Running head: PERCEPTUAL ASYMMETRIES AS A MARKER FOR SSRI

RESPONSIVENESS

Words and Faces on Left and Right: Perceptual Asymmetries as a Marker for SSRI Responsiveness.

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Abstract

Vulnerability to depression has been associated with greater relative right hemisphere frontal activity, as measured by EEG recordings of alpha activity. However, there is much heterogeneity in the patterns of hemispheric asymmetries in people at risk for depression. These different patterns of hemispheric asymmetries may be related to whether an individual responds to Selective Serotonin Reuptake Inhibitor (SSRI) medication. Response to SSRIs is associated with a pattern of overall relative LH activity, whereas non-response to SSRIs is associated with a pattern of overall relative RH activity. Very little is known about how these asymmetries in neural activity relate to asymmetries in cognition. The current study investigated hemispheric differences in the processing of emotional faces and words, in individuals not vulnerable to depression (a Never Depressed group) and in individuals vulnerable to depression (a Previously Depressed group). In the chimeric faces task, the Previously Depressed group had a significantly larger left hemispatial bias compared to the Never Depressed group. This may reflect relatively greater posterior RH activity/arousal in the Previously Depressed group. No differences were found between SSRI Responders and Non-responders in the chimeric faces task. In the divided visual field task, hemispheric differences in the processing of emotional words were found between the SSRI Responders and SSRI Non-responders. In contrast to SSRI Responders and Never Depressed controls, SSRI Non-responders showed a relative advantage for negative over positive words when they were presented to their LVF/RH; and an advantage for negative words presented to their LVF/RH compared to their RVF/LH. Additionally, they were more sensitive to perceiving the valence of a word that was presented to their LVF/RH. This suggests that their RH semantic systems may differ from that of SSRI Responders and Never

Depressed controls. Genetic, hormonal and cognitive factors are discussed in relation to these patterns of hemispheric asymmetries and responsiveness to SSRI medication.

Words and Faces on Left and Right: Perceptual Asymmetries as a Marker for SSRI Responsiveness

Depression is the most prevalent mood disorder, with 16% of people in New Zealand experiencing an episode of depression in their lifetime (Oakley-Brown, Wells, Scott, & McGee, 2006). Depression is characterised by a distinct neuropsychological profile of hemispheric asymmetry, and by atypical processing of emotional stimuli. Although both neuropsychological and emotional correlates of depression are well documented, little is known about how these asymmetric characteristics of depression are related to emotional processing. This study will explore hemispheric differences in the perception of emotional words and faces in women at risk for depression.

Hemispheric asymmetries related to the *experience* of emotion are well established, showing increased frontal right hemisphere (RH) activity during the experience of negative emotion and increased frontal left hemisphere (LH) activity during the experience of positive emotion (Davidson, Ekman, Saron, Senulis, & Friesen, 1990a; Tomarken, Davidson, & Henriques, 1990). Hemispheric differences in the *perception* of emotional information are less clear. The two major hypotheses are the RH hypothesis and the valence hypothesis. The RH hypothesis implicates the posterior RH in the processing of emotional stimuli, regardless of valence (Borod, Koff, & Caron, 1983; Borod, Zgaljardic, Tabert, & Koff, 2001); whereas the valence hypothesis proposes that, similarly to the experience of emotion, processing of positive (or approach-motivated) emotional information involves the LH; while processing of negative (or withdrawal-motivated) emotional information involves the RH (Ahern & Schwartz, 1979).

Not only are patterns of hemispheric asymmetries related to the experience and perception of emotion, they are also linked to vulnerability to depression. Davidson's (1992) diathesis-stress hypothesis suggests that some individuals have a predisposing negative affective processing style, which influences their stress reactivity, increasing their risk for depression. This negative affective style has been linked to relative right hemisphere (RH) frontal activity in people vulnerable to depression (Davidson & Fox, 1989; Gotlib, Ranganathand, & Rosenfeld, 1998; Henriques & Davidson, 1990; Tomarken, Dichter, Garber, & Simien, 2004). The atypical asymmetry is most often shown in electroencephalogram (EEG) studies. Despite a large body of evidence on EEG hemispheric asymmetries in depression, and on the negative cognitive processing style in depression, little has been done to relate these hemispheric asymmetries to cognitive processes. Thus, little is known about what these asymmetries in activity actually mean in terms of cognition in depression. For example, it has not yet been investigated how this characteristic hemispheric asymmetry relates to how people at risk for depression process emotional information from their environment. This may be particularly relevant, as depressed individuals have an interpretive processing style favouring negative information (for reviews see Beck, 2008; Mathews & MacLeod, 1994; Mathews & MacLeod, 2005). A negative processing style may be the mediating factor between a genetic predisposition and increased stress reactivity in the development of depression (Beck, 2008).

A secondary goal of the study is to investigate potential differences in perceptual asymmetries in individuals who respond to Selective Serotonin Reuptake Inhibitor (SSRI) medication, compared to those who do not respond to SSRIs. Only approximately two thirds of patients treated with SSRIs respond favourably to the medication (Kornstein & Schneider, 2001). Many people experience side effects

which range from mild to severe (Ferguson, 2001). Thus it would be beneficial to have methods to predict whether patients are likely to benefit from SSRI medication. Depression is a heterogeneous disorder, and SSRI responders may have a different neuropsychological profile than SSRI non-responders. Differences in hemispheric and perceptual asymmetries (measured by EEG recordings and dichotic listening studies; Bruder et al., 1996; Bruder et al., 2001; Bruder et al., 2004; Bruder et al., 2008) have been found between SSRI responders and non-responders, with a pattern of overall greater relative LH activity in responders, and overall greater relative RH activity in non-responders. However, little is known about the consequences of these asymmetries on the processing of emotional information.

Perceptual asymmetry tasks which assess hemispheric differences in the processing of emotional faces and words will be administered to a group of Previously Depressed individuals, and a group of Never Depressed controls. People who have experienced depression in the past have over a 70% chance of becoming depressed in the future, and thus they are a group at high risk of depression (Kessler & Walters, 1998). Using a remitted depressed group will allow for the examination of vulnerability for depression, without being confounded by the effects of current depressed mood. Using this group will also allow for the separation of the Previously Depressed group further into those who have responded favourably to SSRIs (SSRI Responders), and those who have not (SSRI Non-responders).

Hemispheric Asymmetries in Emotional Experience

Hemispheric asymmetries related to the *experience* of emotion are well established. These asymmetries are most commonly measured using EEG alpha recordings, which measure electrical brain activity in the range of 8-13Hz while the subject is in a resting state. Alpha power is inversely related to cortical activity, thus

the lower the alpha power, the higher the brain activation (Shagass, 1972). Davidson (1992) has proposed that the activity in the frontal regions of the LH is associated with the experience of approach-motivated emotions (e.g. happiness, anger); while activity in the frontal regions of the RH is associated with the experience of withdrawal-motivated emotions (e.g. sadness, fear). Previously this asymmetry was thought to reflect a valence distinction - i.e. the LH is involved in positive emotions and the RH is involved in negative emotions (Heller, 1993). However, research on anger (a negatively-valenced but approach-motivated emotion) has shown that it is motivation, not valence that distinguishes emotional processing in the two hemispheres (Harmon-Jones, 2003).

These patterns of hemispheric asymmetries are associated with the experience of emotion (Davidson et al., 1990a), generalised trait affect (Tomarken, Davidson, Wheeler, & Doss, 1992), emotional responses to stimuli (Tomarken et al., 1990), and physiological responses to stressful stimuli (Jackson et al., 2003). Greater relative frontal RH activity is associated with the experience of disgust (Davidson et al., 1990a); negative trait affect (Tomarken et al., 1992); responding to negative stimuli with relatively stronger negative affect (Tomarken et al., 1990); and relatively larger startle responses to stressful stimuli (Jackson et al., 2003). Greater relative frontal LH activity is associated with the experience of positive affect (Davidson et al., 1990a; Tomarken et al., 1992), and responding to stressful stimuli with relatively smaller startle responses (Jackson et al., 2003).

Hemispheric Asymmetries in Emotional Perception

In contrast to the *experience* of emotion, which is lateralised in frontal regions, less is known about asymmetries in emotional *perception*. There are two major hypotheses on the lateralisation of emotional perception: The valence hypothesis and

the RH hypothesis. As discussed earlier, the valence hypothesis is associated with the *experience* of emotion, however some evidence indicates that this asymmetry may not only be related to the experience of emotion, but also to the *perception* of emotional information. Theories of embodied cognition suggest that to perceive emotion, one must necessarily also experience elements of that emotion (Niedenthal, 2007). For example, emotional perception is facilitated by being in the congruent mood state, and impaired by being in an incongruent mood state (Niedenthal, 2007). Thus, theories of embodied cognition would predict that the *perceptio*n of emotion would be lateralised similarly to the *experience* of emotion; that the LH is more involved in positive/approach-motivated emotions, while the RH is more involved in negative/withdrawal-motivated emotions.

The RH hypothesis suggests that processing of all types of emotional information is localised in the posterior RH (Borod et al., 1983; Borod et al., 2001; Landis, 2006; Wager, Luan Phan, Liberzon, & Taylor, 2003). Support for the RH hypothesis comes from studies of brain damaged patients (Cicero et al., 1999) in which patients with damage to the RH were significantly impaired in processing emotional words and sentences relative to neutral words and sentences, regardless of valence. Patients with damage to the LH had extensive impairments in word processing, but showed facilitation of processing emotional words and sentences, presumably due to the enhanced RH involvement in processing emotional words. Emotional processing involves functions that are specific to the RH, including organization and integration of the relationships between many elements of information (Rotenberg, 2004). Greater neuronal interconnectivity in the RH allows for ‘coarse semantic coding’ which involves automatic extensive, diffuse activation of the RH semantic network (for reviews see Beeman, 1998; Borod et al., 2001). This

contrasts the localised activation of the LH's semantic network. The LH activates only close lexical semantic relationships to activate one dominant meaning; while the RH spreads activation widely throughout the network, activating many possible meanings (Beeman, 1998; Borod et al., 2001; Rotenberg, 2004). This diffuse pattern of semantic organization may serve the broad categories associated with emotional meaning.

