The Cognitive Correlates of Major Depressive Disorder and Administration of SSRI Antidepressants

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DEDICATION

To those who unconditionally held my hand to make my first steps in the physical, intellectual, and emotional realms …

ABSTRACT OF THE DISSERTATION

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A significant barrier to interpreting past studies of cognition in major depressive disorder (MDD) has been the inadequate dissociation of cognitive changes due to MDD from the side effects of antidepressants used to treat MDD such as Selective Serotonin Reuptake Inhibitors (SSRIs). The two most implicated brain regions in the pathophysiology of MDD are the basal ganglia (BG) and the hippocampus, which are also key areas for cognitive function. In this dissertation, we used cognitive assessment tools that selectively and sensitively evaluate BG and hippocampus function to tease apart the cognitive effects of MDD from those of SSRIs, and explore individual differences in cognitive function resulting from naturally occurring genetic variations. We studied two cognitive functions that have well-characterized neural bases informed by patient work and neuro-computational models: (1) **Learning** stimulus-response rules from positive and negative feedback, known to depend on the *BG*; and (2) **Generalization** of

past stimulus-response learning to novel task demands and contexts, known to depend on the *hippocampus*. Investigating learning from positive and negative feedback revealed that MDD impaired learning from positive feedback in future SSRI-responders and non-responders, but spared learning from negative feedback only in SSRI-responders. SSRI administration, however, did not remediate the deficit in learning from positive feedback, but rather impaired learning from negative feedback in SSRI-responders, thereby bringing learning from positive and negative feedback into 'balance'. Variations in dopamine levels reflected by naturally occurring genetic polymorphisms in the dopamine transporter gene modulated learning from positive feedback in both healthy and MDD states. Studying generalization of past learning revealed that MDD had no effect. However, SSRI-responders exhibited overgeneralization after SSRI administration. Overall, these findings define the cognitive profile of medication-naïve MDD and delineate the cognitive mechanism of action of SSRIs. Further, these results differentiate the cognitive profiles of SSRI responders and non-responders before and after treatment and highlight the cognitive effects of naturally occurring genetic variations. Clinical trials based on these findings could inform innovative individualized treatment protocols for MDD, guiding physician choices among antidepressants according to a patient's individual cognitive and genetic profile upon initial diagnosis.

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CHAPTER 1: INTRODUCTION

Cognitive Correlates of Striatal and Hippocampal Dysfunction in Major Depressive Disorder

1.1. OVERVIEW

Major Depressive Disorder (MDD) is characterized by affective symptoms including persistent low mood, loss of pleasure (anhedonia), and emotional dysregulation. Patients with MDD also exhibit a range of cognitive impairments whose behavioral characteristics and neural bases are still too poorly understood. In this chapter, we will review the most commonly accepted neurobiological theories of MDD, linking these theories to the functional roles of the basal ganglia and hippocampus in mediating cognition. Furthermore, we will discuss the effects of Selective Serotonin Reuptake Inhibitors (SSRI) on basal ganglia and hippocampal-dependent cognitive functions. Finally, we will summarize the cognitive effects of naturally occurring genetic polymorphisms in dopamine and serotonin transporters in MDD. In each section, we will discuss critical gaps in the literature and potential ways to address them.

1.2. OVERVIEW OF NEUROBIOLOGICAL THEORIES OF MDD

The neural systems that underlie MDD have been extensively studied, leading to various theories that link structural and neurochemical dysfunction to behavioral symptoms (Hasler, 2010; Henkel, Bussfeld, Moller, & Hegerl, 2002; Huprich, 1998; Manji, Drevets, & Charney, 2001; Pariante & Lightman, 2008). In summary, the most widely accepted theories of MDD are as follows:

(1) The **monoamine deficiency theory** argues that the underlying pathology in MDD is depletion of the monoamines, serotonin, norepinephrine and dopamine (Charney, 1998; Delgado, 2000; D. J. Nutt, 2006; Rotenberg, 1994). Postmortem studies of MDD patient brains and the remediation of MDD symptoms by pharmacologically replenishing central monoamine levels support this theory (Charney, 1998; Lesch et al., 1993; Perry, Marshall, Blessed, Tomlinson, & Perry, 1983). Unfortunately, no direct evidence has been found to support the primary involvement of monoamine systems in MDD (Delgado, 2000). Furthermore, only 30-50% of MDD patients, on average, respond to monoamine pharmacological therapy (Howland, 2008; Labermaier, Masana, & Muller, 2013; McIntyre et al., 2014; Willner, Scheel-Kruger, & Belzung, 2014).

(2) The hypothalamic-pituitary-adrenal (HPA) axis is key for initiating response to stress. Many researchers have explored the link between **HPA axis dysfunction and MDD** demonstrating abnormal HPA axis activity in patients and animal models of MDD (Nikisch, 2009; Pariante, 2003; Pariante & Lightman, 2008). Studies on MDD patients

demonstrated high concentrations of plasma corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol (the final product of HPA axis activity) (Claes, 2004; Holsboer & Barden, 1996).

(3) The **neurogenesis theory of MDD** proposes that disruption of hippocampal neurogenesis in the dentate gyrus leads to the expression of affective and emotional symptoms of MDD (Kempermann, 2002; Kempermann & Kronenberg, 2003; Vaidya, Fernandes, & Jha, 2007). Various reports support the claim that MDD impairs hippocampal neurogenesis (Sahay, Drew, & Hen, 2007). However, suppression of neurogenesis in mice does not induce depression-like symptoms (Santarelli et al., 2003). Nevertheless, intact neurogenesis is instrumental for antidepressants to remediate depressive symptoms (Mendez-David, Hen, Gardier, & David, 2013; Perera et al., 2011).

Other theories of MDD highlight the involvement of other neurochemical systems, such as the cholinergic system, glutamatergic system, GABAergic system, substance P, and neural growth factors (Lanni, Govoni, Lucchelli, & Boselli, 2009). However, none of these theories properly explains the neural basis of the variability seen in MDD symptom expression or the large proportion of MDD patients who do not respond to pharmacological treatment (Labermaier et al., 2013; McIntyre et al., 2014; Willner et al., 2014).

The overlap in all of these theories is their reference to the two most

commonly implicated brain regions in the pathogenesis of MDD, the **basal ganglia** and the **hippocampus**, which are also key areas for cognitive function. Many prior studies have suggested structural and neurochemical impairments in MDD that are specific to the basal ganglia which antidepressant administration may normalize (Di Simplicio, Norbury, & Harmer, 2012; Godlewska, Norbury, Selvaraj, Cowen, & Harmer, 2012) (Stoy et al., 2011). However, reports on the effects of MDD and antidepressants on hippocampal function have been ambiguous and contradictory (Vythilingam et al., 2004). In the next section, we will discuss the involvement of these two neural systems in cognitive dysfunction in MDD and the further effects on cognition of antidepressant administration.

1.2.1. Basal Ganglia Dependent Cognitive Dysfunction in MDD

Research from the past three decades argues that the basal ganglia play an important role in cognitive function. The connections between the basal ganglia and all lobes of cortex increase their involvement in cognitive, emotional, and motor regulation (Haber, 2003). The basal ganglia are involved in many aspects of cognitive function (Da Cunha et al., 2009; Packard & Knowlton, 2002). Recent fMRI and neurophysiological studies have implicated the basal ganglia in habit learning, skill learning, instrumental conditioning, emotional processing as well as positive-vs.-negative feedback learning and decision-making (Da Cunha, Gomez, & Blaha, 2012; Isoda & Hikosaka, 2011; Ward, Seri, & Cavanna, 2013).

While once viewed primarily as systems for motor regulation, the basal ganglia are now recognized as key hubs for diverse aspects of learning and memory.

An extensive literature suggests that the basal ganglia are disrupted in MDD (Dunlop & Nemeroff, 2007; Nestler & Carlezon, 2006; Perona et al., 2008). Anhedonia, the major symptom of MDD, has been linked to dopaminergic dysfunction in the basal ganglia (Bressan & Crippa, 2005; Dhillon, Yang, & Curran, 2008; Heinz et al., 1999; Miller et al., 1996; Schmidt et al., 2001). Further, MDD is prevalent in patients affected by basal ganglia strokes (Fang & Cheng, 2009; Kanner, 2004). Other studies have found that MDD is associated with smaller striatal volume (Lorenzetti, Allen, Fornito, & Yucel, 2009). Imaging studies show that patients with MDD have structural abnormalities directly related to lower levels of nigrostriatal dopamine (Robinson, Cools, Carlisi, Sahakian, & Drevets, 2011; Walter et al., 2007). Furthermore, patients with MDD have a three-fold higher risk of developing Parkinson's disease (Schuurman et al., 2002), in which nigrostriatal dopaminergic neurons decay (Kish, Shannak, & Hornykiewicz, 1988). Also, 50% of patients with Parkinson's disease eventually develop MDD (Cummings, 1992; Leentjens, Van den Akker, Metsemakers, Lousberg, & Verhey, 2003; Schuurman et al., 2002; Veiga et al., 2009). These links between MDD and Parkinson's disease may be attributed to striatal dopamine depletion (Kish et al., 1988; Walter et al., 2007). However, it is not clear whether this overlap between the two disorders is a consequence of dopaminergic dysfunction alone, or results from a mixture of different

monoaminergic effects (Delaville, Navailles, & Benazzouz, 2012; Kitaichi et al., 2010).

Brain imaging and neuropsychological studies of Parkinson's patients suggest a key role for the basal ganglia dopaminergic system in learning from both positive and negative feedback about the consequences of one's choices (Packard & Knowlton, 2002). Unmediated patients with Parkinson's disease and MDD patients exhibit hyposensitivity to positive feedback and rewarding events (Bodi et al., 2009; Henriques, Glowacki, & Davidson, 1994; McFarland & Klein, 2009; Robinson, Cools, Carlisi, Sahakian, & Drevets, 2012) as well as hypersensitivity to negative feedback and aversive events (Henriques et al., 1994; Robinson et al., 2011) (Beats, Sahakian, & Levy, 1996; Elliott, Sahakian, Herrod, Robbins, & Paykel, 1997; Elliott et al., 1996). These results implicate dopaminergic dysregulation in the cognitive correlates of MDD (Dunlop & Nemeroff, 2007). Numerous studies show that patients with MDD have attenuated striatal response to positive feedback (Henriques et al., 1994; McFarland & Klein, 2009; Robinson, Cools, Carlisi, et al., 2012), while event-related potential studies argue that patients with MDD have lower than normal responses to positive feedback (Foti, Carlson, Sauder, & Proudfit, 2014).

MDD has been associated with various cognitive deficits, including alterations to learning from positive and negative feedback (Eshel & Roiser, 2010). Behavioral studies suggest that patients with MDD show hypersensitive

responses to negative feedback (Beats et al., 1996; Elliott et al., 1997; Elliott et al., 1996), while being hyposensitive to positive feedback (Henriques et al., 1994; McFarland & Klein, 2009; Robinson, Cools, Carlisi, et al., 2012). These findings fit with psychological theories of MDD, which argue that patients with MDD manifest abnormally negative attitudes and thoughts (Bower, 1981), while being unable to modulate their behavioral responses when presented with positive reinforcement, which results in misconception of environmental information to confirm these biases (Gotlib & Joormann, 2010; Roiser & Sahakian, 2013). Such cognitive biases relate to the underlying neural circuits that are affected by MDD, namely the basal ganglia and the limbic system (Dunlop & Nemeroff, 2007; D. J. Nutt, 2006; Sheline et al., 2001). Accordingly, we can draw two major conclusions from the literature on MDD patients' ability to process information in the context of positive and negative feedback. The first is that patients with MDD show exaggerated responses to negative feedback (Beats et al., 1996; Elliott et al., 1997; Elliott et al., 1996), while the second is that MDD patients show hyposensitivity to positive feedback (Henriques et al., 1994; McFarland & Klein, 2009; Robinson, Cools, Carlisi, et al., 2012).

Aside from dopaminergic inputs, the basal ganglia receive extensive serotonergic afferents from the dorsal raphe nucleus (Kelland, Freeman, & Chiodo, 1990; Moore, Halaris, & Jones, 1978), which can also play an important role in cognitive deficits associated with MDD (Cools, Nakamura, & Daw, 2011; Cools, Roberts, & Robbins, 2008). Serotonin has been prominently associated

with aversive processing as well as behavioral inhibition, which are related to basal ganglia function. Serotonin levels correlate with inhibition induced by negative feedback and aversive processing but not overall inhibition of motor responses to aversive outcomes (Crockett, Clark, & Robbins, 2009; Deakin & Graeff, 1991; Geurts, Huys, den Ouden, & Cools, 2013). Depletion of central serotonin enhances aversive learning in healthy subjects (Cools, Robinson, & Sahakian, 2008; Evers et al., 2005), which mimics the hypersensitivity to negative feedback in patients with MDD (Beats et al., 1996; Elliott et al., 1997; Elliott et al., 1996). However, it remains unclear how dopamine and serotonin interact in the basal ganglia in the context of MDD.

Critical Gaps in the Literature and Possible Future Directions

Unfortunately, limited research has been conducted to characterize basal ganglia-dependent cognitive dysfunction in MDD, and most studies that have addressed this issue have not differentiated the effects of MDD from the consequences of antidepressant treatment. Furthermore, there has been inadequate attention to individual difference across patients in MDD symptoms, MDD subtypes, and genetic variations, and how these fundamental heterogeneities influence basal-ganglia-dependent cognitive function and response to antidepressants. Resolving these limitations in our understanding of MDD and cognition will improve our understanding of the neural basis of MDD while highlighting the large variability in symptom expression and response to medications.

1.2.2. Hippocampal Dependent Cognitive Dysfunction in MDD

The hippocampus has long been regarded as a critical brain system for memory (Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011; Howard & Eichenbaum, 2013; Wixted & Squire, 2010). Hippocampal lesions induce declarative, contextual, spatial and associative memory deficits (Packard & McGaugh, 1992, 1996; Vann & Albasser, 2011). The hippocampus has also been identified as critically involved in associative learning, especially discrimination learning involving stimuli with multiple attributes (Moss, Mahut, & Zola-Morgan, 1981; Mumby, Astur, Weisend, & Sutherland, 1999; Winocur, 1979). Studies using computational modeling (Gluck, Meeter, & Myers, 2003; Gluck & Myers, 1993; Gluck, Myers, Nicolle, & Johnson, 2006), brain imaging (Johnson, Schmitz, Asthana, Gluck, & Myers, 2008; Poldrack et al., 2001), and neuropsychological techniques in hippocampal-impaired clinical populations (Farkas et al., 2008; Keri, Nagy, Kelemen, Myers, & Gluck, 2005; Myers et al., 2002; Myers, Kluger, Golomb, Gluck, & Ferris, 2008; Myers, Shohamy, Gluck, Grossman, Kluger, et al., 2003; Myers, Shohamy, Gluck, Grossman, Onlaor, et al., 2003) have demonstrated that the hippocampus is critical for encoding the stimulus-stimulus regularities that are present during learning (including contextual cues). This in turn facilitates subsequent generalization of past learning to novel task demands and new contexts (Gluck & Myers, 1993; Poldrack et al., 2001). More specifically, Gluck and Myers have argued that the hippocampus provides for both compression of redundancy (of reliably co-

occurring inputs) and differentiation of stimuli predicting upcoming events during associative learning (Gluck & Myers, 1993, 2001).

A large body of literature suggests that MDD affects the structure and function of the hippocampus, including evidence for reduced hippocampal volume in MDD patients (Campbell & Macqueen, 2004; Kaymak et al., 2010; MacQueen et al., 2003; Vakili et al., 2000; Vythilingam et al., 2004). In line with the hyper-cortisolemia in MDD, and the toxic effect of high cortisol concentrations on hippocampal neurons, this suggests one mechanism by which MDD can lead to hippocampal shrinkage. Further, the suppression of hippocampal neurogenesis in MDD can also lead to the loss of new cells, thus leading to a decrease in hippocampal volume (Boldrini et al., 2009). More detailed analyses have shown that MDD differentially affects the different subfields of the hippocampus, with the most pronounced MDD-related dysfunction and shrinkage seen on the dentate gyrus, followed by less in CA1 and CA3 (Boldrini et al., 2009; Fujii, Saito, Yanaka, Kosaka, & Okazawa, 2014; Willard, Riddle, Forbes, & Shively, 2013). However, these findings are not consistent throughout the literature, and some researchers have found no volume differences between MDD patients and healthy subjects. Recent meta-analyses have, in fact, argued that there are no differences in this regard between MDD and healthy subjects (Kaymak et al., 2010; Kroes, Rugg, Whalley, & Brewin, 2011; MacQueen et al., 2003; Vythilingam et al., 2004). Some researchers have argued that hippocampal volume is affected by the chronicity of MDD, not its pathogenesis,

such that the more depressive episodes the patient has, the more pronounced the hippocampal shrinkage becomes (Cobb et al., 2013; MacQueen et al., 2003). Accordingly, hippocampal volume reduction may be a consequence, not a cause of MDD. Consistent with this view is evidence that patients with MDD in their first episode have normal hippocampal volume, and that only after recurrent depressive attacks do patients start showing hippocampal volumetric changes (Cobb et al., 2013; McKinnon, Yucel, Nazarov, & MacQueen, 2009).

In general, a wealth of research suggests that MDD, especially chronic MDD, impairs many facets of hippocampal-dependent functions (Kaymak et al., 2010; MacQueen et al., 2003). Patients with MDD are impaired on episodic memory measures such as the delayed paragraph recall of Wechsler Memory Scale, the Selective Reminding Test, and recollection memory tests (Vythilingam et al., 2004). Recent work suggests that MDD leads to impaired discrimination of highly similar objects (Dery et al., 2013), thus impairing pattern separation (Fujii et al., 2014; Leal, Tighe, Jones, & Yassa, 2014). Further, studies found that patients with MDD perform worse than healthy subjects on novel spatial memory tasks (Porter, Gallagher, Thompson, & Young, 2003). However, these studies remain inconclusive, because they failed to control for age and medication status.

Critical Gaps in the Literature and Possible Future Directions

Most previous research failed to control for key factors that affect

hippocampal-dependent cognitive function, such as medication status, age, severity of MDD symptoms, and response to antidepressants. Most prior research studies of learning and memory in MDD have used tests that are not specific to the hippocampus or sufficiently sensitive to mild degrees of hippocampal dysfunction (Loewenstein et al., 2009; Myers et al., 2002). This lack of neural specificity limits the generalizability of past results. Moreover, the absence of studies that dissociate effects of MDD and antidepressants on hippocampal-dependent learning is a major limitation to progress in this area.

1.3. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) AND COGNITIVE FUNCTION

SSRIs may achieve some of their therapeutic mood-enhancing effects through one or more mechanisms of action including modifying synaptic availability of serotonin, improving dopaminergic function in the brain (D. J. Nutt, 2006), and possibly also by enhancing neurogenesis in the hippocampal region (Malberg, 2004). Neuroimaging and animal studies suggest that SSRIs increase the size of the hippocampus by augmenting the rate of neurogenesis in the dentate gyrus (Boldrini et al., 2009; Malberg & Schechter, 2005; Sahay et al., 2011). Furthermore, it has been shown in animal studies that neurogenesis in the dentate gyrus is key for the mood augmenting effect of antidepressants (David et al., 2009), although the blockage of neurogenesis does not induce depression-like behavior in animals (Santarelli et al., 2003).

If SSRIs induce neurogenesis, we might expect this to lead to an improvement in learning. However, past studies have shown ambiguous effects of SSRIs on hippocampal-dependent cognitive processes. While some studies show improved cognitive function with SSRI administration, others show no effect or even an SSRI-induced cognitive impairment (Carlini et al., 2012; Igelstrom & Heyward, 2012; Sass & Wortwein, 2012; Vythilingam et al., 2004). SSRI-induced neurogenesis produces cells that are different from cells that are naturally generated in the dentate gyrus (Kobayashi et al., 2010; Liu, Pinnock, & Herbert, 2011; O'Leary, Wu, & Castren, 2009). These immature newborn cells have different functions than mature cells (Kesner, Lee, & Gilbert, 2004) in that they are more excitable (Snyder, Kee, & Wojtowicz, 2001), and tend to inhibit mature neurons in the dentate gyrus (Kobayashi et al., 2010). Thus newborn cells in the dentate gyrus might lead to impaired function in tasks that depend on older mature dentate gyrus neurons. (Ming & Song, 2011). Moreover, recent evidence suggests that hippocampal neurogenesis in rodents can impair memory retrieval when animals are tested in a radial arm maze (Saxe et al., 2007). This might be the result of having too many immature cells in the hippocampal network which negatively impact memory processes (Saxe et al., 2007). Thus, one possible source of cognitive deficits seen after administration of SSRIs may be excessive neurogenesis in the dentate gyrus leading to an imbalance between immature and mature neurons.

Recent studies in humans and rodents argue that SSRI administration in MDD results in restoration of normal activity patterns in the prefrontal cortex, striatum and amygdala (Di Simplicio et al., 2012; Godlewska et al., 2012) (Stoy et al., 2011), as well as normalization of the functional connectivity between the prefrontal cortex and both the hippocampus and amygdala (Di Simplicio et al., 2012; Godlewska et al., 2012; McCabe et al., 2011). The administration of SSRI also diminishes the processing of both positive and negative feedback in healthy human subjects (McCabe, Mishor, Cowen, & Harmer, 2010), but diminishes learning from negative feedback stimuli and enhances learning from positive feedback stimuli in rats (Bari et al., 2010). Accordingly, there is evidence from human and rodent research that SSRI administration normalizes brain activity in key regions for learning from positive and negative feedback, and might also enhance learning from positive feedback.

SSRI may also ameliorate MDD symptoms by inhibiting processing of negative feedback (Boureau & Dayan, 2011; Cools et al., 2011). Increasing the central level of serotonin by administration of SSRI counteracts MDD-related negative biases in aversive learning paradigms in animals (Bari et al., 2010) as well as emotional learning paradigms in humans (McCabe et al., 2010). Various studies show that the adminstration of SSRI normalizes the BOLD response in the dorsomedial PFC and across the functional connectivity between PFC and both hippocampus and amygdala (McCabe et al., 2011). For example, administration of SSRIs causes normal rats to lose selectivity for positive

outcomes, and, instead, select more balanced outcomes (Watts, Gritton, Sweigart, & Poe, 2012). This could support either an SSRI-induced learning deficit or a loss of the power of negative motivation, or both. SSRI administration could have selectively impaired learning from positive or negative outcomes, given the evidence that SSRI diminish learning from positive and negative feedback. Alternatively, SSRI administration may have diminished learning from all outcomes, leading to a balanced, but suppressed, learning of outcome contingencies. Unfortunately, no prior studies have examined the effect of SSRI administration on the balance between positive and negative feedback learning.

