

To Go or Not to Go?

Differential Activation during Response Inhibition in Major Depressive Disorder

by

Laura B. Gabriel

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Advisor: Dr. Scott A. Langenecker

Abstract

Major depressive disorder (MDD) is often the result of a long list of factors, one such factor is a disruption in frontal brain circuitry. More specifically, MDD is characterized by the inability to set shift and inhibit past negative memories, thoughts, and feelings. Based on the literature, it was hypothesized that individuals with MDD will have bilateral frontal hyperactivation and slower response time during behavioral inhibition, as both are thought to be the manifestation of greater effort extended on the part of individuals with MDD to maintain similar accuracy as healthy individuals. The current study used a computer-based inhibitory control (IC) paradigm, the Parametric Go/No-go (PGNG), and functional MRI to illuminate differences in neural activation during response inhibition for MDD versus healthy control participants. The task was administered to 26 healthy controls (Females, $n = 17$) and 26 subjects with MDD (Females, $n = 18$). Results indicated no difference in “Go” and “No-go” target accuracy between the two groups, and significantly slower response time for the MDD group, as well as bilateral frontal hypoactivation in the MDD group. A reduction in response time might be a sign of increased interference in set-shifting, and/or psychomotor slowing, a common symptom of MDD. Likewise, unexpected hypoactivation suggests that the MDD group has an overall decrement in functioning within IC circuitry. Further research is needed to better inform the source and consequences of this neural dysfunction.

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When you type “depression” into Google you receive 77,800,000 hits and the first three are shaded in the distinct pink denoting those websites as sponsored links that sell medications used to treat the condition. An individual can use these medications to treat the symptoms that are listed on a corresponding page. In the current era of readily available information, it looks as though it would be easy to treat a nasty bout with depression. Unfortunately this is far from the truth; clinical depression affects 6.7% of the U.S. adult population according to the NIMH website (<http://www.nimh.nih.gov/statistics/index.shtml>), which goes on to report that it is the leading cause of disability in those between the ages of 15 and 44. Depression is a common cause of suicidal ideation, attempts and success. The widespread age range of individuals with depression and the sheer prevalence of the disorder beg a response from clinicians and researchers with the resources to solve the elusive riddle.

Definition and Symptoms Necessary for Diagnosis

Major Depressive Disorder (MDD) is defined as one or more Major Depressive Episodes (MDEs; American Psychiatric Association [*DSM-IV-TR*], 2000). MDEs are made up of numerous features that tend to consolidate around the heading of sadness. An individual can have a single MDE and be clinically diagnosed with MDD or an individual can have multiple episodes and be diagnosed with recurrent MDD. Whether they experience one or many episodes, the characteristics of an MDE are the same. An MDE is a period of at least two weeks in which an individual is unable to find pleasure in nearly any activity. The loss of pleasure or persistent sadness associated with an MDE needs to be compounded by at least four additional symptoms to meet the criteria for MDD. There can be changes in weight/appetite, sleep, or

psychomotor activity, or loss of energy, feelings of worthlessness or guilt, difficulty with thinking or making decisions, or persistent thoughts of death or suicidal ideation (*DSM-IV-TR*, 2000). Clinically one can experience a variety of symptoms to be diagnosed with MDD, including, but not limited to: irritability, an inability to sleep through the night with subsequent fatigue, decreased productivity at work, or the belief that current troubles are insurmountable. In its most severe forms, depression may lead to suicidal planning or attempts. It is common for most individuals to experience some of these features throughout their lives, but what separates clinically depressed patients is that they experience these symptoms for 2 weeks or more, often on multiple occasions, to the point where it negatively impacts their daily functioning.

Societal and Individual Impact

People who suffer from MDD are not just momentarily down; they have uncontrollable and often devastating sadness that can prevent them from functioning within work and social settings. Thus MDD not only affects the individual experiencing it, but the friends and family who are frequently unable to help or find a cure. Thirty-two is the current median age of onset of depression (*DSM-IV-TR*, 2000) so in many situations the cure is confounded by a combination of past and recent experiences. In depression, an individual's past experiences can shape the way they handle their melancholy and instead of evaluating how their current cognitions and behaviors might contribute to their mood, the feelings of helplessness and stress are often too frequently present and therefore difficult to manage. Characteristics of MDD, such as severe melancholy and constant sadness, may be an important clue in differentiating between the brains of healthy individuals and those with depression. The mere persistence of the emotional symptoms of MDD is a function of its relationship with the executive control portion of the brain. Instead of inhibiting thoughts and behaviors that elicit or exacerbate a depressed mood,

patients seem to have difficulty successfully engaging the systems that might inhibit or modify unwanted or persistent negative thoughts (Dai & Feng, 2011). In this sense, those with MDD may not necessarily have more intense or contextually negative emotions, but rather they cannot regulate their emotions like a healthy person (Joorman, 2010; Joorman & Gotlib, 2010). This theory has been further prompted by the distinct differences that appear between functional neuroimaging of depressed versus healthy study participants during executive functioning tasks (Langenecker et al., 2007b; Rogers et al., 2004).

Precipitating Factors and Course of Illness

It is often thought that a neurotransmitter imbalance between norepinephrine, serotonin, and dopamine is a contributing factor in depression (Goddard et al., 2010; Levinson, 2006), although other possibilities have been hypothesized. The serotonin transporter gene (5-HTTLPR) is responsible for reducing the amount of serotonin within the synapse and is thought to be dysfunctional in MDD (Joensuu et al., 2010); many antidepressants work to address this dysfunction. The short allele of the serotonin transporter gene is thought to interact with stress to increase the risk for MDD. Relatives of those diagnosed with affective disorders are at increased risk themselves and it is thus important to conduct genetic studies (Weissman, Kidd, & Prusoff, 1982). A recent meta-analysis on the serotonin transporter gene, stress, and depression found that the short allele made individuals more sensitive or vulnerable to stressful events, specifically childhood maltreatment and stress from specific medical conditions (Karg, Burmeister, Shedden, & Sen, 2010). The authors commented that previous analyses that did not reach significance had used subjective instead of objective measures of stress and not taken type of stressor into account. Brain abnormalities and traumatic life events have also been shown to contribute to MDD diagnoses (Weniger, Lange, & Irle, 2006). Hsu, Langenecker, Kennedy, Zubieta, and

Heitzeg (2010) found a positive correlation between activity in orbitofrontal cortex (OFC) during presentation of negative emotional stimuli and recent stressful events in individuals with MDD relative to controls. Because the active portions of the orbitofrontal cortex are implicated in emotional impacts (Kringelbach & Rolls, 2004) this finding suggests that current or recent stress had primed the OFC pathway, which in turn elicited greater activation with the presentation of negative emotional stimuli. Further, recent stress was negatively correlated with activity in ventrolateral prefrontal cortex (VLPFC) which was interpreted to be a result of stress on cognitive control centers.

Individual characteristics conducive to depression are low self-esteem, a distorted view of others' perception of oneself, a pessimistic outlook, or an inability to acknowledge personal achievement (McKenzie et al., 2010; Sha, 2006). These traits are often compounded by external issues such as a history of physical and/or sexual abuse, familial alcoholism, death of a loved one, growing up in a broken home or any number of similar stressful life events (Buzi, Weinman, & Smith, 2007; Schoedl et al., 2010). Individuals with these traits or with traumatic experiences are more likely to experience depression or depressive symptoms and women are also twice as likely as men to be diagnosed with MDD (Kuehner, 2003). Once diagnosed, people often experience different courses of the illness. Recurrent episodes can either occur in clusters with long breaks of remission in between or the episodes might occur sporadically with shorter periods of remission. Longer periods of remission often occur earlier in the life course of the illness and the greater the number of prior episodes, the greater the chance an individual will experience subsequent episodes. Most disturbing are statistics regarding MDD recovery, in which 40% of patients may still experience full MDD symptoms one year after treatment has

begun and only 40% make a full recovery (*DSM-IV-TR*, 2000; Rush et al., 2006; Trivedi et al., 2006). Twenty percent continue to experience less severe symptoms (*DSM-IV-TR*, 2000).

Possible Developmental Determinants and Risk Factors

The presence of emotion dysregulation in MDD can be understood within the context of an individual's wider developmental and historical experiences. Individuals learn how to process and control emotions when they are very young and, if an individual learns effective self control strategies, those strategies are more prone to last. Individuals become vulnerable to depression in response to stressors when they form external control strategies or poor coping methods (Jopp & Schmitt, 2010). Some people choose to play an instrument or engage in strenuous physical activity to alleviate stressful or gloomy thoughts. Unfortunately, people with depression often ruminate about negative thoughts or past events, or employ other ineffective cognitive processes when feeling sad (Takano & Tanno, 2009). It seems appropriate then, to look at parts of the brain that have been implicated in emotion regulation, attention, inhibitory control, and memory. In light of the characteristics of depression mentioned here, the complex interaction of these cognitive and affective processes, and the brain structures that underlie them are plausibly responsible for the emotional and functional manifestations of the disorder, at least in part. The present thesis is targeted to address regulation of thoughts as one possible pathway of dysfunction and risk for illness in MDD.

Executive Functioning (e.g., Inhibitory Control) as a Construct

Executive functioning is a broad term that encompasses many jobs of a managerial nature supported by the frontal and parietal cortical areas. Executive functioning is subsumed under the larger heading of metacognition, which is loosely defined as "thinking about thinking." As an aspect of metacognition, executive function involves monitoring one's behavior, regulating that

behavior, and inhibiting inappropriate responses. Healthy adults are able to perform many executive functioning tasks with moderate effort, whereas an inability to effectively control executive functioning is a marker for several types of neuropathology. Examples of these tasks include selective and sustained attention, set shifting or cognitive flexibility, error monitoring, emotion regulation, memory, rule acquisition, abstract thinking, theory of mind, and—significant to the current study—inhibitory control or response inhibition. Without much consideration, the average individual uses most or even all of the aforementioned executive functions in a day's time. For example, selective attention and sustained attention are necessary if one wants to attend to a single auditory event amidst several other auditory disturbances for any period of time (Lamers, Roelofs, & Rabeling-Keus, 2010). Rule acquisition enables one to quickly and efficiently pick up on patterns in the environment (Anderson, Fincham, & Douglass, 1997). Theory of mind facilitates the understanding of intentions, desires, and beliefs of the self and of others (Drubach, 2008). Set shifting or cognitive flexibility would be helpful if an individual had to improvise a dinner recipe after finding out that she was missing a key ingredient (Stemme, Deco, & Busch, 2007). Error monitoring produces a signal if an individual misspeaks (van de Meerendonk, Kolk, Chwilla, & Vissers, 2009). Inhibitory control (IC) is the ability to restrain responses that have been habituated and is, for example, required in activities such as dieting or playing the game, 'Simon Says' (Nederkoorn, Van Eijs, & Jansen, 2004). IC can also be used to describe the process by which unwanted thoughts or ideas are regulated, often described as set-shifting or suppression IC (Hasher & Zacks, 1979). As mentioned earlier, the inability to regulate negative thoughts and emotions is a major symptom of MDD and the focus of the current thesis (Fladung, Baron, Gunst, & Kiefer, 2010; Santesso, 2008).