However, not all studies have supported the RH hypothesis of emotional perception (e.g. Smith & Bulman-Fleming, 2005, discussed below). Some support has been found for the valence hypothesis (Ahern & Schwartz, 1979); the notion that the LH is more involved in the perception of approach/positive emotions, while the RH is more involved in the perception of withdrawal/negative emotions. In a review of the literature on hemispheric differences in emotional word processing, Borod et al. (2001) concluded that when valence is not taken into account, most studies find the expected RVF/LH advantage on emotional language processing tasks (due to the LH's dominance for language processing). Similarly, for processing positive words, there were a larger number of RVF/LH advantages found. However, for negative words, there were an equal number of LVF/RH and RVF/LH advantages found, indicating greater relative RH involvement in the processing of negative words. This is inconsistent with the RH hypothesis, and is consistent with the valence hypothesis of emotional perception.

Hemispheric Asymmetries in Depression

Relative activation in the left and right frontal regions can influence a person's emotional responsiveness. Thus, a person with relative RH frontal activity at rest may be particularly vulnerable to withdrawal-motivated emotions, and may have a higher threshold for experiencing approach-motivated emotions. This leads to more negative

affect, and a vulnerability to developing depression (Davidson, 1998; Davidson, 2003). Consistent with this, patients with damage to the LH are more likely to develop depression compared to patients with damage to the RH (Robinson et al., 1984). This greater relative RH frontal activity is state-independent, as it is found in currently depressed individuals (Gotlib, et al., 1998), previously depressed individuals (Gotlib, et al., 1998; Henriques & Davidson, 1990), adolescents at risk for depression (Tomarken et al., 2004) and infants who cry in response to maternal separation (Davidson & Fox, 1989). Furthermore, greater relative RH frontal activity is present before the onset of depression. Possel, Lo, Fritz and Seemann (2008) found that in adolescents, relative RH frontal activity at time one significantly predicted depression one year later. Thus, this pattern of frontal asymmetry is a stable trait characteristic which is present in those both at risk for and in remission from depression. This is consistent with Davidson's (1992) diathesis-stress hypothesis; that relative RH frontal activity is a predisposing marker for depression, rather than being a 'scar' left from past episodes of depression.

Some researchers have questioned the reliability of these patterns of asymmetries in relation to depression. For example, Reid, Duke and Allen (1998) failed to find differences in frontal asymmetries between sub-clinical and clinically depressed individuals compared to healthy controls. However, in a meta-analysis of the literature, Thibodeau, Jorgensen and Kim (2006) concluded that despite methodological issues and the heterogeneity of depressed patients, overall, depressed individuals show a relative RH frontal activity compared to never depressed individuals. Due to the heterogeneous nature of depression, only some individuals with depression show this pattern of hemispheric asymmetry. Differences in patterns

of hemispheric asymmetries between depressed individuals may be related to other individual neuropsychological differences (e.g. responsiveness to SSRIs).

Patterns of brain activity in depression are related to changes in cognitive function. Depression is characterised by a pattern of brain activity in which (relative to healthy controls) activity is decreased in some regions and increased in others. The extent of resting activity of a brain region has been shown to correlate with performance on cognitive tasks that rely on that region (Heller & Nitschke, 1997; see Levin et al., 2007 for a review); and performance advantages are often associated with relative increases in EEG activity in the relevant region (Chapman, Chapman, & Henriques, 1990; Heller & Nitschke, 1997). For example, Davidson et al. (1990b) found relatively more left central activation during a verbal task (measured using EEG recordings); and relatively more right parietal activation during a spatial task.

Consistent with this, depressed individuals show deficits in tasks involving regions with suppressed activity. In depressed patients, a bilateral suppression of PFC activity is associated with deficits in executive functions (for reviews see Levin et al., 2007; Rogers et al., 2004). Larger decreases in activity are found in the left PFC compared to the right PFC, which may be related to specific deficits in left PFC executive functions (e.g. initiation of strategies, cognitive flexibility; Heller and Nitschke, 1997; for reviews see Levin et al., 2007; Rogers et al., 2004). The PFC has inhibitory connections to limbic sites, therefore decreased PFC activity in depression is associated with increased limbic activity, which is related to increased emotional responsiveness (for reviews see Davidson, 2002; Levin et al., 2007).

When depression is accompanied by relative RH frontal activation, it is typically also associated with suppressed RH posterior activation (Bruder et al., 2004; Bruder, Tenke, Warner, & Weissman, 2006; Heller, 1993; Henriques & Davidson,

1990). This reduced RH posterior activity is also found in people at risk for depression. Bruder et al. (2004) measured EEG alpha asymmetries in individuals with a family history of depression. They found that individuals whose parents both had depression had less activation over RH central and parietal regions compared to individuals with one or no parents with depression. Similarly, Bruder et al. (2006) found that individuals with a parent and grandparent with depression had relatively less RH parietal activation compared to the LH and to individuals with either one or no parents or grandparents with depression.

Suppression of right posterior activity has been related to performance deficits in tasks known to rely on this region. Henriques and Davidson (1997) found that depressed patients showed a deficit in performance in the spatial dot localization task (a task involving the posterior RH) compared to non-depressed controls, and failed to show the same relative RH posterior activation as controls during the spatial task. Similarly, in a sub-clinical sample, Rabe, Debener, Brocke and Beauducel (2005) found that higher levels of depression were associated with relative right hypoactivation during performance of a spatial task. Depressed patients have also shown deficits in other tasks involving the RH posterior cortex, such as the ability to interpret facial expressions, prosody and gesture; as well as various spatial tasks including line bisection and orientation (for reviews see Levin et al., 2007; Rotenberg, 2004).

The relationship between hemispheric asymmetry and depression is further complicated by the frequent co-occurrence of anxiety, which may have the opposite effect to depression on RH posterior activity (Heller et al., 1998; Keller et al., 2000). The RH posterior suppression of activity may be a reflection of decreased arousal, associated with the anhedonic symptoms of depression (Bruder et al., 1997; Heller et

al., 1998). Heller et al. (1998) suggests that RH posterior regions are involved in anxious arousal, which is characterised by somatic symptoms: panic, shortness of breath, pounding heart, dizziness, and sweating, induced by a specific stimulus in the environment (Heller et al., 1998; Nitschke, Heller, Palmieri, & Miller, 1999). Anxious apprehension is associated with activation of the frontal regions of the LH (perhaps due to its verbal component; Heller et al., 1998). Anxious apprehension is characterised by worry, cognitive anxiety, anticipatory anxiety, verbal rumination, muscle tension, restlessness, and fatigue (Nitschke et al., 1999). Using correlational and confirmatory factor analyses, Nitschke et al. (2001) found that anxious arousal and anxious apprehension are distinct dimensions, which are also separate from depression and general negative affect.

Thus, depression and anxious arousal have opposing effects on RH posterior regions: depression suppresses posterior RH activation; while anxious arousal increases posterior RH activation (Heller et al., 1998; Keller et al., 2000). This may account for some of the inconsistent findings in the literature on the relationship between hemispheric asymmetries and depression, as many studies have not controlled for the effect of anxiety on asymmetry (Keller et al., 2000). Bruder et al. (1997) measured EEG alpha asymmetries and found that depressed patients without an anxiety disorder showed less activity over RH compared to LH posterior sites; whereas depressed patients with a co-morbid anxiety disorder showed greater activity over RH compared to LH posterior sites. Nitschke et al. (1999) examined EEG alpha asymmetries in non-depressed individuals high in either anxious arousal or anxious apprehension, and found that the high anxious arousal group showed greater relative RH asymmetry, while the high anxious apprehension group showed no asymmetry. This may be due to the relative involvement of the LH in anxious apprehension.

Hemispheric Asymmetries in SSRI Responders and SSRI Non-responders

Approximately one third of depressed patients who take SSRIs do not respond to the treatment (Kornstein & Schneider, 2001). There are currently no tests used to determine the likelihood of a patient responding to SSRIs. Patterns of hemispheric and perceptual asymmetries may be markers which could be predictive of a patient's response to treatment. Responders to Fluoxetine (a SSRI) show a pattern of greater relative LH activity in frontal, posterior (Bruder et al., 2001) and occipital (Bruder et al., 2008) regions; while non-responders to Fluoxetine show the opposite pattern of greater relative RH activity in frontal, posterior (Bruder et al., 2001) and occipital (Bruder et al., 2008) regions. These asymmetries do not significantly change after treatment, suggesting that alpha asymmetry is a state-independent trait (Bruder et al., 1996; Bruder et al., 2008).

In Bruder et al. (2008), individuals with greater overall LH than RH activity had a positive response rate to SSRI medication of 77.8%. Individuals with greater overall RH than LH activity had a positive response rate of 44.4%. Thus, the potential for hemispheric asymmetry tests to determine likelihood of response is strong, but would best be combined with other predictive measures, possibly including perceptual asymmetry tasks. Additionally, different patterns of hemispheric differences in the processing of auditory information have been found between SSRI responders and non-responders. Typically (consistent with the EEG asymmetries), a pattern of asymmetry consistent with relatively greater overall LH activity in SSRI responders and relatively greater overall RH activity in non-responders is found (Bruder et al., 1996; Bruder et al., 2001; Bruder et al., 2004). Dichotic listening tasks measure these hemispheric differences in the auditory domain. A dichotic listening task involves two different words or sounds being presented simultaneously, one to each ear. The sound

from the right ear is initially processed by the LH and the sound from the left ear is initially processed by the RH (Bryden, 1988). When using linguistic stimuli, a right ear/LH advantage is usually found, presumably due to the LH's advantage for processing verbal information (Bryden, 1988). A left ear/RH advantage is found when processing prosodic features of verbal stimuli, due to the RH's advantage for processing emotional information (Grimshaw, Godfrey, & Seguin, 2009).