It is estimated that only 30-50% of people with MDD respond to an SSRI regimen with a clinically significant reduction in depressive symptoms (Howland, 2008; Labermaier et al., 2013; McIntyre et al., 2014; Willner et al., 2014). In responders, SSRI administration normalizes aberrant hyperactivity in the striatum, amygdala and prefrontal cortex (Di Simplicio et al., 2012; Godlewska et al., 2012; Stoy et al., 2011). Unlike SSRI responders, non-responders often show persistently diminished striatal activity and functional connectivity with cortical regions before and after SSRI administration (Downar et al., 2013; Forgeard et al., 2011). SSRI non-responders also exhibit an increase in hippocampal activity that is not seen in responders (Goldapple et al., 2004). Several studies have also found a positive correlation between insula activity (a cortical area with connections to both the basal ganglia and the hippocampus) and potential response to SSRI administration in MDD (McGrath et al., 2013).

However, it remains unclear what are the cognitive correlates of positive clinical responsiveness to SSRIs.

Critical Gaps in the Literature and Possible Future Directions

Very few prior studies have examined the effect of SSRI administration on cognitive function in MDD. Those that have did not use sensitive and neuroanatomically-specific measures of cognitive function. Moreover, no studies have examined the cognitive differences between responders and non-responders to SSRI treatment.

1.4. INDIVIDUAL DIFFERENCE DUE TO NATURALLY OCCURRING GENETIC POLYMORPHISMS IN THE DOPAMINE TRANSPORTER GENE (DAT1) AND THE SEROTONIN TRANSPORTER GENE (SLC6A4)

Understanding the impact of genetic variations in the dopaminergic and serotonergic systems is key for understanding the pathophysiology of MDD and the mechanisms of action of SSRIs. Serotonin has been associated with aversive processing as well as behavioral inhibition (Crockett et al., 2009; Deakin & Graeff, 1991). The depletion of central serotonin by acute tryptophan depletion enhances learning of aversive cues (Cools, Robinson, et al., 2008), (L. Clark, Chamberlain, & Sahakian, 2009; Eshel & Roiser, 2010). On the other hand, dopamine is key for learning from positive feedback (Schultz, Dayan, &

Montague, 1997). Thus, dopaminergic dysregulation may play a central role in the cognitive correlates of MDD (Dunlop & Nemeroff, 2007; D. Nutt et al., 2007; D. J. Nutt, 2006). As seen in functional imaging studies, patients with MDD exhibit blunted behavioral and striatal response to presentation of reward (Henriques et al., 1994; McFarland & Klein, 2009; Robinson, Cools, Carlisi, et al., 2012). Accordingly, low serotonergic and dopaminergic states could represent the neurochemical basis for some of the observed cognitive biases in MDD (Cools et al., 2011). However, few research techniques offer the opportunity to examine variations in dopamine and serotonin levels in the human brain. One of the commonly used non-invasive techniques takes advantage of naturally occurring genetic polymorphisms in the dopamine and serotonin genes (Haddley et al., 2008).

Polymorphisms in the dopamine transporter gene (DAT1) and the serotonin transporter gene (SLC6A4) influence expression of the dopamine transporter (DAT) protein and the serotonin transporter (SERT) protein and, ultimately, dopamine and serotonin levels in the brain. Naturally occurring genetic variations have been related to individual differences in basal ganglia and hippocampal-dependent cognitive function (Aarts et al., 2010; Frank, Moustafa, Haughey, Curran, & Hutchison, 2007; Hariri & Holmes, 2006). Further, previous reports indicate a role of polymorphisms in the dopamine and serotonin genes for increasing risk of developing MDD (Ueno, 2003). Converging evidence suggests that DAT1 polymorphisms, which regulate the availability of striatal dopamine

(van de Giessen et al., 2009), play an especially salient role in striatal-dependent learning (Simon et al., 2011) as well as in the pathophysiology of MDD (Kirchheiner et al., 2007; Ueno, 2003). Further, carriers of the 10-repeat polymorphism exhibit faster response to antidepressants than 9-repeat homozygotes (Kirchheiner et al., 2007). Unfortunately, no previous studies have investigated the effect of DAT1 VNTR polymorphism on cognitive function in patients with MDD.

Aside from dopamine, polymorphisms in the serotonin transporter (SERT) gene (SLC6A4) have also been associated with individual differences in cognitive function and the risk to developing MDD and other psychiatric disorders (Furr, Lapiz-Bluhm, & Morilak, 2012). These polymorphisms can define individual differences in MDD-related cognitive function and response to antidepressants.

Critical Gaps in the Literature and Possible Future Directions

Unfortunately, little is known about the cognitive correlates of genetic polymorphisms in DAT1 and SLC6A4 in MDD, and how they might be affected by response to SSRI treatment regimen.

1.5. SUMMARY: MAJOR GAPS IN LITERATURE AND FUTURE DIRECTIONS

Major critical gaps in the MDD-cognition literature can be defined as the lack of proper control for medication status, response to medications, MDD

subtype, age, specific and sensitive measures of cognition, and naturally occurring genetic variations. Studies that address these problems can significantly improve our understanding of the neural and cognitive correlates of MDD, and may lead to clinically useful new methods to *a priori* differentiate between SSRI responders and non-responders.

CHAPTER 2

Learning from Negative Feedback in Patients with Major Depressive Disorder is Attenuated by SSRI Antidepressants

2.1. OVERVIEW

To better understand how remediation of depressive symptoms affects cognitive function in MDD, we used between-subjects and within-subjects designs to test patients with MDD and matched healthy controls. All were administered a category-learning task that allows for dissociation between learning from positive feedback versus negative feedback. In the between-subjects study (experiment #1), we evaluated three groups: medication-naïve patients with MDD, SSRI-treated and responding patients with MDD and healthy controls. Healthy subjects learned significantly better from positive feedback than medication-naïve and medicated MDD groups, whose learning accuracy did not differ significantly. In contrast, medicated patients with MDD learned significantly less from negative feedback than medication-naïve patients with MDD and healthy subjects, whose learning accuracy was comparable. A comparison of the subjects' relative sensitivity to positive versus negative feedback showed that both the medicated MDD and healthy control groups exhibited 'balanced' learning, whereas medication-naïve MDD were biased towards learning from negative feedback.

To extend the findings of experiment #1, using the same learning paradigm, we conducted a within-subjects design (experiment #2) in which medication-naïve MDD patients were tested both before and 4-6 weeks after they were stabilized on SSRI regimen. Response to SSRI administration was assessed 6 weeks after diagnosis. Healthy control subjects were also tested twice at the same time interval. We replicated the findings of experiment #1, showing that medication-naïve patients showed a selective deficit for positive feedback learning. Further, SSRI administration significantly suppressed learning from negative feedback in SSRI responders, bringing learning from positive and negative feedback into balance. Conversely, SSRI administration did not affect learning from negative feedback in non-responders. In fact, non-responders expressed balanced learning from positive and negative feedback at the medication-naïve state.

2.2. INTRODUCTION

Major depressive disorder (MDD) is a debilitating psychiatric disease, characterized by persistent low mood and significant loss of pleasure (Belmaker & Agam, 2008). In addition to being implicated in the pathophysiology of MDD, the monoamines serotonin and dopamine have been shown to play major roles in reinforcement learning (Cools et al., 2011; Deakin, 1991; Dunlop & Nemeroff, 2007). Serotonin has been associated with aversive processing as well as behavioral inhibition. Central serotonin levels positively correlate with negative feedback-induced inhibition and aversive processing but not overall inhibition of

motor responses to aversive outcomes (Crockett et al., 2009; Deakin & Graeff, 1991). Studies have shown that acute tryptophan depletion (a dietary technique used to reduce central serotonin concentrations) enhances reversal learning of aversive cues in healthy subjects (Cools, Robinson, et al., 2008). This enhancement of aversive learning mimics the feedback sensitivity bias in patients with MDD (L. Clark et al., 2009; Eshel & Roiser, 2010).

Aside from being key for learning from positive feedback (Schultz et al., 1997), it has been suggested that dopaminergic dysregulation plays a central role in the cognitive correlates of MDD (Dunlop & Nemeroff, 2007; D. Nutt et al., 2007; D. J. Nutt, 2006). Imaging studies have shown that patients with MDD exhibit hyposensitivity to positive feedback alongside attenuated striatal response to presentation of positive feedback (Henriques et al., 1994; McFarland & Klein, 2009; Robinson, Cools, Carlisi, et al., 2012). These reports highlight the low serotonergic and low dopaminergic state in MDD, which could represent the neurochemical basis for the observed cognitive biases in MDD (Cools et al., 2011).

A substantial proportion of patients with MDD respond to pharmacological treatment with antidepressants, including serotonin-selective reuptake inhibitors (SSRI) (Carvalho, Cavalcante, Castelo, & Lima, 2007). SSRIs are thought to achieve their therapeutic effect, primarily, by modifying synaptic availability of monoamines, namely serotonin, dopamine, and norepinephrine (Malberg &

Schechter, 2005). Recent studies argue that SSRI administration in MDD results in normalization of BOLD activity in the prefrontal cortex (PFC) and amygdala (Di Simplicio et al., 2012; Godlewska et al., 2012), normalization of the the functional connectivity between PFC and both hippocampus and amygdala (McCabe et al., 2011), and enhancement of learning from positive feedback and striatal BOLD activity (Stoy et al., 2011). Reports suggest that the administration of SSRI diminishes the processing of both positive and negative feedback stimuli in healthy subjects (McCabe et al., 2010). On the other hand, SSRI administration diminishes learning from negative feedback stimuli but enhances learning from positive feedback stimuli in rats (Bari et al., 2010).

Accordingly, there is evidence that SSRI administration normalizes brain activity in key regions for learning from positive and negative feedback, and enhances learning from positive feedback. However, this only applies to healthy subjects and patients with MDD who respond to SSRI (Kennedy et al., 2001). It is estimated that SSRI administration fails to remediate MDD symptoms in about 30-50% of patients with MDD (Howland, 2008; Labermaier et al., 2013; McIntyre et al., 2014; Willner et al., 2014). Unfortunately, relatively little is known about how the response to SSRI impacts the balance between learning from positive and negative feedback in MDD.

In this study, our main aim was to investigate the effect of remediation of depressive symptoms by SSRI administration on the balance between learning

from positive and negative feedback in MDD. Using between-subjects and within-subjects designs, we conducted two experiments on patients with MDD and matched healthy control subjects. In experiment #1, we tested medication-naïve patients with MDD, SSRI-treated and responding patients with MDD, and matched healthy controls. In experiment #2, we evaluated medication-naïve MDD patients both before and 4-6 weeks after they were stabilized on SSRI regimen, and compared them to matched healthy controls who were also evaluated twice 4-6 weeks apart. All subjects were tested on a computer-based learning task that uses a mix of positive feedback and negative feedback (Bodi et al., 2009). To our knowledge, this is the first study to dissociate the effects of MDD and response to SSRI on positive and negative feedback learning in the same study.

2.3. METHODS

2.3.1. PARTICIPANTS:

Experiment #1: We recruited and tested 13 medication-naïve patients with MDD (MDD), 18 SSRI-responding patients with MDD (MDD-T) and 22 healthy control (HC) subjects (patient companions), from various psychiatric clinics, mental health care centers and primary health care centers throughout the West Bank, Palestine. All SSRI-treated and responding patients with MDD were maintained on 10-30 mg of paroxetine per day (Mean=18.333, SD=5.941) as part of their normal ongoing treatment. Inclusion criteria for HC subjects were absence of

psychiatric, neurological, or other disorders that might affect cognition. MDD-T patients' average exposure to SSRI was 12.833 (SD=18.912) months. MDD-T patients' response to SSRI was assessed using subjective reports and scores on the Beck Depression Inventory II (BDI-II).

Experiment #2: We recruited and tested 45 medication-naïve patients with MDD at baseline and 4-6 weeks after starting SSRI regimen. We also tested and retested 16 matched healthy control (HC) subjects 4-6 weeks apart. We recruited the subjects from various psychiatric clinics, mental health care centers and primary health care centers throughout the West Bank, Palestine. Medication-naïve patients that we recruited were all prescribed the SSRI paroxetine by their treating psychiatrist, and were maintained on 10-30 mg of paroxetine per day (Mean=19.78, SD=9.63). Retesting and assessment of response to paroxetine was done 4-6 weeks after initiation of treatment. Response to SSRI was defined as improvement of the BDI-II results by more than 50% from baseline. SSRI non-responders, with less than 25% decrease in BDI-II scores, 4-6 weeks after starting SSRI, were retested immediately once their treating psychiatrist recommended stopping/changing their treatment regimen. Of the recruited patients with MDD, 32 (71%) responded to SSRI, while 13 (29%) were non-responders 4-6 weeks after initiation of treatment.

All subjects were white, ranging from 18–60 years of age. Participants were group matched for age, gender and years of education, as shown in Table

2.1. All subjects underwent screening evaluations that included a medical history and a physical examination. Psychiatric assessment was conducted using an unstructured interview with a psychiatrist using the DSM-IV-TR criteria for the diagnosis of MDD (melancholic subtype), and the Mini International Neuropsychiatric Interview (MINI) (Amorim, Lecrubier, Weiller, Hergueta, & Sheehan, 1998). We recruited medication-naïve patients with MDD after meeting the DSM-IV-TR criteria for MDD and completing the MINI structured clinical interview to confirm the diagnosis and absence of comorbidities. We tested medication-naïve patients with MDD immediately prior to their initiating treatment with SSRI. Exclusion criteria for all subjects included psychotropic drug exposure, except for the SSRI paroxetine in the SSRI-treated MDD group, major medical or neurological illness, illicit drug use or alcohol abuse within the past year, lifetime history of alcohol or drug dependence, psychiatric disorders other than major depression (excepting comorbid anxiety symptoms), current pregnancy or breastfeeding. After receiving a complete description of the study, participants provided written informed consent as approved by both the Al-Quds University Ethics Committee and the Rutgers Institutional Review Board.

2.3.2. PSYCHOMETRIC AND PSYCHOPATHOLOGY TEST BATTERY

All subjects completed the validated Arabic version (Herzallah et al., 2010; Herzallah, Moustafa, Natsheh, Danoun, et al., 2013) of a battery of psychometric and psychopathology test questionnaires: Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), BDI-II (A. T. Beck, Steer, Ball, &

Ranieri, 1996), and Beck Anxiety Inventory (BAI) (A. T. Beck, Epstein, Brown, & Steer, 1988). All results are summarized in Table 2.1.

2.3.3. COMPUTER-BASED COGNITIVE TASK

Learning from Positive and Negative Feedback

Experiment #1:

Participants were administered a deterministic computer-based classification task (Bodi et al., 2009). On each trial, participants viewed one of eight images (Figure 2.1), and were asked to guess whether that stimulus predicts rainy weather (Rain, Figure 2.1) or sunny weather (Sun, Figure 2.1). For each participant, the eight images were randomly assigned to be stimuli S1-S8. On any given trial, stimuli S1, S3, S5, and S7 predicted Rain, while stimuli S2, S4, S6, and S8 predicted Sun. Stimuli S1-S4 were used in the positive feedback-learning task. Four stimuli per valence were employed in order to balance category outcome frequencies, so that one stimulus in each task would be associated with each outcome. Thus, if the participant correctly guessed category membership on a trial with either of these stimuli, a positive feedback of +25 points was received; if the participant guessed incorrectly, no feedback appeared. Stimuli S5-S8 were used in the negative feedback-learning task. Thus, if the participant guessed incorrectly on a trial with either of these stimuli, a negative feedback of –25 was received; correct guesses received no feedback.

The experiment was conducted on a Macintosh MacBook, programmed in the SuperCard language. The participant was seated in a quiet testing room at a comfortable viewing distance from the screen. The keyboard was masked except for two keys, labeled 'Sun' and 'Rain' which the participant was presented with to enter responses. At the start of the experiment, the participant read the following instructions: 'Welcome to the Experiment! You will be trained as a fortune teller to predict the weather. You will learn to do this by using cards that either predict rain or sun. Your goal is to learn which cards predict rain and which cards predict sun'. During the practice phase the participant was shown an example of a correct and an incorrect response to a sample trial in the positive feedback-learning task and an example of a correct and response to a sample trial in the negative feedback-learning task. These examples used images other than those assigned to S1–S8. The participant saw a practice image, with a prompt to choose either 'Sun' or 'Rain', and a running tally of points in the lower right corner of the screen. The tally was initialized to 500 points at the start of practice. The participant was first instructed to press the 'Sun' key, which resulted in a positive feedback of +25 and updated point tally and then the 'Rain' key, which resulted in no feedback. The participant then saw a second practice figure and was instructed first to press the 'Rain' key, which resulted in a negative feedback of –25 and updated point tally and then the 'Sun' key, which resulted in no feedback. After these two practice trials, a summary of instructions appeared: 'So . . . for some pictures, if you guess CORRECTLY, you WIN points (but, if you guess incorrectly, you win nothing). For other pictures, if you guess

INCORRECTLY, you LOSE points (but, if you guess correctly, you lose nothing). Your job is to win all the points you can and lose as few as you can. Press the mouse button to begin the experiment'. From here, the experiment began. In each trial, the participant saw one of the eight stimuli (S1-S8) and was prompted to guess whether it was a 'Sun' or a 'Rain' card. On trials in the positive feedback-learning task (with stimuli S1-S4), correct answers were rewarded with positive feedback and a gain of 25 points; incorrect answers received no feedback. On trials in the negative feedback-learning task (with Stimuli S5-S8), incorrect answers were punished with negative feedback and a loss of 25 points; correct answers received no feedback. The task contained 160 trials, distributed over 4 blocks of 40 trials. Within a block, trial order was randomized. Trials were separated by a 1-second interval, during which time the screen was blank. Within each block, each stimulus appeared 5 times. Thus, training on the positive feedback-learning task (S1-S4) and negative feedback-learning task (S5-S8) were intermixed. The no-feedback outcome, when it arrived, was ambiguous, as it could signal lack of positive feedback (if received during a trial with S1-S4) or lack of negative feedback (if received during a trial with S5-S8).

Experiment #2:

Participants were administered a computer-based similar to that used in Experiment #1, except for the use of probabilistic classification (Bodi et al., 2009). As shown in Figure 2.1, the subject is asked whether the stimulus predicts rainy weather (Rain) or sunny weather (Sun), as shown in Figure 2.1-A.

The manipulation that differentiated this task from that used in Experiment #1 is that half the four stimuli (S1-S4) were trained using only positive feedback for correct answers (S1-S2, Figure 2.1-C) and no feedback for incorrect answers (Figure 2.1-B) in 90% of the trials, while the other 10% received the opposite feedback (either positive feedback or no feedback). The same applied to stimuli that were trained using negative feedback for incorrect answers (S3-S4, Figure 2.1-D) and no feedback for correct answers (Figure 2.1-B).

2.3.4. STATISTICAL ANALYSIS

The normality of data distribution was checked using Kolmogorov–Smirnov tests. All data were normally distributed ($p>0.1$). We used mixed-design three-way ANCOVA followed by mixed-design two-way ANOVA and one-way ANOVA post-hoc tests, Tukey's Honestly Significant Difference (*HSD*) post-hoc tests and Bonferroni post-hoc tests. The level of significance was set at $\alpha=0.05$.

2.4. RESULTS

2.4.1. EXPERIMENT #1

We used one-sample t-test on the percentage of correct responses in the 4^{th} block of learning in both positive and negative feedback to ensure that subjects learned significantly better than chance in different groups. In positive feedback learning, MDD-T and HC learned significantly better than chance, with Bonferroni correction adjusted $\alpha=0.017$ to protect the level of significance (MDD-

T: $t(17)=3.264$, $p=0.005$; HC: $t(21)=9.997$, $p<0.001$), while MDD did not ($t(12)=0.925$, $p=0.373$). In negative feedback learning, all groups learned significantly better than chance, with Bonferroni correction adjusted $\alpha=0.017$ to protect the level of significance (MDD: $t(12)=7.704$, $p<0.001$; MDD-T: $t(17)=3.394$, $p=0.003$; HC: $t(11)=13.231$, $p<0.001$).

Using mixed-design three-way ANCOVA, we analyzed the data obtained from the cognitive task with group as the between-subjects variable, learning block and feedback type as within-subjects variables, BDI-II scores as a covariate, and the percentage of correct responses on positive and negative feedback as the dependent variables. There was a significant effect of group ($F(2,51)=9.433$, $p<0.001$, $\eta^2=0.270$) and block ($F(3,153)=11.880$, $p<0.001$, $\eta^2=0.189$) as illustrated in Figure 2.2. However, there was no significant effect of feedback type ($F(1,51)=1.337$, $p=0.253$). We conducted two post-hoc mixed-design two-way ANOVAs, with group as the between-subjects variable, learning block as within-subjects variable, the percentage of correct responses on positive feedback as the dependent variable in one of the ANOVAs and the percentage of correct responses on negative feedback in the other, and Bonferroni correction adjusted $\alpha=0.025$ to protect the level of significance. The positive feedback post-hoc revealed a significant effect of group ($F(2,50)=5.094$, $p=0.010$, $\eta^2=0.169$) and block ($F(3,150)=6.000$, $p=0.001$, $\eta^2=0.107$) along with an interaction between group and block ($F(6,150)=3.098$, $p=0.007$, $\eta^2=0.110$). We used four post-hoc one-way ANOVAs to explore the significant interaction between group and block,

with group as the between-subjects variable, and the percentage of correct responses on a each one of the four positive feedback learning block was the within-subjects variable, with a Bonferroni correction adjusted $\alpha=0.0125$ to protect the level of significance. One-way ANOVA and Tukey's *HSD* results are summarized in Table 2.2. The negative feedback post-hoc two-way ANOVA showed a significant effect of group ($F(2,50)=4.512$, $p=0.016$, $\eta^2=0.153$) and block ($F(3,150)=45.644$, $p<0.001$, $\eta^2=0.477$), but no interaction between group and block ($F(6,150)=2.426$, $p=0.029$). Tukey's *HSD* post-hoc test revealed a significant difference between MDD-T and both MDD and HC ($p<0.05$), but not between MDD and HC.

To investigate the balance between positive and negative feedback learning, we subtracted negative feedback learning accuracy in a particular block from that of positive feedback in the same block. Two-way ANOVA, with group as the between-subjects variable, block of learning as the within-subjects variable, and the mean difference between percentage correct responses in positive and negative feedback trials as the dependent variable, revealed a significant effect of block ($F(3,150)=11.147$, $p<0.001$, $\eta^2=0.182$) and an interaction between block and group ($F(6,150)=3.145$, $p=0.006$, $\eta^2=0.112$), but no significant effect of group ($F(2,50)=2.486$, $p=0.094$), as illustrated in Figure 2.3. We used four post-hoc one-way ANOVA and Tukey's *HSD* post-hoc analyses on each block of mean difference between percentage correct responses in positive and negative feedback trials to investigate the interaction between block and

group, with group as the between-subjects variable and the mean difference between percentage correct responses in positive and negative feedback trials as the dependent variable. ANOVA and Tukey's *HSD* results are reported in Table 2.3.

