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Inhibition and response to error in remitted major depression

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ABSTRACT

Depression is a common illness which tends to have a relapsing progression. Revealing vulnerability factors is an important step towards improved treatment and prevention. Previous studies of individuals in remission indicate that inhibitory control is more strongly impaired than other cognitive functions. Studies have mostly used Stroop tasks; it is unclear how this population performs on other measures of inhibition. Abnormal reactions to errors may also promote depression relapse, but this has rarely been studied in remitted depression. We used a Stop Signal task and Stroop inhibition task to investigate inhibitory function and post-error reaction time adjustments in 54 individuals with a history of depression and 185 never-depressed controls. Inhibitory processing was slower among the remitted depressed individuals on the Stop Signal task, but no difference was found in Stroop inhibition. The groups were not different on post-error adjustments. This finding extends the understanding of inhibitory deficiency in this population and offers insight into trait markers of depression.

1. Introduction

Unipolar depression is the leading cause of burden of disease in middle- and high-income countries, and the third leading cause of burden of disease worldwide (World Health Organization, 2008, Part 4). Several psychological and pharmacological treatments for depression have been developed, but their effects are inadequate (Cuijpers et al., 2010; Turner et al., 2008). Many recover from acute depression either spontaneously or with help from the established treatments. However, following recovery from a first episode of major depression, 65–75% experience relapse (Boland and Keller, 2009; Solomon et al., 2000). By revealing psychological vulnerability factors that increase the probability of relapse, we may lay the ground for targeted preventive interventions and fight the major challenge in modern mental health care constituted by recurring depression.

Depression is an emotional disorder, but it is associated with disturbances in cognitive functioning. Cognitive disturbances include reduced concentration and attention, and biases in memory and in the prediction of future outcomes (American Psychiatric Association, 2000; Disner et al., 2011). For a long time it was customary in philosophy and psychology to view cognition and emotion as separate phenomena, but modern cognitive neuroscience has shown that cognition and emotion are indeed connected, both neurologically and phenomenologically (Disner et al., 2011; Okon-Singer et al., 2015). Progress in the neuroscience of emotion may have important clinical implications. Issues of particular importance to psychiatry include the impact of cognitive control functions on psychosocial functioning, in the regulation of emotion, and whether cognitive control functions can be effectively targeted in treatment and prevention of depression. Herein lays the purpose of studying cognitive function in previously depressed individuals.

Cognitive performance in individuals that have recovered from Major Depressive Disorder (MDD) varies considerably between studies. The general tendency is that individuals with a history of depression are moderately impaired on a broad range of cognitive functions, including the domains processing speed, memory, attention, and executive function (Bora et al., 2013; Hasselbalch et al., 2011). A recent meta-analysis suggested that inhibitory control is most strongly affected (Bora et al., 2013). Cognitive deficits in depression are particularly related to difficulties in return to function, including psychosocial difficulties (Bortolato et al., 2014). Inhibitory control is functionally linked to depression through its impact on emotional processing. The inability to inhibit attention to negative stimuli may lead to enhanced processing of such stimuli, which induces negative emotion and prevents recovery from a negative mood (Joormann and D'Avanzato, 2010).

Abbreviations: MDD, Major Depressive Disorder; SST, Stop Signal task; SSRT, Stop Signal Reaction Time; SSD, Stop Signal Delay; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory

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A similar mechanism has been proposed for depressive rumination, in which impaired inhibition of self-referent negative material prevents the person from disrupting the repetitive depressive thoughts (Disner et al., 2011; Koster et al., 2011).

Previous studies of inhibition in remitted depressed populations have largely relied on one specific task of inhibitory capacity, the Stroop task (see Bora et al., 2013). This is a disregard of the multi-factorial nature of the construct; inhibition comprises the suppression of prepotent responses as well as internal and external distractors (Friedman and Miyake, 2004; Nigg, 2000). In the Stroop task, colors are printed in letters with a different color than the word names, and the participant is required to name the printed color and to inhibit the prepotent reading response. The consistency of inhibition on every trial in this task may result in partial automaticity, rather than top–down driven executive control. An alternative to Stroop is the Go/NoGo task, which requires a response to "go" stimuli, and no response to "no-go" stimuli. Three studies have used this task to study inhibition in remitted MDD participants. One study found impaired inhibition, but two studies did not (Georgiadi et al., 2011; Nixon et al., 2013; Westheide et al., 2007). However, learning and automaticity may confound the assessment of inhibition in the Go/NoGo task. The ability to avoid commission errors may be based on automatic bottom-up inhibitory processes due to a simple association between the stimuli and correct response (Verbruggen and Logan, 2008). These confounds are less likely to occur in a third inhibitory paradigm, the Stop Signal task. This paradigm presents the go signal in every trial, and in the event of a stop trial, a Stop Signal is presented after the go signal. The go response has already been initiated when the Stop Signal occurs. Consequently, inhibition is less predictable and requires more dynamic top–down control. Evidence suggests that the Go/NoGo and Stop Signal paradigms rely on different kinds of response inhibition (Verbruggen and Logan, 2008), and they activate overlapping, but distinct, neural circuits (Swick et al., 2011).