Due to the complex interaction between the many facets of executive functioning, assessing a single component can be difficult. There are currently numerous neuropsychological tests that assess specific components of executive functioning, although not often in ideal ways. For example, the tests vary in difficulty level, in which executive functions they test, and in how many executive functions are at use during their completion. Depending on the type and number of executive functions in use, this can in turn confound the interpretation and validity of the results. Few tests are able to narrow in on one executive function and therefore interpretation of the corresponding fMRI results are a combination of functional activation from multiple processes. An ideal imaging test would be able to test specific executive processes while eliminating ceiling effects and/or influences from other types of executive functions, or indeed other cognitive processes. One of the more recent neuropsychological computer tasks, which can be used inside or outside of the scanner, is the Parametric Go/No-go (PGNG; Langenecker et al., 2005). The task has three levels of increasing difficulty to better account for performance by group by activation interactions. The PGNG is unique in that it begins at a relatively easy level where most everyone performs well (>95% accuracy) and increases in difficulty to the point where many individuals find themselves considerably challenged. The first level of difficulty is similar to other types of tasks that have been described as GNG tasks, what we have come to refer to as static IC tasks. These tasks are defined by finite and unchanging Go and No-go sets. We add two more levels of difficulty, so that the final level is challenging for even the healthy control participants (60-70% accuracy). The PGNG is specific in the functions it tests while controlling for ceiling effects often exhibited by young, healthy controls. The PGNG can be performed by patients and participants while inside an fMRI scanner. By comparing the fMRI blood oxygenation level dependent (BOLD) signal data of controls and MDD patients during IC,

it is likely that differences at the neural level will become apparent. The sensitivity of spatial and temporal resolution of the fMRI and the parametric variability in difficulty of the PGNG will hopefully shed light on differential activation between the two groups that would otherwise remain undetected (Langenecker et al., 2007a).

Individuals with MDD have an inability to cope with and regulate negative emotions that appears to be manifest within differential neural activation (Abler et al., 2010). Evidence for the lack of emotional control in MDD lies within the fMRI data gathered during a number of neuropsychological tests of IC/response inhibition (Berman et al., 2011). Our underlying thesis is that the regulation of thoughts and emotions is subserved by a common, non-specific IC network (Rubia et al., 2001). While overwhelming behavioral differences between patients and healthy controls are not yet fully clear, a plethora of imaging data tend to reveal differences within the inferior frontal cortex (IFC) and the anterior cingulate cortex (ACC; Berman et al., 2011; George, Ketter, Parekh, & Rosinsky, 1997; Harvey et al., 2005; Holmes et al., 2005; Matthews et al., 2009; Wagner et al., 2006). In controls, dorsolateral prefrontal cortex (DLPFC) has been shown to activate when the individual must perform a novel action, right ventrolateral prefrontal cortex (VLPFC) activates in the face of irrelevant responses, and ACC is active when performance and goals are assessed (Matthews et al., 2009; Wagner et al., 2006). When female participants with MDD and current anhedonia were shown pleasant stimuli, they showed decreased activation in medial frontal cortex (MFC) and increased activation in IFC, ACC, thalamus, putamen, and insula, relative to healthy controls (Mitterschiffthaler et al., 2003). The latter was a study of affect processing in MDD, but these brain regions have also been implicated during tasks of IC. In tasks of IC, individuals with MDD also tend to activate ventral IFC and superior temporal gyrus (Langenecker et al., 2007b). It is also possible that different groups

utilize separate networks to accomplish the same level of behavioral performance in a task, often referred to as compensation, or recruitment (Cabeza, 2002; Langenecker & Nielson, 2003).

There are several plausible explanations for why MDD patients have differential activation in areas of the prefrontal cortex typically implicated by IC paradigms. Activation that is muted relative to the activation of healthy controls might be a result of brain regions that do not function at an efficient level. For instance, perhaps the uncontrollable emotional response in MDD is a result of an inability to activate the inhibitory network. When activation is much greater than that of healthy controls, there is reason to believe that those regions are working harder in order to maintain a certain level of performance on an inhibitory task (Langenecker et al., 2007b; Schöning et al., 2009). Differential activation and performance speaks to the evolving conclusion that MDD is a more serious disorder than once thought. Brain dysfunction in chronic MDD is in the same playing field with schizophrenia and other historically serious disorders. The disability data related to long term depression may not be that ominous, but the monetary, familial, and interpersonal cost of depression is still staggering.

Development of IC and Measurement Strategies and Tasks. Executive functioning abilities develop at different stages of an individual's life. The development of IC in those who eventually become depressed is likely atypical, and techniques for examining these constructs in childhood have been investigated (Halari et al., 2009). Surprisingly, even though executive functions are complex in nature, children experience their inception around similar ages, often earlier than once thought. For instance, false beliefs are a type of theory of mind in which one has knowledge about the world that is not true to reality (e.g., a woman left her reading glasses on her dresser, her husband moved them, and the woman therefore had a false belief of their location). Adults and even 4-year-old children understand false belief, but children 3-years-old

and younger perform below chance on these tasks. False belief is pertinent because the literature points to IC as a mechanism that aids in successful performance. The development of IC, or lack thereof, is crucial because impulsive children who lack IC are often diagnosed ADHD (Rubia et al., 2010). These individuals, and others, may fail to ever learn adequate impulse control, often to their detriment. There are academic and social sequelae of the poor IC that might subsequently result in poor long term outcomes in these and other domains (Banich et al., 2009).

Infants and young children were once thought to be solely dependent beings who must be taught everything if they were ever going to mature into functioning adolescents and adults. Further, the executive skill set of an infant was not thought to exist, let alone be related to their skill set as an adult (Piaget, 1962). Diamond (1990, 2000) and many others have been working for the last 25 years to contradict Piagetian thought. Piaget theorized that infants and young children moved chronologically through a developmental schedule, that developmental markers were inflexible, and that the functioning adult was the epitome of cognitive maturity. Diamond and others have worked to dispel the myth that children are truly incapable of seemingly simple tasks. These researchers argue that just because children have not reached the final stage of cognitive development, they can still grasp cognitively-demanding concepts. Diamond and Gilbert (1989) found that children understand contiguity—a developmental milestone—if they are able to inhibit the reflex to touch one part of the contiguous object. These children can grasp the concept if they are not held back by an underdeveloped skill set. Much like in tests measuring false beliefs, in the contiguity tasks it is not necessarily that children are unable to perform tasks, it is that they have not yet developed stable IC. Functional neuroimaging findings also support this hypothesis, in that neurocircuitry underlying IC in children has been shown to

approximate that of adults, although children may not employ such neural mechanisms as efficiently (Casey et al., 1997).

The relation of childhood and adult IC was creatively investigated by Shoda, Mischel, and Peake (1990) when they asked 4-year-old children to wait in a room with a marshmallow. If the children waited “until they got back” without eating the marshmallow, then they would receive two marshmallows. In a follow-up study with the same children between 15 and 18-years old, those children who were able to inhibit eating the marshmallow at age 4 were rated as having more self control and success in resisting temptations as a teen. The IC at age 4 also correlated with participants’ subsequent verbal and quantitative scores on the SAT.

In adolescence, cognitive control is often challenged because teenagers seem to be more sensitive to reward than they are to punishment. Geier and colleagues (2010) found that adolescents show hyperactivation in prefrontal regions, relative to adults, during response preparation. The researchers took the over-activity during anticipation of reward as a sign that adolescent cognitive control is underdeveloped relative to adults. In light of the marshmallow study by Shoda, Mischel, and Peake (1990), there is a good chance that some adolescents are better able to regulate cognitive control. Depression is quickly becoming a common diagnosis among adolescents. During a behavioral inhibition task, adolescents with MDD have been shown to exhibit reduced activation in right DLPFC, ACC, and IFC (Favre et al., 2009; Halari et al., 2009).

Executive Functioning Tasks and Dysfunction in Executive Functioning and IC in MDD

Similar to the tasks designed for children, IC can be assessed in adults using any of a variety of clinical measures including, but not limited to, the Wisconsin Card-Sort Test (WCST), Stroop Color-Word Test, Go/No-go tests (e.g., the Parametric Go/No-go in the current study),

and any task emphasizing a switch from a prepotent to a non-habituated response. As noted previously, tasks designed to assess IC may also assess other executive functions, which is a confound that reflects a weakness in the literature.

The Wisconsin Card Sorting Test (WCST). The WCST (Heaton, 1993) has four key cards that participants use to guide their organization of a deck of like-faced cards, and all the while the category by which they must match is changing. WCST standardization prevents the examiner from describing how to perform the task, or providing any feedback beyond whether a move is correct or incorrect. Cards are matched on form, number, or color and once the participant has achieved ten of any category the next category begins and the participant must inhibit the response with which they just became accustomed to responding. Individuals who continue to use one category after receiving feedback that the formerly correct choice is now incorrect are said to be making perseverative errors. This perseveration impairs the participants' ability to complete the highest number of categories in the fewest number of cards. Likewise, 'failure to maintain set' explains the behavior of participants that have trouble completing ten sets of any category. Due to the negative emotional perseveration in MDD, the WCST enables researchers to gauge impaired perseveration in a more neutral context.

Grant, Thase, and Sweeney (2001) found that, while depressed younger adults were not significantly more impaired in verbal fluency, attention, learning, and memory tasks (for a list of tasks and description see Grant et al., 2001), they performed significantly worse on the WCST. Outpatients with MDD, matched with controls, displayed a reduced ability in terms of learning and maintaining rules of the task, and in shifting set. Similar findings were also reported by Channon and colleagues (1996). The research findings related to WCST performance among individuals with depression are important, but can be interpreted in multiple ways. For instance,

perhaps the patients were not ill enough to cause difficulty within all of the tests or the other tests were not sensitive enough to illuminate differences between patients and controls.

Oren and Boone (1991) used the WCST to assess higher-order cognitive impairments in MDD because impairments on memory, motor dexterity, and mental processing speed had already been observed (Bulmash et al., 2006; Fairhall, Sharma, Magnusson, & Murphy, 2010). The researchers compared an MDD outpatient group to matched controls, and also included a group of outpatients with dysthymia to judge whether severity or type of depression had a significant effect. Participants underwent measures of symptom severity (i.e., SCID, BDI, HDRS) and then completed the WCST. In regards to the WCST, a depressive diagnosis of Dysthymia or MDD predicted the percentage of perseverative errors, whereas severity of depression predicted scores on total errors, failure to maintain set, and percent perseverative responses. Overall, the more depressed the patient, the worse the performance. A high level of perseverative responding, indicating a lack of problem solving and hypothesis testing, was found in the MDD patient group.

The Stroop Color-Word test. The Stroop task (Stroop, 1935) is another test often used to measure IC in depression and is comprised of three tasks. The first part asks the subject to read down a list of three color words printed in black ink as quickly as possible, the second part presents series of letters (i.e., XXXX) printed in three colors and they must name the color, and the last part shows a list of color words that are printed in incongruent colors (e.g., the word “red” printed in blue ink) and the participant must name the ink color. The latter part is the experimental component, as response time increases due to the interference of the printed word. Theoretically, participants who have more frontal interference at baseline (i.e., those with MDD, OCD, PTSD, or ADHD, etc.) will have even more trouble responding in a timely manner. The

Stroop effect has also been used to develop tasks examining the effect of emotional salience on IC (e.g., George et al., 1997). McNeil and colleagues compared three patient groups (PTSD, MDD, and OCD) across three Stroop measures, one General Anxiety Stroop, one Depression Stroop and the original Color-Word Stroop. The researchers did not use a control group, but found the largest effect of the Stroop on the PTSD group. However, differences within the three patient groups did not prove to be significant. In fact, the MDD group had the faster response times. While a comparison with a control group would likely have revealed interference in the three patient groups, the Stroop was not sensitive enough a measure to distinguish between these seemingly very different clinical populations (McNeil, Tucker, Miranda, Lewin, & Nordgren, 1999).

