   matlabbatch{5}.spm.spatial.normalise.write.woptions.prefix = 'w';
   matlabbatch{6}.spm.spatial.smooth.data(1) = cfg_dep('Normalise: Write: Normalised
Images (Subj 1)', substruct('.','val', '{}',{5}, '.','val', '{}',{1}, '.','val', '{}',{1}, '.','val', '{}',{1}),
substruct('()',{1}, '.','files'));
   matlabbatch{6}.spm.spatial.smooth.fwhm = [8 8 8];
   matlabbatch{6}.spm.spatial.smooth.dtype = 0;
   matlabbatch{6}.spm.spatial.smooth.im = 0;
   matlabbatch{6}.spm.spatial.smooth.prefix = 's';
   save preprocess_batch matlabbatch
   spm_jobman('run', matlabbatch)
   clear matlabbatch
   toc
end
```

MATLAB scripts for fMRI First-level analysis

```
clear all; clc
root = '/data/project/SIMBAphd/COPY/';
onsets_folder = '/data/project/SIMBAphd/COPY/onsets/POPFACES'
cd(root)
task ='FACES'
folders= dir('SIMBA*');

% i = 33 skipped, needs re-prepprocessing
for i = 1: length(folders)
targetdir= [root folders(i).name '/NIFTI/data/' task ];
cd(targetdir)
fmri =spm_select('EXTFPList',pwd,['^swa0*.*' task '*.*_reo.nii'])
rp = spm_select('FPList', pwd,'^rp_0*.*_reo.txt')
mkdir analysis_block
cd analysis_block
analysis_dir = pwd
```

```
delete SPM.mat

cd(onsets_folder)
onset_file = dir(['onsets_Simba_*' folders(i).name '*.mat'])
clear ons
load(onset_file.name)
ons{1}.missed = sort([ons{1}.neu_miss; ons{1}.fea_miss; ons{1}.hap_miss])
ons{1}.incorrect = sort([ons{1}.neu_incor; ons{1}.fea_incor; ons{1}.hap_incor])

matlabbatch{1}.spm.stats.fmri_spec.dir{1} = analysis_dir;
matlabbatch{1}.spm.stats.fmri_spec.timing.units = 'secs';
matlabbatch{1}.spm.stats.fmri_spec.timing.RT = 2;
matlabbatch{1}.spm.stats.fmri_spec.timing.fmri_t = 41;
matlabbatch{1}.spm.stats.fmri_spec.timing.fmri_t0 = 21;
%%
matlabbatch{1}.spm.stats.fmri_spec.sess.scans = cellstr(fmri)

%%
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).name = 'Neutral';
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).onset =
[ons{1}.neu_cor(1);ons{1}.neu_cor(1+find(diff(ons{1}.neu_cor)>20))]
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).duration = 17.5; % Perf{1}.neu_corr_rt:
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).tmod = 0;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).pmod = struct('name', {}, 'param', {},
'poly', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).orth = 1;


matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).name = 'Happy';
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).onset =
[ons{1}.hap_cor(1);ons{1}.hap_cor(1+find(diff(ons{1}.hap_cor)>20))]
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).duration = 17.5; % Perf{1}.hap_corr_rt:
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).tmod = 0;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).pmod = struct('name', {}, 'param', {},
'poly', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).orth = 1;


matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).name = 'Fearful';
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).onset
=[ons{1}.fea_cor(1);ons{1}.fea_cor(1+find(diff(ons{1}.fea_cor)>20))];
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).duration = 17.5; % Perf{1}.fea_corr_rt:
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).tmod = 0;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).pmod = struct('name', {}, 'param', {},
'poly', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).orth = 1;

nCond  =3;

if ~isempty(ons{1}.incorrect)
```

```
   nCond = nCond +1;
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).name = 'incorrect responses';
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).onset = ons{1}.incorrect
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).duration = 1.75; %
nanmean([Perf{1}.neu_incorr_rt; Perf{1}.fea_incorr_rt; Perf{1}.hap_incorr_rt]);
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).tmod = 0;
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).pmod = struct('name', {}, 'param',
{}, 'poly', {});
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).orth = 1;
end


if ~isempty(ons{1}.missed)
   nCond = nCond+1;
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).name = 'misses';
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).onset = ons{1}.missed
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).duration = 1.75;
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).tmod = 0;
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).pmod = struct('name', {}, 'param',
{}, 'poly', {});
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).orth = 1;
end