Bruder et al. (1996), Bruder et al. (2001) and Bruder et al. (2004) found that SSRI responders have a significantly larger right ear or LH advantage in the dichotic listening rhymed fused word task; and a smaller left ear or RH advantage in the complex tone task compared to SSRI non-responders. A characteristic perceptual asymmetry (PA) score can be obtained combining PA scores for both tasks. This is based on the assumption that people have a tendency towards relatively greater LH or RH activation, and thus relatively better performance of the LH or RH, regardless of the task at hand (Heller & Nitschke, 1997; Levin et al., 2007). Characteristic PA in Bruder et al. (1996) significantly predicted response to treatment. Participants with a characteristic PA of relative LH asymmetry had a 76% response rate; while patients with a characteristic PA of relative RH asymmetry had only a 50% chance of responding to Fluoxetine.

Despite the relatively strong relationship between asymmetry and SSRI response in females, there is some evidence that patterns of asymmetry do not predict responsiveness to SSRIs in males. Further analyses by Bruder et al. (1996) showed that for the verbal task, the difference between SSRI responders and non-responders was significant for females but not for males. In females completing the verbal task, patients with a relative LH asymmetry had a 94% response rate to Fluoxetine, while patients with a relative RH asymmetry had a 25% response rate. Thus, perceptual

asymmetry scores in this task were a better predictor of treatment response than hemispheric asymmetry scores obtained using EEG measures (e.g. Bruder et al., 2008), but only for females. In Bruder et al. (2004) in the verbal task, asymmetry differences between SSRI responder groups were again significant for women but not for men. Patients with a relative LH asymmetry above the mean had a 94% response rate for Fluoxetine, while patients with an asymmetry below the mean had a 43% response rate for Fluoxetine. These studies indicate that at least for females, perceptual asymmetry tasks may be a particularly effective predictor of SSRI response.

The differences in frontal and posterior asymmetries between responders and non-responders found in Bruder et al. (2001) were significant for females, but not males. However, in the mostly male sample studied in Bruder et al. (2008), differences in asymmetries between responders and non-responders were found at occipital (but not frontal) sites. It is difficult to speculate on reasons for these sex differences, as so little is known about what EEG alpha asymmetries are actually measuring. More women than men experience depression (Heller, 1993); and the nature of depression differs in males and females. For example, women are more likely than men to engage in rumination (Heller, 1993). As this is a verbal, LH process, the neuropsychological profile of activity and asymmetry in depressed men and women may differ. There are also hormonal differences between men and women which are likely to affect patterns of asymmetry (Landis, 2006).

Thus, there is a tendency (at least in females) for SSRI responders to be more LH lateralised, and for SSRI non-responders to be more RH lateralised. This has been shown in both EEG and dichotic listening studies. However, it is unknown whether there are hemispheric differences in SSRI responders and non-responders in the

perception of emotional stimuli (specifically faces and words). As people vulnerable to depression respond to emotional stimuli in the environment differently to those not vulnerable to depression (Beck, 2008; Gotlib & Neubauer, 2000; for reviews see Mathews & MacLeod, 1994; Mathews & MacLeod, 2005), then the processing of emotional stimuli may be where the largest hemispheric differences between groups lie.

Negative Cognitive Processing Style in Depression

Vulnerability to depression has been associated with a negative cognitive processing style which interacts with life stress to increase the likelihood of development of depression (for reviews see Beck, 2008; Davidson, 1992). Depression has been associated with a processing style favouring attention and memory for negative information, and in the interpretation of ambiguous information (for reviews see Mathews & MacLeod, 1994; Mathews & MacLeod, 2005). In contrast to healthy controls (who have a positive interpretive bias; Hirsch & Mathews, 2000) depressed individuals demonstrate a bias towards attending to negative stimuli, but only when the stimuli are presented for longer durations (which allows for the conscious direction of attention), but not when the stimuli are presented for shorter durations (assessing unconscious, automatic control of attention; for reviews see Mathews & MacLeod, 1994; Mathews & MacLeod, 2005). Depressed individuals may also interpret ambiguous information more negatively than non-depressed individuals, however research has not determined whether this is the effect of a response bias (a tendency to report negative information), rather than a negative perceptual bias; (for reviews see Mathews & MacLeod, 1994; Mathews & MacLeod, 2005). Depressed individuals have a robust bias for recalling negative information, especially for self-referential stimuli (for reviews see Mathews & MacLeod, 1994; Mathews &

MacLeod, 2005). This advantage is probably caused by conscious encoding/retrieval strategies (including rumination), as this effect is not found in implicit memory tasks (Mathews & MacLeod, 1994). Thus, the negative cognitive style in people vulnerable to depression appears to influence the processing of emotional information in a top-down, conscious manner. However, possibly due to the heterogeneity of depression, results on this topic have not always been consistent (for reviews see Mathews & MacLeod, 1994; Mathews & MacLeod, 2005).

There is some evidence that a negative cognitive style is a causal factor preceding the development of depression. For example, a tendency towards interpreting ambiguous information as negative can later predict stronger negative responses to impending stress (Pury, 2002). MacLeod et al. (2002) induced a negative interpretive bias in healthy individuals by forcing attention towards negative stimuli. People with the induced negative interpretive bias subsequently showed relatively greater increases in negative mood in response to a stressor compared to those without the induced negative bias. This suggests that a negative interpretive style has a causal influence on emotional response to stress. This is consistent with the diathesis-stress hypothesis (Davidson, 1992), that people with a negative processing style react to stress in more maladaptive ways, increasing their negative affect and susceptibility to depression. Remitted depressives may exhibit similar cognitive characteristics as currently depressed individuals, but only under certain conditions (e.g. negative mood induction; for a review see Mathews & MacLeod, 2005).

The negative cognitive processing style in depression may depend on the extent of the processing involvement of each hemisphere. Thus, these effects may be more robustly demonstrated by the use of perceptual asymmetry tasks. For example, Atchley, Ilardi and Enlow (2003) and Atchley et al. (2007) found an advantage for

processing negative words over positive words in currently and previously depressed individuals, but only when the words were presented to the LVF/RH.

Perceptual Asymmetry Tasks

Thus, there is a large body of research examining EEG hemispheric asymmetries in depression; and examining negative cognitive style in depression. However, little research has examined how these asymmetries in brain activity relate to this negative cognitive style, and more specifically to asymmetries in the processing of emotional stimuli. Perceptual asymmetry tasks measure hemispheric differences in information processing. Divided visual field tasks measure these hemispheric differences in the visual domain. Words are briefly presented laterally and different responses to the words can be obtained (e.g. affective judgement, lexical decision). A word shown in the left visual field (LVF) will be initially processed by the contralateral hemisphere (the RH) and similarly, a word shown in the right visual field (RVF) will be initially processed by the LH (Beaumont, 1983). As most people's LHs are dominant for language processing, there is usually a RVF/LH advantage in this task (Borod et al., 2001). However, people differ in the strength (and sometimes in the direction) of their perceptual asymmetry in this task. Emotional content may be a factor which influences the relative contribution of each hemisphere. By looking at performance when sounds are presented to each ear, or words to each visual field (VF), perceptual asymmetry scores can be obtained, reflecting the relative performance of each hemisphere.

Hemispheric differences in the processing of emotional faces can be measured using the chimeric faces task (Levy, Heller, Banich, & Burton, 1983), in which photos of faces are presented with half the face smiling, and half the face in a neutral expression. Each trial consists of two faces, shown one above the other, which are

mirror images of each other (see Figure 1). The task is to choose which of the two faces looks happier in each trial. There is a consistent left hemispatial bias found in this task (i.e. a bias to choosing the face with the smile on the left side; Borod et al., 2001; Levy et al., 1983) even under free viewing conditions. The leftward bias is often interpreted as an attentional bias to the left side of the face (Levy et al., 1983).This leftward bias is found in children at least as young as six years, increases until the age of 10, and then plateaus (Chiang, Ballantyne, & Trauner, 2000).

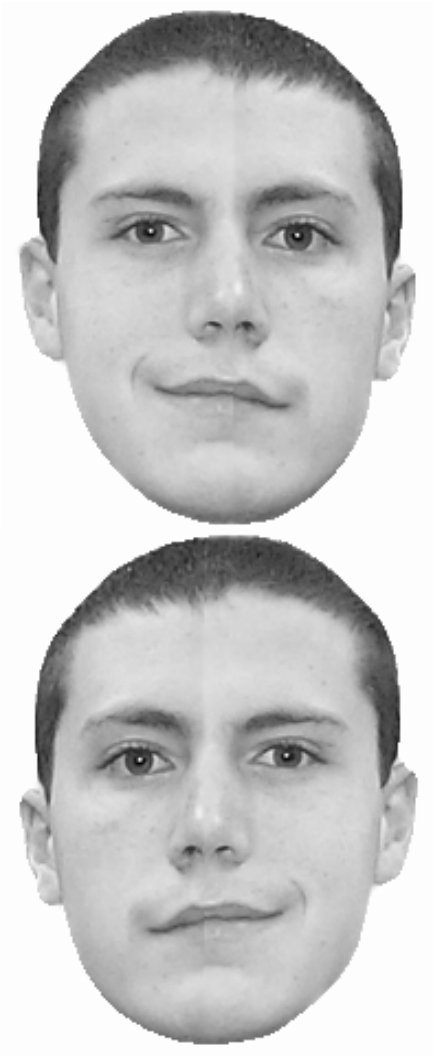

Figure 1. An example of a chimeric face image.