2.4.2. EXPERIMENT #2

We used one-sample t-test on the percentage of correct responses in the 4th block of learning in both positive and negative feedback to ensure that subjects learned significantly better than chance in different groups. All groups learned significantly better than chance (50%) from both the positive and negative feedback at test and retest (p<0.05).

We categorized our subjects into three groups: SSRI-responding MDD, SSRI non-responders and HC. Each subject was tested twice, 4-6 weeks apart. Using mixed-design four-way ANOVA, we analyzed the data obtained from the cognitive task with group as the between-subjects variable, learning block, feedback type, and test-session as within-subjects variables, and the percentage of correct responses on positive and negative feedback as the dependent variables. There was a significant effect of group ($F(2,58)=22.54$, p<0.001, $\eta^2=0.437$), feedback type ($F(1,58)=4.11$, $p=0.047$, $\eta^2=0.066$) and block ($F(3,174)=75.36$, p<0.001, $\eta^2=0.565$), along with a significant interaction between feedback type and group ($F(2,58)=5.91$, $p=0.005$, $\eta^2=0.169$), block and group ($F(6,174)=3.16$, $p=0.006$, $\eta^2=0.098$), and test-session, feedback type and group ($F(2,58)=5.49$, $p=0.007$, $\eta^2=0.159$).

To explore the significant interaction between the test-session, feedback type and group, we conducted three repeated-measures ANOVA tests (one test per group), with test session and feedback type as the within-subjects variables, and the accuracy in learning accuracy in 4th block of positive and negative feedback as the dependent variables. In the SSRI-responder repeated-measures ANOVA, there was a significant effect of feedback type ($F(1,31)=18.65$, $p<0.001$, $\eta^2=0.376$) and a significant interaction between test-session and feedback type ($F(1,31)=8.38$, $p=0.007$, $\eta^2=0.213$). However, repeated-measure ANOVA tests on SSRI non-responders and HC did not reveal any significant results (Figure 2.4). To explore the interaction between test-session and feedback type in SSRI responders, we used two paired-samples t-tests to compare the learning accuracy in 4th block of positive and negative feedback across test-sessions. There was a significant effect of test-session on learning from negative feedback ($t(31)=2.64$, $p=0.013$, Cohen's $d=0.47$, Figure 2.4-A) but not from positive feedback ($t(31)=-1.93$, $p=0.062$, Cohen's $d=0.34$, Figure 2.4-B).

To explore the interaction between feedback type and group, we used four one-way ANOVA tests (one per test-session), with group as the between-subjects variable, and learning accuracy in 4th block of positive and negative feedback as the dependent variables. There was a significant effect of group on learning from positive feedback in the 4th block at baseline ($F(2,58)=13.43$,

p<0.001, η^2=0.32) and retesting (F(2,58)=11.94, p<0.001, η^2=0.29). Also, there was a significant effect of group on learning from negative feedback in the 4th block at baseline (F(2,58)=5.07, p=0.009, η^2=0.15) and retesting (F(2,58)=6.60, p=0.003, η^2=0.18). Tukey's *HSD* post-hoc test revealed significant differences between HC at the two MDD groups in learning from positive feedback at both baseline and retest (p<0.05). However, at baseline, SSRI non-responders were significantly different from both HC and SSRI-responders in learning from negative feedback. At retest, there was a significant difference between HC and both SSRI-responders and non-responders in learning from negative feedback (p<0.05).

Similar to Experiment #1, we investigated the balance between positive and negative feedback learning by subtracting negative feedback learning accuracy in a particular block from that of positive feedback in the same block. Using a three-way ANOVA, with group as the between-subjects variable, block of learning and test-session as the within-subjects variables, and the mean difference between percentage optimal responses in positive and negative feedback trials as the dependent variable, revealed a significant effect of group (F(2,58)=5.91, p=0.005, η^2=0.169) and an interaction between test-session and group (F(2,58)=5.49, p=0.007, η^2=0.159). Tukey's *HSD post-hoc* test revealed a significant difference between SSRI-responders and HC (p<0.05). To explore the interaction between test-session and group, we used three paired-samples t-tests (one test per group) to compare the 4th blocks of the difference between

positive and negative feedback learning accuracy. There was a significant effect of test-session only on the SSRI-responders group ($t(31)=-2.89$, $p=0.007$, Cohen's $d=0.34$, Figure 2.5).

2.5. CONCLUSIONS

In Experiment #1, we have three main findings. First, SSRI-treated patients with MDD were less sensitive to negative feedback than either medication-naïve patients with MDD or HC subjects, based on their accuracy in the cognitive task. Second, both medication-naïve and SSRI-treated patients with MDD were less sensitive to positive-feedback than HC subjects. Third, a comparison of subjects' learning from positive versus negative feedback, showed that both the HC and SSRI-treated MDD groups conform to Kahneman and Tversky's (1979) Prospect Theory, which expects losses (negative feedback) to loom psychologically larger than gains (positive feedback) (Kahneman & Tversky, 1979). In contrast, the medication-naïve MDD patients violate Prospect Theory by being significantly more biased towards negative. In experiment #2, we replicate the three main findings of experiment #1 using a within-subjects design, and further add that SSRI administration significantly modulates both learning from positive and negative feedback in responders. Furthermore, we report that potential SSRI responders and non-responders learn significantly differently from negative feedback before administration of SSRIs.

2.6 LIMITATIONS AND FUTURE DIRECTIONS

An important limitation of the current study is that the different severity of depressive symptoms in SSRI-treated vs. medication-naïve patients in Experiment #1 might have contributed to the difference between the groups. We did not have access to SSRI-treated patients' BDI-II scores before they were placed on the SSRI regimen. Therefore, it is impossible to conclude that the observed behavioral effects originate from the medication alone. However, we added BDI-II scores as a covariate in our main analysis in Experiment #1, and matched the different groups on a number of psychometric measures. Further, we replicated the findings of Experiment #1 using a within-subjects design in Experiment #2.

Another major limitation of the current study is the low number of recruited subjects. However, given that the focus of the current study is cognitive function assessment, all *a priori* power analyses indicated the need for 14 subjects per group to achieve power levels higher than 90%, which confirms the sufficiency of the number of subjects in the analysis of our primary cognitive results. Unfortunately, it was not possible to recruit a sufficient number of SSRI non-responders. Future studies, however, should address this limitation and better control for possible confounding variables.

CHAPTER 3

Depression Impairs Learning, whereas the Selective Serotonin Reuptake Inhibitor, Paroxetine, Impairs Generalization in Patients with Major Depressive Disorder

3.1. OVERVIEW

To investigate how medication status and task demands affect cognition in Major Depressive Disorder (MDD), we used between-subjects and within-subjects designs to evaluate patients with MDD and matched healthy controls. All subjects were administered a computer-based cognitive task with two phases, an initial phase in which a sequence is learned through positive feedback (which our prior studies suggest is striatal-dependent), followed by a generalization phase that involves a change in the context where learned rules are to be applied (which our prior studies suggest is hippocampal-region dependent). Using between-subjects design (Experiment #1), we tested medication-naïve patients with MDD, medicated patients with MDD receiving and responding to the Selective Serotonin Reuptake Inhibitor (SSRI) paroxetine, and healthy controls. Medication-naïve MDD patients were slow to learn the initial sequence but were normal on subsequent generalization of that learning. In contrast, medicated patients learned the initial sequence normally, but were impaired at the

generalization phase. Experiment #2 utilized a within-subjects design, where we tested medication-naïve MDD patients both before and 4-6 weeks after they were stabilized on SSRI regimen. We assessed response to SSRI administration 6 weeks after diagnosis. Healthy control subjects were also tested twice at the same time interval. Healthy subjects exhibited significantly better sequence-learning and generalization than patients with MDD at both baseline and retest. However, the effect sizes of these differences differed between baseline and retest. We argue that these data suggest (i) an MDD-related impairment in striatal-dependent sequence-learning which can be remediated by SSRIs and (ii) an SSRI-induced exacerbation of impairment in hippocampal-dependent generalization of past learning to novel contexts.

3.2. INTRODUCTION

MDD is a condition characterized by a long-lasting depressed mood or marked loss of interest or pleasure in all or nearly all activities (Belmaker & Agam, 2008). Relatively little is known about the effects of MDD on striatal-based learning, although it is well known that the striatum is a key brain region disrupted in MDD (Dunlop & Nemeroff, 2007; Nestler & Carlezon, 2006; D. J. Nutt, 2006; Perona et al., 2008). Converging evidence from the literature confirms the involvement of the basal ganglia dopaminergic system in the pathophysiology and cognitive changes related to MDD. Studies have reported reductions in the size of the striatum in patients with MDD (Lorenzetti et al.,

2009) that have been linked to impairments in motor sequence learning (Naismith, Hickie, Ward, Scott, & Little, 2006).

However, because psychomotor retardation is a common feature of MDD (Buyukdura, McClintock, & Croarkin, 2011), it is unclear whether such deficits reflect learning deficits or just motor slowing. The present study addresses this issue by using a computer-based test of sequence learning (Shohamy et al., 2005; Nagy et al., 2007a). In this task, participants learn to execute a chain of actions leading to positive feedback. The chain is gradually lengthened until a complete sequence is learned. Subjects are first trained to learn A→positive-feedback, followed by B→A→positive-feedback, and so forth until a full sequence is acquired (D→C→B→A→positive-feedback). Learning is evaluated by the number of errors that are committed at each stage of the task, and therefore, learning does not depend on response speed. Converging evidence from the literature suggests that the basal ganglia dopaminergic system is vital for this type of positive feedback-based sequence learning (Haber & Knutson, 2010; Schultz, 1997). For example, a previous study from our group utilizing the same task as in the current study showed that medication-naïve patients with PD were significantly impaired on sequence-learning (H. Nagy et al., 2007). A different study showed that dopaminergic medication (L-dopa) remediated this deficit (Shohamy, Myers, Grossman, Sage, & Gluck, 2005).

The task also contains a subsequent generalization phase, designed to

test the generalization of learned stimulus-response associations. In this phase, subjects are presented with a choice between the door that was previously correct in this room, a door that was previously-correct in a different room, and a "distractor" door that was never correct in any room. To successfully pass this phase, subjects are required to apply their previously learned door-room associations from the sequence-learning phase to new contexts with novel distractors. Animal and human work has shown that the medial temporal lobe plays an important role in generalization of learning over multiple contexts (Eichenbaum, Schoenbaum, Young, & Bunsey, 1996; Myers et al., 2002; Myers, Shohamy, Gluck, Grossman, Onlaor, et al., 2003). Specifically, a previous study using this task found that PD patients with nigrostriatal dysfunction (but presumed intact medial temporal lobe function) showed no impairment in generalization, while those with amnestic mild cognitive impairment (aMCI, and presumed medial temporal lobe dysfunction) did show an impairment (H. Nagy et al., 2007), consistent with the view that the positive feedback-based sequence learning phase is striatal-dependent while the subsequent generalization phase is hippocampal/medial temporal lobe dependent. This finding is important because patients with MDD are also thought to have a smaller-than-average hippocampus, a key brain region for memory formation located within the medial temporal lobe (Campbell & Macqueen, 2004; MacQueen et al., 2003; Vakili et al., 2000; Vythilingam et al., 2004). Moreover, studies indicate that medication-free patients with MDD are impaired on hippocampal-dependent memory measures such as the delayed paragraph recall of Wechsler Memory Scale and the

Selective Reminding Test (Austin, Mitchell, & Goodwin, 2001; Vythilingam et al., 2004). Thus, we seek to address how MDD influences hippocampal-based generalization, in addition to striatal-based sequence learning. Of note, a previous study on this task found a sequence-learning deficit but spared generalization in patients with MDD (Polgar et al., 2007). However, this experiment did not control for medication use and so it is still not clear how antidepressants affect cognitive performance. However, it has not been sufficiently tested what SSRIs would do for medial temporal lobe dependent learning using sensitive measures of cognitive function similar to the task we use in our current study.

Thus, it remains unclear how MDD and medication use influences cognitive function on a learning and generalization task. To our knowledge, few studies have conducted thorough assessments of striatal- and hippocampal-dependent learning-and-memory function on patients with MDD both with and without SSRI treatment. In this study, we investigated the cognitive correlates of striatal and hippocampal function in two groups of patients with MDD, those that were medication-naïve and those that have been treated using SSRIs, as well as healthy matched controls. We predicted that medication-naïve patients with MDD would resemble medication-naïve patients with PD, being impaired at initial sequence learning, whereas SSRI treated patients would not show this impairment. Given past studies showing ambiguous effects of SSRIs on medial temporal lobe dependent processes (Carlini et al., 2012; Igelstrom & Heyward,

2012; Sass & Wortwein, 2012; Vythilingam et al., 2004), it was not clear *a priori* what, if any, effect SSRIs would have on the generalization phase of this task. As described below, our results indicated that while patients treated with SSRIs did not have a sequence-learning deficit, these medications led to an additional and heretofore unknown impairment in generalization of this learning.

3.3. METHODS

3.3.1 PARTICIPANTS

Experiment #1: We recruited 16 medication-naïve patients with MDD (MDD), 15 SSRI-responding patients with MDD (MDD-T), and 25 HC subjects, from various psychiatric clinics, mental health care centers and primary health care centers throughout the West Bank, Palestine. All SSRI-treated patients with MDD received 10-30 mg of paroxetine per day (M=16.67, SD=7.78) as part of their normal ongoing treatment. Inclusion criteria for HC subjects were absence of any psychiatric or other disorders that might affect cognition. MDD-T patient average exposure to SSRIs was 35.35 (SD=43.96) months. MDD-T patients' response to SSRIs was assessed using subjective reports and scores on the Beck Depression Inventory II (BDI-II).

Experiment #2: We recruited and tested 31 medication-naïve patients with MDD at baseline and 4-6 weeks after starting SSRI regimen. We also tested and retested 15 matched healthy control (HC) subjects 4-6 weeks apart. We

recruited the subjects from various psychiatric clinics, mental health care centers and primary health care centers throughout the West Bank, Palestine. Medication-naïve patients that we recruited were all prescribed the SSRI paroxetine by their treating psychiatrist, and were maintained on 10-30 mg of paroxetine per day (Mean=18.75, SD=10.20). Retesting and assessment of response to paroxetine was done 4-6 weeks after initiation of treatment. Response to SSRIs was defined as improvement of BDI-II results by more than 50% from baseline. SSRI non-responders, with less than 25% decrease in BDI-II scores, 4-6 weeks after starting SSRIs, were retested immediately once their treating psychiatrist recommended stopping/changing their treatment regimen. Of the recruited patients with MDD, 19 (61%) responded to SSRI, while 12 (39%) were non-responders 4-6 weeks after initiation of treatment. A subgroup of 6 of the SSRI non-responders and 7 of the SSRI responders failed to pass the learning criterion of the computer-base task. Therefore, their data were dropped from the study.

All subjects were white, ranging from 18–60 years of age. Participants were group matched for age, gender and years of education, as shown in Table 3.1. All subjects underwent screening evaluations that included a medical history and a physical examination. Psychiatric assessment was conducted using an unstructured interview with a psychiatrist using the DSM-IV-TR criteria for the diagnosis of MDD, and the Mini International Neuropsychiatric Interview (MINI) (Amorim et al., 1998). Exclusion criteria for all subjects included psychotropic

drug exposure, except for the SSRI paroxetine in the SSRI-treated MDD group, major medical or neurological illness, illicit drug use or alcohol abuse within the past year, lifetime history of alcohol or drug dependence, psychiatric disorders other than major depression (excepting comorbid anxiety symptoms), current pregnancy or breastfeeding. After receiving a complete description of the study, participants provided written informed consent as approved by the Al-Quds University Ethics Committee and the Rutgers Institutional Review Board.

3.3.2. NEUROPSYCHOLOGICAL TEST BATTERY

In both experiments, subjects completed the Arabic version (Inzelberg et al., 2007) of a battery of neuropsychological test questionnaires: Mini-Mental Status Examination (MMSE (Folstein et al., 1975)), BDI-II (A. T. Beck et al., 1996), Beck Anxiety Inventory (BAI) (A. T. Beck et al., 1988) and the digit span subtest of the Revised Wechsler Adult Intelligence Scale (WAIS-R digit span) (Burgess, Flint, & Adshead, 1992). All results are summarized in Table 3.1.

In Experiment #1, one-way ANOVAs, with a Bonferroni correction of $\alpha=0.01$ to protect the level of significance (5 comparisons), revealed a significant effect of group on BDI-II ($F(2,53)=79.65$, $p<0.001$, $\eta^2=0.75$), BAI ($F(2,53)=17.90$, $p<0.001$, $\eta^2=0.40$) and WAIS-R scores ($F(2,53)=9.22$, $p<0.001$, $\eta^2=0.26$). Tukey's *HSD* post-hoc test revealed significant differences between MDD and both MDD-T and HC in BDI-II and BAI scores, and between HC and both MDD and MDD-T in WAIS-R scores. However, BDI-II and BAI scores were

significantly correlated. Further, only BDI-II scores significantly correlated to behavioral task results. Hence, we only included BDI-II as a covariate in the analysis of cognitive data (for more details see Figure 3.3-A).

In Experiment #2, one-way ANOVAs at test and retest with a Bonferroni correction of $\alpha=0.005$ to protect the level of significance (10 comparisons), revealed a significant effect of group on BDI-II (TEST: $F(2,30)=58.92$, $p<0.001$, $\eta^2=0.80$; RETEST: $F(2,30)=44.64$, $p<0.001$, $\eta^2=0.74$), BAI (TEST: $F(2,30)=31.21$, $p<0.001$, $\eta^2=0.68$; RETEST: $F(2,30)=18.96$, $p<0.001$, $\eta^2=0.56$) and WAIS-R scores (TEST: $F(2,30)=3.68$, $p=0.037$, $\eta^2=0.20$). Tukey's *HSD* post-hoc test showed a significant difference between HC and both SSRI-responder and non-responders at baseline. At retest, each pairwise comparison between the three groups was significant. In BAI baseline scores, there was a significant difference between HC and both responders and non-responders. At retest, all pairwise comparisons between the three groups were significant except between HC and responders. WAIS-R scores were significantly different between HC and responders at baseline. At retest, there were no difference between groups. However, none of the aforementioned variables was correlates with the behavioral task results. Therefore, they were not included as covariates in subsequent analysis.

3.3.3. COMPUTER-BASED COGNITIVE TASK

Sequence Learning Followed by Generalization with a Context-Shift

We used same task as previously described by Nagy et al. 2007 (H. Nagy et al., 2007). It was run on a Macintosh computer, programmed in the SuperCard language. In this task, participants were instructed to guide an animated character (nicknamed “Kilroy”) through a sequence of four rooms with different colored doors to reach a goal point, the outside world. The rooms had a uniform white background and were drawn using perspective lines, with three black doors appearing on the far wall. The doors were depicted about 2″ high, the colored cards each approximately 1″ high by 0.5″ wide, and outlined in white for visual clarity. The animated figure (Kilroy) was shown to be about 1-1/2″ tall.

On each trial, Kilroy appeared in a room with three doors, each represented by a different colored card (see Figure 3.1-A). The three colored cards in each room were consistent for every participant, but no color appeared in more than one room during training. For example, room A might have red, green, and purple doors; room B might have yellow, blue, and brown doors, and so on. The colored cards marking the doors in each of six rooms were selected from a set of eighteen unique and highly discriminable colors. Assignment of colors was randomized across subjects. Spatial layout of these three colored cards on the doors (left, center, right) was randomized on each trial, so that the correct answer (left, center, right) varied across trials in a room. Thus, the color

of the card, not the location of the door, determined the correct response on each trial.

In each room, the subject used the computer mouse to move the cursor to click on one of the doors. When the subject selected a door, Kilroy would turn, walk to that door, and try to open it. If the subject's choice was incorrect, the door would be "locked", thus preventing Kilroy from opening it. In that case, he would place his hands on his hips and make a disappointed face, and the caption at the bottom of the screen would read "Locked!" (Figure 3.1-C). Kilroy would then move back to the center of the room and await the subject's next choice. If the subject's choice was correct, Kilroy would succeed in opening the door and stepping through. If this room was at the end of the sequence, Kilroy would reach the outside, at which point he would turn and give a thumbs-up sign (Figure 3.1-B); if the room was shown at an earlier stage of the sequence, Kilroy would step through into the next room (Figure 3.1-D) and, once there, would wait for further instructions (as in Figure 3.1-A). In either case (correct or incorrect response), the outcome would appear on the screen for 1 second; this was followed by a 0.33 second interval before Kilroy would appear at the bottom of the screen again, ready for new instructions. There was no limit on response times.

One trial consisted of Kilroy traversing a full sequence of rooms until (eventually) reaching the outside. The length of this sequence increased from

one to four rooms over the course of training, starting in the room leading directly to the outside world and progressively moving further inside, into the more interior rooms. A trial was scored as correct if the subject chose the correct door on the first opportunity for every room in the sequence. However, a subject could make one or more errors on a trial, by choosing an incorrect door one or more times before finally choosing the correct door, in each of one or more rooms in the sequence. This would mean that a subject could make more than one error per trial. Each learning phase continued until the subject completed four consecutive correct trials or up to a maximum of fifteen trials. If a subject failed to reach criterion within the maximum number of trials for any phase, that phase was terminated, further training and context-shift phases were skipped, and the subject proceeded directly to the last (retraining) phase of the task.

Procedure

The subject was seated in a quiet testing room at a comfortable viewing distance from the screen. Before the test, the subject was informed that the aim of the game was to help an animated figure get out of the house as many times as possible. The following instructions were shown on the screen: “Welcome to the Experiment. In this experiment, you will see a character named Kilroy who is trying to get out of the house. Each room in the house has three doors, and each door has a colored card on it. On each trial, two of the doors are locked, and one door is unlocked. In each room, click on the color card of the door that you think

is unlocked. If you are correct, Kilroy will get outside. Good luck!" The task then consisted of the following phases (Table 3.2):

1. *Practice*. The Practice Room was shown containing three colored doors ($P_1P_2P_3$) and Kilroy in his "waiting-for-instructions" position at the front bottom of the screen. If the subject chose the correct door (P_1), Kilroy would reach the outside and the trial would be concluded. Every trial terminates with Kilroy (eventually) reaching the outside. The practice phase continued until the subject made four consecutive correct trials (i.e. by choosing the correct door on the first response in each of four trials).