Go/No-go (GNG) tests. Go/No-go tasks reflect a broad category including any task that habituates a participant to one response and then asks them to inhibit responding on some cue. These tasks are increasingly being used in studies of depression and related disorders, although there has been some confusion between what is a Stroop-like and what is a Go/No-go task. The PGNG is one such task with three levels in which participants must first respond to any X, Y, or Z in a string of rapidly presented letters (500ms between letters), on the second level they can only respond to X and Y if they are in alternating order, and the last level is similar to the second, but they are responding to all three X, Y, and Z. The first level habituates participants to a prepotent response and IC is not necessary because X, Y, and Z can be responded to in any order; the second and third levels add a component of IC. Langenecker et al. (2007a) found that within a cognitive battery including tests of attention, set shifting, and IC, attention and set shifting performance was weakly correlated with IC performance which suggests they are different executive functions. Moreover, PGNG was a sensitive enough measure to detect

differences within several patient and non-patient groups; controls were marginally better than depressed and bipolar patients in inhibitory processing speed, ($p = 0.077$) and ($p = 0.079$), respectively. Further, Anxiety groups were shown to perform better than the Bipolar and MDD/dysthymia in IC accuracy.

More recently, a wider breadth of neuropsychological tests were employed by Degl'Innocenti, Agren, and Bäckman (1998) to evaluate executive functioning in MDD. The researchers used the WCST to assess the ability of participants to use working memory and feedback to form conceptual sets, to set shift when told to do so, and to hypothesize appropriate problem solving strategies. The researchers also used the Stroop Test to test inhibition and the Controlled Oral Word Association (COWA) test to measure verbal fluency under timed-retrieval. These are all executive functions that are hypothesized to be disrupted in MDD. The results revealed selective impairment within the MDD group compared with matched controls. Controls were significantly more successful on the WCST in the number of trials, the number of errors, the number of non-perseverative errors and the percentage of conceptual level responses. The MDD group was slower in all trials of the Stroop in comparison with controls and there were significant effects for all three trials of the COWA, with the MDD group naming fewer words for each of the three letters. These results suggest that the MDD group is impaired in the ability to alter behavior based on feedback. Although this study found no differences in inhibition between groups, the Stroop test might not be sensitive enough to reveal them. Lastly, the results of COWA indicate a slowing of retrieval from the lexicon.

Two characteristics of MDD, diminished motivation and impaired decision making, have foundations in functioning of the frontal and parietal lobes. Cella, Dymond, and Cooper (2010) used the Iowa Gambling Task (IGT) to assess plasticity of decision-making in individuals with

MDD currently on medication compared to a group of matched healthy controls. The IGT allows participants to choose from a deck of cards for a monetary gain and/or loss. Two decks immediately reward large sums, but eventually lead to long term loss and the second two decks offer small immediate rewards, but produce fewer losses and thus end in an overall gain. The researchers used the contingency shifting variant IGT which is on a computer and involves two slightly different phases, but is otherwise similar to the original IGT in what it measures. Not surprisingly the researchers found that the MDD group performed below chance, especially in the final three blocks of the standard IGT. During the shifts in reinforcement in the contingency shifting variant IGT, the MDD group again performed worse than the control group. These results can be interpreted as impaired sensitivity to reward and punishment in MDD. The results of the contingency shifting variant IGT suggest an inability to reevaluate decisions based on changing environments, similar to findings related to performance on the WCST.

The executive functioning tasks designed to hone in on IC are different because they many utilize various additional executive functions, but they share the commonality of better assessing individuals' ability to contain their desire to respond prematurely or inappropriately. This includes control of both thoughts and actions. Although the tasks can be discussed independently to detail their relative benefits and shortcomings, they do share a universal requirement; participants must engage with a particular concept to the point that they are habituated in their response to it, and then they are forced to respond in a way that is unnatural relative to how they have been responding. The aforementioned tasks all meet this latter condition, but vary in the amount of effort necessary for successful completion. As a result, one must take into account how taxing a test is *and* how the related challenge on other cognitive functions like working memory would in turn alter how much of an individual's performance can

be attributed to their response inhibition and how much is attributable to the challenging nature of the task.

Response inhibition is an effortful activity, especially when there are other factors involved that may degrade its function and efficiency (Lindqvist & Thorell, 2009). Very young children are known to hit, kick, and scream at inappropriate times, but most learn to curb that aggression as they develop, through a process of socialization. The process of socialization suggests that certain behaviors must be, at least at first, consciously inhibited (Côté, Vaillancourt, LeBlanc, Nagin, & Tremblay, 2006). Most adults understand that certain behaviors can be appropriate within some contexts and disrespectful in others. Few would blame an individual that swears at his team in a sports bar, but the same man who swears in church has a lack of IC. Regardless of the inappropriate behavior, a lack of IC can have relatively detrimental effects.

Poor IC is certainly not the only contributing factor for MDD; individuals experiencing either the bar or church scenario might describe their actions as uncontrollable. These examples are relevant because the current study focuses on another ‘uncontrollable’ response; patients with MDD often have overwhelming and unmanageable sadness. Instead of regulating these emotions, individuals with MDD find that these negative emotions seep into all aspects of their lives. This may contribute to even more negative feelings. The developmental acquisition of executive function is important because some individuals do not learn adequate coping methods and thus resort to ineffective responses to pain and loss (Nolen-Hoeksema, 2000). Through use, these responses develop prepotency and then few opportunities arise in which an individual can undo a maladaptive response or replace one response with a more adaptive one. In this respect, stressful life events may exacerbate poor IC, thereby provoking unusually intense negative

emotions. To date, no sole determining allele linking some people to MDD has been found. Rather, it is this culmination of factors—reduced IC, excessive emotional reactivity at the neurological level, and stressors and life events—that likely contribute to the illness (Hsu et al., 2010; Joorman, 2010; Langenecker et al., 2007a).

MDD is manifested in many other areas of cognitive dysfunction including memory, emotion processing, and motor dexterity and speed. For the purposes of this paper, memory, emotion processing, visual-spatial abilities, and motor dexterity and speed are all viewed as problems in MDD that are beyond the purview of the present study. These areas of difficulty are well known in the literature and have been addressed in a recent review by Langenecker, Lee, and Bieliauskas (2009).

The deficiencies in IC in the MDD population are the focus of the current study. The aforementioned study by Murphy et al. (1999) found a bias of MDD participants to respond normally to sad targets and slowly to happy targets on an inhibition and set-shifting paradigm. Alongside this finding, depressed participants, when compared to matched controls and to manic participants, were unable to shift attention from one target emotion to another. These results, in conjunction with the emotional bias, suggest an inability for the depressed group to inhibit previously salient emotions.

Langenecker et al. (2005) found that even mildly depressed women exhibited deficits in IC in relation to matched healthy controls. Using the PGNG, the researchers assessed IC on two of three levels of the task. As in previous studies, Langenecker et al. found that depressed women performed significantly worse on the more challenging level three of the PGNG (i.e., alternatively responding to X, Y, and Z stimuli). Contrary to hypotheses, the differential performance of MDD and healthy controls on the easier level two of the PGNG (i.e.,

alternatively responding to X and Y) did not reach significance. These findings suggest dysfunction within IC in depressed individuals; most reliably on sensitive tasks (see Langenecker et al., 2007a).

Brain Areas Supporting Executive Functioning, Specifically Inhibitory Control

As with other studies using fMRI, the literature on neurocircuitry related to IC proves somewhat inconsistent. Nevertheless, there appears strong evidence for functional activation within the DLPFC, ACC, IFC and basal ganglia (BG; Aron, Robbins, & Poldrack, 2004; Goghari & MacDonald, 2009). More specifically, activation appears to lie within the dorsal ACC (dACC) and the right IFC, although Rubia et al. (2002) found left lateralized activation in the IFC. Often researchers combine either a Stop-Signal Task, Go/No-go task or another task measuring IC during fMRI (e.g., Chevrier, Noseworthy, & Schachar, 2007).

There are different aspects of cognitive control that, when activated together, enable an individual to inhibit a prepotent response. One aspect of cognitive control is focusing attention on the relative or important features of a situation while ignoring other extraneous parts of the environment. Weissman et al. (2004) examined the relationship between dACC activation and ability to complete a cued global/local selective attention task. The task consisted of either global ('G') or local ('L') images that were either a large letter or a bunch of small letters making up a larger letter, respectively. Participants had to press one button if the letter was an 'H' or an 'S' and another button if the letter was an 'X' or an 'O'. This way, the experimenters were able to create congruent trials in which the global and local letters needed the same key press, neutral trials in which a random letter was used or incongruent trials in which the local letter did not warrant the same key press as the global letter. Weissman and colleagues predicted that participants would have more difficulty responding to local than to global cues and indeed

reaction times (RTs) were slower for local trials. Further, the researchers had also predicted greater dACC activity during local cue trials. Interestingly, within the first three of the six trials, there was significantly more dACC activation during local trials. This study highlights both the relationship between controlled responding and dACC activation, as well as the importance of taking practice effects, which tend to increase processing speed, into account.

While attention is an important element of inhibiting prepotent responses, there are other measures that, when used within an fMRI setting, serve to better elucidate the role of neural mechanisms in IC. One of these tasks is the Go/No-go (GNG), which has been used successfully outside the context of fMRI as described above, and has also been used in a variety of forms with fMRI. Konishi et al. (1999) compared prefrontal activation during a GNG task with activation during the Wisconsin Card-Sort Test (WCST). The researchers found substantial overlap between the tasks in their activation of the right IFC and less significantly of the left IFC, although the significance did not withstand statistical correction. Not only does the former provide evidence for a specific location within the PFC that corresponds to IC, but it appears that inhibiting a ‘go’ response and inhibiting a cognitive set are functionally similar. Likewise, in a review by Aron, et al. (2004), the researchers discussed evidence for rIFC and DLPFC activation during other versions of GNG, the WCST, tasks measuring ‘switch cost,’ and tasks requiring inhibition of inappropriate memories.

In the studies by Aron et al. (2004) and Konishi et al. (1999) participants were shown to activate right IFC during the inhibitory trials of GNG and WCST, which suggests that right IFC is involved in at least motor and cognitive IC. Berkman, Burklund, and Lieberman (2009) investigated whether intentional motor inhibition might not have a “spillover” effect within affective inhibitory structures if a task implicitly presented negatively-valenced stimuli. They

found activation within right IFC, ACC and DLPFC during no-go trials. Further, negatively-valenced inhibitory (i.e., no-go) trials produced a reduction in amygdala activity as compared with go trials and with baseline. In other words, active motor inhibition produced “spillover” emotional inhibition during trials with implicit negative emotion. This finding is relevant for the current study because an oft-cited trait of MDD is an inability to inhibit negative emotional affect.

If inhibition is truly localized within these specific parts—right IFC, ACC, DLPFC—of the PFC, the next question is what effect do individual differences in brain activation have on function, if any. Forstmann et al. (2008) used a cued version of the Simon task, fMRI, and diffusion tensor imaging (DTI) to map the connection amongst IC, brain function and brain structure, respectively. The computer version of the Simon task displayed a signal for either ‘congruent’ or ‘incongruent’ and then displayed a screen with either a green or red circle to the right or left of center. In all trials, green meant press left and red meant press right, but they could appear on either side of center (i.e., spatially congruent or spatially incongruent). Further, the label of congruent or incongruent on the first screen was either valid or invalid. For trials that were invalidly labeled, the comparison of good versus poor inhibitors (as measured by reaction time) revealed significant BOLD activation of the right IFC during invalidly cued trials only. Forstmann and colleagues hypothesized that behavioral success, as identified by faster response time, would in turn be related to the connectivity of white matter in the structure activated during the task. The results revealed a positive correlation between right IFC BOLD activation and right IFC structural differences; more proficient inhibitors were found to have greater connectivity within white matter tracks of the right IFC. As stated earlier, individuals

with MDD have been found to have trouble inhibiting negative emotions and the current study sheds light on a potential link between functional difficulty and structural inadequacy.