Do between-subjects differences in perceptual asymmetries actually reflect genuine individual trait differences, and how do these perceptual asymmetries relate

to patterns of resting EEG asymmetries? EEG and behavioural studies suggest that individual variation in activity in the RH posterior region partly accounts for perceptual asymmetries (Heller, 1993). Asymmetry in arousal is a stable characteristic, with high reliability (Kim, Levine, & Kertesz, 1990). Davidson and Hugdahl (1996) found that in a dichotic listening syllables task, participants with greater relative LH posterior asymmetry (as measured with EEG recordings) had a greater right ear/LH advantage than those with greater relative RH posterior asymmetry. Bruder et al. (2001) found a large significant correlation in female participants (but not males) between perceptual asymmetry in a dichotic listening word task, and overall alpha asymmetry ($r = 0.51$, $p < .01$) indicating that (at least for females) performance in this perceptual asymmetry task is significantly related to patterns of EEG alpha asymmetries. Green et al. (1992) found that EEG alpha asymmetry scores measured at temporal and parietal regions were significantly predictive of perceptual asymmetries in a divided visual field lexical decision task. Together, temporal and parietal asymmetry accounted for 50% of the variance in perceptual asymmetry in the task. These studies indicate that perceptual asymmetries in divided visual field and dichotic listening tasks at least partly reflect hemispheric asymmetries of activity/arousal in the posterior regions of the brain.

Thus, perceptual asymmetry tasks can be used to examine how hemispheric asymmetries are related to the perception of emotional information. People vulnerable to depression process emotional information differently than people who have never experienced depression (Atchley, et al., 2003; Atchley et al., 2007; Beck, 2008; Gotlib & Neubauer, 2000; for reviews see Mathews & MacLeod, 1994; Mathews & MacLeod, 2005). If relative RH frontal activity is related to this negative cognitive processing style, which affects how people respond to emotional stimuli in the

environment, then asymmetries in the perception of emotional information may be particularly relevant to individuals with depression. Therefore, Previously Depressed individuals may differ considerably from Never Depressed individuals in their asymmetries for processing emotional information. The current study will use two tasks to examine asymmetries in how people who were previously depressed process emotional information. An additional advantage of using perceptual asymmetry tasks is that they are relatively quick, simple and inexpensive to administer, and are less invasive compared to imaging and EEG techniques.

Chimeric Faces Task

The first task used in the current study will be the chimeric faces task. Butler et al. (2005) proposed that the left hemispatial bias in the chimeric faces task is caused by a combination of a directional scanning bias to the left side and lateralisation of brain function. That is, when a face is initially presented, the left side of the face is projected to the RH, and the right side of the face is projected to the LH. The RH is specialised for face processing, and so more attention is drawn to the left side of the face. This combines with a directional scanning bias (due to reading from left to right on the page) which initially draws more attention to the left side. In a gender identification chimeric faces task (with half the face male and half female), Butler et al. (2005) found that when a left hemispatial bias was present, participants made a greater number of fixations to the left and looked at the left side of the face for longer than the right side. There was no effect of eye movements on trials with a right hemispatial bias. On the vast majority of trials the first saccade was made to the left side of the face. In a subsequent study, Butler and Harvey (2006) presented chimeric faces for 195ms, too short a duration to allow for eye movements. The leftward bias

was attenuated but present, demonstrating that eye movements to the left side of the face contribute to, but are not necessary for the left hemispatial bias to occur.

The posterior RH is involved in directing attention in space to different locations (Heller, 1993), recognising faces and emotional expressions (Borod et al., 2001; David, 1989; Kucharska-Pietura, Phillips, Gernand. & David, 2003; Levy et al., 1983) and modulating emotional autonomic and behavioural arousal (Borod et al., 2001; Heller, 1993). Thus it has been suggested that the leftward bias may be partly dependent on the extent of RH posterior activity or arousal compared to the posterior LH (Borod et al., 2001; David, 1989; Heller, 1993; Levy et al., 1983). Depressive symptoms have been associated with a decreased left hemispatial bias in the chimeric faces task. This may reflect the decreased RH posterior activity/arousal associated with anhedonic symptoms of depression (Bruder et al., 1997; Heller et al., 1998; Heller, Etienne, & Miller, 1995; Voelz et al., 2001). In support of this, over half of the variance in self-reported behavioural arousal can be accounted for by differences in the size of the bias in the chimeric faces task; with increased arousal being associated with increased left hemispatial biases (Heller, 1993).

The size of a person's left hemispatial bias on this task can predict future anxiety and positive affect, with smaller biases being associated with positive affect, and larger biases being associated with anxiety. Voelz et al. (2001) administered the chimeric faces task to a non-clinical sample to examine whether the size of a left hemispatial bias at time one can predict measures of anxiety and positive affect at time two. They found that increased left hemispatial biases at time one significantly predicted increased anxiety at time two. Voelz et al. interpret these increased left hemispatial biases as reflecting increased physiological arousal in the posterior RH, which is consistent with the increase in anxiety at time two for this group. Decreased

left hemispatial biases at time one significantly predicted decreased positive affectivity at time two. They interpret these decreased left hemispatial biases as reflecting reduced RH posterior activity, resulting in lower levels of positive affect, consistent with the suggestion that suppression of RH posterior activity reflects anhedonia.

Response to stress may be a mediating variable in the relationship between depressive symptoms and the size of the left hemispatial bias on this task. Compton et al. (2003) examined the relationship between individuals' coping styles and their left hemispatial biases on the chimeric faces task. They found that in women, rumination was associated with reduced left hemispatial biases in the chimeric faces task. As rumination is thought to involve LH processes (due to the verbal component; Heller et al., 1998), the reduced left hemispatial bias may reflect increased activation of the LH. Similarly, Flynn and Rudolph (2007) examined the relationship between youths' responses to stress and their left hemispatial biases on this task. They found that youths with a reduced left hemispatial bias were more likely to engage in less adaptive responses to stressful events. In youths who reported high levels of stress (but not those who reported low levels), responses to stress significantly contributed to the association between a reduced left hemispatial bias and depressive symptoms.

To investigate the opposing effects of anxiety and depression on RH posterior activation, Heller et al. (1995) examined the effects of anxiety and depressive symptoms (in a non-clinical sample) on performance in the chimeric faces task. Participants were classed as either high or low anxious, and high or low depressed, depending on their scores on self-report anxiety and depression measures. They found that the high depressed group had a smaller left hemispatial bias compared to the low depressed group; and that the high anxious group had a larger left hemispatial bias

than the low anxious group. Heller et al. interpreted these findings as reflecting the decreased RH posterior activation seen in depression and the increased RH posterior activation seen in patients with anxiety disorders (Heller et al., 1995).

The reduced left hemispatial bias and associated suppressed RH posterior activity may be related to the anhedonic symptoms of depression. Bruder et al. (2002) used a clinical sample to examine asymmetries in the perception of chimeric faces in patients with atypical depression (depression without melancholia), melancholic depression (depression with melancholia), and healthy control participants. The main feature of melancholic depression is marked anhedonia, whereas patients with atypical depression do not experience anhedonia (Leventhal, & Rehm, 2005). The atypical depression group showed a larger left hemispatial bias compared to controls and the melancholic depression group. The melancholic group showed no left hemispatial bias at all. The authors interpret the lack of a left hemispatial bias as reflecting anhedonia in the melancholic group, due to decreased arousal/activation in the posterior RH. Consistent with this, the atypical depressed group did not show this decreased left hemispatial bias.

Divided Visual Field Task

The second task used in the current study used a divided visual field paradigm (based on Atchley et al., 2007), to examine hemispheric differences in the perception of emotional words. The limited research on hemispheric differences in processing emotional words indicates that even in healthy participants, emotional words may be processed differently from non-emotional words (Landis, 2006), and that valence may affect the lateralisation of emotional word processing (for a review see Borod et al., 2001). Although the LH is the dominant hemisphere for language comprehension in almost all right handed people, this does not mean that the RH is incapable of

language comprehension (Lindell, 2006). The RH may be involved more in the processing of emotional compared to non-emotional words. For example, Landis (2006) administered a lexical decision task using simultaneous lateralised presentation of emotional and non-emotional words (and non-words). They found that for words presented to the RVF/LH there was an overall superiority for word recognition, but no difference in processing emotional vs. non-emotional words; whereas for words presented to the LVF/RH, there was significantly better processing of emotional vs. non-emotional words.

However, some studies that assess performance for positive and negative words separately find that the RH advantage for emotional information may only be observed for negative but not positive words (as predicted by the valence hypothesis of emotional perception; Ahern & Schwartz, 1979). Smith and Bulman-Fleming (2005) measured the perception of positive, negative and neutral words presented laterally for 17ms. They found that for negative words, there was a LVF/RH advantage, but for positive words, there was no VF advantage. If the RH is involved equally in the processing of all emotional information, there should have also been a RH advantage for positive stimuli. Thus, this lends support to the valence hypothesis of emotional perception (Ahern & Schwartz, 1979). Many studies attempting to test the valence hypothesis have failed to control for the effects of arousal. Negative words tend to be more highly arousing than positive words (see Bradley & Lang, 1999), thus valence effects may be confounded by arousal in previous studies.

Atchley et al., (2003) performed a study using the DVF paradigm with Previously Depressed, Currently Depressed, and Never Depressed participants. Participants made affective valence judgements (i.e. is the word positive or negative?) about laterally presented emotional words. The words were person-descriptive

adjectives (e.g. smart, dirty) and were presented following a centrally presented prime word which was either related or unrelated to the target word. In a subsequent study, Atchley et al. (2007) again used the divided visual field paradigm to examine perceptual asymmetries in Previously Depressed, Currently Depressed, and Never Depressed participants. They performed an affective valence judgement task with laterally presented emotional person-descriptive adjectives. This time no primes were used. In both studies, Atchley et al. (2003; 2007) found that for words presented to the LVF/RH, Currently Depressed and Previously Depressed participants were significantly more accurate for negative target words than for positive target words; and that Never Depressed controls were significantly faster for positive target words than for negative target words. They found no valence effects in the RVF/LH. These results indicate that individuals vulnerable to depression may process negative words more effectively than positive words when words are presented to their RH.