2. *Phase 1: Sequence training*. At this point, new instructions appeared: "You've successfully finished practice! Now Kilroy will be put in some new rooms. Again, in each room, two doors are locked and one door is unlocked. Each time, click on the door that you think is unlocked. Sometimes, Kilroy will have to go through more than one room to reach the outside. Good luck!" Kilroy then appeared in his "waiting-for-instructions" position in Room 1. This phase was identical to the practice phase, except that three new colored cards were used ($A_1A_2A_3$). Here, subjects had to learn to open the correct door (A_1, see Table 3.2). Once this was learned, phase 2 began, in which Kilroy appeared in Room 2, which contained three new colored cards; here, choice of the correct door (B_1) would lead Kilroy to Room 1, where a correct answer led him outside. Once this was learned, subjects worked through phase 3 (door C_1 in Room 3 leading to Room 2 and so on) and phase 4 (door D_1 in Room 4 leading to Room

3 and so on) until, by the end of phase 4, subjects should have been choosing the correct door in each room: $D_1 \rightarrow C_1 \rightarrow B_1 \rightarrow A_1 \rightarrow$positive-feedback.

3. *Phase 2: Generalization with Context-shift*. Next came a generalization with context-shift phase, unsignaled to the subject. At the start of a trial, Kilroy appeared in Room 4. Correct responses would, as usual, allow him to progress through the sequence of rooms and reach the outside. However, now the three cards included one that was previously correct in that room, one that was previously correct in a different room, and a distractor that was never correct in any room. Thus, in Room 2, Kilroy might have been presented with a choice between card B_1, card A_1, and card C_3. Card B_1 was the correct choice and should have been chosen by a subject who had learned the sequence; that is, what choice to make at each step in the sequence. But a subject who had merely learned non-sequential stimulus-response associations might have chosen A_1, since that was a stimulus that had been directly associated with positive feedback in the past. The generalization with context-shift phase contained six trials, each trial consisting of a passage through the usual four rooms. This phase enabled dissociation between-subjects who learned the correct sequence (i.e., what choice to make at each step in the sequence) versus subjects who merely learned non-sequential stimulus-response associations (i.e., knowing a stimulus has been associated with positive feedback regardless of the sequence). Participants who broadly generalize from the distractor doors that are correct in other rooms, will be expected to make more errors.

4. *Phase 3: Retraining*. The final phase was a retraining phase, in which subjects were required to learn a new room with three new colored cards ($Y_1Y_2Y_3$), one of which led directly to the outside. The purpose of this phase was to determine whether any learning deficits observed on the sequence learning or generalization phase were due to fatigue effects or other non-associative factors.

At the end of the test, the subject was shown a screen reporting the total number of trials on which Kilroy had gotten outside, which was equal to the total number of trials (regardless of intervening errors).

3.3.4 STATISTICAL ANALYSIS:

The normality of data distribution was checked using Kolmogorov–Smirnov tests. All data were normally distributed ($p>0.1$). Mixed-design ANCOVA using SPSS 20 was used to compare HC subjects, medication-naïve and SSRI-treated patients with MDD, followed by planned one-way ANOVAs and Tukey's Honestly Significant Difference (*HSD*) post-hoc tests. Spearman's rho correlation coefficients were calculated between test performance and neuropsychological measures. The level of significance was set at $\alpha=0.05$.

3.4. RESULTS

3.4.1. EXPERIMENT #1

3.4.1.1. Behavioral Results

Five participants failed to complete one of the steps of the sequence-learning phase within the maximum allowed trials (2 of 25 HC, 2 of 16 medication-native MDD, and 1 of 15 SSRI-treated MDD). Data from these subjects were excluded from subsequent analyses.

We conducted mixed-design ANCOVA, with group as the between-subjects variable, learning phase (sequence-learning, context-shift generalization and retraining) as the within-subjects variable, BDI-II results as a covariate (there was a significant correlation between BDI-II scores, and the number of errors in the sequence-learning phase, see *3.4 Correlational Studies*), and number of errors in sequence-learning, context-shift generalization and retraining as the dependent variable.

The ANCOVA revealed a significant effect of group ($F(2,47)=6.282$, $p=0.004$, $\eta^2=0.211$) and learning phase ($F(2,94)=16.018$, $p<0.001$, $\eta^2=0.254$). In addition, there was a significant interaction between group and learning phase ($F(4,94)=9.835$, $p<0.001$, $\eta^2=0.295$) as well as between BDI-II scores and learning phase ($F(4,94)=3.633$, $p=0.030$, $\eta^2=0.072$). Although there was a significant correlation between BDI-II scores and the number of errors in the sequence-learning phase, BDI-II did not have a significant effect on the between-subjects effects of the covariance analysis ($p>0.05$), and was dropped from subsequent analyses.

To further investigate the differences between groups and within phases, we conducted one-way ANOVA on the sequence-learning, generalization and retraining phases separately, with a Bonferroni correction of α=0.017 to protect the level of significance (for three comparisons):

Phase 1: Sequence Learning

Using one-way ANOVA, with group as the independent variable, and the total number of errors in the sequence-learning phase (A-D, see Table 3.2) as the dependent variable, we found a significant effect of group ($F(2,48)=8.64$, $p=0.001$, $\eta^2=0.26$). Tukey's *HSD* post-hoc test revealed that medication-naïve patients with MDD made significantly more errors than either SSRI-treated patients with MDD or HC ($p<0.05$, Figure 3.2-A).

Phase 2: Generalization with Context-Shift

One-way ANOVA, with group as the independent variable, and the total number of errors in the context-shift generalization phase as the dependent variable, revealed significant effect of group ($F(2,48)=10.60$, $p<0.001$, $\eta^2=0.31$). Follow up post-hoc analysis using Tukey's *HSD* post-hoc test showed that SSRI-treated patients with MDD made significantly more errors than either medication-naïve patients with MDD or HC ($p<0.05$, Figure 3.2-B).

Phase 3: Retraining

One-way ANOVA, with group as the independent variable, and the total number of errors in the retraining phase as the dependent variable, showed no effect of group ($F(2,48)=0.43$, $p=0.64$).

3.4.1.2. Correlational studies

Spearman's rho correlation coefficients were calculated between test performance on our sequence learning task and neuropsychological measures. There was a significant correlation between BDI-II scores, and the number of errors in the sequence-learning phase. Specifically, the more depressed subjects were, the worse they did at the sequence-learning phase (Spearman's rho, r_s=0.410, N=51, *p*=0.003, Figure 3.3-A). However, the same correlation did not hold significance when subjects were distributed to their corresponding groups (HC: Spearman's rho, r_s=0.036, N=23, *p*=0.871; medication-naïve MDD: Spearman's rho, r_s=−0.373, N=14, *p*=0.188; SSRI-treated MDD: Spearman's rho, r_s=0.139, N=14, *p*=0.636). The negative correlation between WAIS-R digit-span results, which represent a measure of short-term memory, and the number of errors on the generalization phase, approached significance; specifically, better working memory scores were associated with better performance (fewer errors) on the generalization phase of the task (Spearman's rho, r_s=−0.246, N=51, p=0.082, Figure 3.3-B). When subjects were split into groups, correlations between WAIS-R digit-span results and the number of errors on the generalization phase only in HC and SSRI-treated patients with MDD were approaching significance (HC: Spearman's rho, r_s=−0.304, N=23, *p*=0.159; medication-naïve MDD: Spearman's rho, r_s=0.317, N=14, *p*=0.270; SSRI-treated MDD: Spearman's rho, r_s=0.438, N=14, *p*=0.119).

3.4.2. EXPERIMENT #2

Twelve participants failed to complete one of the steps of the sequence-learning phase within the maximum allowed trials (7 of 19 SSRI-responders MDD, and 6 of 12 SSRI non-responders). Data from these subjects were excluded from subsequent analyses.

We conducted mixed-design ANOVA, with group (MDD SSRI-responder, MDD SSRI non-responder and HC) as the between-subjects variable, learning phase (sequence-learning, context-shift generalization and retraining) and test-session as the within-subjects variables and number of errors in sequence-learning, context-shift generalization and retraining as the dependent variable. There was a significant effect of group ($F(2,30)=19.76$, $p<0.001$, $\eta^2=0.57$), learning phase ($F(2,60)=63.08$, $p<0.001$, $\eta^2=0.68$), and a significant interaction between learning phase and group ($F(2,60)=8.94$, $p<0.001$, $\eta^2=0.37$), learning phase and test-session ($F(2,60)=4.47$, $p=0.016$, $\eta^2=0.13$), and learning phase, test-session and group ($F(2,60)=3.08$, $p=0.023$, $\eta^2=0.17$). Tukey's *HSD* post-hoc test revealed a significant difference between HC and both SSRI-responders and non-responders.

To investigate the interaction between learning phase and test-session, we used nine paired-samples t-test on each one of the learning phases per group, with test-session as the within-subjects variable, and the number of errors

in each phase as the dependent variables. The tests revealed no significant effects.

We explored the interaction between learning phase, test-session and group using six one-way ANOVAs on each learning phase per session, with group as the between-subjects variable, and the number of errors in each phase as the dependent variables. There was a significant effect of group on the number of errors in the sequence-learning phase at baseline ($F(2,30)=9.76$, $p=0.001$, $\eta^2=0.39$, Figure 3.4-A) and retest ($F(2,30)=4.88$, $p=0.015$, $\eta^2=0.24$, Figure 3.4-A). Tukey's *HSD* post-hoc test revealed a significant difference between HC and both MDD groups at baseline, and between HC and SSRI non-responders at retest ($p<0.05$). Further, there was a significant difference between groups in the number of errors in the generalization phase at baseline ($F(2,30)=4.28$, $p=0.023$, $\eta^2=0.22$, Figure 3.4-B) and retest ($F(2,30)=11.26$, $p<0.001$, $\eta^2=0.43$, Figure 3.4-B). Tukey's *HSD* post-hoc test showed a significant difference between HC and SSRI-responders at baseline, and between SSRI-responders and both HC and SSRI non-responders at retest ($p<0.05$).

3.5. CONCLUSIONS

The present study investigated the effects of MDD and SSRI administration on sequence learning phase and generalization. In Experiment

#1, as predicted, medication-naïve patients with MDD were impaired on the initial sequence-learning phase of the task. This impairment was not present in the paroxetine-treated MDD group. On the other hand, paroxetine-treated patients with MDD, but not medication-naïve patients with MDD, showed impairment on the generalization phase in which the previously learned rules needed to be applied in a novel context, a function that has been attributed to the medial temporal lobe in a previous study using this task (H. Nagy et al., 2007). In Experiment #2, both SSRI-responder and non-responder patients with MDD were more impaired in sequence learning than HC at baseline and retest 4-6 weeks after MDD patients received SSRI. However, SSRI administration in SSRI-responders partially remediated the sequence-learning impairment more than what was observed in non-responders. In generalization, SSRI-responders showed broader generalization than non-responders and HC at baseline. SSRI administration exacerbated generalization impairment (broader generalization) only in SSRI-responders. In SSRI-responders, the effect size of difference in sequence-learning accuracy was larger at baseline than at retest, while in generalization, the effect size was larger at retest than baseline.

3.6. LIMITATIONS AND FUTURE DIRECTIONS

An important limitation of the current study is that the different severity of depressive symptoms in SSRI-treated vs. medication-naïve patients might have

contributed to the difference between the groups in Experiment #1. We did not have access to SSRI-treated patients' BDI-II scores before they were placed on the SSRI regimen. Therefore, it is impossible to conclude that the observed behavioral effects originate from the medication alone. However, we matched the different groups on almost all measures of neuropsychological and neuropathology tests we used in this study. Further, we used the same cognitive task in a within-subjects design to avoid the effect of this variable.

Another limitation of the current study is the low number of recruited subjects. This becomes evident in the correlational analyses in Experiment #1, where we collapsed all groups together to investigate correlations within the larger group. Further, Experiment #2 also included a limited number of subjects. However, given that the focus of the current study is task-measured cognitive function, all *a priori* power analyses indicated the need for 14 subjects per group to achieve power levels higher than 90%, which confirms the sufficiency of the number of subjects in the analysis of our primary cognitive results in Experiment #1. Future larger studies, however, should address these imitations and better control for possible confounding variables. Despite these power limitations, we found a double dissociation between medication naïve and SSRI-treated patients with MDD in learning and generalization.

In sum, our results show that SSRI have both enhancing and deleterious effects on cognition in MDD. To our knowledge, this is the first study to

dissociate the effects of MDD and SSRI treatment on cognitive function. Our results examine the effects of chronic (longer than eight weeks) administration of SSRI. However, there is still much to explore regarding the time course of the effects of SSRI on cognition, and how this time course might relate to the time course of remediation of depressive symptoms. Moreover, given the heterogeneity of MDD and the wide range of individual differences among people suffering from MDD, further research is needed to better characterize the cognitive correlates of various subcategories of MDD. Additional research is also needed to study other antidepressants in use, such as selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and dopamine agonists. In addition, the cognitive correlates of other treatment modalities, such as cognitive behavioral therapy, repetitive TMS, and electroconvulsive therapy, and how that might interact with antidepressant treatment regimen also needs further investigation.

CHAPTER 4

Dopamine Transporter 3'-UTR VNTR Polymorphism Modulates Learning from Positive and Negative Feedback in Healthy Subjects and Patients with Major Depressive Disorder

4.1. OVERVIEW

Understanding the impact of genetic variations in the dopaminergic system is key for clarifying how such variations contribute to individual differences in cognition, as well as to risk factors for mental disorders and differential responses to therapy. To examine the influence of the 3' variable number of tandem repeats (VNTR) polymorphism in the dopamine transporter gene (DAT1) on cognitive function, we used a probabilistic category-learning task that allowed for dissociation between the acquisition of positive and negative feedback. Of note, the DAT1 polymorphism influences expression of the DAT protein and ultimately dopamine levels in the striatum, and previous research has shown that variations in dopamine levels can influence whether one learns more from positive or negative feedback. We tested racially homogenous, healthy volunteers as well as SSRI-treated and responding patients with Major Depressive Disorder (MDD) and grouped them according to DAT1 VNTR genotype into 9-repeat carriers and 10-repeat homozygotes. Both healthy and

MDD carriers of the 9-repeat allele, who should express less DAT1 and thus have higher levels of dopamine, were more efficient in learning from positive feedback. On the other hand, among healthy subjects, there was no difference between genotypes in learning from negative feedback. Overall, patients with MDD learned significantly less well than healthy subjects from both positive and negative feedback. These results contribute to a growing body of data that implicates the dopaminergic system in striatal-dependent feedback-based learning and the pathogenesis of MDD, and add weight to the proposition that individual differences in cognition have a strong genetic basis. Future work is needed to focus on studying the effect of this polymorphism on cognitive function in medication-naïve patients with MDD, and link that to future response to SSRIs.

4.2. INTRODUCTION

Understanding variations in dopaminergic function can shed light on its contribution to individual differences in cognitive function. Various direct and indirect approaches have been used to measure dopamine levels in animals, including genetic approaches to modulate enzymes/proteins that clear dopamine from the synapse (Gainetdinov, Fumagalli, Jones, & Caron, 1997; Saha et al., 2014). In human studies, however, few of these methods are applicable because of technical and ethical limitations. Aside from measuring the concentration of dopamine metabolites in the plasma (Herbert, Kuiperij, Bloem, & Verbeek, 2013), various studies have examined the influence of the naturally occurring 3' variable

number of tandem repeats (VNTR) polymorphism in the dopamine transporter gene (DAT1) (Byerley, Hoff, Holik, Caron, & Giros, 1993; Vandenbergh et al., 1992). Given the key role of the dopamine transporter in clearing dopamine from synapses in the striatum, functional genetic variations (polymorphisms) in the DAT1 gene can influence expression of the dopamine transporter protein and ultimately dopamine levels in the striatum (Fuke et al., 2001; Mill, Asherson, Browes, D'Souza, & Craig, 2002). In particular, subjects who carry a 9-tandem repeat DAT1 allele express lower levels of the dopamine transporter protein and thus exhibit *higher* levels of striatal dopamine (lower dopamine clearance). On the other hand, homozygotes of the 10-repeat allele express higher levels of the dopamine transporter, and therefore have *lower* levels of striatal dopamine (higher dopamine clearance) (Fuke et al., 2001; Mill et al., 2002; van de Giessen et al., 2009). See Figure 4.1 for a schematic illustration of dopamine transporter synaptic location and DAT1 variations.

Several previous studies have investigated the role of the VNTR DAT1 polymorphism in positive feedback learning (Aarts et al., 2010; Wittmann, Tan, Lisman, Dolan, & Duzel, 2013). Healthy carriers of the DAT1 9-repeats show enhanced positive feedback associative learning, implicit sequence learning, and risk-taking behavior when compared to 10-repeat homozygotes (Aarts et al., 2010; Heitland et al., 2012; Simon et al., 2011). In contrast, carriers of 10-repeat exhibit higher levels of perseveration on previously selected wrong choices (den Ouden et al., 2013). Imaging studies show that the DAT1 VNTR polymorphism is

associated with differences in activation in the ventral and dorsal striatum during positive feedback anticipation (Aarts et al., 2010; Wittmann et al., 2013). However, few studies have explored the effects of the DAT1 VNTR polymorphism on other learning processes, such as learning from negative feedback. The effect of negative feedback on dopaminergic activity is controversial (Marinelli & McCutcheon, 2014). Studies have found that learning from negative feedback was significantly higher in 10-repeat carriers (Wittmann et al., 2013). Unfortunately, a very limited number of studies have investigated the effect of the DAT1 VNTR polymorphism on learning from both positive and negative feedback in the same paradigm (Bodi et al., 2009). This limits the ability to understand the interaction between positive and negative feedback learning within each subject.

Previous reports have highlighted the role of polymorphisms in the dopamine genes in increasing risk for developing MDD. Converging evidence suggests that the VNTR DAT1 polymorphism, which regulates the availability of striatal dopamine, plays a role in the pathogenesis of MDD (Kirchheiner et al., 2007; Ueno, 2003). Further, carriers of the 10-repeat polymorphism exhibit faster response to antidepressants than 9-repeat homozygotes (Kirchheiner et al., 2007). Unfortunately, no previous studies have investigated the effect of DAT1 VNTR polymorphism on cognitive function in patients with MDD.

In this study, our main aim was to investigate the effect of the DAT1 VNTR polymorphism on learning from positive and negative feedback in both healthy subjects and SSRI-responding MDD patients. We utilized a computer-based learning task that uses a mix of positive and negative feedback (Bodi et al., 2009).

4.3. METHODS

4.3.1 PARTICIPANTS:

Experiment #1: We recruited and tested 145 (91 females) healthy undergraduates at Al-Quds University, Abu Dis, Palestine. All subjects were white, ranging from 18–25 years of age. Subjects were categorized according to their DAT1 VNTR genotype to 9-repeat carriers (82 subjects (55 females)) and 10-repeat homozygotes (63 subjects (36 females)). Participants were group matched for age, gender and years of education, as shown in Table 4.1. All subjects underwent screening evaluations that included a medical history and a brief physical examination. Psychiatric assessment was conducted using an unstructured interview with a psychiatrist using the DSM-V criteria, and the Mini International Neuropsychiatric Interview (MINI) (Amorim et al., 1998). Exclusion criteria included current or previous neurological or psychiatric disease, psychotropic drug exposure, major medical or neurological illness, illicit drug use or alcohol abuse within the past year, lifetime history of alcohol or drug dependence, psychiatric disorders, current pregnancy or breastfeeding.

Experiment #2: We recruited and tested 38 (18 females) SSRI-responding patients with MDD (MDD-T) from various psychiatric clinics, mental health care centers and primary health care centers throughout the West Bank, Palestine. All subjects were white, ranging from 18–69 years of age. Participants were group matched for age, gender and years of education, as shown in Table 4.1. All subjects underwent screening evaluations that included a medical history and a brief physical examination. Psychiatric assessment was conducted using an unstructured interview with a psychiatrist using the DSM-IV-TR criteria for the diagnosis of MDD (melancholic subtype), and the MINI. SSRI-treated patients with MDD received 10-30 mg of paroxetine per day (Mean=21.84, SD=7.66) as part of their normal ongoing treatment. Inclusion criteria for HC subjects were absence of any psychiatric, neurological, or other disorders that might affect cognition. MDD-T patients' average exposure to SSRIs was 32.36 (SD=44.53) months. MDD-T patients' response to SSRIs was assessed using subjective reports and scores on the Beck Depression Inventory II (BDI-II). Exclusion criteria included psychotropic drug exposure, except for the SSRI paroxetine in the SSRI-treated MDD group, major medical or neurological illness, illicit drug use or alcohol abuse within the past year, lifetime history of alcohol or drug dependence, psychiatric disorders other than MDD (excepting comorbid anxiety symptoms), current pregnancy or breastfeeding.

After receiving a complete description of the study, participants provided written informed consent as approved by both the Al-Quds University Ethics Committee and the Rutgers Institutional Review Board.

4.3.2. PSYCHOMETRIC AND PSYCHOPATHOLOGY TEST BATTERY

All subjects completed the validated Arabic version (Herzallah et al., 2010; Herzallah, Moustafa, Natsheh, Danoun, et al., 2013) of a battery of psychometric and psychopathology test questionnaires: Mini-Mental State Examination (MMSE) (Folstein et al., 1975), BDI-II (A. T. Beck et al., 1996), and Beck Anxiety Inventory (BAI) (A. T. Beck et al., 1988). All results are summarized in Table 4.1.

4.3.3 GENETIC ANALYSIS

Subjects were asked to provide a 3-5 mL blood sample for genetic analysis. The sample was obtained via venipuncture of the median cubital vein following standard procedure and observing universal safety precautions. Blood then was transferred into an EDTA tube, gently inverted a number of times, labeled with a subject ID number and date, and kept in a refrigerator at 4°C, for 48 hours before DNA extraction. Genomic DNA was extracted using the MasterPure™ Genomic DNA Purification Kit. EDTA blood samples were collected, centrifuged at 1,000 x *g* and the buffy coat was transferred to a clean eppindorf tube. RBCs were lysed at RT in excess low ionic strength buffer and samples were then centrifuged for 25 seconds at 10,000 x *g*. The supernatant

was discarded and intact WBCs were re-suspended in a second lysis buffer containing SDS and protinase K, mixed with 6M NaCl; the mixture was centrifuged for 10 minutes at 10,000 x *g* after vigorous vortex. The clean supernatant was transferred to a clean eppindorf tube and mixed with 2 vol ice cold isopropanol. DNA was precipitated after centrifugation at 14000 x g for 15 minutes. Thereafter, the DNA was washed with ice-cold ethanol, air-dried and re-suspended in sterile distilled water. All samples were stored at -30^{0}C until further testing. Purified DNA was diluted 1:50 in a buffer containing 10 mM Tris-HCL, and 1mM Na2EDTA (pH=8). Absorbance was measured at 260 nm and 280nm, using a photometer adapted for micro-samples (Gene Quant II-Pharmacia Biotech). The ratio of 260/280 was calculated to evaluate the purity of DNA in each sample. DNA concentration was calculated according to the formula: 1A unit =50 µg double-stranded DNA. The DNA concentration obtained for all samples was in the range of 0.288 – 1.029 µg/ µl. Genomic DNA was qualified by electrophoresis in 1% (w/v) Agarose prepared in Tris- Acetate DETA (TAE) using 0.5 ul of the extracted genomic DNA. PCR was performed using the AccuprimeTM Taq DNA polymerase system (Invitrogen) with the following PCR program: 94°C for 2 min, followed by 35 cycles of 94°C for 30 sec, 60°C for 30 sec, and 68°C for 1 min. The PCR products were then run out on a 2% agarose gel stained with ethidium bromide. A 100 bp DNA ladder was then used to identify the various repeat alleles by size: 9-repeat (440bp), and 10-repeat (480bp) A standard 100 bp ladder (invitrogen) was used as size marker. The primers and protocols are described below.