It is readily apparent that MDD is a disorder involving irregular activation in the frontal lobes. One meta-analysis concluded that at-rest individuals with MDD have hypoactivation in DLPFC, dACC, insula, and superior temporal gyrus (Fitzgerald, Laird, Maller, & Daskalakis, 2008). Other studies (Okada et al., 2003) have likewise found hypoactivation during executive functioning tasks, including tasks of verbal working memory, but many of these studies have small sample sizes (<10) and rely on block designs. Similarly, studies that fail to report performance or report accuracy and no response time do not allow an adequate comparison between the two groups. The event-related design used in the current study, in combination with the PGNG task is suggested to be more effective than preceding studies using block designs, as it enables a focused examination of individuals' response to stimuli requiring IC. The current event-related design allows a comparison of activation during successful and failed behavioral inhibition.

Studies of Impaired Executive Functioning and Inhibitory Control in MDD

Studies of attention have found that, when an MDD group performs similarly with the control group, they show a relative increase in prefrontal and parietal regions (Holmes et al., 2005). In a Stroop interference task, Wagner et al. (2006) found that, while the MDD and control groups performed similarly on accuracy and reaction time, imaging data revealed hyperactivation in rostral anterior cingulate gyrus (rACG) and DLPFC. One study used a verbal *n*-back task during fMRI and found that, when the MDD and control groups performed similarly with regard to reaction time and accuracy, MDD subjects had greater activation in the lateral PFC and the ACC (Harvey et al., 2005). The latter three studies suggest that individuals with

MDD are able to maintain equivalent behavioral performance relative to controls, but they exhibit greater activation during a task in order to maintain said performance.

Few studies have directly considered IC as a dependent variable in MDD. One study measured response inhibition used the PGNG task and an event-related design to compare three behavioral measures and imaging data for 42 participants (MDD = 20). The control group had better performance on target accuracy and faster response times, but the patient group was more successful on inhibitory lure trials (i.e., correct rejections). Activation during correct rejections was found to be greater in the MDD group, specifically in frontal and anterior temporal regions (Langenecker et al., 2007b). Berman et al. (2011) hypothesized that the ruminative style of MDD might be accounted for by differences in activation (e.g. temporal, spatial, and/or strength) in left IFG in the patient group. The MDD group was significantly worse than the control group at removing negative information from short-term memory. Although the MDD and control groups both activated left IFG to the same degree, the MDD group exhibited greater spatial variation within this region. The researchers rationalized the spatial inconsistency as an artifact of ineffectual activation within the MDD group and a cause of the behavioral discrepancies.

Summary Section and Hypotheses

The prevalence and debilitating toll of major depressive disorder are a call to action for clinicians, psychiatrists, other healthcare providers, researchers and all others that have a stake. MDD is characterized frequently as an inability to regulate emotions, to shift between different emotional contexts, and to override rumination through cognitive control. At a neural level, emotion and cognitive control are connected via the subgenual and rostral cingulate cortex, from the amygdala to the PFC (e.g., Phillips, Drevets, Rauch, & Lane, 2003b), with a primary effortful IC foci in the right IFC (Aron et al., 2004). Studies have repeatedly indicated that depressed

individuals exhibit outward and inward problems with executive control/regulation and differential activation in and around these pathways, relative to healthy controls. Previous studies have attempted to pinpoint differences in activation during various tasks of executive function, but few are able to challenge controls enough to elucidate differences, which causes a disadvantage for the MDD group.

The current study uses a PGNG task that has been shown to be challenging not only for individuals with MDD, but also for control groups (Langenecker et al., 2007a, 2007b, 2010). The difficulty of the PGNG, paired with event-related fMRI analyses, will hopefully more clearly distinguish the MDD from the control group as well as neural differences during successful versus unsuccessful behavioral inhibition. Differential activation during response inhibition in an affectively neutral task would suggest that MDD does not just impact dysregulation in emotion, but cognitive control more generally. Or it might suggest that effortful cognitive and affective control circuits are highly overlapping.

Currently there is a contradiction in the literature as to whether individuals with MDD show hyper- or hypoactivation during executive functioning tasks. A majority of studies using event-related fMRI and larger participant populations have found hyperactivation in MDD groups during executive tasks relative to control groups (Harvey et al., 2005; Holmes et al., 2005; Langenecker et al., 2007b; Wagner et al., 2006). Others have reported no difference between MDD and control groups (Barch, Yvette, Sheline, Csernansky, & Abraham, 2003), or hypoactivation (Berman et al., 2009; Halari et al., 2009; Okada et al., 2003). Likewise, one recent meta-analysis suggests that frontal and some temporal hypoactivation in MDD is apparent at resting states (Fitzgerald et al., 2008). This discrepancy across studies is not unique to depression, and similar contradictory findings have been reported in schizophrenia and mild

cognitive impairment, even in healthy aging. Phillips et al. (2003b) rationalized the contradictions as a combination of hyperactivation within the ventral network and hypoactivation within the dorsal network, dependent on the type of task utilized.

As mentioned above, the current PGNG task is meant to challenge control participants in a way that better disentangles activation in various conditions of the task. In the current study, it is predicted that:

H1. The MDD group will have slower response times, relative to the control group.

H2. The MDD group will have worse accuracy for target trials, relative to the control group.

H3. The MDD group will have better or no different accuracy for inhibitory lure trials, relative to the control group.

H4. The MDD group will exhibit dysfunction in frontal circuitry during successful and unsuccessful behavioral inhibition, relative to controls. Specifically, the MDD group will show bilateral frontal hyperactivation for successful rejection trials.

Method

Participants

This study was conducted using a portion of the existing data from two ongoing studies and one completed study (Langenecker et al., 2007b) examining individuals with major depressive disorder (MDD) and matched healthy controls (HC). The current set of participants included 26 individuals with MDD (18 females) and 26 healthy controls (17 females).

Participants were initially evaluated with the structured clinical interview for the *DSM-IV* (SCID-I; First et al., 1995) to determine psychiatric diagnosis. A score of ≥ 15 on the Hamilton Depression Rating Score (HDRS) was used as inclusion criteria for MDD participants. Healthy controls receiving an HDRS score > 5 were excluded. MDD participants with comorbid

disorders other than panic disorder, GAD, or social phobia were excluded. Exclusion criteria for both groups included any history of serious medical illness, any use of psychoactive substances, history of *DSM-IV* alcohol or drug dependence within the past five years, head injury with loss of consciousness, or any regular tobacco use. Further exclusion criteria for HCs were prior treatment with a mental health professional and first or second degree relatives with alcohol or substance abuse, affective disorders, Schizophrenia, or anxiety disorders. All participants met their respective group's inclusion and exclusion criteria and were further included in the current study if they had completed the PGNG task during an fMRI scan. Therefore the data from a total of 52 individuals (26 MDD) was available for behavioral and imaging analyses.

Independent sample t-tests were performed on the demographic variables of interest in order to determine whether there were differences between the HC and MDD groups. The control group did not differ significantly from the patient group in age, $t(50) = .41, p = .582$, level of education, $t(50) = 1.24, p = .067$, or Shipley IQ (Shipley, 1946), $t(49) = .10, p = .205$. There were no differences between the two groups in gender distribution, $X^2(1) = .087, p = .768$. As expected, the two groups were significantly different on the Hamilton Depression Rating Scale-17 (Hamilton, 1960), $t(50) = -21.88, p < .001$, with the MDD group ($M = 19.52, SD = 4.11$) exhibiting significantly higher scores than the control group ($M = .85, SD = 1.42$).

Demographic data for the two groups are presented in Table 1.

Measures

Hamilton Depression Rating Scale. The Hamilton Depression Rating Scale (HDRS) is a 17-item inventory that is administered by a clinician or trained research associate. The scale attempts to quantify the severity of depression with questions regarding physical, psychological and emotional well-being. The first 17 items of the questionnaire are graded and questions 18-21

give more information about the depression (Hamilton, 1960, 1967) and our group has demonstrated strong interrater reliability in administration (Langenecker et al., 2007b, 2010).

Shipley Institute of Living Scale. The Shipley Institute of Living Scale (Shipley, 1946) is comprised of two subsections aimed at measuring intellectual ability. The first subsection involves vocabulary and the second subsection involves abstract reasoning (Villar, 2005).

Task

Parametric Go/No-go Task. The PGNG task involves three levels of ascending difficulty (Langenecker et al., 2005, Figure 1). Each level consists of a stream of black 40-point Times font letters against a white background on a computer. The letters are presented for 500 ms each with 0 ms in between each letter presentation. The participant is encouraged to respond as quickly as possible by hitting a predetermined computer key (letter “n”) with the index finger of their most comfortable hand.

Level 1 is a static-inhibition task that allows the participant to develop a prepotent response to a set of three target letters (here “x,” “y,” and “z”). The target letters appear interspersed among other letters and the participant is instructed to respond every time they see a target letter, regardless of the order in which they are presented (e.g., respond to both x, y, z and y, z, x). Because the participant must respond to the target letters every time regardless of their order, the first level of PGNG is a simple executive functioning test of attention and response time (Langenecker et al., 2007a). Dividing the number of correct target responses by the total number of possible target responses for Level 1 gives the percentage of correct target trials (PCTT—sustained attention and set maintenance), or total hits in the fMRI analyses. The average response time for correct targets for Levels 1, 2, and 3 is labeled as the reaction time to hits (RT—simple processing speed).

Unlike Level 1, Level 2 only consists of two target letters (“x” and “y”) and context is a factor in determining whether an “x” or a “y” is a target (hence go/no-go). The participant is instructed to press the “n” key every time they see an “x” or a “y” in alternating order. This is labeled as the “non-repeating rule.” The participant must use working-memory (WM) to remember which target they just responded to and thus cannot respond to again until they respond to the alternate letter (e.g., after responding to “y,” the WM target is “x” and the WM inhibit set is “y”). Level 2 is seemingly more difficult than Level 1 as participants are required to inhibit the learned prepotent response from Level 1. However, only two letters must be kept in WM at a time and a good approach is to remember only the letter that must be responded to next and thus not use resources otherwise necessary to keep both the to-be responded to letter *and* the letter to inhibit in WM at once. Level 2 also measures sustained attention and set shifting (PCTT) along with complex processing speed (RT) and response inhibition (PCIT). For both Levels 2 and 3, response inhibition was measured by dividing the total number of times a participant successfully inhibited a response by the total number of times it was necessary to inhibit a response.

Level 3 is again a go/no-go level, but the aforementioned anticipation strategy is hindered by the addition of a third target (now “x,” “y,” and “z”) with the same non-repeating rule in effect. The three targets must now be responded to in alternation such that once “y” is responded to, both “x” and “z” must be held as potential targets in WM while “y” must be held in the WM inhibit set. In Level 3 the participant loses some ability to anticipate the next target response and must constantly shift the target set. Although Level 3 is much more difficult than Level 2 (and Level 1), it requires sustained attention, response inhibition, and set shifting similar with Level 2. PGNG Levels 2 and 3 have been shown to measure more complex executive functioning skills

and context-based inhibition while addressing oft-encountered ceiling effects in the performance on young, healthy adults (see Langenecker et al., 2005, 2007a). The PGNG task is pertinent to the current study because it will allow for a more sensitive measure of the differences between healthy controls and participants with MDD in regards to IC, set shifting and other complex executive functions. By using a sensitive measure like the PGNG during fMRI, the current study hopes to better elucidate any differences in functional activation that exist between MDD and healthy control participants.

Procedures

The current studies were advertised in local newspapers, in outpatient clinics, and within the Mood Disorders Program at the University of Michigan. Interested participants were screened over the phone and made aware of the inclusion and exclusion criteria. Informed consent was obtained and participants were further screened for items that would prohibit their engagement with the fMRI (e.g., pacemakers, metallic surgical devices, etc.).