In studies of current MDD, as in the remitted population, Stroop type tasks are most frequently employed (Snyder, 2013). Patients with current MDD are significantly impaired on Stroop performance compared to healthy controls, but it has been difficult to delineate whether this is due to inhibitory deficiency *per se* or to overall slowing (Snyder, 2013). In the Stop Signal task, general psychomotor slowing is easily accounted for by the calculation of inhibitory processing efficiency (i.e. Stop Signal Reaction Time, SSRT), and the task is therefore apt in the pursuit of clear-cut inhibitory deficiency in this population. Previous investigations of Stop Signal inhibition in depressed populations suggest there may be no impairment, but the results are uncertain. Two studies found no significant difference in SSRT between depressed individuals and controls (Halari et al., 2009; Lyche et al., 2010), but a third study indicated possible improvement in SSRT following recovery from depression (Gruber et al., 2007). These studies used the mean method for estimating SSRT, a method which is sensitive to skewed reaction times and test-wide slowing (Verbruggen et al., 2013). The studies are therefore limited by potential inaccuracies in the estimated SSRT. In a fourth study, Lau et al. (2007) used an emotional Stop Signal task of positive, negative and neutral words, and similar non-words. The observed SSRTs were substantially higher in depressed individuals for both neutral as well as emotional words and non-words, indicating slower inhibition. However, the differences were marginally statistically significant due to relatively small samples and unusually large standard deviations.

In individuals recovered from depression, we recently found no difference in SSRT compared to never-depressed controls (Aker et al., 2014). This was based on an adapted Stop Signal task which included pictures of human faces as emotional distracters. This task included fewer trials than other established versions such as the Cantab Stop Signal task (Cambridge Cognition Ltd., Cambridge, UK). It therefore remains to be fully assessed whether Stop Signal inhibition is impaired as a trait marker in remitted depression.

Another set of variables which can be derived from the SST relates to response monitoring. Response monitoring is the ability to detect conflict or performance error, and adjust behavior accordingly (Thakkar et al., 2014). These variables might give clue to how participants react to their own mistakes, which is valuable in terms of understanding how this population handles correctives and adversities. If a mistake is committed, it may be adaptive to slow down responses in order to increase probability of success on the next trial; however, it is not adaptive to be overly conservative and withdrawn in response to feedback. Depressed patients exhibit a rapid deterioration of performance once a mistake is committed (Beats et al., 1996; Pizzagalli et al., 2006; Steffens et al., 2001). Elliott et al. (1997, 1996) showed that abnormal response to negative feedback was correlated with depression severity and specific to depression. Similarly, students with high self-reported level of depressive symptoms show slower and less accurate response in post-error trials, in various types of tasks (Compton et al., 2008; Farrin et al., 2003; Steele et al., 2007). Studies of response to feedback as reflected in behavioral adjustments following errors, are scarce in recovered individuals (but see Elliott et al., 1997). This is an intriguing issue because such behavioral patterns in remitted MDD patients may indicate specific vulnerability and promote relapse.

In summary, inhibition as indicated by the Stroop test is impaired in remitted MDD, but research based on other measures of inhibition, specifically the SST, is needed. The first aim of this study was to investigate inhibitory function in remitted depressed individuals compared to controls, using the Stop Signal task from the Cantab neuropsychological test battery. We predicted less effective Stop Signal inhibition in remitted depressed participants. A Stroop inhibition task was included for comparison. Our second aim was to investigate post-error behavioral adjustments. Based on the reviewed literature on post-error behavior in MDD, we hypothesized larger post-error adjustments in remitted MDD.

2. Methods

2.1. Participant inclusion and procedure

Participants were recruited from the general public using advertisements in a local newspaper in Oslo, Norway. After giving written informed consent, the participants provided information about their medical status and underwent psychiatric evaluation including the Structured Clinical Interview for DSM-IV, Axis I disorders (SCID I). Depression and anxiety symptoms were assessed using the Beck Depression Inventory (Beck et al., 1996) and the Beck Anxiety Inventory (Beck and Steer, 1990), respectively. The SCID interviews were administered by trained clinicians; they were also audio-recorded and subjected to consensus diagnoses. Diagnostic exclusion criteria were current depressive disorder, current drug or alcohol abuse or dependency, current or previous bipolar or psychotic disorder. Other exclusion criteria were lifetime head trauma with loss of consciousness for 30 min or more, or other neurological disorder. The full procedure of clinical and behavioral assessment was completed in one day. Participant characteristics are presented in Table 1.

2.2. General cognitive functioning

General cognitive functioning was assessed with Picture Completion and Similarities from the Wechsler Adult Intelligence Scale III (Wechsler, 2003). Results are reported as scaled scores.