Gene	Polymorphism	Alleles	Genotyping technique	Fragment lengths	Primers
DAT1	3'-UTR VNTR	10-repeat	PCR	9R=440bp	5' – TGTGGTGTAGGGAACGGCCTGAG – 3'
SLC6A3		9-repeat		10R=480bp	5' – CTTCCTGGAGGTCACGGCTCAAGG – 3'

4.3.3. COMPUTER-BASED COGNITIVE TASK

Learning from Positive and Negative Feedback

Participants were administered a computer-based probabilistic classification task (Bodi et al., 2009). As shown in Figure 4.2, subjects were asked to choose whether the stimulus predicted rainy weather ('Rain') or sunny weather ('Sun'), as shown in Figure 4.2-A. The critical manipulation that differentiates this task from many previous studies of probabilistic category learning is that half the four presented stimuli (S1-S4) were trained using only positive feedback for correct answers (S1-S2, Figure 4.2-C) and no feedback for incorrect answers (Figure 4.2-B), while the other half were trained using only negative feedback for incorrect answers (S3-S4, Figure 4.2-D) but no feedback for correct answers (Figure 4.2-B). Thus, across all stimuli, the no-feedback trials are ambiguous and can occur following correct responses for negative feedback stimuli or incorrect responses for positive feedback stimuli. This made it difficult for subjects to infer the implicit meaning of the no-feedback trials and encouraged them to focus, instead, on learning from the positive and negative feedback trials. Across four blocks of 40 trials (160 trials total), subjects learned to categorize the stimuli into the two outcome categories, 'Rain' and 'Sun'. This experimental design allowed us to measure and compare individuals' sensitivity

to learning from positive feedback versus from negative feedback. Half the four stimuli were trained using only positive feedback for correct answers (S1-S2) and no feedback for incorrect answers in 90% of the trials, while the other 10% received the opposite feedback (either positive feedback or no feedback). The same applied to stimuli that were trained using negative feedback for incorrect answers (S3-S4) and no feedback for correct answers.

4.3.4. STATISTICAL ANALYSIS

The normality of data distribution was checked using Kolmogorov–Smirnov tests. In Experiment #1, some of the variables were not normally distributed ($p<0.05$). Therefore, we used the Mann-Whitney U test to compare groups. In Experiment #2, all variables were normally distributed ($p>0.1$). Therefore, we used a mixed-design ANOVA and follow up one-way ANOVAs and pairwise independent-samples t-tests with Bonferroni corrections to protect the significance level. To compare results from Experiment #1 and Experiment #2, we used the Kruskal-Wallis test along with pairwise Mann-Whitney U test with Bonferroni correction. The level of significance was set at $\alpha=0.05$.

4.4. RESULTS

4.4.1. EXPERIMENT #1

We used the Mann-Whitney U test to examine the effect of the VNTR DAT1 polymorphism on learning from both positive and negative feedback in the

4th block, which is considered the most sensitive measure of learning (Bonferroni correction α=0.025 to protect the significance level). Carriers of the 9-repeat learned from positive feedback significantly better than 10-repeat homozygotes in the 4th block (Mann-Whitney U=2043, N=145, *p*=0.005, Figure 4.3-A). Conversely, there was no difference between groups in learning from negative feedback in the 4th block (Mann-Whitney U =2525, N=145, *p*=0.756) as shown in Figure 4.3-B.

4.4.2 EXPERIMENT #2

We applied one-sample t-test on average positive and negative feedback learning to confirm that subjects in the MDD-T group learned better than chance (50%). The test revealed that on average, MDD-T subjects learned significantly better than chance from positive (t(37)=17.987, *p*<0.001) and negative feedback (t(37)=26.671, *p*<0.001) as shown in Figure 4.4-A. We also used one-sample t-test to examine the average difference between learning from positive and negative feedback across blocks against baseline (zero). Although figure 4.4-B illustrates a difference between learning bias and baseline, MDD-T subjects' learning bias did not significantly differ from zero (t(37)=-1.254, *p*=0.218) indicating that MDD-T show balanced learning from positive and negative feedback (see Chapter 2).

Mixed-design ANOVA, with feedback type and block as the within-subjects variables, genotype as the between-subjects variable, and accuracy of learning

from positive and negative feedback as the dependent variable revealed a significant effect of block ($F(3,108)=10.567$, $p<0.001$, $\eta^2=0.227$), a significant interaction between feedback type and group ($F(1,108)=6.087$, $p=0.019$, $\eta^2=0.145$), and a significant interaction between feedback type and block ($F(3,108)=2.826$, $p=0.042$, $\eta^2=0.073$). However, there was no significant effect of feedback ($F(1,36)=3.338$, $p=0.076$) or interactions between block and group ($F(3,108)=2.470$, $p=0.066$) or feedback type, block and group ($F(3,108)=0.106$, $p=0.956$). Figure 4.5 shows the MDD-T learning curves from positive feedback (Figure 4.5-A) and negative feedback (Figure 4.5-B).

To explore the interaction between feedback type and group, we used two mixed-design ANOVAs with block as the within-subjects variable, genotype as the between-subjects variable, and accuracy of learning from positive or negative feedback as the independent variables. The mixed-design ANOVA on positive feedback revealed a significant difference between carriers of the 9-repeat allele and 10-repeat homozygotes ($F(1,36)=5.585$, $p=0.022$, $\eta^2=0.136$), where 9-repeat carriers learned significantly better from positive feedback than 10-repeat homozygotes (Figure 4.5-A). However, there was no significant effect of block ($F(3,108)=2.296$, $p=0.082$) or interaction between block and genotype ($F(3,108)=1.678$, $p=0.176$). The mixed-design ANOVA of negative feedback showed a significant effect of block ($F(3,108)=26.880$, $p<0.001$, $\eta^2=0.427$), but no significant effect of genotype ($F(3,108)=0.048$, $p=0.828$) or interaction between block and genotype ($F(3,108)=1.136$, $p=0.294$), showing that 9-repeat carriers

and 10-repeat homozygotes did not learn significantly different from negative feedback (Figure 4.5-B).

4.4.3. COMPARING HEALTHY AND MDD-T LEARNING PROFILES

We used the Kruskal-Wallis test to examine the effect of the VNTR DAT1 polymorphism on learning from both positive and negative feedback in the 4th block as well as the positive-negative learning bias (difference between learning from positive and negative feedback in the 4th block) in both the healthy and MDD-T groups (Bonferroni correction α=0.017 to protect the significance level). There was a significant effect of group (healthy 9-repeats, healthy 10/10, MDD-T 9-repeats, and MDD-T 10/10) on learning from positive feedback (Kruskal-Wallis H=64.534, df=3, N=183, p<0.001), negative feedback (Kruskal-Wallis H=31.263, df=3, N=183, p<0.001), and learning bias (Kruskal-Wallis H=15.245, df=3, N=183, p=0.003). *Post-hoc* Mann-Whitney U tests (with Bonferroni correction α=0.002 to protect the significance level) revealed significant differences in all pairwise comparisons for learning from positive feedback (p<0.001) where MDD and HC were significantly different, and 9-repeat carriers and 10-repeat homozygotes were also significantly different within each group (Figure 4.6-A). Also, there were significant pairwise comparisons between MDD-T 10-repeat homozygotes and both healthy groups (p=0.001) and between MDD-T 9-repeat carriers and the two healthy groups in the negative feedback (p=0.001, Figure 4.6-B). *Post-hoc* Mann-Whitney U test showed a significant difference between

MDD-T 10-repeat homozygotes and the two healthy groups (p<0.001, Figure 4.6-C), but the rest of the comparisons did not reach statistical significance.

4.5. CONCLUSIONS

In this study, we found that the DAT1 VNTR polymorphism modulates learning from positive feedback, but not negative feedback, in both healthy subjects and SSRI-treated patients with MDD. Carriers of the DAT1 VNTR 9-repeat allele in both the healthy and MDD-T groups exhibited better learning from positive feedback than 10-repeat homozygotes. Healthy subject groups learned significantly better from positive and negative feedback than the MDD-T groups. Further, we replicated our earlier findings by showing that the MDD-T group showed balanced learning from positive and negative feedback (Herzallah, Moustafa, Natsheh, Abdellatif, et al., 2013).

To our knowledge, this is the first study to investigate the cognitive correlates of the DAT1 VNTR polymorphism in MDD. Future work is needed to focus on studying the effect of this polymorphism on cognitive function in medication-naïve patients with MDD, and link that to future response to SSRIs.

CHAPTER 5: Discussion

5.1. OVERVIEW

In the previous chapters, we found significant and comparable cognitive effects of MDD and SSRIs in responder and non-responder patients. While both SSRI responders and non-responders showed impaired learning from positive feedback before treatment, only non-responders also exhibited impaired learning from negative feedback. Only in responders, SSRI administration impaired learning from negative feedback, thereby balancing the persistent impairment in learning from positive feedback. On the other hand, MDD impaired sequence-learning in both SSRI responders and non-responders at the medication-naïve level, whereas SSRIs relatively remedied that deficit. SSRI responders were significantly more overgeneralizing than non-responders and healthy subjects at baseline. After SSRI administration, responders' overgeneralization exacerbated, while non-responders performance did not change. In this chapter, we discuss potential cognitive, neurochemical, and neuroanatomical interpretations of the reported results.

5.2. DISSOCIATING THE EFFECTS OF MDD AND SSRIS ON LEARNING FROM POSITIVE AND NEGATIVE FEEDBACK

Abnormal exaggerated reactions to negative events, and overlooking positive events are considered central features of MDD (Beats et al., 1996; Elliott et al., 1996). These abnormal responses to positive and negative feedback represent an important link between emotional and cognitive disturbances in MDD (Elliott et al., 1997; Wright & Beck, 1983), showing an increased elaboration of negative information (I.H. Gotlib, 2010), while ignoring positive information. As explained by the cognitive theory of depression (D. A. Clark & Beck, 2010), depressed people tend to demonstrate selective attention to negative information, thereby magnifying the importance and meaning placed on negative events (A. Beck, 1979; Bower, 1981). Our results show that medication-naïve patients with MDD learn from negative feedback as efficiently as HC subjects, but fail to learn from positive feedback. However, the task design we used in the current study is not the most ideal approach to delineate higher-than-normal learning from negative feedback in MDD due to a possible ceiling effect (Figure 2.2-b). Further research is needed in this domain to further investigate the differential sensitivity to negative feedback in MDD as compared to healthy subjects, and properly correlate cognitive measures with symptom distribution and severity in patients with MDD.

MDD patients' bias toward negative stimuli and away from positive ones highlights the role of serotonin in the processing of affective stimuli, inhibitory

control of behavior and adaptation to aversive events (Graeff, Guimaraes, De Andrade, & Deakin, 1996). Further, this underpins the attentional bias in MDD towards negative feedback (Harmer, Goodwin, & Cowen, 2009; Mogg, Bradley, & Williams, 1995). Lowering brain serotonin level by acute tryptophan depletion in healthy volunteers results in increased sensitivity to negative feedback without affecting positive feedback (Cools, Robinson, et al., 2008; Robinson, Cools, & Sahakian, 2012). These alterations in positive and negative feedback processing implicate a neural circuit that is composed of brain regions strongly innervated by serotonin, namely, the medial PFC and the ventral striatum (L. Clark et al., 2009).

Recent imaging studies argue that patients with MDD manifest cognitive and neurochemical dysfunction directly related to the nigrostriatal dopaminergic system (Dunlop & Nemeroff, 2007; Robinson, Cools, Carlisi, et al., 2012; Walter et al., 2007). Consistent with this, previous research has shown that the basal ganglia dopaminergic system is vital for learning to predict positive outcomes (Haber & Knutson, 2010; Schultz et al., 1997). In a previous study using a positive-negative feedback learning task (similar to the tasks we used), medication-naïve patients with Parkinson's disease learned very well from negative feedback but were impaired on positive feedback learning (Bodi et al., 2009). Our findings indicate that medication-naïve patients with MDD show similar cognitive profile to *de novo* patients with Parkinson's (Bodi et al., 2009). Both disorders were shown to suppress learning from positive feedback (Bodi et al., 2009; Henriques et al., 1994; McFarland & Klein, 2009; Robinson, Cools,

Carlisi, et al., 2012), without altering learning from negative feedback (Beats et al., 1996; Bodi et al., 2009; Elliott et al., 1997; Elliott et al., 1996). This observation might be attributed to the effect of both disorders on the striatal dopamine system (Kish et al., 1988; Walter et al., 2007). Further, there is a very high level of comorbidity between MDD and Parkinson's disease (Cummings, 1992; Leentjens et al., 2003; Schuurman et al., 2002; Veiga et al., 2009). However, it is not clear whether this overlap between the two disorders is a consequence of dopaminergic dysfunction alone, or can be attributed to deficits in other monamine systems (Delaville, Navailles, et al., 2012; Kitaichi et al., 2010). In addition, our findings suggest that SSRI-treated MDD learn significantly less from positive-feedback than HC subjects, similar to medication-naïve patients with MDD. Future studies ought to compare the cognitive correlates of SSRI administration in MDD and depression in Parkinson's disease.

Increasing the central level of serotonin by administration of SSRI counteracts negative biases in aversive learning paradigms in animals (Bari et al., 2010) as well as emotional learning paradigms in humans (Harmer 2009; (McCabe et al., 2010). Various studies show that the adminstration of SSRIs normalizes the BOLD response in the dorsomedial PFC and across the functional connectivity between PFC and both hippocampus and amygdala (McCabe et al., 2011). Hence, it has been proposed that SSRIs may ameliorate MDD sympoms by inhibiting processing of negative feedback (Boureau & Dayan, 2011; Cools et al., 2011). In agreement with these results, we found that SSRI-

treated patients with MDD are less sensitive to negative feedback as compared to both medication-naïve patients with MDD and HC subjects in both experiments #1 and #2 (in responders only) in Chapter 2.

Based on the SSRI-related suppression of negative feedback learning, we found that SSRI-treated patients with MDD expressed balanced positive-negative learning bias similar to HC subjects. This balance can be the underlying mechanism for SSRI-induced restoration of mood in patients with MDD. However, SSRI non-responders show similar balance between positive and negative feedback both at baseline and after SSRI administration. Unlike SSRI responders, non-responders often show persistently diminished striatal activity and connectivity before and after SSRI administration (Downar et al., 2013; Forgeard et al., 2011). Further, several studies have also found a positive correlation between insula activity (a cortical area with connections to both the basal ganglia and limbic system) and potential response to SSRI administration in MDD (McGrath et al., 2013). Given that the insula has repeatedly been implicated in learning from negative feedback (Garrison, Erdeniz, & Done, 2013; Liljeholm, Dunne, & O'Doherty, 2014), the suppressed learning from negative feedback we observe in non-responders at baseline might be attributed to insula activity and used to *a priori* predict response to SSRI.

It is worth noting, however, that SSRI-treated MDD (both responders and non-responders) and HC profiles are not similar. This indicates that the state of

SSRI-treated MDD is not ‘normal’ (when compared to HC), but rather balanced with less learning from both positive and negative feedback. The negative values observed in the bias graphs of HC and MDD-T groups indicated a higher sensitivity to learn slightly more quickly from negative feedback than positive feedback. This findings is in line with Kahneman’s and Tversky (1979) Prospect Theory (Kahneman & Tversky, 1979) expects that losses from negative feedback should loom larger than gains from positive feedback. Only medication-naïve MDD patients failed to conform to the Prospect Theory with significantly exaggerated bias towards negative feedback.

5.3. LEARNING AND GENERALIZATION ARE AFFECTED DIFFERENTLY BY MDD AND SSRIs

The results of our studies in Chapter 3 indicate that medication-naïve patients with MDD show a similar cognitive profile to medication-naïve patients with Parkinson’s disease. Both patient groups showed impaired learning but spared generalization (H. Nagy et al., 2007). This observation might be attributed to the effect of both disorders on striatal dopamine (Kish et al., 1988; McCabe et al., 2010; Walter et al., 2007) as well as a deficit in raphe serotonin (Gervais & Rouillard, 2000; Guiard, El Mansari, Merali, & Blier, 2008). Furthermore, there is an overlap between MDD and Parkinson’s disease, where patients with MDD are at a higher risk to develop Parkinson’s disease later in life (Leentjens et al., 2003; Schuurman et al., 2002). Further, 50% of patients with

PD develop MDD during the course of the disease (Cummings, 1992; Veiga et al., 2009). The comorbidity of the two disorders can be a consequence of both serotonergic and dopaminergic effects (Delaville, Chetrit, et al., 2012; Kitaichi et al., 2010), which could also have caused the deficit in sequence learning. Studies comparing dopaminergic and serotonergic antidepressants would dissociate the involvement of serotonergic and dopaminergic systems in cognitive function in MDD.

SSRIs are the first line of treatment for MDD due to their well-documented mood-elevating effect (Belmaker, 2008). It is believed that SSRIs achieve their therapeutic outcome by increasing synaptic concentrations of not only serotonin, but also dopamine and norepinephrine (Dunlop & Nemeroff, 2007; D. J. Nutt, 2006). SSRI-treated patients in our studies received paroxetine mono-therapy to remedy their depressive symptoms. Compared to medication-naïve patients with MDD and HC, paroxetine-treated patients with MDD showed no impairment on the sequence-learning phase in Experiment #1, Chapter 3. It is worth noting that the severity of depressive symptoms, as reflected by BDI-II scores, significantly correlates with the number of errors on the sequence-learning phase of the cognitive task, such that the more depressed people performed most poorly on this learning phase. However, in Experiment #2, Chapter 3, both SSRI-responders and non-responders showed a larger impairment in sequence-learning at the medication-naïve state than that observed in SSRI-treated state. Unlike non-responders, the improvement of sequence-learning accuracy in SSRI-

responders is approaching significance. Further, BDI scores of responders at retest were still significantly different from those of HC. The slight remediation of the sequence-learning deficit in responders might be a result of paroxetine modulating serotonin and dopamine concentrations, leading to a reduction of positive feedback learning deficit in SSRI-responders (Cools et al., 2011; Stoy et al., 2011). Minimizing the deficit in positive feedback learning in paroxetine-treated patients with MDD could explain the remediation of learning of sequence-learning phase. Alternatively, the remediation of the sequence-learning deficit in the paroxetine-treated group could be attributed to diminished neural processing of both positive and negative feedback during SSRI treatment, bringing positive and negative feedback into balance (Kish et al., 1988; McCabe et al., 2010; Walter et al., 2007). On the other hand, the low number of subjects in the non-responder group limits the interpretation of current results. It has been shown, however, that non-responders have persistently diminished striatal activity and connectivity before and after SSRI treatment (Downar et al., 2013; Forgeard et al., 2011). MDD impairs cognitive function at multiple levels, and SSRI also affect many other neurotransmitter systems that could contribute to the changes in behavioral performance (Belmaker & Agam, 2008).

In the generalization phase, the performance of medication-naïve patients with MDD was not significantly different from that of HC subjects in Experiment #1, Chapter 3. In Experiment #2, Chapter 3, however, only SSRI-responders were significantly more overgeneralizing than HC subjects. In contrast, SSRI-

responders expressed more overgeneralization in both Experiment #1 and Experiment #2, Chapter 3. Non-responders were not different from HC at baseline or retest. The overgeneralization impairment in SSRI-responders in both experiments resembles that of patients with amnestic mild cognitive impairment previously studied using this same task (H. Nagy et al., 2007). The discrepancy between the SSRI-responder results of Experiment #1 and Experiment #2 in Chapter 3 can be attributed to the length of exposure to SSRIs. While SSRI-responders in Experiment #1 were exposed to SSRIs for more than 36 months on average, patients in Experiment #2 were only placed on SSRIs for 4-6 weeks. This might be the case where length of exposure to SSRIs can precipitate hippocampal-dependent cognitive deficits. Alternatively, these results can be attributed to the effect of chronicity of MDD on hippocampal function. Repetitive episodes of MDD lead to shrinkage in hippocampal volume, not otherwise seen upon initial diagnosis (Campbell and Macqueen, 2004; MacQueen et al., 2003). Patients with MDD in Experiment #2 were diagnosed 4-6 weeks before the final testing session, whereas patients in Experiment #1 were diagnosed at least 36 months before testing. Further, in Experiment #2, the effect size of difference in generalization performance after SSRI administration was larger than that at baseline. On the other hand, non-responders did not show any deficit in generalization before or after SSRI administration. These results are in agreement with previous studies showing that positive response to SSRI leads to a decrease in hippocampal activity that is not otherwise seen in non-responders (Goldapple et al., 2004). Therefore, future research ought to

follow cognitive function at multiple time points to track when hippocampal changes become evident in responders and non-responders.

Previous work has argued that SSRI administration remediates "hippocampal-related" cognitive deficits in SSRI-responder patients with MDD (Vythilingam et al., 2004). More recent evidence suggests that there are no hippocampal volume differences between patients with MDD and normal healthy controls (Kroes et al., 2011; Vythilingam et al., 2004). This finding does not rule out non-volumetric dysfunctions. However, we argue that most prior studies of learning and memory in MDD have used the delayed paragraph recall test (Vythilingam et al., 2004) which is (i) not *specific* to the medial temporal lobe, as performance can be affected by disrupted frontal function (Loewenstein et al., 2009), and (ii) not sufficiently *sensitive* to mild degrees of hippocampal atrophy or dysfunction (Loewenstein et al., 2009; Myers et al., 2002).