Participants meeting all inclusion criteria were brought in for an initial personal interview that was comprised of the Structured Clinical Interview for DSM-IV (SCID-I). The participants then completed the Hamilton Depression Rating Scale (HDRS) and Shipley Institute of Living Scale, as well as other neuropsychological tests beyond the purview of the present study.

Participants' second visit consisted of the fMRI, acquired on a GE Sigma 3T scanner (release VH3, Milwaukee, Wisconsin). They performed a practice run of the PGNG before entering the scanner and, after all of their questions had been addressed, they completed the experimental protocol inside the scanner. During fMRI, participants also performed facial emotion perception, monetary incentive delay, and resting state tasks. The data for the latter three tasks are not examined in the current study.

MRI Acquisition and Processing

Imaging was performed using a GE Signa 3 T scanner (release VH, Milwaukee, Wisconsin). The fMRI series consisted of 30 contiguous oblique-axial sections; 4 mm thick to cover the brain acquired using a forward-reverse spiral sequence. The typical image matrix was 64 x 64 over a 24 cm field of view for a 3.75 x 3.75 x 4 mm voxel. The 30-slice volume was acquired serially at 2000 ms temporal resolution for a total of 720 time points over six runs. The entire scanning procedure and protocol for processing is described in detail in a prior work (Langenecker et al., 2007b) and includes coregistration, normalization, and smoothing (5 FWHM). First level individual models include regressors for correct hits and rejections, as well as incorrect responses (commissions and omissions). Missed opportunities (i.e., lure stimuli following an omission), were also entered as nuisance regressors. Analyses of neural activation were conducted with Statistical Parametric Mapping (SPM; version 5) software.

Statistical Analyses

The alpha threshold of significance was $p < .05$ for all behavioral tests. The first hypothesis concerned differences in response time between the MDD and control groups, predicting that the MDD group would have greater response times across trials. In order to test hypothesis one, a 2 x 3 repeated measures analysis of variance (ANOVA) was performed on response time for the three levels of the task with group (MDD x control) as the independent variable and response times for levels one through three as the dependent variable. To test the second hypothesis, predicting that the MDD group would have worse accuracy for target trials, a 2 x 3 repeated measures ANOVA was performed on target accuracy with group (MDD x control) as the independent variable and accuracy to target trials in the three levels of the task as the dependent variable. Likewise, to test the third hypothesis, predicting that the MDD group would

have equal or better accuracy for inhibitory lure trials, a 2 x 2 repeated measures ANOVA was performed, with group (MDD x control) as the independent variable and accuracy for inhibitory lure trials in the latter two levels of the task as the dependent variable.

The functional analyses were done using SPM-5. The whole brain corrected threshold for significance for all analyses ($p < .04$) was computed with a monte carlo simulation using the program AlphaSim. This program takes into account the probability of height by extent thresholding, considering voxel size and spatial smoothing. As such, a $p < .001$, extent of 264 mm³, and smoothing of 5 FWHM with the acquisition parameters results in 4% whole brain significance detection errors in the monte carlo simulation. Hypothesis four, regarding differences in activation between the MDD and control groups was tested using four separate ANOVAS with group (MDD x control) as the independent variable and each of four variables in the PGNG task as the dependent variables. These independent variables were BOLD fMRI changes due to hits in the static Level 1 (3 target go condition), hits in the context-dependent levels two and three, correct rejections (successful response inhibition), and commissions (failed response inhibition). A planned ROI analysis was also conducted for each of the four behavioral regressors in comparison between HC and MDD in right IFG (Brodmann areas 44-47), with a $p < .01$ and $mm^3 > 120$.

Results

Correlations

Table 2 shows the correlations between the behavioral measures for each Level of the PGNG task. As indicated, RT and PCTT variables intracorelate for all three Levels of the task. Likewise, PCIT variables correlate for levels two and three of the task. There is no measure of IC in level one, but RT and PCTT are modestly correlated, $r(52) = -.24, p = .09$. For Level 2 of

the task, RT correlated with PCTT, $r(52) = -.27, p = .05$, RT correlated with PCIT, $r(52) = -.35, p = .01$, and PCTT correlated with PCIT, $r(52) = .46, p < .01$. None of the dependent variables correlate on Level 3 of the task.

Repeated Measures ANOVAs for Performance Variables

A series of three repeated measures ANOVAs were conducted for response time, accuracy in target trials, and accuracy in inhibitory trials, respectively. The means and standard deviations for these dependent variables are reported in Table 3. Each ANOVA was followed by paired posthoc t-tests as warranted by significant main effects.

Response time to hits. First, response time (RT) was compared across the three levels of the PGNG using a 2 (group) x 3 (level) repeated measures ANOVA. There was a significant effect of Level on RT, with RT decreasing as the levels increase in difficulty, $F(2, 49) = .151, p < .001$. There was no interaction between group and Level, $F(2, 49) = .959, p = .357$. The difference in RT between groups was significant, with slower performance in the MDD group, $F(1, 50) = 4.602, p = .037$ (see Figure 2).

A paired-sample t-test was used to evaluate the effect of PGNG level on response time (RT). There was no significant difference in RT between Level 1 and Level 2, $t(51) = -1.76, p = .084$, but there was a significant difference in RT between Level 2 ($M = 485.30, SD = 60.95$) and level 3 ($M = 543.61, SD = 58.93$), $t(51) = -12.55, p < .001$. Both the control group, $t(25) = -10.66, p < .001$, and the MDD group, $t(25) = -7.51, p < .001$, showed significant slowing from Level 2 to Level 3. The change in response time between Level 1 and 2 was not significant for either group.

Accuracy for target trials. Accuracy for target trials was compared across the three Levels using a 2 (group) x 3 (level) repeated measures ANOVA. There was a significant effect

of Level on target trial accuracy, with accuracy decreasing with Level, $F(2, 49) = .578, p < .001$. There was no interaction between group and Level, $F(2, 49) = .967, p = .441$, and the difference in target trial accuracy between groups was not significant, $F(1, 50) = .10, p = .753$.

A paired t-test was used to evaluate the effect of Level on general target accuracy. Overall, there was a significant difference in target accuracy between Level 1 ($M = .96, SD = .05$) and Level 2 ($M = .93, SD = .09$), $t(51) = 2.45, p = .018$. There was a significant effect of Level 3 on target accuracy, in comparison to Level 1, $t(51) = 6.05, p < .001$, and level 2, $t(51) = 5.05, p < .001$. The change in accuracy between Level 1 and 2 was not significant for either group. Both the control group, $t(25) = 3.31, p = .003$, and the MDD group, $t(25) = 3.77, p = .001$, showed a significant decrease in target accuracy between Levels 2 and 3.

Accuracy for inhibitory trials. Accuracy for inhibitory trials was compared between Levels 2 and 3 using a 2 (group) x 2 (level) repeated measures ANOVA. There was a significant effect of level on inhibitory accuracy, with Level 3 decreasing in accuracy, $F(1, 50) = .629, p < .001$. There was no interaction between group and level, $F(1, 50) = 1.0, p = .998$. The difference in inhibitory target trial accuracy between groups was not significant, $F(1, 50) = .161, p = .690$.

Again, paired t-tests were performed to evaluate the effect of level on accuracy for inhibitory trials. Inhibitory trials were only present for Levels 2 and 3. There was a significant difference in inhibitory accuracy between Level 2 and 3, $t(51) = 5.49, p < .001$. Both the control group, $t(25) = 3.60, p = .001$, and the MDD group, $t(25) = 4.14, p < .001$, showed a significant decrease in inhibitory accuracy between Levels 2 and 3.

Functional Imaging Results

Event-related responses to hits (correct targets) in the Level 1, 3 target go condition (i.e., Level 1). For both groups there was significant activation for hits bilaterally in ACC and middle occipital cortex. There was also activation in right paracentral frontal, medial frontal, superior frontal, and superior temporal gyrus. Areas of left activation included precentral, posterior insula, and superior temporal, within the insula. The control group did not show significantly more activation than the MDD group, but the MDD group showed greater activation in left precentral and midbrain and in right cerebellum. Regions of activation for hits in Level are located in Table 4.

Event-related responses to hits in the Level 2 and 3 Go/No-go conditions (i.e., Levels 2 and 3). For both groups there was significant activation for hits bilaterally in middle frontal and middle temporal regions. There was also activation in right precentral, medial frontal, superior frontal, middle occipital, and superior parietal regions as well as left fusiform and inferior parietal lobule. The MDD group did not show significantly more activation than the control group, but the control group showed greater activation in right inferior frontal gyrus. Regions of activation for hits in the Level 2 and 3 Go/No-go conditions are located in Table 5.

Event-related responses to correctly rejected lures in the Levels 2 and 3, Go/No-go conditions. For both groups there was significant activation for correctly rejected lures bilaterally in medial frontal gyri. There was also activation in right lingual and supramarginal gyrus and in the left hippocampal tail. The control group did not show significantly more activation than the MDD group, but the MDD group showed greater activation in left dorsal cingulate. Regions of activation for correctly rejected lures in the Level 2 and 3 Go/No-go conditions are located in Table 6. The planned region of interest (ROI) analyses for rejections within the inferior frontal gyrus are reported below.

Event-related responses to commission errors in the Level 2 and 3, Go/No-go

conditions. For both groups there was significant activation for responses to commission errors bilaterally in middle frontal and posterior lobule. There was also activation in left medial frontal, inferior frontal, and cuneus. The MDD group did not show significantly more activation than the control group, but the control group showed greater activation in right middle frontal and superior frontal regions. Regions of activation for responses to commission errors are located in Table 7.

Event-related responses to all events of interest within right inferior frontal gyrus

(IFG). A final planned analysis was conducted within the right inferior frontal gyrus in comparison of the HC and MDD subjects. As right IFC is thought to play the most pivotal role in IC, we used a relaxed threshold and focused set of analyses on Brodmann areas 44-47. Using the Wake Forest Pick Atlas and these Brodmann areas, with a dilation of 2 to cover all gray matter areas, we used a combined height by extent threshold of $p < .01$ and $\text{mm}^3 > 120$. There was activation in right IFG that was greater in HC relative to MDD for rejections (50, 20, 18, $Z = 2.91$, $p = .002$, 1640 mm^3). There was also a larger IFC cluster more active for HC relative to MDD in a more anterior right IFG cluster in the commissions analysis (46, 44, 20, $Z = 3.98$, $p < .0001$, 2696 mm^3). There were no areas of greater activation for HC relative to MDD for the Level 2 and 3 Hits only condition that could be considered within the right IFG. An area of anterior insula/orbital frontal cortex (36, 24, 4, $Z = 3.43$, $p < .0001$, 784 mm^3) was more active in HC relative to MDD for the Level 1 targets, which includes set shifting and maintenance components. The MDD subjects exhibited activation greater than HCs in two small ventral IFG clusters for commissions (44, 0, 6, $Z = 2.49$, $p = .006$, 464 mm^3 and 48, 22, 10, $Z = 2.17$, $p = 0.015$, $\text{mm}^3 = 136$). A smaller right IFG cluster was more active in MDD relative to HC for Level

1 hits only (60, 18, 18, $Z = 2.31$, $p = .01$, $mm3 = 168$), with no areas in right IFG more active for MDD relative to controls for either rejections or hits in Levels 2 and 3. The areas of greater activation in HC relative to MDD, several of which survive FDR correction, are shown in Figure 7.