if ~isempty(ons{1}.fp)
   nCond = nCond +1;
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).name = 'false positives';
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).onset = ons{1}.fp
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).duration = 1.75 %;
Perf{1}.fp_mean_rt;
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).tmod = 0;
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).pmod = struct('name', {}, 'param',
{}, 'poly', {});
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(nCond).orth = 1;
end



matlabbatch{1}.spm.stats.fmri_spec.sess.multi = {''};
matlabbatch{1}.spm.stats.fmri_spec.sess.regress = struct('name', {}, 'val', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.multi_reg = cellstr(rp)
matlabbatch{1}.spm.stats.fmri_spec.sess.hpf = 128;
matlabbatch{1}.spm.stats.fmri_spec.fact = struct('name', {}, 'levels', {});
matlabbatch{1}.spm.stats.fmri_spec.bases.hrf.derivs = [0 0];
matlabbatch{1}.spm.stats.fmri_spec.volt = 1;
matlabbatch{1}.spm.stats.fmri_spec.global = 'None';
matlabbatch{1}.spm.stats.fmri_spec.mthresh = 0.8;
matlabbatch{1}.spm.stats.fmri_spec.mask = {''};
matlabbatch{1}.spm.stats.fmri_spec.cvi = 'AR(1)';
```

```
matlabbatch{2}.spm.stats.fmri_est.spmmat(1) = cfg_dep('fMRI model specification:
SPM.mat File', substruct('.','val', '{}',{1}, '.','val', '{}',{1}, '.','val', '{}',{1}),
substruct('.','spmmat'));
matlabbatch{2}.spm.stats.fmri_est.write_residuals = 0;
matlabbatch{2}.spm.stats.fmri_est.method.Classical = 1;
matlabbatch{3}.spm.stats.con.spmmat(1) = cfg_dep('Model estimation: SPM.mat File',
substruct('.','val', '{}',{2}, '.','val', '{}',{1}, '.','val', '{}',{1}), substruct('.','spmmat'));

matlabbatch{3}.spm.stats.con.consess{1}.tcon.name = 'Neutral';
matlabbatch{3}.spm.stats.con.consess{1}.tcon.weights = 1
matlabbatch{3}.spm.stats.con.consess{1}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{2}.tcon.name = 'Happy';
matlabbatch{3}.spm.stats.con.consess{2}.tcon.weights = [0 1];
matlabbatch{3}.spm.stats.con.consess{2}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{3}.tcon.name = 'Fearful';
matlabbatch{3}.spm.stats.con.consess{3}.tcon.weights = [0 0 1];
matlabbatch{3}.spm.stats.con.consess{3}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{4}.tcon.name = 'Happy>Neutral';
matlabbatch{3}.spm.stats.con.consess{4}.tcon.weights = [-1 1];
matlabbatch{3}.spm.stats.con.consess{4}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{5}.tcon.name = 'Fearful>Neutral';
matlabbatch{3}.spm.stats.con.consess{5}.tcon.weights = [-1 0 1];
matlabbatch{3}.spm.stats.con.consess{5}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{6}.tcon.name = 'Fearful>Happy';
matlabbatch{3}.spm.stats.con.consess{6}.tcon.weights = [0 -1 1];
matlabbatch{3}.spm.stats.con.consess{6}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.delete = 0;
cd(analysis_dir)
save batch matlabbatch
spm_jobman('run',matlabbatch)
end
```

added contrasts

```
clear all; clc
root = '/data/project/SIMBAphd/COPY/';
onsets_folder = '/data/project/SIMBAphd/COPY/onsets/POPFACES'
cd(root)
task ='FACES'
folders= dir('SIMBA*');


for i = 1:length(folders)
targetdir= [root folders(i).name '/NIFTI/data/' task '/analysis_block' ];
cd(targetdir)
```

```
mat_file = spm_select('FPList', pwd,'^SP*.*.mat')

matlabbatch{1}.spm.stats.con.spmmat= cellstr(mat_file)

matlabbatch{1}.spm.stats.con.consess{1}.tcon.name = 'allfaces';
matlabbatch{1}.spm.stats.con.consess{1}.tcon.weights = [1 1 1]
matlabbatch{1}.spm.stats.con.consess{1}.tcon.sessrep = 'none';
matlabbatch{1}.spm.stats.con.delete = 0;
save batch matlabbatch
spm_jobman('run',matlabbatch)
end
```

Appendices for Chapter 4

N-back paradigm

MATLAB scripts for fMRI First-level analysis