One possible explanation of our results–and their seeming paradoxical conflict with these past other reports–might be that SSRI administration in responders results in hippocampal dysfunction via induction of excessive neurogenesis in the dentate gyrus (Meltzer, Yabaluri, & Deisseroth, 2005; Ming & Song, 2011). This, of course, is only a conjecture. However, some studies suggest that SSRI-induced neurogenesis produces cells that are characteristically different than cells that are naturally generated in the dentate gyrus (Kobayashi et al., 2010; Liu et al., 2011; O'Leary et al., 2009). These

immature newborn cells have different functions than mature cells (Kesner et al., 2004); they are more excitable (Snyder et al., 2001) and tend to inhibit mature neurons in the dentate gyrus (Kobayashi et al., 2010). In fact, this might lead to impaired function of the dentate gyrus in pattern separation of input to the dentate gyrus (Ming & Song, 2011). Moreover, recent evidence in the animal literature also suggests that hippocampal neurogenesis can impair memory retrieval in a radial arm maze (Saxe et al., 2007). Thus, it is possible that the production of immature cells in the hippocampal network as a result of SSRI administration negatively impact memory processes (Saxe et al., 2007). Future research, of course, is needed to evaluate this hypothesis. The near-significant negative correlation between errors on the generalization phase and WAIS-R digit-span scores (a measure of short-term memory) indicates that those who were most impaired on generalization (more errors) had the worst scores on short-term memory (Figure 3.3-B). This is in line with previous literature that suggests a negative effect of dentate gyrus neurogenesis on some types of memory (Aimone, Wiles, & Gage, 2009; Saxe et al., 2007; Weisz & Argibay, 2009). A larger study will be required to see if this trend holds consistently and significantly.

Another possible way in which SSRIs could affect hippocampal function in responders is via their impact on rapid eye movement (REM) sleep. Studies suggest that SSRI administration suppresses REM sleep (Brooks & Gershon, 1977; Ross, Ball, Gresch, & Morrison, 1990), which impairs hippocampal–but not

striatal–dependent learning (Fogel, Smith, & Cote, 2007; Hennevin, Hars, Maho, & Bloch, 1995; Hennevin, Huetz, & Edeline, 2007; Watts et al., 2012). This is in agreement with our findings where SSRI-responding patients with MDD show deficit on the hippocampal-dependent generalization phase, but improved striatal-dependent learning phase of the cognitive task we used. However, it is still unclear how SSRI administration leads to REM suppression and related cognitive deficit. More research is required to disentangle MDD-related from sleep-related cognitive deficits, and further explore the role of SSRI in subsequent cognitive changes. It will be particularly important in future research to better understand how individual differences in SSRI-related changes in REM correlate with SSRI-mediated changes in both clinical symptoms and cognitive function.

Another possible interpretation of overgeneralization in SSRI-responders is that paroxetine, the SSRI that was used to treat MDD in our sample, has a weak anti-nicotinic anticholinergic effect (Fortin et al., 2011; Mertens & Pintens, 1988). The hippocampus has a high concentration of nicotinic cholinergic receptors (Martin & Aceto, 1981). Previous studies have shown that using multiple SSRI with anticholinergic properties might impair hippocampal dependent memory functions (Fortin et al., 2011; Herzallah et al., 2010). Thus, this weak anticholinergic effect of paroxetine could have contributed to the deficit we observe in the generalization phase of cognitive task in the SSRI treated MDD patients. However, compared to other anticholinergic agents, paroxetine

has been found to have a relatively weak anticholinergic effect (Chew et al., 2008), suggesting that this explanation is unlikely. Further, it is not clear why the anticholinergic effect of paroxetine would not be evident in non-responders.

We base some of our interpretations of the current study by drawing on findings obtained using the same task in patient populations with amnestic mild cognitive impairment and Parkinson's disease (H. Nagy et al., 2007; O. Nagy et al., 2007; Shohamy et al., 2005). However, various studies suggest that amnestic mild cognitive impairment affects many brain systems, other than the medial temporal lobe, and these might contribute to the deficit we found in the generalization phase of the cognitive task (Van Dam et al., 2013). Further, Parkinson's disease has been shown to affect several systems in the brain other than the nigrostriatal dopamine system (Jellinger, 1991; Mann & Yates, 1983). Subsequently, generalizing earlier results to our findings in MDD might require further research into the overlapping biological correlates between these disorders.

5.4. POLYMORPHISMS IN THE DOPAMINE TRANSPORTER GENE MODULATE LEARNING FROM POSITIVE FEEDBACK IN HEALTHY SUBJECTS AND MDD PATIENTS

Studies suggest that DAT1 VNTR 9-repeat carriers have lower striatal dopamine transporter density than 10-repeat homozygotes (VanNess, Owens, &

Kilts, 2005). Therefore, 9-repeat carriers are expected to have higher synaptic levels of striatal dopamine, and therefore learn better from positive feedback given the wealth of evidence linking that to striatal dopaminergic function (Schultz et al., 1997). Further, enhanced dopaminergic function in the striatum in 9-repeat carriers leads to higher activity in the prefrontal cortex, which is also an important structure for learning from positive feedback (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Yacubian et al., 2007). Imaging studies have shown that 9-repeat carriers not only learn well from positive feedback, they also have greater activity in the dorsomedial striatum when anticipating positive feedback (Aarts et al., 2010). These findings are consistent with our results in Chapter 4 showing enhanced learning from positive feedback in 9-repeat carriers. However, we found no effect of the DAT1 VNTR on learning from negative feedback.

The link between learning from negative feedback and dopaminergic function is not well established (Boureau & Dayan, 2011; Cools et al., 2011). Various studies report conflicting results regarding dopaminergic neuronal activity during negative feedback learning. Negative feedback learning increased, decreased, or did not change the rate of dopaminergic neuronal firing across several different published reports (Marinelli & McCutcheon, 2014). Furthermore, recorded neuronal activity in the substantia nigra during negative feedback learning was linked to the firing of GABAergic neurons, and not dopaminergic neurons (Henny et al., 2012). On the other hand, human studies show that 10-

repeat homozygotes exhibit better recognition of cues associated with negative feedback (Wittmann et al., 2013). Accordingly, dopamine level variations due to naturally occurring genetic polymorphisms in the dopamine transporter gene might not be robust enough to illustrate a significant difference in learning from negative feedback in our current learning task. Our finding here that there is no effect of DAT1 VNTR on learning from negative feedback warrants further investigation and better characterization of the role of dopamine in learning from negative feedback in healthy and disease states.

Dopaminergic dysfunction has repeatedly been implicated in the pathophysiology of MDD (Dunlop & Nemeroff, 2007; D. Nutt et al., 2007; D. J. Nutt, 2006). MDD patients show neurochemical, structural, and functional impairments related to dopaminergic dysfunction (Lorenzetti et al., 2009; Walter et al., 2007). Further, MDD patients' selective impairment in learning from positive feedback has been attributed to dysfunction in the nigrostriatal dopaminergic pathway (Robinson, Cools, Carlisi, Sahakian, & Drevets). Various studies have linked the DAT1 polymorphisms to the pathophysiology of MDD (Kirchheiner et al., 2007; Ueno, 2003). Unfortunately, no previous studies examined the effect of the DAT1 VNTR polymorphism on cognitive function in MDD. In our study, 9-repeat carriers MDD-T learned significantly better from positive feedback than 10-repeat homozygotes, although both groups had impaired learning compared to healthy subjects (Figure 4.5-A). This finding suggests that the DAT1 VNTR polymorphism can be used to predict the speed

and level of response to SSRI treatment (Kirchheiner et al., 2007), given that SSRI administration successfully reversed mild, but not severe, deficits in learning from positive feedback (Der-Avakian, Mazei-Robison, Kesby, Nestler, & Markou, 2014).

SSRI administration modulates the dopaminergic system, in part, by increasing the availability of dopamine transporter in the striatum and decreasing dopamine levels (Kugaya et al., 2003). MDD patients who are homozygous for the 9-repeat allele have been shown in past studies to respond to SSRI treatment much slower than 9/10 heterozygotes or 10-repeat homozygotes (Kirchheiner et al., 2007). The larger difference in learning from positive feedback between the MDD-T groups when compared to the difference between the healthy groups can be attributed to the low dopaminergic state that is exacerbated by SSRI administration (Kugaya et al., 2003). Such variability in learning from positive feedback in MDD should be further investigated as a predictive factor of response to SSRI administration.

As illustrated in Figure 5.1, learning from positive feedback in healthy and MDD-T subjects seems to follow a nonlinear relationship that relates variations in dopamine levels with cognitive performance (i.e., inverted U-shaped function: "∩") (Cools, Barker, Sahakian, & Robbins, 2001; Williams & Goldman-Rakic, 1995; Zahrt, Taylor, Mathew, & Arnsten, 1997). Emerging evidence suggests that the effects of naturally occurring polymorphisms in dopamine genes on

cognition should be magnified in individuals with greater losses in their dopamine resources (Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013). In particular, the effect of the DAT1 VNTR polymorphism on learning from positive feedback is thought to increase as dopamine levels are reduced (towards the left-hand side of the curve in Figure 5.1). The difference in learning from positive feedback in the healthy groups is smaller in magnitude than that between MDD-T subjects (Figure 4.6-A) given that both healthy groups are close to the optimal region of the curve where differences in dopamine levels (due to the DAT1 VNTR polymorphism) translate to small changes in learning from positive feedback. However, both MDD-T groups are shifted to the left of the curve, where variations in dopamine levels of the MDD-T groups due to DAT1 VNTR variations result in a larger difference in learning from positive feedback, indicating that MDD is a state of low dopamine where differences in cognitive function are amplified. However, it seems that SSRIs do not remediate the deficit in learning from positive feedback (Herzallah, Moustafa, Natsheh, Abdellatif, et al., 2013). These findings highlight the role of dopamine in MDD, and argue that SSRI treatment does not remediate the neurochemical and cognitive deficits associated with MDD.

One of our key findings in Chapter 4 is that, in our task, DAT1 VNTR polymorphism does not have any effect on learning from negative feedback in the MDD-T group. Further, the DAT1 VNTR polymorphism did not have any effect on learning from negative feedback in healthy subjects either. This can be considered a second line of evidence that the DAT VNTR polymorphism does not

affect learning from negative feedback. Further, we can argue that learning from negative feedback engages neurochemical systems other than dopamine, such as the serotonergic system (Cools et al., 2011). Future research is needed to identify other functional polymorphisms in the DAT1 gene, which can serve, alone or together with the DAT1 VNTR, as more accurate measures of dopamine level variability.

Our findings shed the light on the significance of the DAT1 VNTR polymorphism to learning from positive feedback in healthy and MDD patients. Introduction of more sensitive cognitive tasks in the future may better differentiate the effects of the DAT1 VNTR polymorphism on both positive and negative feedback learning. It remains unclear, however, what role SSRIs play in modulating learning from positive and negative feedback in the context of the DAT VNTR polymorphism.

5.5. THE COGNITIVE PROFILE OF MDD VS. THE COGNITIVE MECHANISM OF ACTION OF RESPONSE TO SSRIS

The findings in the aforementioned studies can be organized in three main themes: (1) defining the cognitive profile of medication-naïve MDD, (2) delineating the cognitive mechanism of action of SSRIs, and (3) differentiating the cognitive profiles of SSRI responders and non-responders before and after treatment.

According to our findings and previous literature, MDD is characterized by a selective deficit in learning from positive feedback. Learning from negative feedback, however, showed bimodality that was previously described in the literature as “catastrophic response to punishment” (Beats, Sahakian, & Levy, 1996; L. Clark et al., 2009; Eshel & Roiser, 2010). A subgroup of MDD patients showed increased sensitivity to negative feedback, while others were impaired at learning from negative feedback. Our results replicate these findings and argue that these cognitive differences might implicate different subtypes of MDD as defined by their response to SSRIs.

Contradictory to previous reports, we found that MDD does not impair hippocampal-dependent generalization. These results support the current view that hippocampal dysfunction in MDD is a result of chronicity of MDD rather than being a precursor (Cobb et al., 2013; MacQueen et al., 2003). Unfortunately, we had a limited data set to explore sources of individual differences within the MDD group.

Our studies suggest that SSRI administration balances the deficit in learning from positive feedback by inducing a new deficit in learning from negative feedback. Converging evidence suggests that SSRI-induced changes in feedback-based learning happen much earlier than remediation of MDD symptoms. Therefore, this “balancing process” can be viewed as a significant

contributor to the mood-elevating effects of SSRIs. However, it seems that the "balancing process" takes effect only if MDD patients have a bias towards negative feedback prior to administration of SSRIs.

We found that SSRI administration induced impairment in hippocampal-dependent generalization that was not otherwise seen in medication-naïve patients with MDD. These results provide a valid explanation for recent findings that SSRIs antagonize the effects cognitive behavioral therapy (CBT) (Browning et al., 2011). Psychological treatments of MDD rely on learning new skills and generalizing them to novel situations. If SSRIs impair the patient's ability to generalize new skills, then the combination of CBT and SSRIs will improve the outcomes of treatment.

According to NIMH's STAR*D clinical trial, only 30% of patients with MDD respond to SSRIs (Howland, 2008). Here, we characterize a cognitive marker that *a priori* differentiates SSRI responders and non-responders. We found that potential SSRI non-responders exhibit impairment in learning from negative feedback before administration of SSRIs. In the context of the "balancing process" that SSRIs seem to utilize to remedy MDD symptoms, non-responders will not benefit from SSRI administration given that their biases are already balanced.

This research can lead to clinically significant transformations of the field of psychiatry, which can ultimately improve treatment of MDD by translating emerging neuroscience knowledge into large-scale clinical trials and treatment protocols. Since only 30% of MDD patients receiving SSRIs show significant reduction in symptoms (Howland, 2008), it is of significant clinical importance to develop convenient diagnostic tools to *a priori* identify SSRI responders and non-responders. Furthermore, utilizing an animal model of MDD facilitates the characterization of behavioral and physiological subtypes of MDD.

5.6. FUTURE DIRECTIONS

According to NIMH's STAR*D clinical trial, only about 30% of patients with MDD respond to SSRIs (Howland, 2008). Unfortunately, clinicians cannot predict, *a priori*, who will or will not respond to SSRI administration. Furthermore, in animal models of MDD, researchers often overlook bimodality in response to SSRIs, where about 50% of animals with MDD-like symptoms do not respond to SSRIs (Christensen, Bisgaard, & Wiborg, 2011; Jayatissa, Bisgaard, Tingstrom, Papp, & Wiborg, 2006). If, however, simple behavioral and neural markers in patients and animal models of MDD could differentiate those who are, or are not, likely to respond to subsequent SSRI administration, this would: (1) provide immediate clinical relevance, helping identify those most likely to benefit from SSRIs, and (2) inform future drug discovery by characterizing behavioral and neural mechanisms associated with SSRI non-responders. Future studies ought

to examine the behavioral and neural mechanisms of response to SSRIs in both humans and rat models of MDD.

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APPENDICES

FIGURES

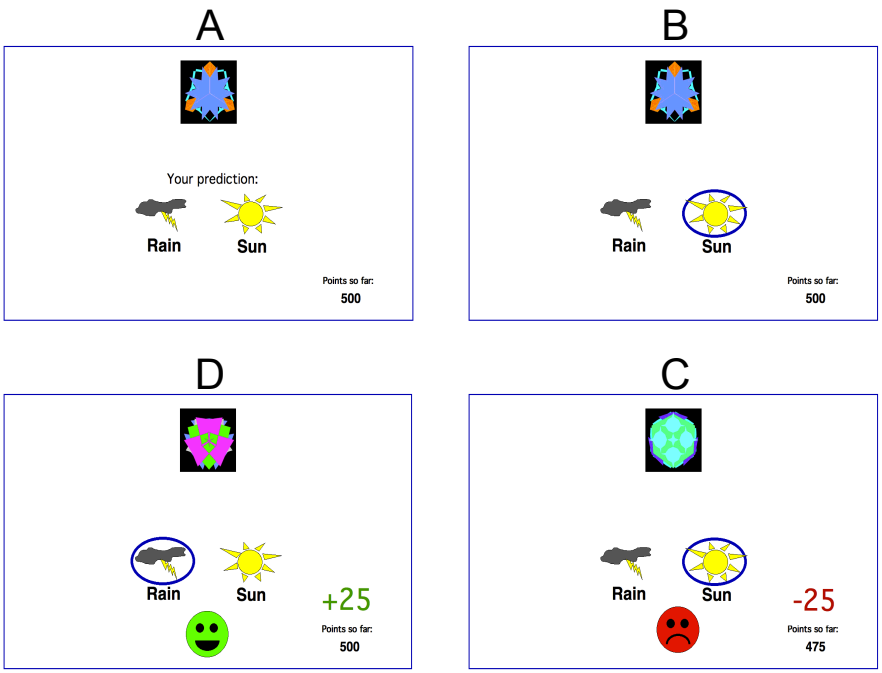

Figure 2.1. *The feedback-based classification task. (A) On each trial, the participant saw one of four stimuli and was asked whether this stimulus predicts rain or sun. (B) No feedback is given for incorrect answers in positive feedback stimuli or correct answers in negative feedback stimuli (C) For positive feedback stimuli, correct responses get positive feedback with visual feedback and 25 points winnings. (D) For negative feedback stimuli, incorrect responses get negative feedback with visual feedback and the loss of 25 points.*

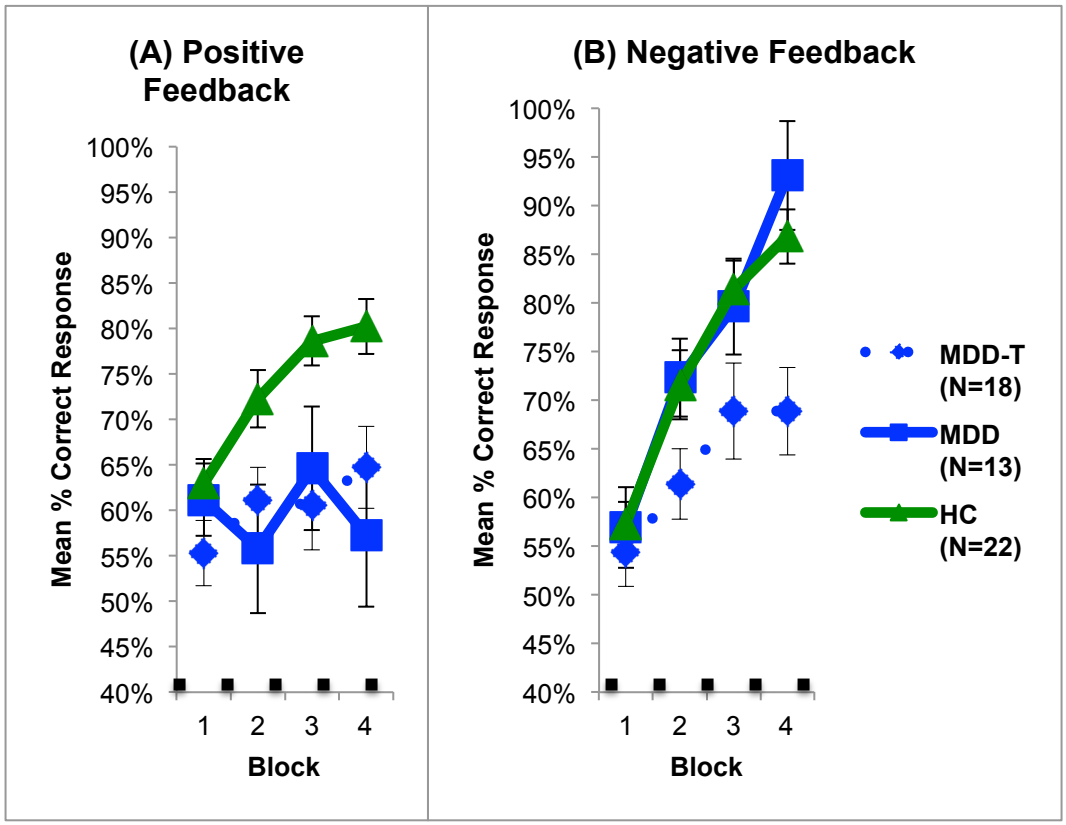

Figure 2.2. *Performance on the positive and negative feedback learning task in Experiment #1. (A) The mean number of correct responses in the four phases for the positive feedback stimuli (±SEM). (B) The mean number of correct responses in the four phases for the negative feedback stimuli (±SEM). MDD is medication naïve, MDD-T is on medication MDD patients, and HC is healthy controls.*

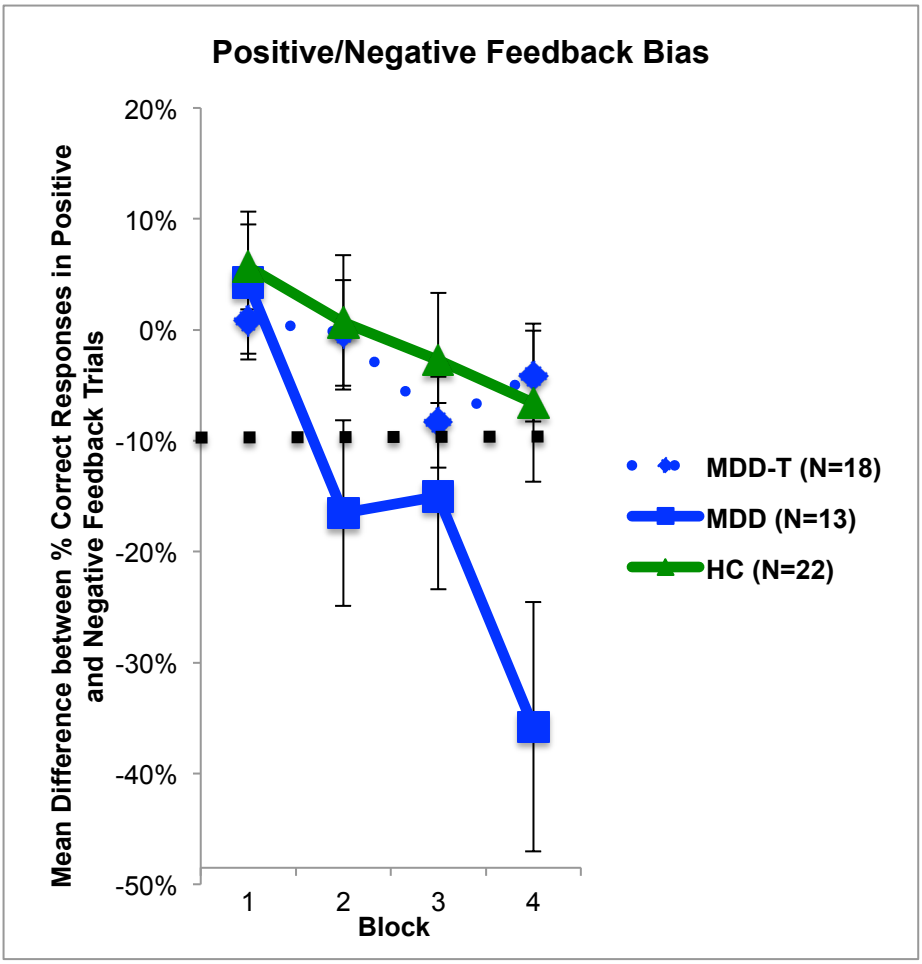

Figure 2.3. *Mean difference between percentage correct responses in positive and negative feedback trials per block (±SEM) in Experiment #1.* MDD is medication naïve, MDD-T is on medication and HC is healthy controls.