In addition to valence effects, VF effects can also be examined using this paradigm. In the Atchley et al. (2003) study, all three groups had a RVF/LH advantage for processing both negative and positive words. In the Atchley et al. (2007) study, the Currently and Previously Depressed groups both had this same RVF/LH advantage for processing both negative and positive words. The Never Depressed participants shared this RVF/LH advantage for processing negative words, however they did not have a VF advantage for positive words. This is unexpected, as usually healthy participants typically demonstrate a robust RVF/LH advantage for positive words (for a review see Borod et al., 2001).

In both studies, Atchley et al. analysed percentage correct as their accuracy measure. This does not differentiate between the effects of sensitivity and bias on performance. Sensitivity or *d'* is a measure of accuracy which takes into account both

hits (indicating that a word is positive when it is positive) and false alarms (indicating a word is positive when it is actually negative). The *d'* measure takes into account both hits and false alarms, to determine how sensitive the participant actually is to the correct valence of the word. This eliminates any effects of biased responding. Bias or *c* is a measure of how biased a participant is to responding a certain way, regardless of the actual valence of the word. For example, a participant may tend to respond '*positive*' if they are not sure whether the valence is positive or negative. This would result in a large number of hits for positive words (responding that a word is positive, when it is in fact positive), but also a large number of false alarms (responding that a word is positive when it is in fact negative). This would also result in low accuracy on negative words. Given that biased interpretation of emotional information may be characteristic of vulnerability to depression (for reviews see Beck, 2008; Mathews & MacLeod, 1994; Mathews & MacLeod, 2005), it is important to separately consider independent contributions of bias and sensitivity on task performance. Atchley et al. (2003; 2007) only examined hit rates as their accuracy measure, which does not take into account any bias effects. This may explain Atchley et al.'s (2007) unusual finding of no VF advantage for positive words in Never Depressed individuals.

The present study

The current study investigated hemispheric differences in the processing of emotional faces and emotional words in Previously Depressed and Never Depressed individuals. Studying Previously Depressed instead of Currently Depressed participants allowed for the examination of the effects of vulnerability to depression, without being confounded by the effects of depressed mood. Due to the high co-morbidity of anxiety and depression, using participants who are not currently depressed may remove some of the effects of anxiety that may be more prevalent in a

currently depressed sample. Anxiety was assessed and used as a covariate in the analyses. All participants were right-handed females, to keep the groups as homogenous as possible, and because the relationships between hemispheric asymmetry and depression, and between hemispheric asymmetry and SSRI response, are more robust in women than in men (Bruder et al., 1996; Bruder et al., 2004; Bruder et al., 2008). Participants completed a chimeric faces task and a divided visual field task with emotional words.

Previous research using the chimeric faces task has examined both sub-clinical and clinical depressed samples, but not a Previously Depressed sample. The current study will examine these perceptual asymmetries in a group of Previously Depressed individuals. If Previously Depressed individuals demonstrate a reduced left hemispatial bias compared to Never Depressed controls (as currently depressed individuals do), then that would indicate that the associated suppressed arousal in the posterior RH is a state-independent trait, which remains after recovery from depression. However, if Previously Depressed individuals do not demonstrate a relatively smaller left hemispatial bias compared to Never Depressed controls, then that would indicate that the associated suppressed arousal in the posterior RH is dependent on being in a depressed mood state. This would be consistent with the idea that suppressed activity in the posterior RH is associated with current anhedonia (Bruder et al., 1997; Heller et al., 1998). The size of the SSRI Responder and SSRI Non-responder groups' left hemispatial biases will be compared. It is possible that the SSRI Non-responders may have a comparatively larger left hemispatial bias compared to the SSRI Responders, based on their increased RH involvement in dichotic listening tasks and greater relative RH activity.

Participants will also complete a divided visual field affective judgement task using emotional words. This is partly to replicate the findings of Atchley et al. (2003; 2007), and to extend their findings. Atchley et al. (2007) did not examine response times, and only examined accuracy as a percentage correct. As explained earlier, using this measure of accuracy does not differentiate between how sensitive someone is to detecting whether a word is positive or negative, or whether they are biased towards responding a certain way when they are unsure of the correct valence of the word. The current study will also extend Atchley et al.'s findings by examining hemispheric differences between SSRI Responders and Non-responders on this task.

Based on the results on Atchley et al., (2003; 2007), it is expected that for words presented to the RVF/LH, both Never Depressed and Previously Depressed participants will have an advantage for positive over negative words. However, for words presented to the LVF/RH, the Never Depressed group may have an advantage for positive words; whereas the Previously Depressed group may have an advantage for negative words. It is expected that the Never Depressed group will have an overall RVF/LH processing advantage seen in this task. Based on studies of perceptual asymmetries in dichotic listening tasks with SSRI Responders and SSRI Non-responders (which find increased RH involvement in Non-responders) it is expected that the SSRI Responders will resemble control participants, showing a RVF/LH advantage, whereas SSRI Non-responders may show a decreased RVF/LH advantage, or a reversal towards a LVF/RH advantage.

Method

Participants

The 78 Never Depressed participants were female psychology students from an introductory psychology course. Student participants were screened for their past

history of depression, and no control participants had a history of treatment for depression. The 53 Previously Depressed female participants were recruited through advertisements in the university magazine and posters around campus, and from an introductory psychology course. Students in the psychology course received course credit for participation. Other participants were given movie vouchers as compensation. The mean age in the Never Depressed group was 19.35 years (*SD* = 3.44) and in the Previously Depressed group was 22.65 years (*SD* = 6.20).

All Previously Depressed participants completed a Depression history questionnaire (see Appendix C) asking whether they were treated with SSRI medication, other medication, and/or therapy, and whether they thought the SSRI medication helped their depression. It would have been preferable to have access to the participants' medical records to confirm diagnosis and treatment, however this was not possible in this study. The Previously Depressed group were further divided into a 'SSRI Responders' group (*n* = 27), a 'SSRI Non-responders' group (*n* = 11) , and an 'Other Treatment' group (*n* = 15) depending on their self-reported treatment history. All participants were right handed, spoke fluent English, and were without vision or hearing impairments.

Measures

The Zung self-rating depression scale (Zung, 1965; Appendix A) and the Zung self-rating anxiety scale (Zung, 1971; Appendix B) were given to all participants. Both scales consist of 20 items, with five reversed items in the anxiety scale and 10 reversed items in the depression scale. For each item participants tick one option out of '*a little of the time*'; '*some of the time*'; ' *a good part of the time*'; and '*most of the time*'. Examples of items from the anxiety scale include '*I get upset easily or feel panicky*' and '*I can breathe in and out easily*'. Examples of items from the depression

scale include '*I feel downhearted and blue'* and '*I am more irritable than usual*'. A questionnaire on their depression treatment history was administered to all remitted depressed participants (Appendix C). Psychology Software Tools' E-Prime Suite version 1.0 was used to design and administer the experiments (Schneider, Eschman, & Zuccolotto, 2002), and to record the reaction time and accuracy for each task. Tasks were presented on a Dell PC. SPSS 16.0 was used to analyse the data.

Chimeric faces. To assess asymmetries in the perception of emotional faces, a chimeric faces task was administered to all participants. This task was based on that of Levy et al. (1983) Participants were presented with a series of 20 chimeric faces (see Figure 1 for an example). The faces were adapted from Levy et al. (1983). The faces show half the face smiling and half with a neutral expression. Two faces were presented, one above the other, which were mirror images of one another. The face pairs were presented in random order. The participants chose which face appeared happier by responding on one key to indicate that the top face was happier, and one key to indicate that the lower face was happier. Half the participants pressed '*top*' with their index finger and '*lower*' with their middle finger, and half the participants pressed '*top*' with their middle finger and '*lower*' with their index finger. The responses were recorded in E-Prime.

Divided visual field task with emotional words. To assess perceptual asymmetries in the perception of emotional words, a divided visual field task using emotional words (based on Atchley et al., 2003; Atchley et al., 2007) was administered to all participants. The target words were a mixture of positive and negatively valenced words, of either high or low arousal. All participants saw the same 96 words, 24 of which were of a negative valence, and high arousal; 24 of which were of a negative valence and low arousal; 24 of which were of a positive valence

and high arousal; and 24 of which were of a positive valence and low arousal (Appendix D). The words were selected from the list of Affective Norms for Emotional Words (ANEW; Bradley & Lang, 1999). Independent samples t-tests were administered to ensure that the positive and negative lists significantly differed in valence ratings: $t(46) = -36.51$, $p < .05$ (low arousal lists) and $t(46) = -33.70$, $p < .05$ (high arousal lists); and that the low and high arousal lists significantly differed in arousal ratings: $t(46) = -27.33$, $p < .05$ (positive lists) and $t(46) = 0.64$, $p < .05$ (negative lists). The positive lists did not significantly differ from each other in valence, $t(46) = -1.78$, $p = .08$; the negative lists did not significantly differ from each other in valence, $t(46) = 1.0$, $p = .17$; the high arousal lists did not significantly differ from one another in arousal, $t(46) = 0.96$, $p = .30$; and the low arousal lists did not significantly differ from one another in arousal, $t(46) = 0.77$, $p = .45$. None of the lists significantly differed from each other in word frequency or word length.