```
clear all; clc
root = '/data/project/SIMBAphd/COPY/';
onsets_folder = '/data/project/SIMBAphd/COPY/onsets/NBACK'
cd(root)
task ='NBACK'
folders= dir('SIMBA*');

for i = 1: length (folders)
targetdir= [root folders(i).name '/NIFTI/data/' task ];
cd(targetdir)
fmri =spm_select('EXTFPList',pwd,['^swa0*.*' task '*.*_reo.nii'])
rp = spm_select('FPList', pwd,'^rp_*.*.txt')
mkdir analysis
cd analysis
analysis_dir = pwd
delete SPM.mat

cd(onsets_folder)
onset_file = dir(['onsets_Simba_*' folders(i).name '*.mat'])
clear ons
load(onset_file.name)
ons{1}.hits = sort([ons{1}.corr_Resp_B0 ons{1}.corr_Resp_B1 ons{1}.corr_Resp_B2
ons{1}.corr_Resp_B3])

matlabbatch{1}.spm.stats.fmri_spec.dir{1} = analysis_dir;
matlabbatch{1}.spm.stats.fmri_spec.timing.units = 'secs';
matlabbatch{1}.spm.stats.fmri_spec.timing.RT = 2;
matlabbatch{1}.spm.stats.fmri_spec.timing.fmri_t = 41;
matlabbatch{1}.spm.stats.fmri_spec.timing.fmri_t0 = 21;
%%
matlabbatch{1}.spm.stats.fmri_spec.sess.scans = cellstr(fmri)

%%
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).name = 'Instruction';
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).onset = ons{1}.Instruction
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).duration = 3;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).tmod = 0;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).pmod = struct('name', {}, 'param', {},
'poly', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(1).orth = 1;


matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).name = 'zero back';
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).onset = ons{1}.X;
```

```
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).duration = 28;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).tmod = 0;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).pmod = struct('name', {}, 'param', {},
'poly', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(2).orth = 1;


matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).name = 'one back';
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).onset = ons{1}.B1;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).duration = 28;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).tmod = 0;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).pmod = struct('name', {}, 'param', {},
'poly', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(3).orth = 1;


matlabbatch{1}.spm.stats.fmri_spec.sess.cond(4).name = 'two back';
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(4).onset = ons{1}.B2
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(4).duration = 28;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(4).tmod = 0;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(4).pmod = struct('name', {}, 'param', {},
'poly', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(4).orth = 1;



matlabbatch{1}.spm.stats.fmri_spec.sess.cond(5).name = 'three back';
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(5).onset = ons{1}.B3
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(5).duration = 28;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(5).tmod = 0;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(5).pmod = struct('name', {}, 'param', {},
'poly', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(5).orth = 1;


matlabbatch{1}.spm.stats.fmri_spec.sess.cond(6).name = 'hits';
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(6).onset = ons{1}.hits;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(6).duration = 2;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(6).tmod = 0;
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(6).pmod = struct('name', {}, 'param', {},
'poly', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.cond(6).orth = 1;

if ~isempty(ons{1}.missed)
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(7).name = 'misses';
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(7).onset = ons{1}.missed
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(7).duration = 2;
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(7).tmod = 0;
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(7).pmod = struct('name', {}, 'param', {},
'poly', {});
```

```
   matlabbatch{1}.spm.stats.fmri_spec.sess.cond(7).orth = 1;
end

matlabbatch{1}.spm.stats.fmri_spec.sess.multi = {''};
matlabbatch{1}.spm.stats.fmri_spec.sess.regress = struct('name', {}, 'val', {});
matlabbatch{1}.spm.stats.fmri_spec.sess.multi_reg = cellstr(rp)
matlabbatch{1}.spm.stats.fmri_spec.sess.hpf = 128;
matlabbatch{1}.spm.stats.fmri_spec.fact = struct('name', {}, 'levels', {});
matlabbatch{1}.spm.stats.fmri_spec.bases.hrf.derivs = [0 0];
matlabbatch{1}.spm.stats.fmri_spec.volt = 1;
matlabbatch{1}.spm.stats.fmri_spec.global = 'None';
matlabbatch{1}.spm.stats.fmri_spec.mthresh = 0.8;
matlabbatch{1}.spm.stats.fmri_spec.mask = {''};
matlabbatch{1}.spm.stats.fmri_spec.cvi = 'AR(1)';
matlabbatch{2}.spm.stats.fmri_est.spmmat(1) = cfg_dep('fMRI model specification:
SPM.mat File', substruct('.','val', '{}',{1}, '.','val', '{}',{1}, '.','val', '{}',{1}),
substruct('.','spmmat'));
matlabbatch{2}.spm.stats.fmri_est.write_residuals = 0;
matlabbatch{2}.spm.stats.fmri_est.method.Classical = 1;
matlabbatch{3}.spm.stats.con.spmmat(1) = cfg_dep('Model estimation: SPM.mat File',
substruct('.','val', '{}',{2}, '.','val', '{}',{1}, '.','val', '{}',{1}), substruct('.','spmmat'));