Discussion

This study explored the differences between healthy individuals (HC) and individuals diagnosed with Major Depressive Disorder (MDD) using an IC task. The MDD group exhibited significantly slower reaction times than the HC group in each of the three levels of the task, although there were no significant differences between the two groups on either target trial accuracy or inhibitory lure accuracy. The imaging results indicated that the task was successful in engaging activity within regions typically implicated in IC and sustained attention (e.g., ACC, DLPFC, and right IFG; Aron, Robbins, & Poldrack, 2004; Berkman, Burkland, & Leiberan, 2009; Ckikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Hedden & Gabrieli, 2010; McNab et al., 2008; Rubia et al., 2001). The task was also designed in a way that allowed for enough error events that differences in sustained attention and IC activation between MDD and control participants could be compared across levels for hits, successful rejections, and errors of commission.

Engagement of Attentional Control and Set Maintenance Areas in Level 1 Go-Only Condition

Activation for hits in Level 1 of the task registered significant activation for both groups bilaterally in ACC and middle occipital cortex, as well as right lateralized activation in paracentral, medial and superior frontal and temporal regions. The ACC has been implicated in focusing attention on relevant stimuli in order to minimize distraction by irrelevant ones. Orr

and Weissman (2009) used an attentional cueing task and found that dorsal ACC is more involved in focusing attention on relevant stimuli, while rostral ACC is involved earlier in spotting potential conflict with competing stimuli. ACC activation for hits in level 1 of the PGNG is suggested to be a mechanism whereby individuals focus attention on the relevant stimuli (i.e., X, Y, and Z in any order) and prevent distraction from irrelevant stimuli (i.e., other letters).

Interestingly, although Level 1 has only a static inhibitory component, the ROI analysis revealed two areas of significant activation in right IFG that were greater in the MDD group, relative to the controls. There is a static measure of IC because there are three items that are perpetually within the target group of memory (i.e. X, Y, and Z in any order) and all of the other letters serve as incorrect lures, or distracters, in memory. This does not provide the contextual, set-shifting IC challenge to HC or MDD that Levels 2 and 3 provide. However, it is noteworthy that MDD had significantly greater activation in right IFG in Level 1, an area of major import within the IC network (Hedden & Gabrieli, 2010; Rubia et al., 2001). This might suggest that the MDD group were working harder than the control group to maintain accuracy in the classically “easiest” of PGNG levels. However, this hypothesized pattern of frontal hyperactivation was to a large extent absent within the MDD group in the current study in more challenging levels of the task, inconsistent with the earlier work by our group (Langenecker et al., 2007b). Still, regions in which the MDD group exhibited significantly more activation included the cerebellum and precentral motor areas, indicating greater necessity for regions implicated in fine and more general motor movements during Level 1 of the task.

Addition of Set-Shifting and Contextual Inhibitory Control for Hits in Levels 2 and 3, Go/No-go Conditions

Levels 2 and 3 of the PGNG involve a higher demand on working memory and IC because the appropriate target is dependent on changing context, or the last response made. Both groups activated middle frontal cortex, which is likely a result of this increase in demand on working memory (Provost, Petrides, & Monchi, 2010). There were no significant differences in hit accuracy between groups, although the MDD group was significantly slower in levels two and three of the task. These results suggest either that the MDD group was decidedly slower in order to maintain accuracy in the more difficult go trials of Levels 2 and 3 or that reduced response time was an artifact of insufficient activation within inhibitory circuits.

The right IFG is a region that is suggested to play a major role in inhibiting prepotent responses (Aron, Robbins, & Poldrack, 2004; Berkman, Burkland, & Leiberan, 2009; Ckikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; McNab et al., 2008), with greater activation commonly manifesting as a function of the inhibitory response demands (Goghari & MacDonald, 2009). However, right IFG has also been shown to become active when important stimuli are perceived in the environment and not just under instances of behavioral inhibition (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). It is also noteworthy that many tests of IC focus mainly on behavioral inhibition of a prepotent response. The contextual set-shifting required in the Level 2 and 3 Go/No-go tasks includes elements of inhibition in working memory, as described previously by Hasher and Zacks (1979). It is possible that the IFG is also important for inhibition of unwanted thoughts within working memory. The hypoactivation in MDD is related to slower set maintenance and shifting in response time to hits, or changing of the target and lure working memory sets. In the present study, the control group exhibited significantly more activation in right IFG, relative to the MDD group for rejections and commissions. Due to the context-dependent nature of Levels 2 and 3, as opposed to the static

nature of Level 1, response demands are greater, and therefore significantly more attention and inhibition must be placed on important stimuli. This suggests that the control group might have been able to ramp up engagement with the task to a greater degree, which might reflect the faster response times present for controls.

Behavioral Inhibition Successes and Failures in Level 2 and 3 Go/No-go Conditions

Successful behavioral inhibition involves attention, working memory, and the activation of the IC network within the brain (Aron, Robbins, & Poldrack, 2004; Berkman, Burkland, & Leiberman, 2009). Our whole-brain between-group analyses revealed that the MDD group had greater activation in dorsal cingulate cortex during correct rejections, but planned ROI analyses showed that controls had greater activation in right IFG. During errors of commission (i.e., unsuccessful behavioral inhibition), the control group had greater activation in more anterior regions of right IFG and also bilateral superior and middle frontal gyri, while the MDD group had greater activation in a smaller cluster in ventral IFG. The comparison between correct rejections and errors of commission is the crux of the PGNG task as it reveals differentiation in neural circuits between and within groups during successful and unsuccessful behavioral inhibition. Contrary to hypothesis 4, it appears that the current MDD group had hypoactivation relative to controls in regions implicated in IC.

Activation in anterior regions of right IFG might seem counterintuitive in the face of unsuccessful behavioral inhibition because right IFG is implicated in successful IC. However, more anterior regions of right IFG have also been shown to be active in instances of failed or “lost” inhibition. For instance, one study found activation in anterior right IFG when participants were instructed to lose to a computer in a game of rock, paper, scissors (Matsubara, Yamaguchi, Xu, & Kobayashi, 2004). The activation in ventral IFG present in the MDD group during errors

of commission might suggest a broader role of ventral IFG in the response inhibition task in general, whereas a combination of IFG, dACC, and DLPFC might be necessary to fully process lures and targets and make successful rejections (Cai & Leung, 2009). While both groups performed similarly in inhibitory lure trials, the control group was able to do so with a significantly quicker response time, suggesting better efficiency of inhibitory circuitry.

The relative hypoactivation in MDD contradicted hypothesis 4, and is somewhat puzzling in that it included some of the same patients as a previous study (Langenecker et al., 2007b). Many of the newest recruits to the MDD group had a current diagnosis of MDD with comorbid anxiety. It is quite possible that comorbid anxiety confounded the results because anxiety has been found to have a dulling effect on the frontal lobes, which is manifest in hypoactivation and irregularity relative to controls (Britton et al., 2010; Etkin, Prater, Hoefl, Menon, & Schatzberg, 2010). Analysis of comparisons between those MDD subjects with and without comorbid anxiety is an appropriate area for future investigation. There is also the possibility that a larger sample size with a larger number of individuals with pure MDD might have increased the significance of the activation in the MDD group.

The PGNG task did not attempt to evoke any affective state, with the aim of investigating general cognitive inhibition without the confound of emotional stimuli. This distinction was made as a result of recent data suggesting that MDD might not only be characterized by the inability to inhibit negatively salient stimuli, but that different inhibitory mechanisms (e.g. emotional and cognitive) might share the same neural pathways (Berkman, Burklund, & Lieberman, 2009). Berkman and colleagues found evidence for a form of “inhibitory spillover” in affective inhibition in a task that only intentionally engaged cognitive inhibitory networks. In addition, cognitive reappraisal tasks with MDD subjects demonstrate hyperactivation in right

IFG, suggesting greater general IC needed to regulate unwanted emotions (Johnstone, Reekum, Urry, Kalin, & Davidson, 2007). While the current study did not assess the similarities and differences between emotional and cognitive inhibitory circuitry, the imaging data suggest differences in inhibitory networks for affectively neutral stimuli.

One study found that lesions in right IFC, which cause an obvious decrement in function, were significantly associated with reductions in reaction time in response inhibition, measured by Stop-Signal Reaction Time (Aron, Robbins, & Poldrack, 2004; Verbruggen & Logan, 2009). One of the hallmarks of MDD is psychomotor slowing (Bulmash et al., 2006); with the current task, the MDD group was significantly slower than the controls in each of the three levels. It is hypothesized that hypoactivation in frontal circuitry—regions often implicated in planning and executing (Hedden & Gabrieli, 2010)—might underlie psychomotor slowing and other common higher order dysfunctions in depression. The current study argues that the hypoactivation in right IFC during the PGNG task is linked to the negative rumination and often overwhelming feelings of worthlessness common to MDD (Berman et al., 2011; Young & Nolen-Hoeksema, 2001). Future research should aim to answer the question of directionality of these findings. Does inadequate activation of right IFC lead to reduced cognitive and emotional control and thus depressive symptomology? Or alternatively, does depression put some form of strangle-hold on the activity of the frontal lobes, specifically right IFC, BG, and dACC, i.e., regions shown to be involved in IC?

Recent work with a combination of fMRI and diffusion tensor imaging (DTI) has revealed that both the function and the structure of right IFC play a role in response inhibition (Forstmann et al., 2008). Specifically, when healthy controls were compared based on their accuracy and RT measures in a cueing version of the Simon task, those that were more proficient

in regards to response inhibition had comparably more activation in right IFC than those with less proficiency in the task. Further, DTI revealed that greater fractional anisotropy or white matter connectivity within rIFC was correlated with more successful outcomes on the task. Future studies should incorporate patients with MDD in studies with DTI in order to elucidate any underlying structural differences.

Depressed individuals have been shown to exhibit impairment in post-error performance in neuropsychological tasks meant to gauge executive function (Pizzagalli, Peccoralo, Davidson, & Cohen, 2006). While impairment in post-error performance was outside the scope of the current study and not included in behavioral or functional analyses, it was a partial basis for the prediction that MDD participants would display worse performance for target and inhibitory lure trials. While the current behavioral results depict otherwise, the functional data reveal a differentiation in activation. In light of these results, perhaps the current PGNG task was not sensitive enough to reveal differences in target accuracy or inhibitory lure accuracy. In fact, as the task was completed twice prior to participants' completion of the task during fMRI, the effects of interest may have been washed out with practice. Some have hypothesized that decrements in inhibitory accuracy will only be revealed for emotionally salient tasks, although it is probably more likely that both dorsal and rostral regions of ACC are important for IC, the former for cognitive control and the latter for emotional control (Mohanty et al., 2007; Orr & Weissman, 2009). The current study provides evidence of dysregulation of the cognitive part of the ACC in MDD, but not for impairment of behavioral inhibition.

This honors thesis attempted to better explain behavioral symptomatology common in MDD with a computer-based task of IC, as well as functional imaging data to inform the neural correlates of performance. As mentioned earlier, one limitation of the current study was that a

large number of participants within the MDD group also met diagnostic criteria for comorbid anxiety disorders. In contrast to earlier studies (Langenecker et al., 2007b) that found frontal hyperactivation in the MDD group relative to the control group, the current study found frontal hypoactivation. The hypoactivation in MDD might be an artifact of the comorbid anxiety as has been the case in previous studies (Britton et al., 2010; Etkin, Prater, Hoefl, Menon, & Schatzberg, 2010). Likewise, the PGNG task did not appear sensitive enough to distinguish between the control and MDD groups on the two accuracy measures (i.e., PCTT and PCIT). However, the slower RT in the MDD group, coupled with the differential activation, suggests that functional imaging data and multiple behavioral measures are necessary to parse apart the frontal dysfunction widely cited in depression. As is the case in most studies that make use of fMRI, the small participant sample size is a factor in whether or not results reach significance, and hopefully future studies will continue to grow in size as more and more individuals fall ill to this disorder and demand a response.