Participants placed their heads in a chin rest which was positioned 60 cm from the computer screen. In this task, a centrally presented fixation cross was followed by a brief presentation of a target word to either the LVF or RVF. The degree of visual angle to the inner edge of the lateralised stimuli was 2º. Participants were required to indicate whether the valence was positive or negative by pressing '*one*' or '*two*' on the number pad, with the index finger or middle finger of their right hand as quickly and accurately as possible. Half the participants pressed '*positive*' with their index finger and '*negative*' with their middle finger, and half the participants pressed '*positive*' with their middle finger and '*negative*' with their index finger. At the beginning of a trial, a fixation cross appeared centrally for 1000ms, followed by the lateralised target word which appeared for 185ms, followed by a pattern mask, which also appeared for 185ms. Participants were required to respond within 2500ms after

target onset, or an incorrect trial was recorded, and they automatically moved on to the next trial. The participants completed a series of 20 practice trials, with the words presented centrally on the screen. They then completed a series of 96 lateralised trials. Participants saw each word only once, and the lists were counterbalanced so that the each word was presented to the left and to the right an equal number of times across participants. Response time and accuracy were recorded by E-Prime.

Procedure

Written informed consent was obtained for all participants. After completion of the chimeric faces task, then the divided visual field task, they were given the Zung self-rating depression and anxiety scales, and (if applicable) completed a questionnaire on their treatment history for depression. Afterwards, they were given a verbal and written debriefing.

Results

For the mean scores and standard deviations for the Depression and Anxiety scales, see Table 1. The Previously Depressed (n = 53) and Never Depressed groups (n = 78) did not significantly differ on their Zung Self-rating Depression; $t(129) = -0.53$, $p = .60$; or Anxiety scores; $t(129) = -1.01$, $p = .31$. Within the Previously Depressed group, the SSRI Responders (n = 27) and the SSRI Non-responders (n = 11) also did not significantly differ on their Zung Self-rating Depression; $t(36) = -1.07$, $p = .77$ or Anxiety scores; $t(36) = -.93$, $p = .94$. People with current depression tend to score over 60 on the Depression scale out of a possible 80 (Thurber, Snow, & Honts, 2002). One participant from the Never Depressed group scored over 60 on the Depression scale. This participant was not removed from the analyses due to relatively small group numbers, and because they were not an outlier in any analyses. No participants scored higher than 60 on the Anxiety scale.

Table 1

The Zung Self-rating Anxiety and Zung Self-rating Depression Scores for the Never Depressed and Previously Depressed Groups.

	Never Depressed (*n* =78)		Previously Depressed (*n* =53)		SSRI Responders (*n* = 27)		SSRI Non-responders (*n* =11)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Anxiety	32.34	7.50	33.64	6.76	33.48	7.25	35.82	6.51
Depression	34.74	8.11	35.53	8.74	34.67	9.39	38.18	8.78

Note. Anxiety scores are from the Zung self-rating anxiety scale. Depression scores are from the Zung self-rating depression scale. Both are out of a possible 80.

Results will examine findings from the chimeric faces task, first comparing the Previously Depressed and Never Depressed groups; and then comparing SSRI Responders, SSRI Non-responders and Never Depressed groups. The divided visual field task results will then be discussed, first comparing the Previously Depressed and Never Depressed groups; and then comparing SSRI Responders, Non-responders and Never Depressed groups. For the analyses of the responder groups, 15 subjects were removed from the analyses as they were Previously Depressed but received treatment other than SSRI medication.

Chimeric Faces Task

Previously Depressed vs. Never Depressed groups. The proportion of times that participants chose the face with the smile on the left as being happier will be referred to as the left hemispatial bias, with greater values indicating a greater left hemispatial bias in this task. A left hemispatial bias of 0.5 indicates that the participant chose the smile on the left and right side of the face an equal number of

times. A bias below 0.5 indicates a bias to choosing the right side of the face; whereas a bias above 0.5 indicates a bias to choosing the left side of the face. Due to computer error, the data for seven participants was not recorded (one participant from the Previously Depressed, No Treatment group, and six participants from the Never Depressed group). The mean left hemispatial bias for the Previously Depressed group (n = 52) was: M = 0.67, SD = 0.18, and the mean left hemispatial bias for the Never Depressed group (n = 71) was: M = 0.57, SD = 0.22. These biases differed significantly from 0.5 for both the Never Depressed $t(70) = 2.53$, $p = .01$; and Previously Depressed groups $t(51) = 6.88$, $p < .01$, indicating that both groups had significant left hemispatial biases.

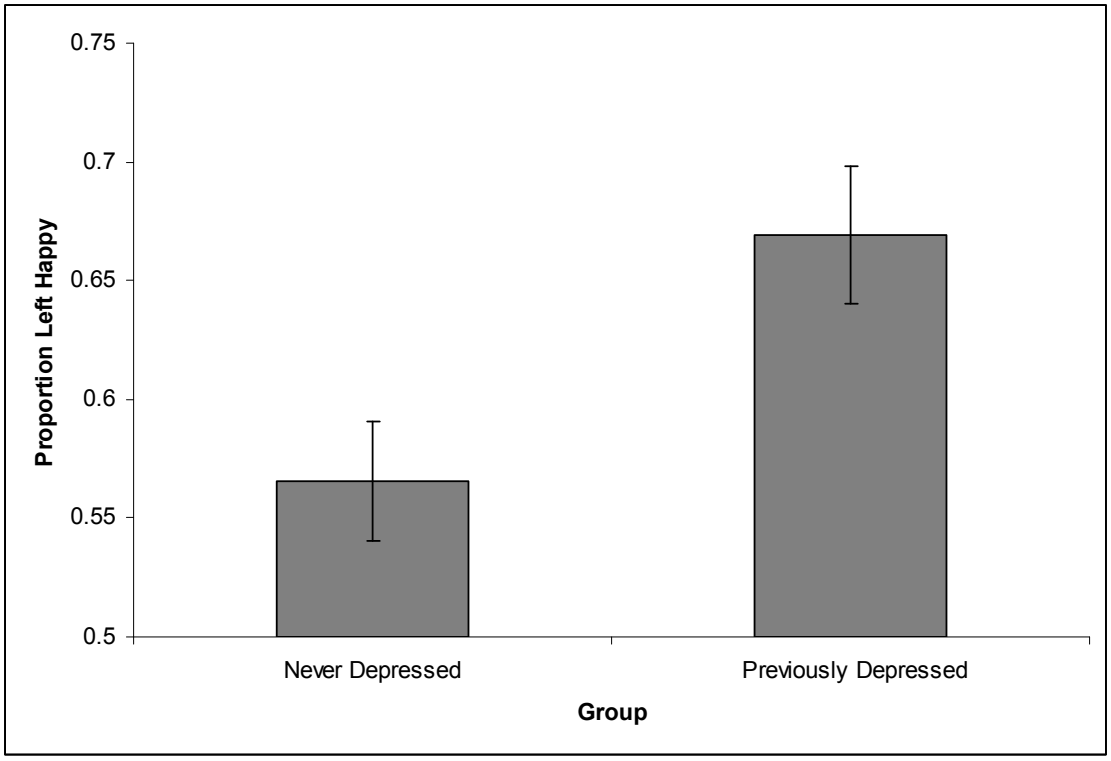

Figure 2. The proportion of left-happy responses for the Never Depressed and Previously Depressed groups. A score of 0.5 would indicate no bias, while scores above 0.5 indicate a left hemispatial bias. The vertical lines are standard error bars.

A univariate ANOVA was performed with group (Previously Depressed, n = 52 and Never Depressed, n = 71) as the fixed factor, anxiety as a covariate, and left

hemispatial bias as the dependent variable. There was a significant effect of group (see Figure 2), $F(1, 121) = 7.63$, $p < .01$, indicating that the groups differed significantly from each other in their left hemispatial biases. More specifically, the Previously Depressed group had a greater left hemispatial bias ($M = 0.67$, $SD = 0.18$) than the Never Depressed group *(*$M = 0.57$, $SD = 0.22$).

SSRI Responder vs. SSRI Non-responder groups. Further analyses were performed to determine whether there were differences in the left hemispatial biases between SSRI Responders, SSRI Non-responders, and Never Depressed controls. The mean left hemispatial biases for each group were: for SSRI Responders ($n = 27$), $M = 0.66$, $SD = 0.18$; for SSRI Non-responders ($n = 11$), $M = 0.66$, $SD = 0.17$; and for Never Depressed controls ($n = 71$), $M = 0.56$, $SD = 0.22$. These left hemispatial biases significantly differed from 0.5 for both SSRI Responders, $t(26) = 4.82$, $p < .01$, and Non-responders, $t(10) = 3.19$, $p = .01$.

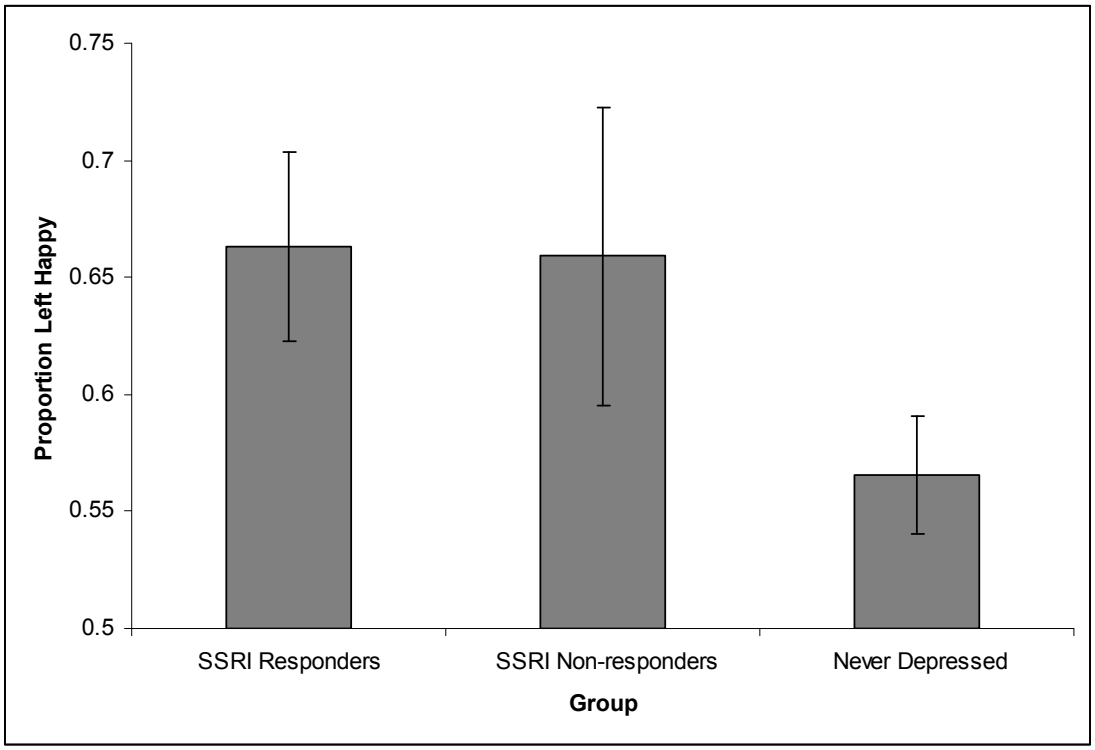

Figure 3. The proportion of left-happy choices for the different Responder groups. A score of 0.5 would indicate no bias, while scores above 0.5 indicate a left hemispatial bias. The vertical lines are standard error bars.