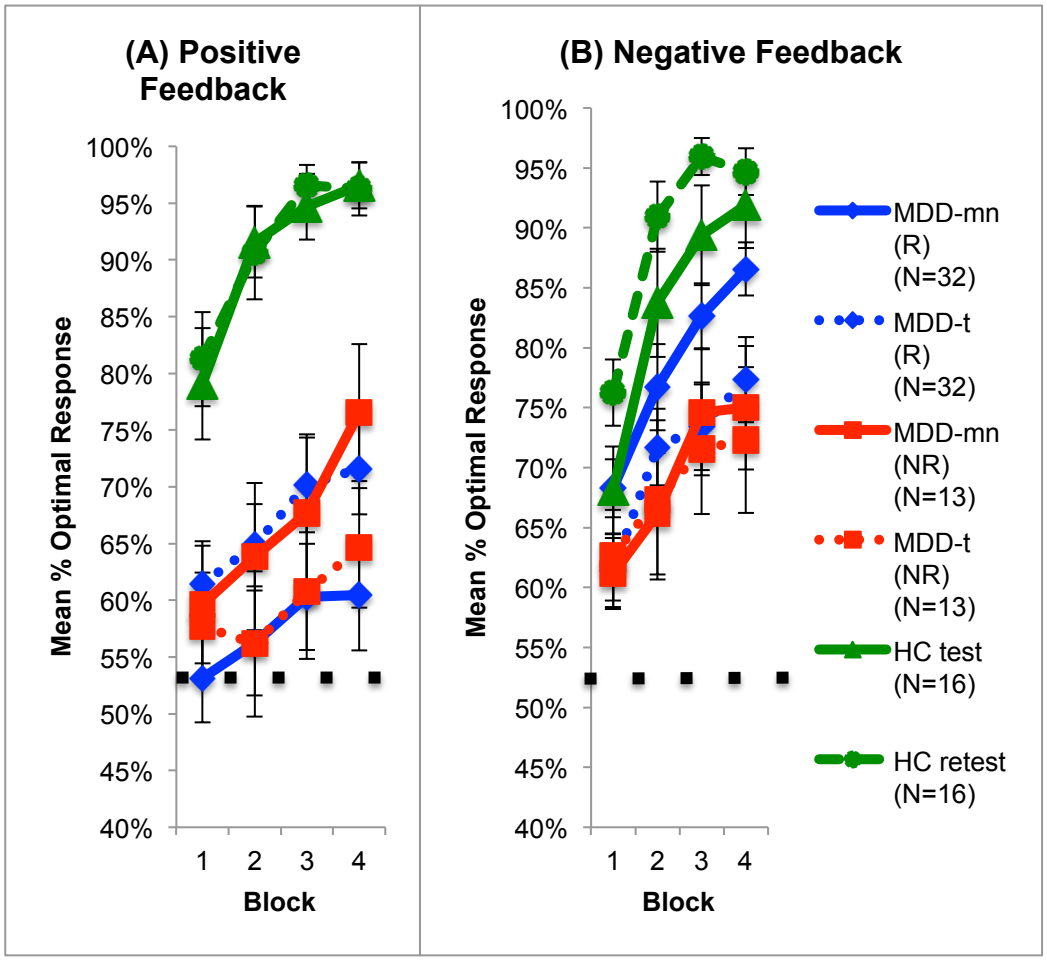

Figure 2.4. *Performance on the positive and negative feedback learning task in Experiment #2. (A) The mean number of optimal responses in the four phases for the positive feedback stimuli (±SEM). (B) The mean number of optimal responses in the four phases for the negative feedback stimuli (±SEM). MDD (R) is medication-naïve MDD who are SSRI responders, MDD-t (R) are SSRI responders, MDD (NR) is medication-naïve MDD who are SSRI non-responders, MDD-t (NR) are SSRI non-responders, HC test are healthy controls at baseline, HC retest are healthy controls tested 4-6 weeks after initial testing.*

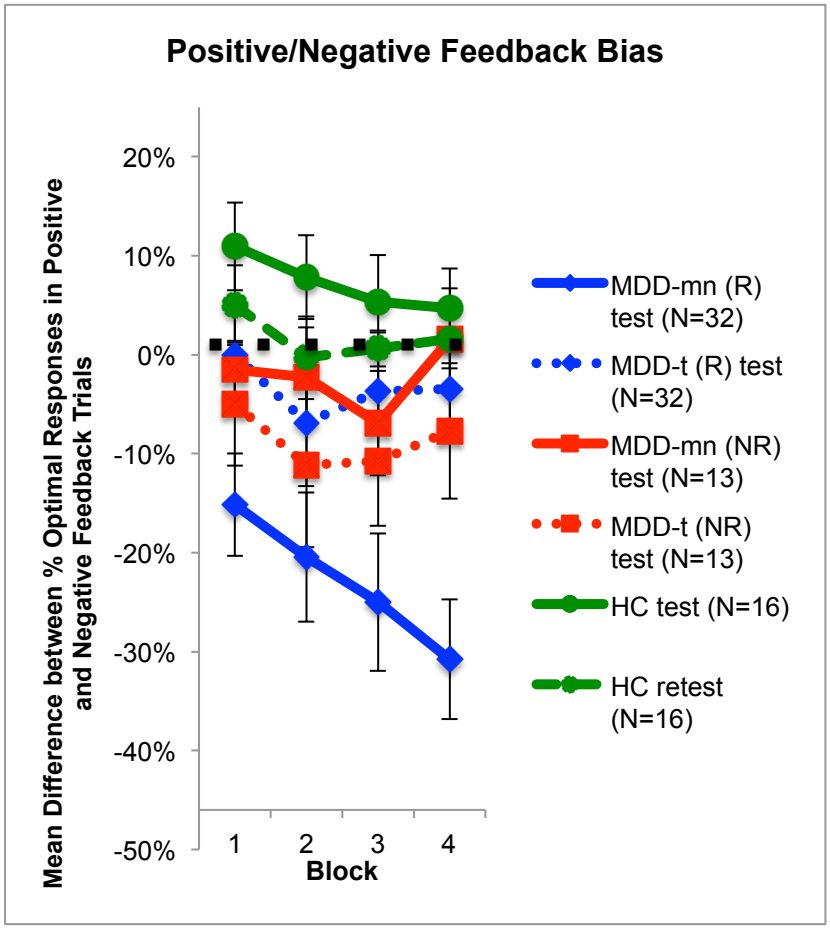

Figure 2.5. *Mean difference between percentage optimal responses in positive and negative feedback trials per block (±SEM) in Experiment #2. MDD (R) is medication-naïve MDD who are SSRI responders, MDD-t (R) are SSRI responders, MDD (NR) is medication-naïve MDD who are SSRI non-responders, MDD-t (NR) are SSRI non-responders, HC test are healthy controls at baseline, HC retest are healthy controls tested 4-6 weeks after initial testing.*

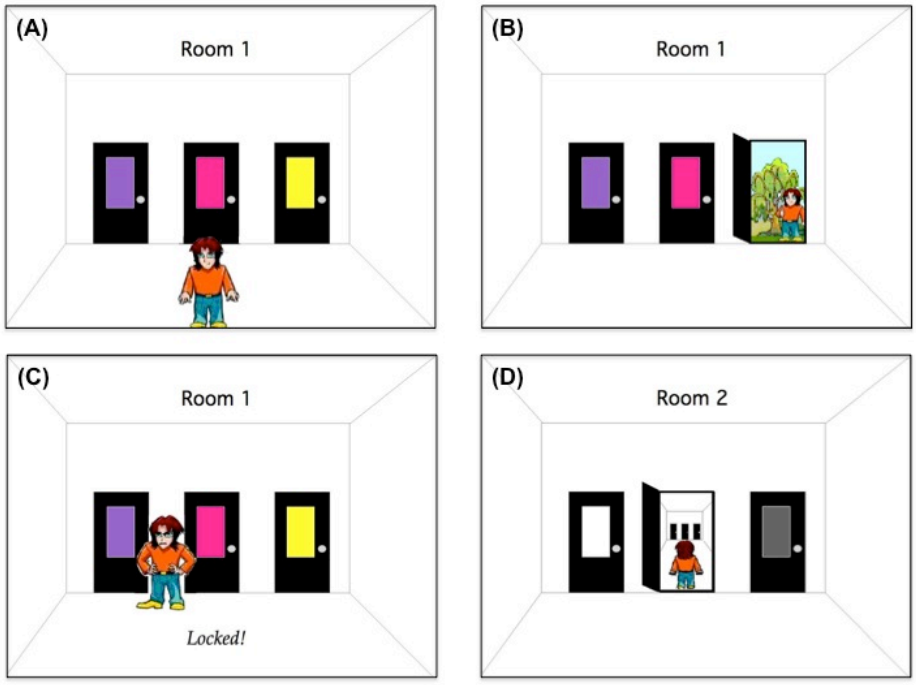

Figure 3.1. *Illustration of the sequence learning with context shift task.*

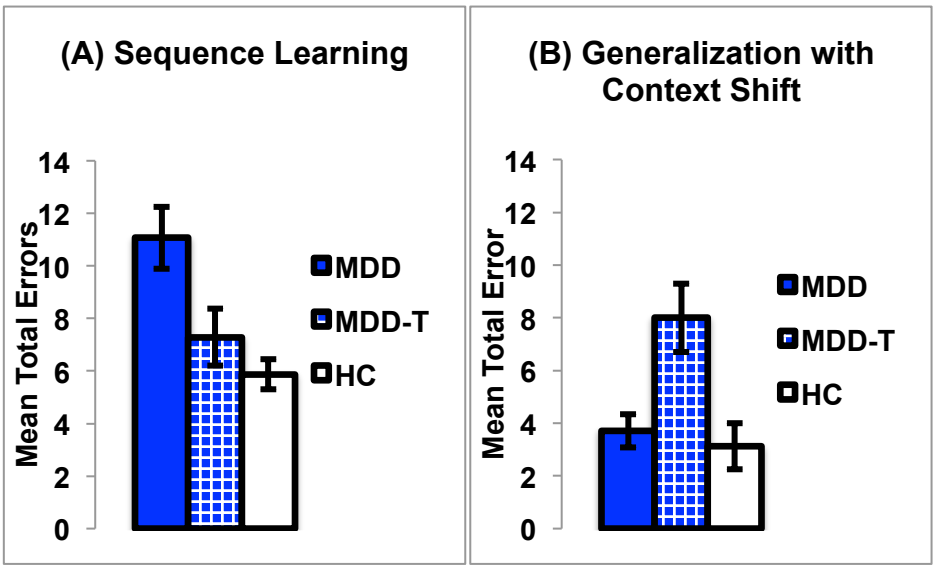

Figure 3.2. *Computer-based cognitive task results in Experiment #1. (A) The mean numbers of errors on the sequence-learning phase of the task (chain steps A-D) (±SEM). (B) The mean numbers of errors on the generalization with context-shift phase (±SEM). MDD are medication-naïve patients with MDD, MDD-T are SSRI-treated patients with MDD, HC are healthy controls.*

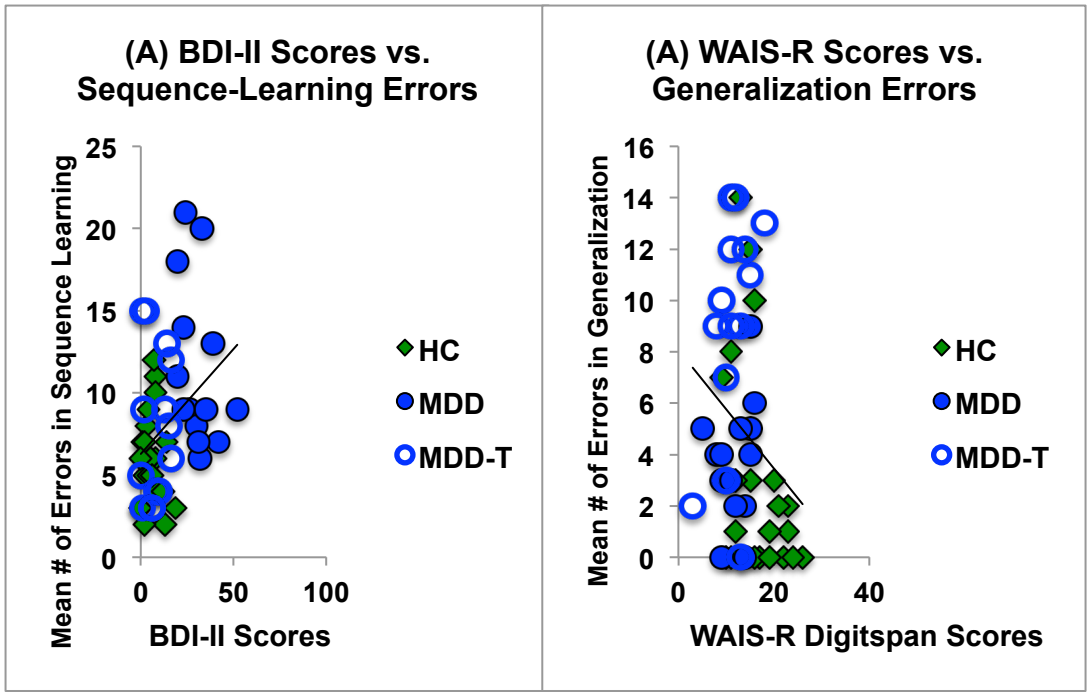

Figure 3.3. *(A) Correlation between BDI-II scores and the numbers of errors on the sequence-learning phase of the task (chain steps A-D) in Experiment #1, Spearman's rho, r_s=0.410, N=51, p=0.003. (B) Correlation between WAIS-R digit-span scores and the number of errors on the context-shift generalization phase in Experiment #1, Spearman's rho, r_s=−0.245, N=51, p=0.083.*

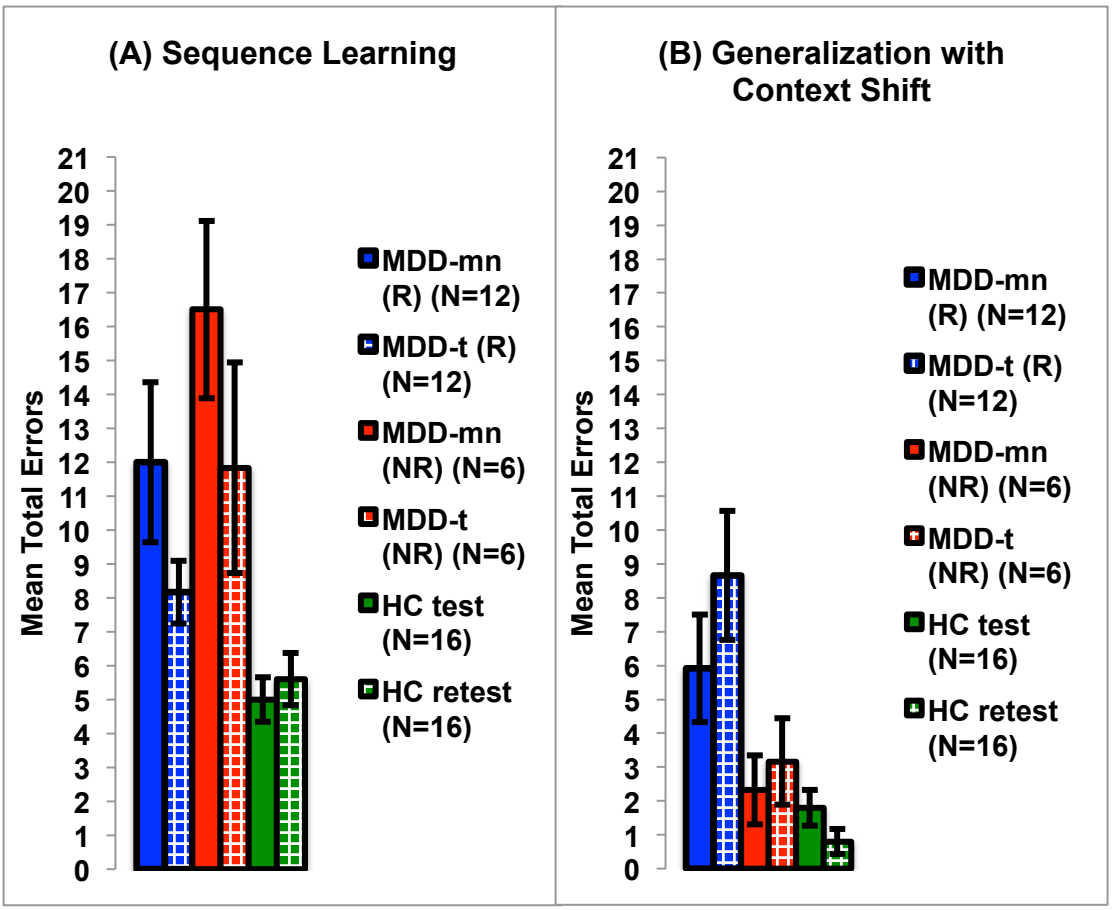

Figure 3.4. *Computer-based cognitive task results. (A) The mean numbers of errors on the sequence-learning phase of the task (chain steps A-D) (±SEM) in Experiment #2. (B) The mean numbers of errors on the generalization with context-shift phase (±SEM). MDD (R) is medication-naïve MDD who are SSRI responders, MDD-t (R) are SSRI responders, MDD (NR) is medication-naïve MDD who are SSRI non-responders, MDD-t (NR) are SSRI non-responders, HC test are healthy controls at baseline, HC retest are healthy controls tested 4-6 weeks after initial testing.*

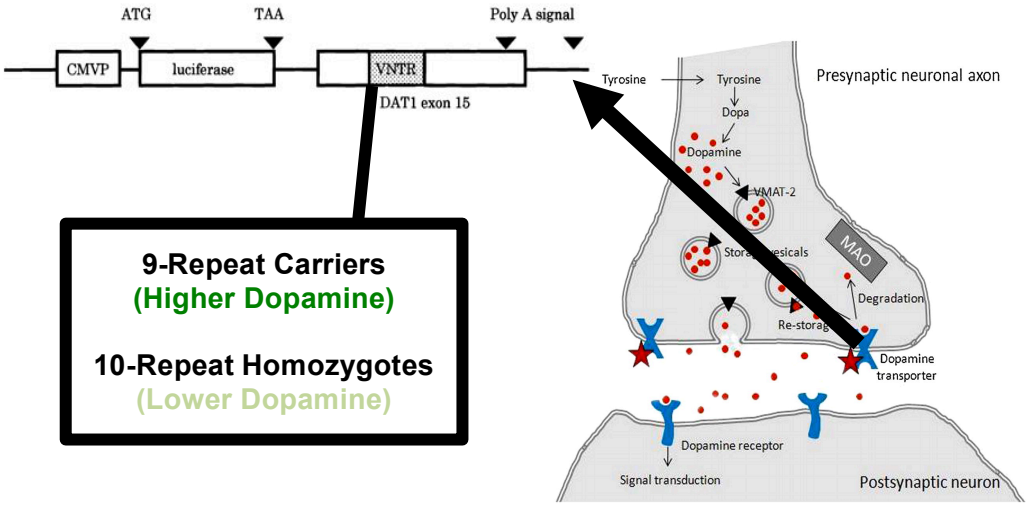

Figure 4.1. *A schematic of the 3' VNTR polymorphism in the DAT1 gene (Fuke et al., 2001). 9-Repeat Carriers (subjects with at least on copy of the 9-repeat DAT1 allele) express relatively a less active dopamine transporter protein, leading to slower clearance of synaptic dopamine, and ultimately higher levels of dopamine. 10-Repeat Homozygotes (subjects homozygous for the 10-repeat DAT1 allele) have more active dopamine transporter, and thus lower levels of synaptic dopamine (Dopamine transporter illustration adapted from Djang et al., 2012.*

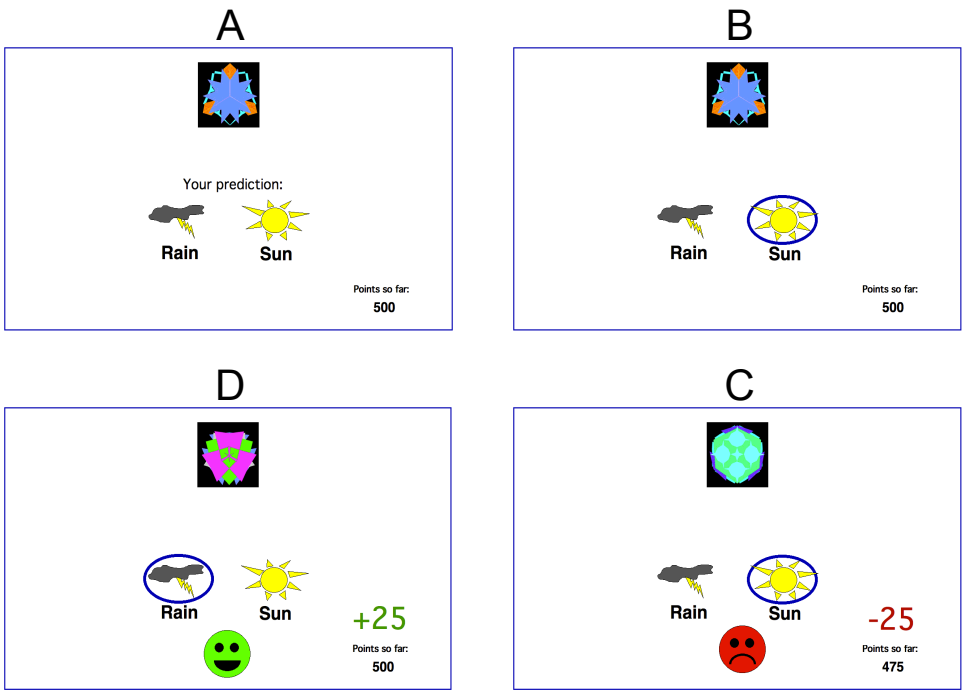

Figure 4.2. *The feedback-based probabilistic classification task. (A) On each trial, the participant saw one of four stimuli and was asked whether this stimulus predicts rain or sun. (B) No feedback is given for non-optimal answers in positive feedback stimuli or optimal answers in negative feedback stimuli. (C) For positive feedback stimuli, optimal responses get positive feedback with visual feedback and 25 points winnings. (D) For negative feedback stimuli, non-optimal responses get negative feedback with visual feedback and the loss of 25 points. The task applied a probabilistic strategy where in 90% of the trials, the associated feedback was provided. In the remaining 10% of trials, the feedback association with sun and rain was exchanged.*