matlabbatch{3}.spm.stats.con.consess{1}.tcon.name = 'AllBack>zeroBack';
matlabbatch{3}.spm.stats.con.consess{1}.tcon.weights = [0 -1 0.333333333333333
0.333333333333333 0.333333333333333];
matlabbatch{3}.spm.stats.con.consess{1}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{2}.tcon.name = '1Back>0Back';
matlabbatch{3}.spm.stats.con.consess{2}.tcon.weights = [0 -1 1];
matlabbatch{3}.spm.stats.con.consess{2}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{3}.tcon.name = '2Back>0Back';
matlabbatch{3}.spm.stats.con.consess{3}.tcon.weights = [0 -1 0 1];
matlabbatch{3}.spm.stats.con.consess{3}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{4}.tcon.name = '3Back>0Back';
matlabbatch{3}.spm.stats.con.consess{4}.tcon.weights = [0 -1 0 0 1];
matlabbatch{3}.spm.stats.con.consess{4}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{5}.tcon.name = '2Back>1Back';
matlabbatch{3}.spm.stats.con.consess{5}.tcon.weights = [0 0 -1 1];
matlabbatch{3}.spm.stats.con.consess{5}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{6}.tcon.name = '3Back>1Back';
matlabbatch{3}.spm.stats.con.consess{6}.tcon.weights = [0 0 -1 0 1];
matlabbatch{3}.spm.stats.con.consess{6}.tcon.sessrep = 'none';

matlabbatch{3}.spm.stats.con.consess{7}.tcon.name = '3Back>2Back';
matlabbatch{3}.spm.stats.con.consess{7}.tcon.weights = [0 0 0 -1 1];
matlabbatch{3}.spm.stats.con.consess{7}.tcon.sessrep = 'none';
```

```
matlabbatch{3}.spm.stats.con.delete = 0;
cd(analysis_dir)
save batch matlabbatch
spm_jobman('run',matlabbatch)
end
```

Appendices for Chapter 5

SPSS Syntax for brain age analysis

```
* create dummy - who (groups)
* gp3: 0 (HC), 1 (BD), 2 (LI)
* change old variable (gp3) into a new variable (who1)
* when old variable (gp3) = 0 (HC)
* for the new variable (who1) = 1 (true).
RECODE gp3 (0=1) (ELSE=0) INTO who1.
VARIABLE LABELS  who1 'HC'.
EXECUTE.

* change old variable (gp3) into a new variable (who2)
* when old variable (gp3) = 1 (BP)
* for the new variable (who2) = 1 (true).
RECODE gp3 (1=1) (ELSE=0) INTO who2.
VARIABLE LABELS  who2 'BP'.
EXECUTE.

* change old variable (gp3) into a new variable (who3)
* when old variable (gp3) = 2 (BPL)
* for the new variable (who3) = 1 (true).
RECODE gp3 (2=1) (ELSE=0) INTO who3.
VARIABLE LABELS  who3 'BPL'.
EXECUTE.

* create dummy - which (study)
* study: sty1 (bliss), sty2 (simba), sty3 (crib), sty4 (brcfmrs)
* change old variable (study) into a new variable (which1)
* when old variable (study) = 1 (bliss)
* for the new variable (which1) = 1 (true).
RECODE study (1=1) (ELSE=0) INTO which1.
VARIABLE LABELS  which1 'bliss'.
EXECUTE.

* change old variable (study) into a new variable (which2)
* when old variable (study) = 2 (simba)
* for the new variable (which2) = 1 (true).
RECODE study (2=1) (ELSE=0) INTO which2.
VARIABLE LABELS  which2 'simba'.
EXECUTE.

* change old variable (study) into a new variable (which3)
* when old variable (study) = 3 (crib)
* for the new variable (which3) = 1 (true).
RECODE study (3=1) (ELSE=0) INTO which3.
VARIABLE LABELS  which3 'crib'.
EXECUTE.
```

```
* change old variable (study) into a new variable (which4)
* when old variable (study) = 4 (brcfmrs)
* for the new variable (which4) = 1 (true).
RECODE study (4=1) (ELSE=0) INTO which4.
VARIABLE LABELS  which4 'brcfmrs'.
EXECUTE.