Another univariate ANOVA was performed with responder group (SSRI Responders, SSRI Non-responders, and Never Depressed controls) as the fixed factor, anxiety as a covariate, and left hemispatial bias as the dependent variable. There was a non-significant trend towards an effect of Responder group (see Figure 3): $F(2, 107) = 2.64$, $p = .08$. Further t-tests were performed to determine where any potential differences between Responder groups lay. SSRI Responders and SSRI Non-responders did not differ in their left hemispatial biases. The difference between Never Depressed controls and SSRI Responders was significant: $t(97) = 2.01$, $p = .05$; indicating that the SSRI Responders have a significantly greater left hemispatial bias than the Never Depressed group. The difference between SSRI Non-responders and Never depressed controls did not reach significance; $t(81) = 1.31$, $p = .19$, but as the mean for the SSRI Responders and SSRI Non-responders was equal ($M = 0.66$), this non-significant result reflects a lack of power due to the small number of SSRI Non-responders.

Divided Visual Field Task

Sensitivity or *d'* is a measure of accuracy which takes into account both hits (indicating that a word is positive when it is positive) and false alarms (indicating a word is positive when it is actually negative). This measure eliminates any effects of biased responding. For example, a participant may tend to respond '*positive*' if they are not sure whether the valence is positive or negative. This would result in a large number of hits (responding that a word is positive, when it is in fact positive), but also a large number of false alarms (responding that a word is positive when it is in fact negative). The *d'* measure takes into account both hits and false alarms, to determine how sensitive the participant actually is to the correct valence of the word. The

formula for calculating *d'* is z(hit rate) - z(false alarm rate) (Macmillian & Creelman, 1991).

For the divided visual field task, 13 participants were removed from all the analyses, as their sensitivity scores were considered too low to reflect task performance. Criterion for removal was having all four *d'* scores less than one. The four *d'* scores were for high arousal words presented to the RVF; low arousal words presented to the RVF; high arousal words presented to the LVF; and low arousal words presented to the LVF. Sensitivity scores below one indicate that the participant may have misunderstood the task; was not trying to answer correctly; or was pressing the wrong response buttons. Five of these were from the Never Depressed group; two from the Previously Depressed, SSRI Responder group; and five from the Previously Depressed, Other Treatment group leaving a total of 73 Never Depressed participants, and 46 Previously Depressed participants, 25 of which were SSRI Responders, 11 of which were Non-responders, and 10 of which received other treatment.

Response times.

Previously Depressed vs. Never Depressed groups. Median RTs for correct trials in each condition were examined. See Table 2 for RT means, standard deviations and RT laterality indices for each group. RT laterality indices are calculated with the formula: (LVF RT - RVF RT). Positive laterality indices indicate a RVF/LH advantage; while negative laterality indices indicate a LVF/RH advantage. A mixed-model ANOVA was conducted to determine whether there were differences in RTs between the Previously Depressed group (n = 46) and the Never Depressed group (n = 73). The within-subjects factors were arousal, valence and VF, the between-subjects factor was group (Previously Depressed and Never Depressed); anxiety was used as a covariate.

Table 2

Median (ms) response times for the Never Depressed and Previously Depressed groups for each arousal, valence, and visual field condition.

	Never Depressed (*n* =73)				Previously Depressed (*n* =46)				Never Depressed	Previously Depressed
	LVF	LVF	RVF	RVF	LVF	LVF	RVF	RVF	Laterality RT	Laterality RT
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*M*
Negative										
High	1034	288	1013	263	904	217	878	195	**21**	**26**
Low	913	193	883	166	877	157	870	165	**30**	**7**
Positive										
High	910	180	883	183	905	201	838	131	**27**	**67**
Low	879	141	861	152	902	146	838	145	**18**	**64**

Note. LVF = Left visual field. RVF = Right visual field. RT = Response time. The Laterality RTs (in bold), positive numbers indicate a RVF/LH advantage, while negative numbers indicate a LVF/RH advantage.

A main effect of group was found, $F(1, 116) = 3.92$, $p = .05$. The Previously Depressed group was faster overall (M = 868 ms, SD = 181.73) than the Never Depressed group (M = 923 ms, SD = 211.58). An Arousal x Group interaction was found, $F(1, 116) = 8.88$, $p < .01$, and a Valence x Group interaction was found, $F(1, 116) = 6.27$, $p = .01$. These two-way interactions are better explained by a three-way interaction among Arousal x Valence x Group; $F(1, 116) = 4.28$, $p = .04$ (see Figure 4). Further analyses examining words of high and low arousal separately showed that the Valence x Group interaction was significant only for high arousal words; $F(1, 116) = 7.63$, $p < .01$, but not for low arousal words; $F(1, 116) = 0.66$, $p = .42$. For high arousal words, the Never Depressed participants were significantly faster at positive compared to negative words, $t(72) = 4.16$, $p < .05$; while the Previously Depressed participants did not differ in their processing of positive and negative words, $t(45) = 0.59$, $p = .56$.

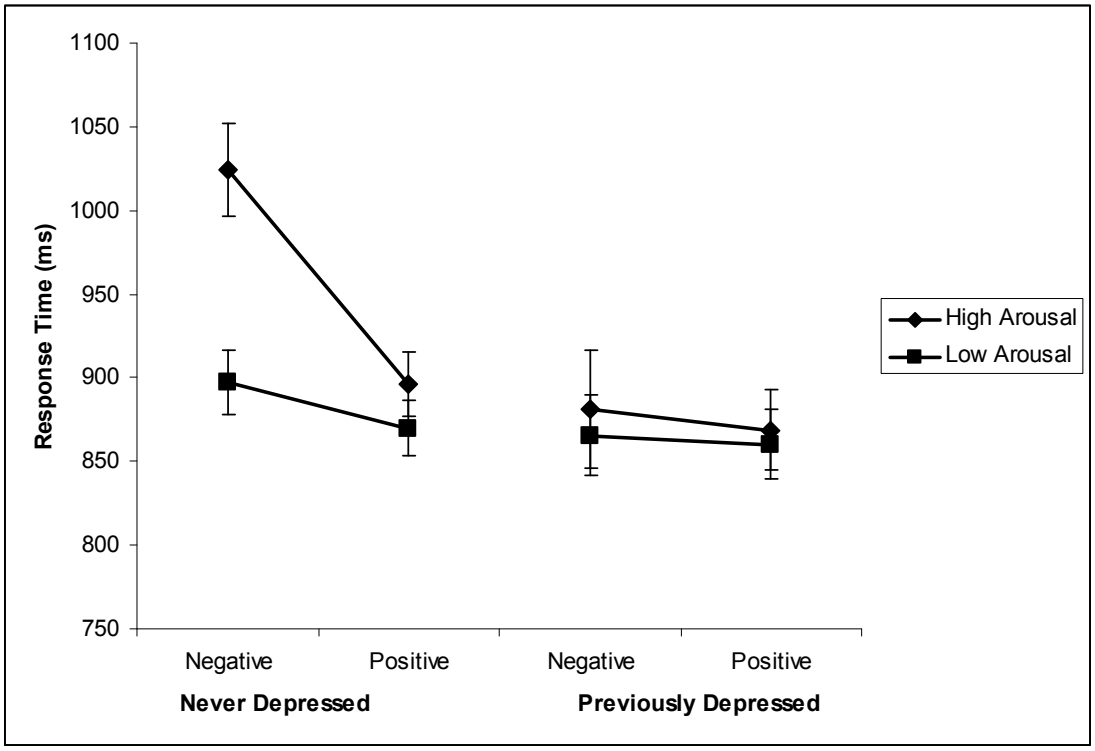

Figure 4. Response times for words of each valence and arousal type, for the Never Depressed and Previously Depressed groups. The vertical lines are standard error bars.

A Valence x VF interaction was found (see Figure 5), $F(1, 116) = 4.48$, $p < .04$. For positive words, there was a significant speed of processing advantage in the RVF compared to the LVF, $t(116) = 4.29$, $p < .01$. For negative words, there was no difference in the speed of processing in the RVF compared to the LVF $t(116) = 1.62$, $p = .11$. No Group x VF interaction was found, indicating that the groups did not differ in their overall VF advantages.

