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Research report

Depression impairs learning, whereas the selective serotonin reuptake inhibitor, paroxetine, impairs generalization in patients with major depressive disorder

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ABSTRACT

To better understand how medication status and task demands affect cognition in major depressive disorder (MDD), we evaluated medication-naïve patients with MDD, medicated patients with MDD receiving the selective serotonin reuptake inhibitors (SSRI) paroxetine, and healthy controls. All three groups were administered a computer-based cognitive task with two phases, an initial phase in which a sequence is learned through reward-based 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). 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. 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 impairment in hippocampal-dependent generalization of past learning to novel contexts, not otherwise seen in the medication-naïve MDD group. Thus, SSRIs might have a beneficial effect on striatal function required for sequence learning, but a detrimental effect on the hippocampus and other medial temporal lobe structures is critical for generalization.

1. Introduction

Major depressive disorder (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 and 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 and Nemeroff, 2007; Nestler and Carlezon, 2006; Nutt, 2006; Perona et al., 2008). Converging evidence from the literature confirms the involvement of the broader basal ganglia dopaminergic system in the patho-physiology and cognitive changes related to MDD. For example, recent imaging studies suggest that patients with MDD show cognitive and neurochemical dysfunction directly related to the nigrostriatal system (Dunlop and Nemeroff, 2007; Robinson et al., 2012; Walter et al., 2007). In addition, the major symptom of MDD, anhedonia, has been linked to dopaminergic dysfunction in the basal ganglia (Bressan and Crippa, 2005; Dhillon et al., 2008; Heinz et al., 1999; Miller et al., 1996; Schmidt et al., 2001). Further, patients with MDD have a three-fold higher than normal risk of developing Parkinson's disease (PD) (Leentjens et al., 2003; Schuurman et al., 2002), in which nigrostriatal dopaminergic neurons decay (Kish et al., 1988). Finally, studies have reported reductions in the size of the striatum in patients with MDD (Lorenzetti et al., 2009) that has been linked to impairments in motor sequence learning (Naismith et al., 2006).

However, because psychomotor retardation is a common feature of MDD (Buyukdura et al., 2011), it is unclear whether such deficits

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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 H. et al., 2007). In this task, participants learn to execute a chain sequences leading to reward. The chain is gradually lengthened until a complete sequence in learned. Subjects are first trained to learn A→reward, followed by B→A→reward, and so forth until a full sequence is acquired (D→C→B→A→reward). Learning is evaluated by the number of errors that are committed at each stage of the task, and therefore, learning does not dependent on response speed. Converging evidence from the literature suggests that the basal ganglia dopaminergic system is vital for this type of reward-based sequence learning (Haber and 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 (Nagy H. et al., 2007). A different study showed that dopaminergic medication (L-dopa) remediated this deficit (Shohamy et al., 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 et al., 1996; Myers et al., 2002, 2003). Specifically, a previous study using this task found that PD patients with nigro-striatal 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 (Nagy H. et al., 2007), consistent with the view that the reward-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 and 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 et al., 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. It has been hypothesized that selective serotonin reuptake inhibitors (SSRIs) achieve their therapeutic mood-enhancing effect, in part, by modifying synaptic availability of serotonin, by enhancing dopaminergic function in the brain (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, a substructure of the hippocampal region (Boldrini et al., 2009; Malberg and 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). 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. SSRI-induced neurogenesis could indicate a learning improvement with SSRIs. However, past studies showed ambiguous effects of SSRIs on medial temporal lobe dependent processes (Carlini et al., 2012; Igelstrom and Heyward, 2012; Sass and Wortwein, 2012; Vythilingam et al., 2004).

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 the SSRI treatment. In our current study, we investigate the cognitive correlates of striatal and hippocampal function in two groups of patients with MDD, those that are 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 and Heyward, 2012; Sass and 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 reveal an MDD-derived sequence-learning deficit, these medications led to an additional and heretofore novel impairment in the medial temporal lobe dependent generalization of this learning.

2. Methods

2.1. Participants

We recruited 16 medication-naïve patients with 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, Palestinian Territories. All subjects were Caucasians, ranging from 18 to 60 years of age. Participants were group matched for age, gender and years of education, as shown in Table 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

Table 1
Summary of demographic and neuropsychological results. HC: healthy controls, MDD: medication-naïve patients with MDD, MDD-T: SSRI-treated 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
HC						
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						
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						
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