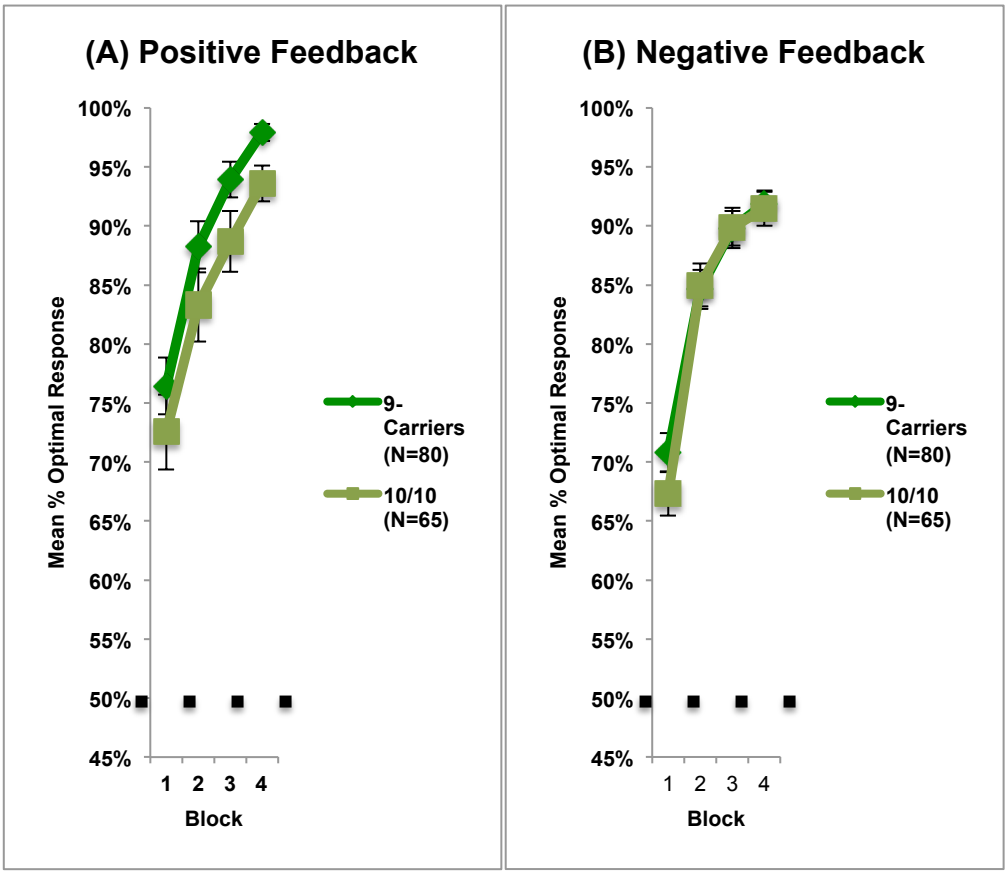

Figure 4.3. *Performance on the positive and negative feedback learning task in Experiment #1. (A) The mean number of optimal responses in the four phases for the positive feedback stimuli (±SEM). (B) The mean number of optimal responses in the four phases for the negative feedback stimuli (±SEM). 9-Carriers: subjects with at least one copy of the 9-repeat DAT1 allele. 10/10: subjects homozygous for the 10-repeat DAT1 allele.*

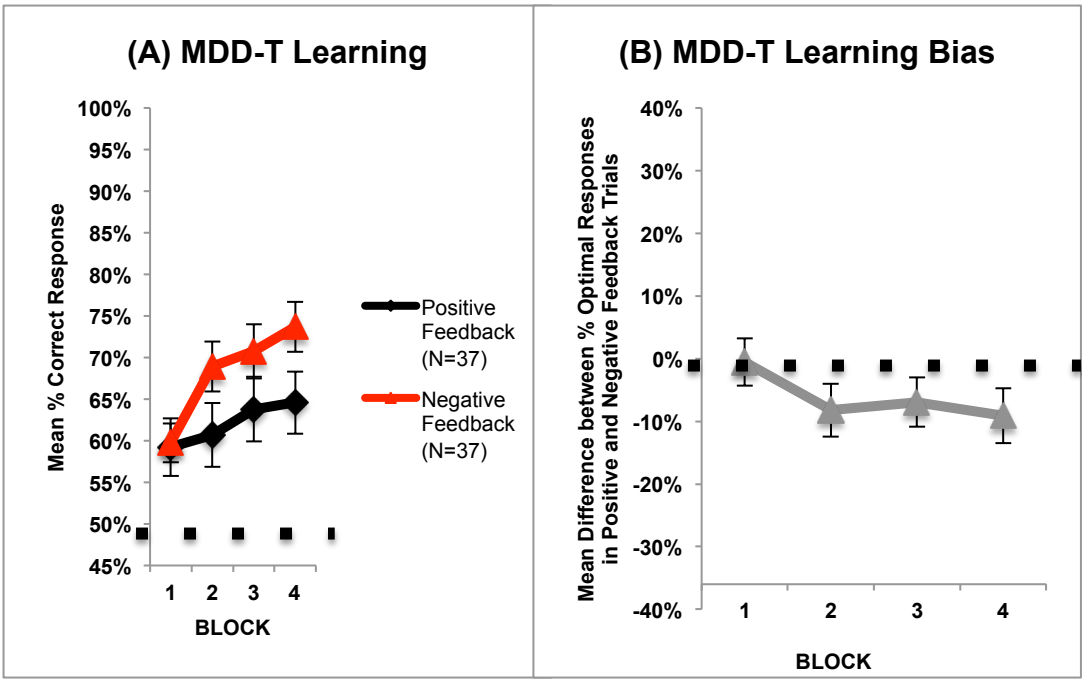

Figure 4.4. *Performance of SSRI-treated patients with MDD on the positive and negative feedback learning task in Experiment #2. (A) The mean number of optimal responses in the four phases for the positive and negative feedback stimuli (±SEM). (B) Mean difference between percentage optimal responses in positive and negative feedback trials per block (±SEM). MDD-T: SSRI-treated MDD subjects.*

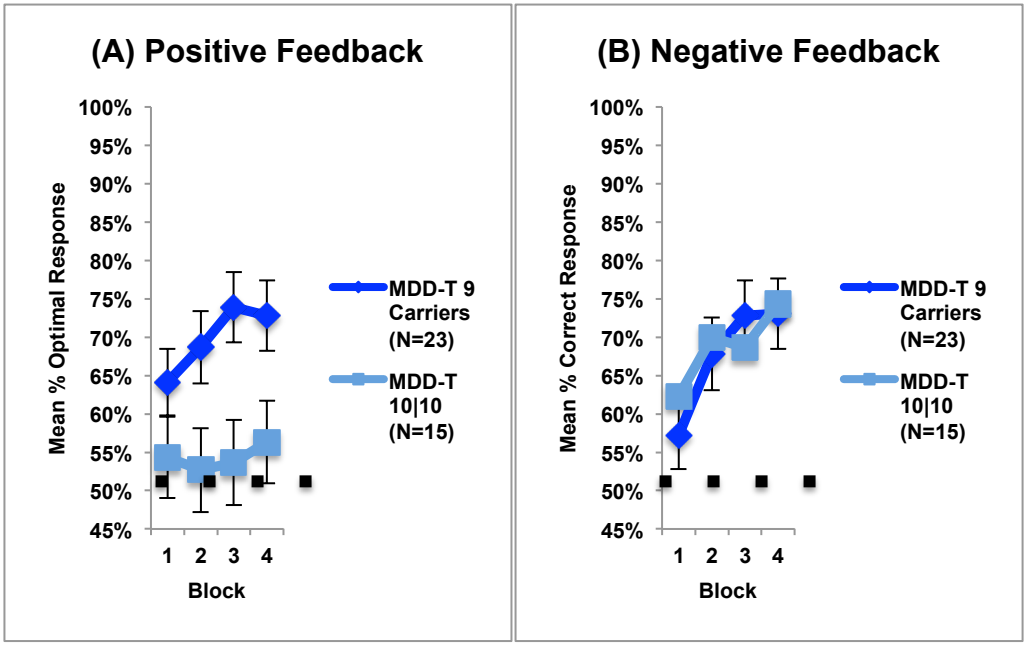

Figure 4.5. *Performance on the positive and negative feedback learning task in Experiment #2. (A) The mean number of optimal responses in the four phases for the positive feedback stimuli (±SEM). (B) The mean number of optimal responses in the four phases for the negative feedback stimuli (±SEM). MDD-T 9-Carriers: SSRI-treated MDD subjects with at least one copy of the 9-repeat DAT1 allele. 10/10: SSRI-treated MDD subjects homozygous for the 10-repeat DAT1 allele.*

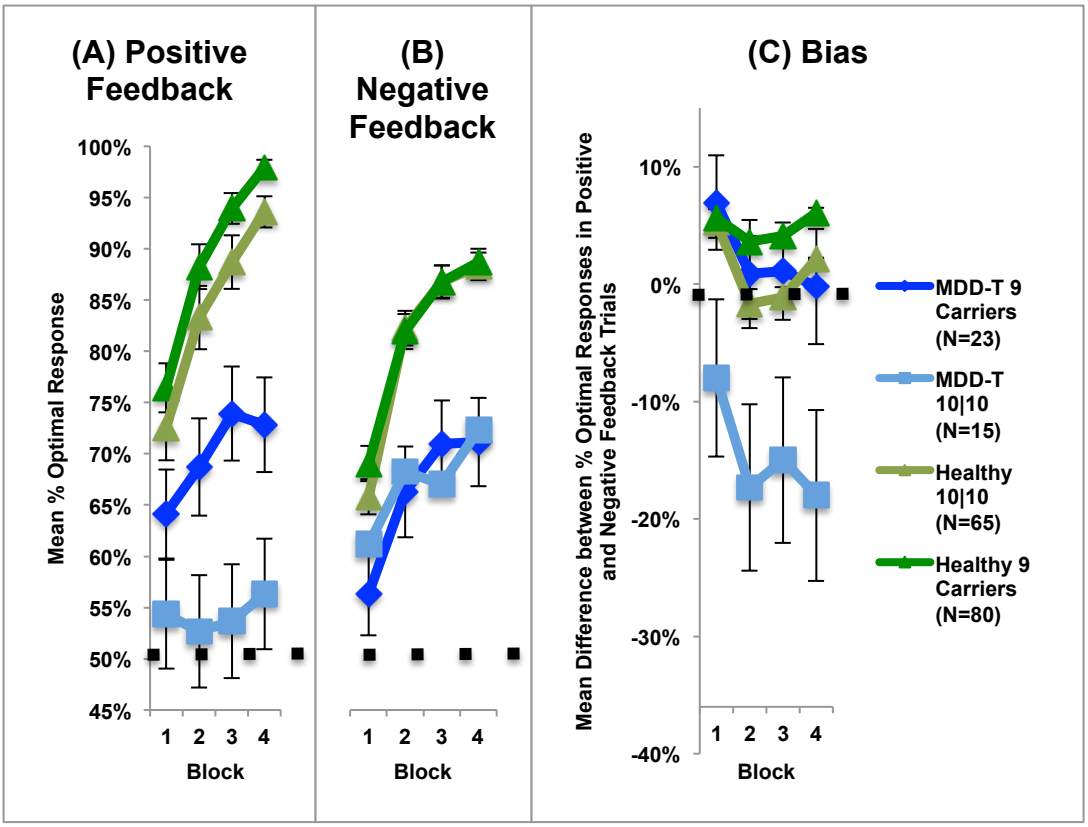

Figure 4.6. *Performance on the positive and negative feedback learning task in Experiments #1 and #2. (A) The mean number of optimal responses in the four phases for the positive feedback stimuli (±SEM). (B) The mean number of optimal responses in the four phases for the negative feedback stimuli (±SEM). (C) Mean difference between percentage optimal responses in positive and negative feedback trials per block (±SEM).* MDD-T 9-Carriers: SSRI-treated MDD subjects with at least one copy of the 9-repeat DAT1 allele. 10/10: SSRI-treated MDD subjects homozygous for the 10-repeat DAT1 allele.

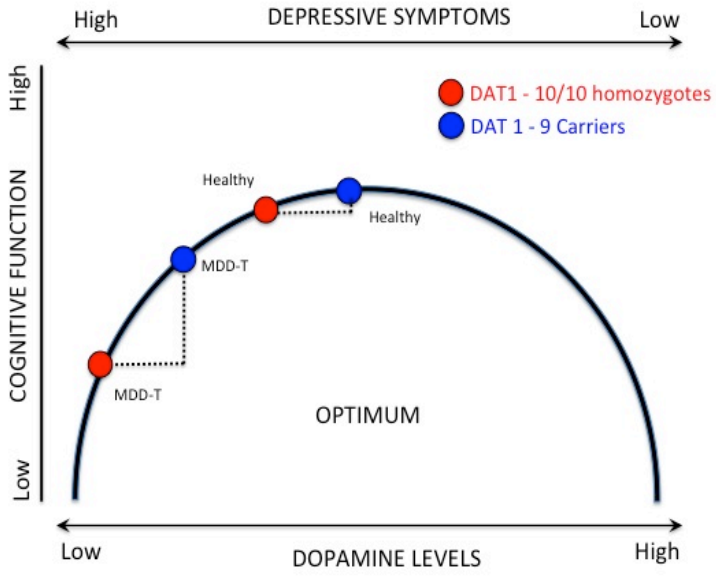

Figure 5.1. The inverted U-shaped function of dopamine and cognitive function. MDD-T: SSRI-treated MDD subjects, 9 Carriers: subjects with at least one copy of the 9-repeat DAT1 allele. 10/10 homozygotes: subjects homozygous for the 10-repeat DAT1 allele.

TABLES

Table 2.1. Summary of demographic and neuropsychological results. HC: healthy controls, MDD: medication-naïve patients with MDD, MDD-T: SSRI-treated patients with MDD*, MDD-R: SSRI-responding patients with MDD, MDD-NR: SSRI non-responder patients with MDD,* MMSE: Mini-Mental Status Exam, BDI-II: Beck Depression Inventory II, BAI: Beck Anxiety Inventory.

				Age	Education	MMSE	BDI-II	BAI
Experiment #1	**HC N=22**		Mean	28.50	15.09	29.91	5.5	6.36
			SD	11.84	1.57	0.29	4.09	5.60
	MDD N=13		Mean	27.23	14.31	28.53	33.77	28.84
			SD	6.24	2.29	1.33	10.02	9.01
	MDD-T N=18		Mean	32.11	13.56	27.83	9.72	9.27
			SD	9.14	2.17	2.71	6.41	5.43
Experiment #2	**MDD-R N=32**	Test	Mean	32.13	11.47	28.53	31.37	27.91
			SD	10.42	3.30	1.27	9.58	11.67
		Retest	Mean	32.13	11.47	28.38	30.15	28.00
			SD	10.42	3.30	1.50	5.94	10.40
	MDD-NR N=13	Test	Mean	28.38	11.54	28.81	10.88	14.22
			SD	8.87	2.96	1.26	6.23	11.10
		Retest	Mean	28.38	11.54	27.92	34.46	32.77
			SD	8.87	2.96	1.32	7.92	10.52
	HC-test N=16	Test	Mean	25.19	16.69	29.56	7.62	7.81
			SD	8.75	1.14	0.81	4.30	4.29
		Retest	Mean	25.19	16.69	29.94	5.19	6.50
			SD	8.75	1.14	0.25	3.87	4.14

Table 2.2. *Summary of the post-hoc one-way ANOVA and Tukey's HSD post-hoc results to explore the significant interaction between group and block in positive feedback learning, with group as the between-subjects variable, and the percentage of correct responses on a each one of the four positive feedback learning block was the within-subjects variable, with a Bonferroni correction adjusted α=0.0125 to protect the level of significance. HC: healthy controls, MDD: medication-naïve patients with MDD, MDD-T: SSRI-treated patients with MDD, * marks significant results.*

Statistical Test	**Within-Subjects Variable**	**Between-Subjects Variable**	**df-1**	**df-2**	**F**	***p***	**η^2**
One-Way ANOVA	Block 1 Positive Feedback	Group (MDD, MDD-T, HC)	2	50	1.571	0.218	-
One-Way ANOVA	Block 2 Positive Feedback	Group (MDD, MDD-T, HC)	2	50	3.862	0.28	-
One-Way ANOVA	Block 3 Positive Feedback	Group (MDD, MDD-T, HC)	2	50	4.973	0.011 *	0.166
Tukey's *HSD*		HC vs. MDD-T	-	-	-	0.04 *	-
		HC vs. MDD	-	-	-	0.097	-
		MDD vs. MDD-T	-	-	-	0.827	-
One-Way ANOVA	Block 4 Positive Feedback	Group (MDD, MDD-T, HC)	2	50	6.038	0.004 *	0.194
Tukey's *HSD*		HC vs. MDD	-	-	-	0.006 *	-
		HC vs. MDD-T	-	-	-	0.049 *	-
		MDD vs. MDD-T	-	-	-	0.572	-

Table 2.3. *Summary of the post-hoc one-way ANOVA and Tukey's HSD post-hoc analyses on each block of mean difference between percentage correct responses in positive and negative feedback trials to investigate the interaction between block and group, with group as the between-subjects variable and the mean difference between percentage correct responses in positive and negative feedback trials as the dependent variable. HC: healthy controls, MDD: medication-naïve patients with MDD, MDD-T: SSRI-treated patients with MDD, * marks significant results.*

Statistical Test	**Within-Subjects Variable**	**Between-Subjects Variable**	**df-1**	**df-2**	**F**	***p***	**η^2**
One-Way ANOVA	Block 1 Difference	Group (MDD, MDD-T, HC)	2	50	0.358	0.701	-
One-Way ANOVA	Block 2 Difference	Group (MDD, MDD-T, HC)	2	50	2.121	0.131	-
One-Way ANOVA	Block 3 Difference	Group (MDD, MDD-T, HC)	2	50	1.035	0.363	-
One-Way ANOVA	Block 4 Difference	Group (MDD, MDD-T, HC)	2	50	5.251	0.009 *	0.173
Tukey's *HSD*		HC vs. MDD	-	-	-	0.017*	-
		HC vs. MDD-T	-	-	-	0.963	-
		MDD vs. MDD-T	-	-	-	0.013 *	-

Table 3.1. *Summary of Demographic and Neuropsychological Results. HC: healthy controls, MDD: medication-naïve patients with MDD, MDD-T: SSRI-treated and responding patients with MDD, MDD-R: SSRI-responding patients with MDD, MDD-NR: SSRI non-responder patients with MDD, Mini-Mental Status Examination (MMSE), the digit span subtest of the Revised Wechsler Adult Intelligence Scale (WAIS-R digit-span), Beck Depression Inventory II (BDI-II), and Beck Anxiety Inventory (BAI).*

				Age	Education	MMSE	WAIS-R digit-span	BDI-II	BAI
Experiment #1	**HC N=25**		Mean	31.08	14.08	29.76	16.24	5.84	8.76
			SD	14.01	1.87	0.44	4.93	4.89	7.01
	MDD N=16		Mean	30.63	12.63	29.19	11.87	31.50	24.43
			SD	8.25	2.06	0.91	3.16	8.80	10.98
	MDD-T N=15		Mean	34.87	13.07	28.93	11.13	8.73	11.87
			SD	7.44	3.49	1.75	3.44	6.47	7.10
Experiment #2	**HC N=16**	Test	Mean	26.67	16.13	29.67	14.60	6.27	8.13
			SD	10.24	2.07	0.62	3.42	4.03	4.53
		Retest	Mean	26.67	16.13	29.87	14.93	4.33	7.27
			SD	10.24	2.07	0.35	4.04	3.18	3.86
	MDD-R N=12	Test	Mean	29.58	11.08	28.83	11.25	30.33	28.83
			SD	9.74	3.32	0.84	3.14	8.34	12.19
		Retest	Mean	29.58	11.08	29.08	11.83	10.42	14.08
			SD	9.74	3.32	0.79	3.16	7.19	10.60
	MDD-NR N=6	Test	Mean	25.00	11.83	28.67	12.33	35.00	36.83
			SD	7.21	2.48	1.21	3.01	8.92	8.35
		Retest	Mean	25.00	11.83	28.50	12.83	30.82	31.17
			SD	7.21	2.48	1.87	3.87	7.83	9.91

Table 3.2. *The sequence learning with context-shift learning paradigm.*

Phase	**Description**	**Doors shown**	**Correct response**
Practice	Cue-association	$P_1P_2P_3$	P_1→positive-feedback
Sequence-Learning	Chain step A Chain step B Chain step C Chain step D	$A_1A_2A_3$ $B_1B_2B_3$ $C_1C_2C_3$ $D_1D_2D_3$	A_1→ positive-feedback B_1 →A_1 → positive-feedback C_1 →B_1 →A_1 → positive-feedback D_1 →C_1 →B_1 →A_1 → positive-feedback
Context-Shift Generalization	Example generalization trial	$D_1B_1X_1$	D_1 →C_1 →B_1 →A_1 → positive-feedback
Retest	Cue-association	$Y_1Y_2Y_3$	Y_1→ positive-feedback

Table 4.1. *Summary of Demographic and Neuropsychological Results. Healthy: healthy undergraduates, MDD-T: SSRI-treated patients with MDD, MMSE: Mini-Mental Status Exam, BDI-II: Beck Depression Inventory II, BAI: Beck Anxiety Inventory, Tridimensional Personality Questionnaire (TPQ) dimensions: HA: harm avoidance, RD: reward dependence, NS: novelty seeking.9-Carriers: subjects with one copy of the 9-repeat DAT1 allele. 10/10: subjects homozygous for the 10-repeat DAT1 allele.*

			Age	Education	MMSE	BDI-II	BAI	WAIS-R	NS	HA	RD
Healthy	**9-Carriers N=80**	Mean	19.48	13.79	29.32	10.67	11.71	14.13	15.72	13.20	17.29
		SD	1.19	1.09	1.01	5.72	6.78	3.06	4.46	6.14	4.10
	10/10 N=65	Mean	19.51	13.78	29.51	10.67	10.60	14.90	15.98	12.73	17.27
		SD	1.366	1.40	0.64	6.40	6.57	3.60	4.29	5.68	4.22
MDD-T	**9-Carriers N=23**	Mean	32.07	11.17	29.04	11.70	10.65	11.39	13.87	14.87	16.00
		SD	11.41	3.04	0.93	8.88	6.51	2.98	5.39	8.45	5.88
	10/10 N=15	Mean	33.77	11.67	28.73	14.40	14.33	11.60	14.13	17.53	16.33
		SD	12.01	3.33	1.28	11.49	10.46	2.23	3.94	5.99	4.04