The importance of this study lies in our illumination of the differences between MDD and HC groups in interference resolution and inhibitory circuitry with an IC paradigm. Specifically, the MDD group exhibited hypoactivation in IC circuitry, suggesting a functional deficiency within this network. Importantly, behavioral data alone might not have been sensitive enough to elucidate this finding. However, this study was not meant to single out IC as the *only* problem within clinical depression. MDD is a multifaceted disorder and clinicians and researchers are just beginning to understand its complexity (Boland & Keller, 2010). Moreover, studies involving genetic testing and behavioral therapies are likewise important pieces to the puzzle. Based on the current findings, it is imperative that future studies seek MDD patient groups without comorbid anxiety, but continue to dissect the neural correlates of dysfunction within

frontal circuitry. Perhaps one day cognitive behavioral therapy will be used to promote efficient neural activation during tasks of cognitive control and thus teach better response to pharmacotherapy.

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Author's Note

Laura B. Gabriel, Department of Psychology, University of Michigan, Ann Arbor.

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Correspondence concerning this article should be sent to Laura Gabriel, 523 S. Fourth Ave., Ann Arbor, MI, 48104, email: lbethgab@umich.edu.

Table 1

Demographic Characteristics

	MDD (<i>n</i> = 26)	HC (<i>n</i> =26)
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)
Age	37.23 (12.37)	38.58 (11.57)
Education	15.62 (2.82)	16.46 (2.02)
HDRS-17	19.52 (4.11)	0.85 (1.42)
Shipley IQ	105.64 (9.02)	105.96 (13.15)

Note. HDRS-17 = Score on the Hamilton Depression Rating Scale (Hamilton, 1960; Hamilton, 1967), MDD = Participants Diagnosed with Major Depressive Disorder, HC = Healthy Control Participants, Education = Participants' years of formal education.

Table 2

Go/No-go Correlations

	2.	3.	4.	5.	6.	7.	8.
1. Level 1 RT	<i>0.71</i>	<i>0.76</i>	-0.24	-0.15	-0.15	-0.19	-0.10
2. Level 2 RT		<i>0.84</i>	-0.08	-0.27	-0.13	<i>-0.35</i>	0.00
3. Level 3 RT			-0.05	-0.12	0.00	-0.06	0.16
4. Level 1 PCTT				0.27	<i>0.46</i>	0.21	0.27
5. Level 2 PCTT					<i>0.62</i>	<i>0.46</i>	0.20
6. Level 3 PCTT						0.25	0.07
7. Level 2 PCIT							<i>0.59</i>
8. Level 3 PCIT							

Note. Numbers in bold and italics are significant at the 0.01 level (2-tailed).

Numbers in bold are significant at the 0.05 level (2-tailed).

Table 3

PGNG Behavioral Data

	MDD (<i>n</i> = 26)	HC (<i>n</i> =26)
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)
Trial1RT	493.58 (54.85)	455.72 (35.08)
Trial2RT	499.71 (63.79)	470.88 (55.46)
Trial3RT	555.30 (65.95)	531.92 (49.49)
Trial1PCTT	.95 (.04)	.96 (.05)
Trial2PCTT	.94 (.06)	.91 (.11)
Trial3PCTT	.85 (.12)	.84 (.17)
Trial2PCIT	.74 (.19)	.72 (.21)
Trial3PCIT	.61 (.21)	.59 (.18)

Note. RT = Response Time, PCTT = Percent Correct Target Trials, PCIT = Percent Correct Inhibitory Trials.

Table 4

Regions of Brain Activation for the Hits (Correct Go Targets) in the Level 1(3 Target Go) Condition

Lobe/Region	Foci	BA	x	y	z	mm3	Z	
HC and MDD								
Frontal	Paracentral	5	4	-40	56	2216	4.75	
	Precentral	4	-41	-17	43	832	4.15	
	Anterior Cingulate		32	1	30	24	11904	4.5
			25	-1	14	-7	376	4.43
	Medial Frontal	6	1	1	58	448	4.3	
	Superior Frontal	9	8	57	27	320	3.9	
Occipital	Middle Occipital	18/19	-45	-71	-9	3224	5.38	
		18	26	-93	6	3672	4.51	
Temporal	Post. Insula	13	-50	-42	19	1240	4.01	
	Superior Temporal	22/21	52	-38	8	2232	4.63	
	Superior Temporal/ Insula	22/13	-45	-21	2	1712	4.54	
HC > MDD								
None								
MDD > HC								
Frontal	Precentral	4	-41	-17	43	336	3.69	
Brainstem	Midbrain		-6	-40	-15	408	3.49	
Cerebellum	Culmen		8	-48	-10	488	3.79	

Note. BA = Brodmann area.

Table 5

Regions of Brain Activation for the Hits in the Level 2 and 3 Go/No-go Condition

Lobe/Region	Foci	BA	x	y	z	mm ³	Z	
HC and MDD								
Frontal	Precentral	6	43	-5	47	3648	4.36	
	Medial Frontal	6	3	28	35	360	3.8	
	Middle Frontal		9	34	41	27	304	3.79
			10	-34	47	18	17984	5.76
	Superior Frontal	6	1	14	53	992	4.23	
Occipital	Middle Occipital	18	38	-83	-10	7176	5.25	
	Fusiform	18	-25	-95	-10	4224	5.48	
Parietal	Superior Parietal	7	24	-63	48	5952	5.16	
	Inferior Parietal	40	-48	-52	41	4648	5.11	
Temporal	Middle Temporal	21	-59	-27	-7	1832	4.52	
		21	59	-34	-9	352	4.17	
HC > MDD								
Frontal	Inferior Frontal	47	26	24	-4	352	4.46	
MDD > HC								
None								

Note. BA = Brodmann area.

Table 6

Regions of Brain Activation for Correct Rejections in the Level 2 and 3 Go/No-go Conditions

Lobe	Foci	BA	x	y	z	mm3	Z
HC and MDD							
Frontal	Medial Frontal	10	6	55	-4	712	4.47
	Medial Frontal	9	3	53	20	448	3.48
Occipital	Lingual	17/18	15	-106	-8	1880	4.86
Parietal	Supramarginal	40	48	-56	37	320	4.01
	Hippocampal Tail		-24	-42	8	264	3.64
HC > MDD							
None							
MDD > HC							
Frontal	Dorsal Cingulate	24	-10	-15	38	904	3.79

Note. BA = Brodmann area.

Table 7

Regions of Brain Activation for Commission Errors in the Level 2 and 3 Go/No-go Conditions

Lobe	Foci	BA	x	y	z	mm3	Z
HC and MDD							
Frontal	Medial Frontal	9	-1	51	29	5088	5.2
	Middle Frontal	10	-34	51	9	1032	4.54
		8	-40	16	41	672	4.11
	Inferior Frontal	47	-48	30	-8	272	4.43
Occipital	Cuneus	18	-17	-102	2	440	3.82
Cerebellum	Posterior Lobe		31	-83	-31	4784	4.73
			-34	-75	-34	792	4.3
HC > MDD							
Frontal	Middle Frontal	6	38	1	49	488	5.01
		6	27	-7	59	376	4.09
		10	40	39	19	360	3.98
	Superior Frontal	8	19	37	40	400	4.17
		6	1	14	59	304	3.68
MDD > Control							
None							

Note. BA = Brodmann area.

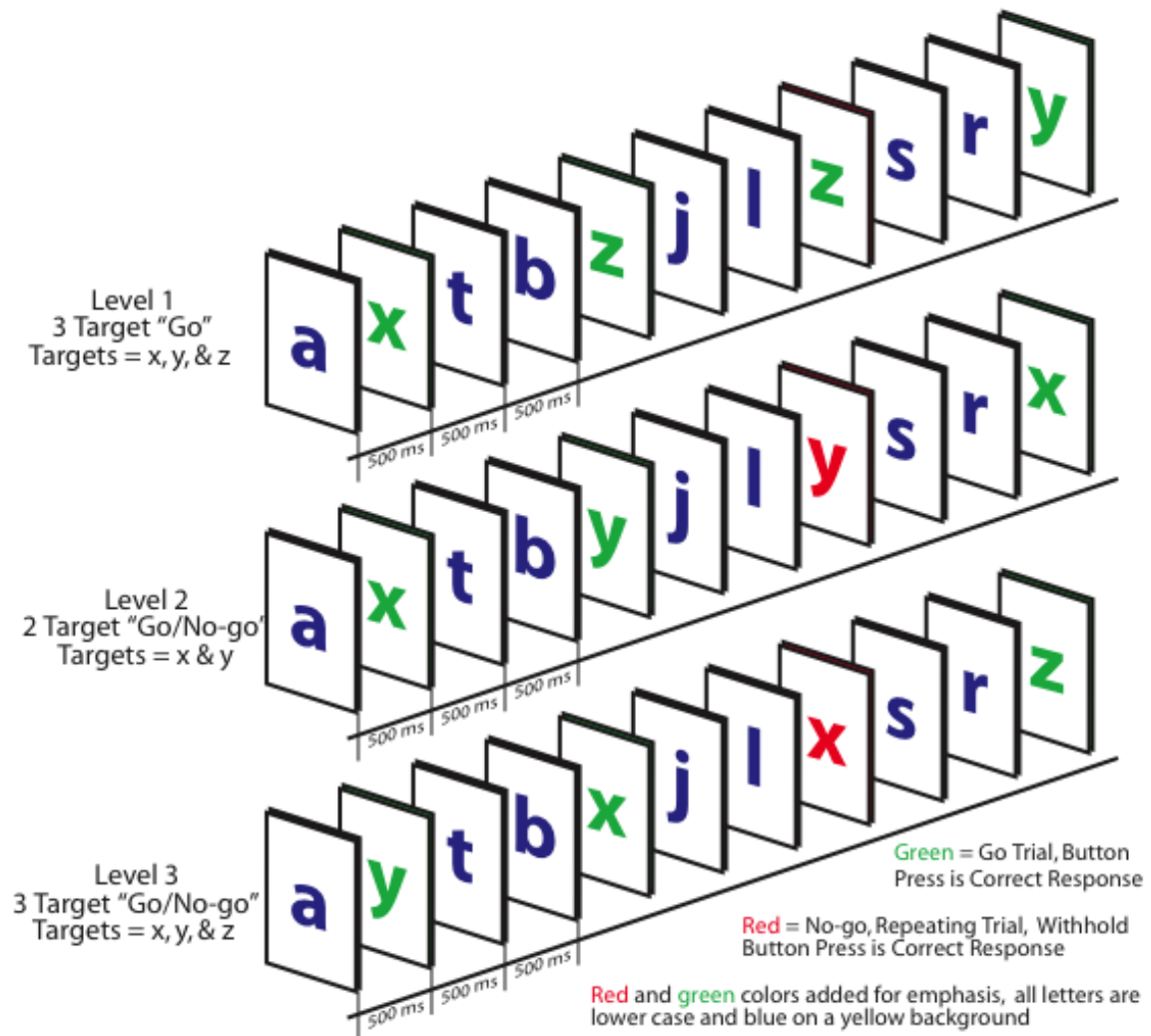


Figure 1. Parametric Go/No-go task. This figure illustrates the three levels of the PGNG task. The first level is static and the second two are context-dependent. All letters appear in blue.