*logic check for grp2.
CROSSTABS
  /TABLES=who1 BY gp2
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT
  /COUNT ROUND CELL.

*logic check for grp2.
CROSSTABS
  /TABLES=who2 BY gp2
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT
  /COUNT ROUND CELL.

*logic check for grp2.
CROSSTABS
  /TABLES=who3 BY gp2
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT
  /COUNT ROUND CELL.


* descriptive of study by 2 groups.
* check how many HC vs BD (grp2) in each study.
CROSSTABS
  /TABLES=study BY gp2
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT
  /COUNT ROUND CELL.

* descriptive of scanage by 2 groups.
* check scanage of HC vs BD (grp2).
EXAMINE VARIABLES=brainage scanage BY gp2
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING PAIRWISE
  /NOTOTAL.

*create variable study by university, 1= BLISS, 2=KCL.

DATASET ACTIVATE DataSet1.
```

```
RECODE study (1=1) (2 thru 4=2) INTO study_u.
VARIABLE LABELS  study_u 'study by university'.
EXECUTE.

* to see if there are correlations between brainage, scanage, and gap between brainage and
scanage (bsgap1).
CORRELATIONS
  /VARIABLES=scanage brainage bsgap1
  /PRINT=TWOTAIL NOSIG FULL
  /MISSING=PAIRWISE.
NONPAR CORR
  /VARIABLES=scanage brainage bsgap1
  /PRINT=SPEARMAN TWOTAIL NOSIG FULL
  /MISSING=PAIRWISE.

* to see if there are differences between two groups (BD & HC) by age, yedu, iqfull (t-test)
and gender (chi square).
T-TEST GROUPS=gp2(0 1)
  /MISSING=ANALYSIS
  /VARIABLES=scanage yedu iqfull
  /ES DISPLAY(TRUE)
  /CRITERIA=CI(.95).

CROSSTABS
  /TABLES=study_u BY gender
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.

* analysis1a - (using brain age) using regression to see if there is difference between 2 groups
with all samples.
* check if patient's brainage is older than healthy people's (BD vs HC).
* regression for brainage with scanage, HC vs BD (grp2) in study 1 - 4.
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT brainage
  /METHOD=ENTER scanage
  /METHOD=ENTER which2 which3 which4
  /METHOD=ENTER gp2.


* analysis1b - (using age gap) - the gap between brainage and scanage with study 1-4
samples.
* create agegap variable.
COMPUTE bsgap1=brainage - scanage.
EXECUTE.
```

```
* descriptive of bsgap - check if there are negative values.
DESCRIPTIVES VARIABLES= bsgap1
  /STATISTICS=MEAN STDDEV MIN MAX SEMEAN.

* see if there is difference between 2 groups in agegap1 (minus, bsgap1: HC & BD).
T-TEST GROUPS=gp2(0 1)
  /MISSING=ANALYSIS
  /VARIABLES=bsgap1
  /ES DISPLAY(TRUE)
  /CRITERIA=CI(.95).
* analysis2 - lithium effects - if brain age gap is larger in BD in 3 gps (BD > LI/HC), using
study1 samples.
* filter to focusing on study1.
USE ALL.
COMPUTE filter_$=(study=1).
VARIABLE LABELS filter_$ 'study=1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.

* check data.
DESCRIPTIVES VARIABLES=study
  /STATISTICS=MEAN STDDEV MIN MAX.

* using ANOVA to see if brain age gap is larger in BD in 3 groups (BD > LI/HC).
* testing bsgap1.
ONEWAY bsgap1 BY gp3
  /STATISTICS DESCRIPTIVES HOMOGENEITY
  /MISSING ANALYSIS
  /CRITERIA=CILEVEL(0.95)
  /POSTHOC=TUKEY ALPHA(0.05).


* analysis3a - to see what types of cognitive functions predict the gap between brainage and
scanage.
* regression to see the relationships between age gap1 (minus) and cognition.
DATASET ACTIVATE DataSet1.
CORRELATIONS
  /VARIABLES=bsgap1 yedu iqfull pcat tmta
  /PRINT=TWOTAIL NOSIG FULL
  /STATISTICS DESCRIPTIVES
  /MISSING=PAIRWISE.

DATASET ACTIVATE DataSet1.
REGRESSION
  /DESCRIPTIVES MEAN STDDEV CORR SIG N
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS CI(95) R ANOVA
```

```
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT bsgap1
  /METHOD=ENTER scanage who1 who2 who3 yedu iqfull tmta pcat.

* remove filter.
FILTER OFF.
USE ALL.
EXECUTE.
```