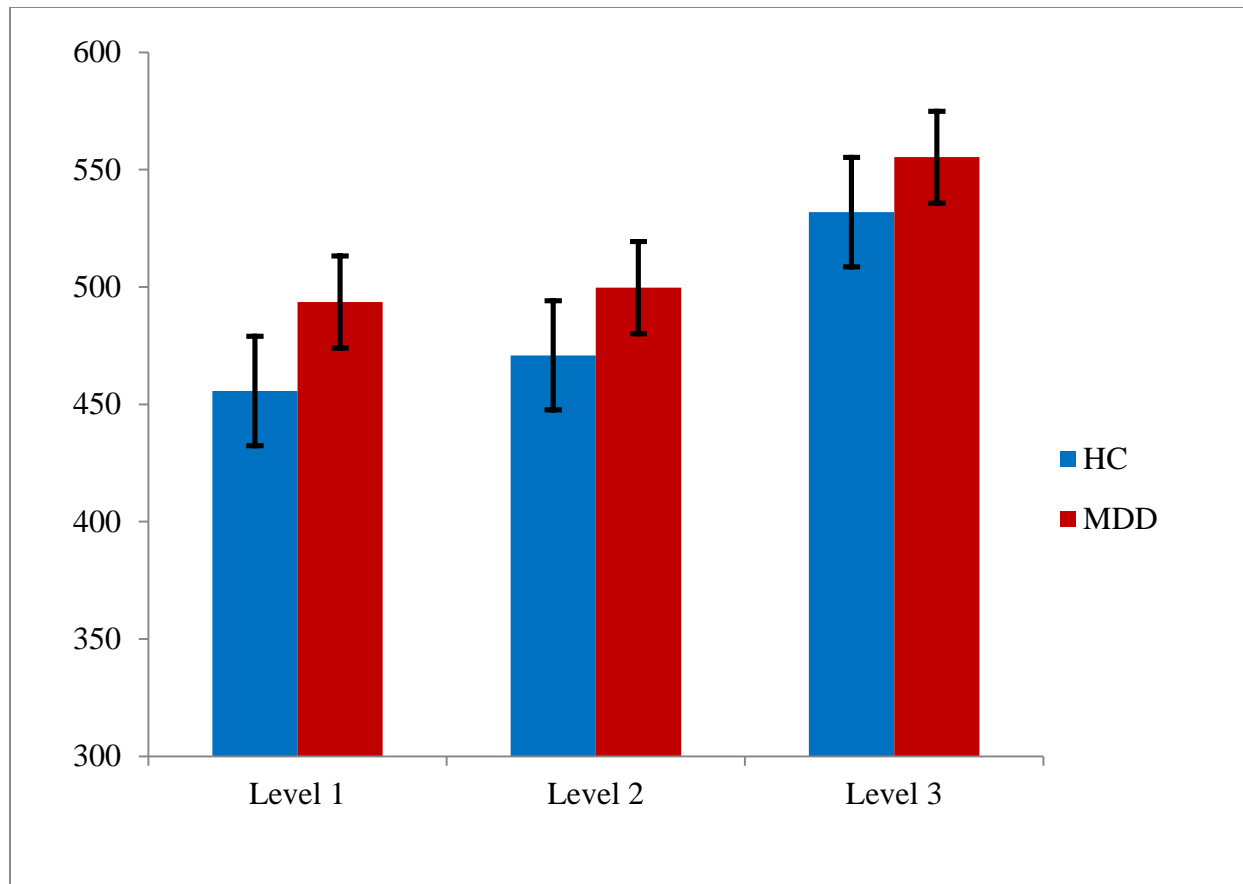


Figure 2. Response times to targets in each level of the PGNG. This figure illustrates the slower response times to targets in the MDD subjects.

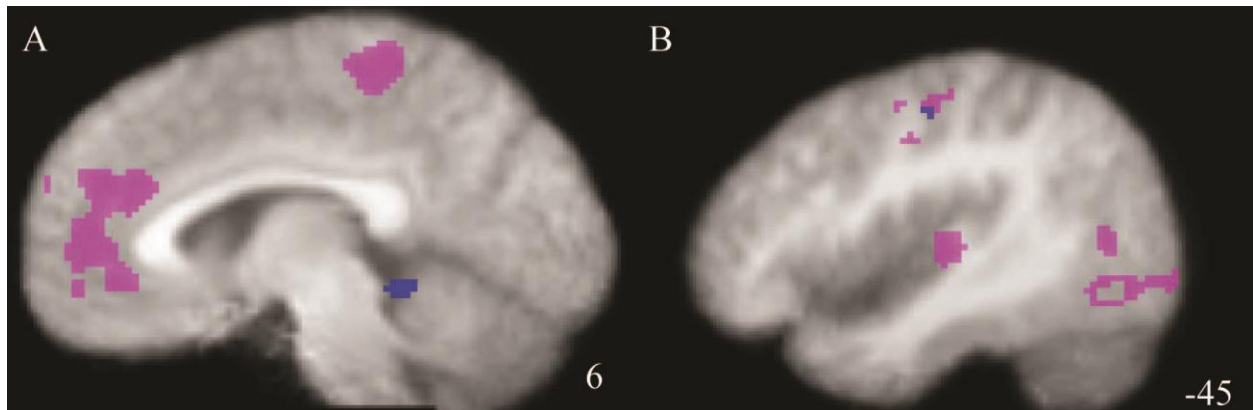


Figure 3. Activation for hits in Level 1 of the PGNG. Pink represents significant activation for both groups and blue represents significant activation for the MDD group.

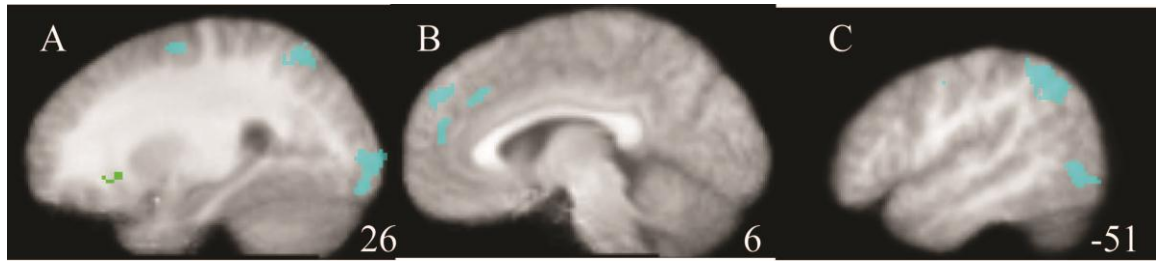


Figure 4. Activation for hits in Levels 2 and 3 of the PGNG. Cyan represents significant activation for both groups and green represents significantly greater activation for the HC group compared to the MDD group.

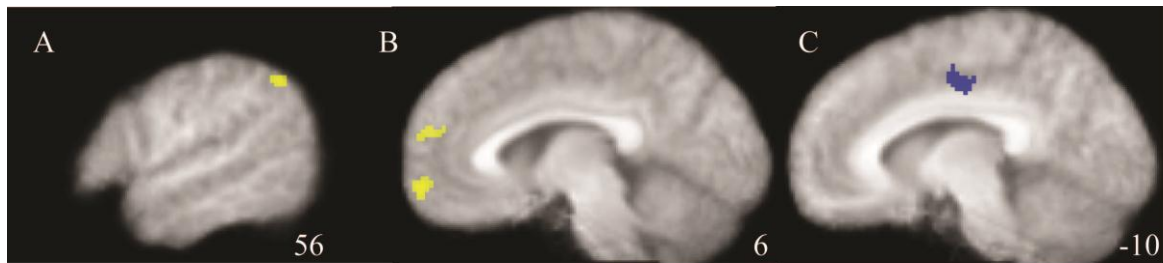


Figure 5. Activation for correct rejections in Levels 2 and 3 of the PGNG. Yellow represents significant activation for both groups and blue represents significantly greater activation for the MDD compared to the control group.

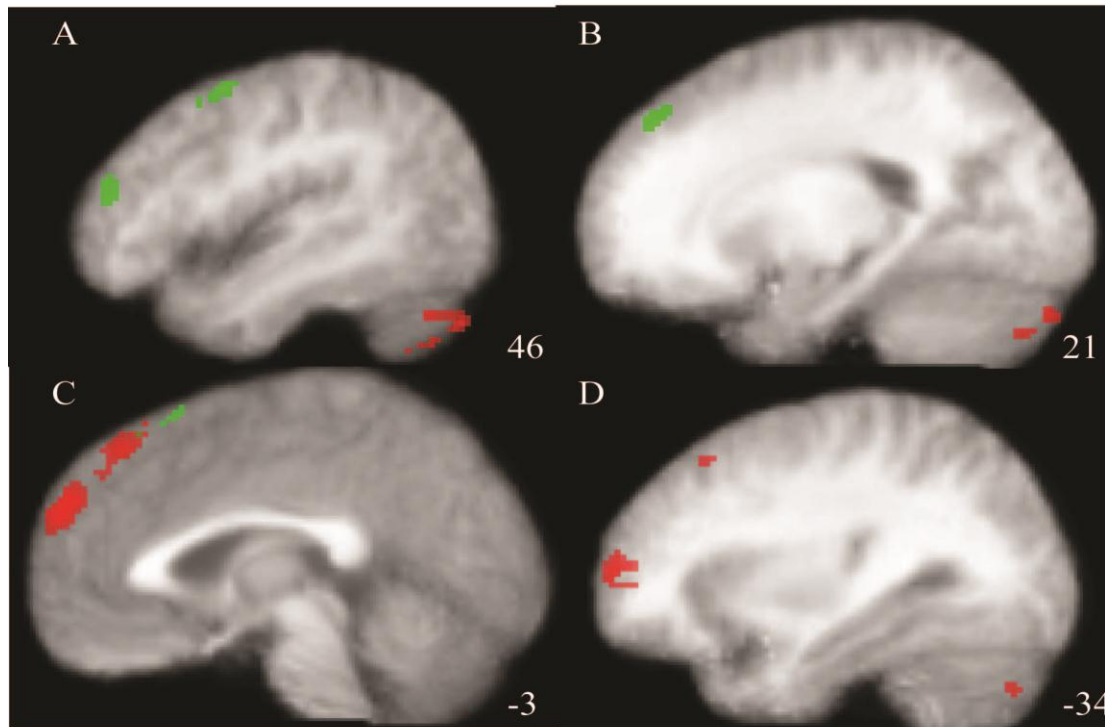


Figure 6. Activation for errors of commission in Levels 2 and 3 of the PGNG. Red represents significant activation for both groups and green represents significantly greater activation in the HC group compared to the MDD group.

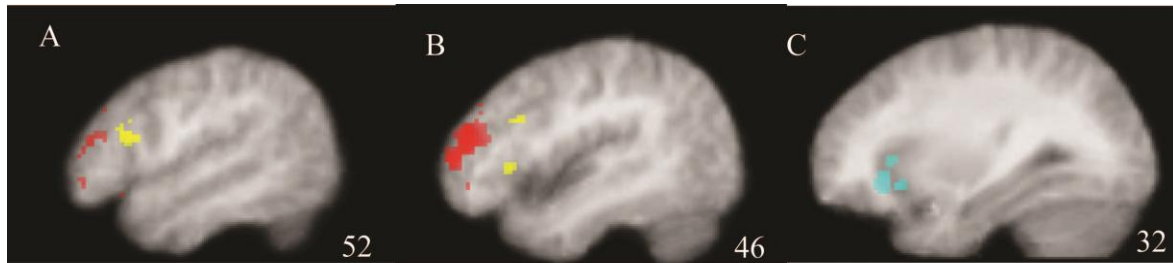


Figure 7. Greater activation in the healthy control subjects compared to the MDD group in regions of the right IFG for targets, rejections, and commissions. Cyan represents greater activation in the HC group for level 2 and 3 hits, yellow represents greater activation in the HC group for rejections, and red represents greater activation in the HC group for commissions, all in comparison to the MDD group. Two clusters in ventral IFG that are greater in MDD relative to HC are not shown.