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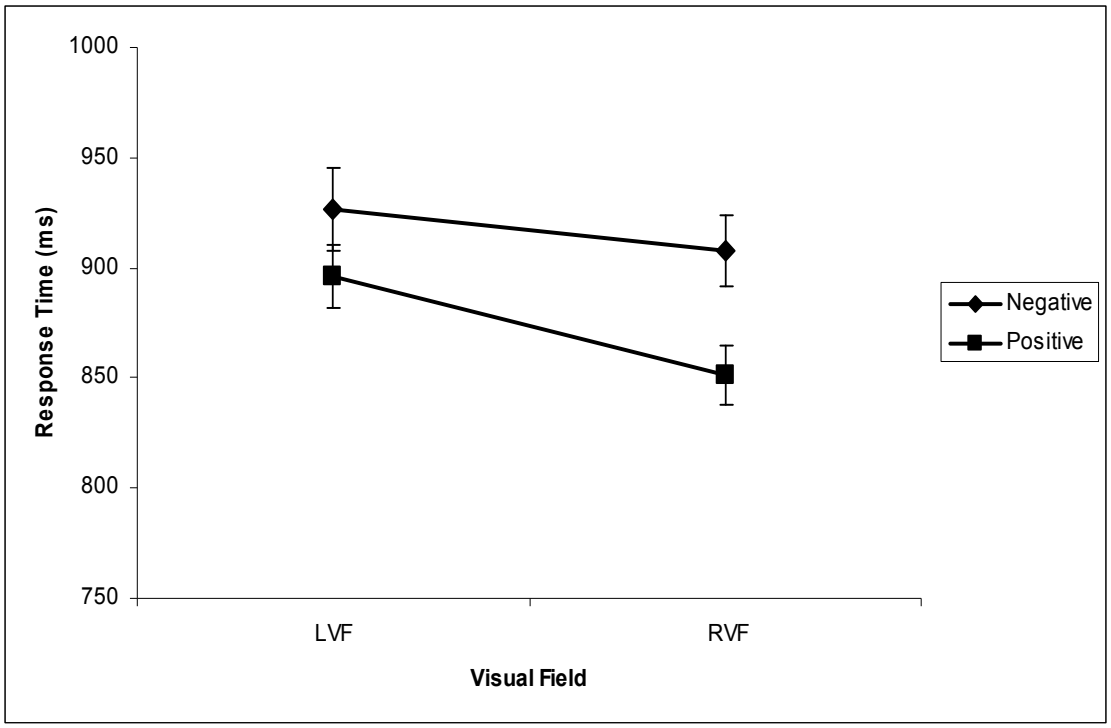

Figure 5. Response times for words of negative and positive valences are shown for each visual field. LVF = left visual field, RVF = right visual field. The vertical lines are standard error bars.

However, a trend towards a Valence x VF x Group interaction was found (See Figure 6); $F(1, 116) = 3.64$, $p = .06$. This can be examined as valence advantages in each VF: The Never Depressed group had a comparable advantage for positive over negative words in the LVF, $t(72) = 3.18$, $p < .01$; and the RVF, $t(72) = 2.89$, $p < .01$. The Previously Depressed group had an advantage for positive over negative words in the RVF, $t(45) = 2.44$, $p = .02$; but showed a non-significant advantage for negative over positive words in the LVF, $t(45) = -.98$, $p = .33$. Alternatively, this interaction can be examined as VF advantages for each valence: The Never Depressed group had a RVF advantage for positive words, $t(72) = 1.96$, $p = .05$, but had no VF advantage for negative words, $t(72) = 1.53$, $p = .13$. The Previously Depressed group also had a RVF advantage for positive words, $t(45) = 4.84$, $p < .01$, and also had no VF advantage for negative words, $t(45) = 0.62$, $p = .54$. Examination of Figure 6 indicates

that the Never Depressed group had a non-significant RVF advantage for negative words; while the Previously Depressed group shows little to no RVF advantage for negative words.

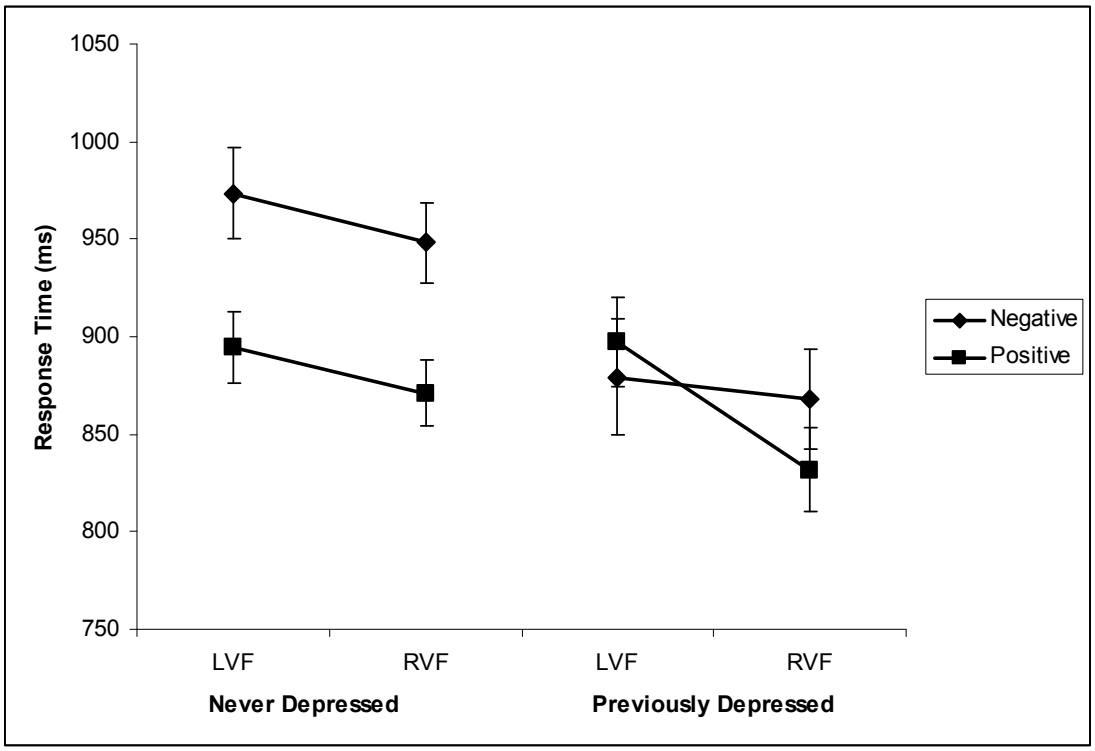

Figure 6. The response times for both visual fields, for positive and negative words, for the Never Depressed and Previously Depressed groups. LVF = left visual field, RVF = right visual field. The vertical lines are standard error bars.

A three way Valence x VF x Anxiety interaction was found, $F(1, 116) = 6.70$, $p = .01$, indicating that anxiety had an effect on the Valence x VF interaction. Specifically, those who scored lower in the anxiety scale did not show a Valence x VF interaction $F(1, 62) = 0.30$, $p = .58$; whereas those who scored higher in the anxiety scale did show a significant Valence x VF interaction $F(1, 54) = 9.34$, $p < .01$. Additional analyses indicated that the low anxious participants showed a trend towards being faster in the RVF compared to the LVF for both positive, $t(62) = 1.70$, $p = .09$ and negative, $t(62) = 1.82$, $p = .07$ words. High anxious participants were significantly faster in the RVF compared to the LVF for positive words, $t(54) = 4.43$,

$p < .01$, but did not significantly differ by VF for negative words, $t(54) = 0.20$, $p = .85$. This suggests that higher anxious participants may have more RH involvement in the processing of negative words than lower anxious participants.

SSRI Responders vs. SSRI Non-responder groups. See Table 3 for RT means, standard deviations and RT laterality indices for the SSRI Responder, SSRI Non-responder and Never Depressed groups. A repeated measures ANOVA was conducted to determine whether there were differences in RTs between the SSRI Responders ($n = 25$), SSRI Non-responders ($n = 11$), and the Never Depressed group ($n = 72$). The within-subjects factors were arousal, valence and VF, the between-subjects factor was group (SSRI Responders, SSRI Non-responders, and Never Depressed); anxiety was used as a covariate.

Table 3

Median (ms) response times for the SSRI Responder and SSRI Non-responder groups, for each arousal, valence, and visual field condition.

	SSRI Responders (*n* =25)				SSRI Non-responders (*n* = 11)				Never Depressed	SSRI Responders	SSRI Non-responders
	LVF	LVF	RVF	RVF	LVF	LVF	RVF	RVF	Laterality RT	Laterality RT	Laterality RT
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*M*	*M*
Negative											
High	912	180	855	181	856	207	891	218	**21**	**57**	**-35**
Low	917	157	869	143	826	187	881	207	**30**	**48**	**-55**
Positive											
High	896	214	829	122	955	220	888	166	**27**	**67**	**67**
Low	898	151	853	162	894	159	825	123	**18**	**45**	**69**

Note. LVF = Left visual field. RVF = Right visual field. RT = Response time. For the Laterality RTs (in bold), positive numbers indicate a RVF/LH advantage, while negative numbers indicate a LVF/RH advantage.

A significant Arousal x Responder Group interaction, $F(2, 105) = 5.72$, $p < .01$, and a significant Valence x Responder Group interaction were found, $F(2, 105) = 3.41$, $p = .04$. These two-way interactions are better explained by the three-way Arousal x Valence x Responder Group interaction; $F(2, 105) = 3.56$, $p = .03$ (see Figure 7). Further analyses examining the words of high and low arousal separately demonstrated that this Valence x Responder Group interaction was significant only for words of high arousal; $F(2, 105) = 4.96$, $p < .01$, but not for words of low arousal; $F(2, 105) = 0.12$, $p = .88$. For high arousal words, the SSRI Responders and Non-responder groups did not significantly differ in their processing of positive vs. negative words: $t(24) = 0.80$, $p = .43$ and $t(10) = -1.30$, $p = .22$, respectively. The Never Depressed group judged positive high arousal words more quickly than negative high arousal words, $t(72) = 4.16$, $p < .01$.

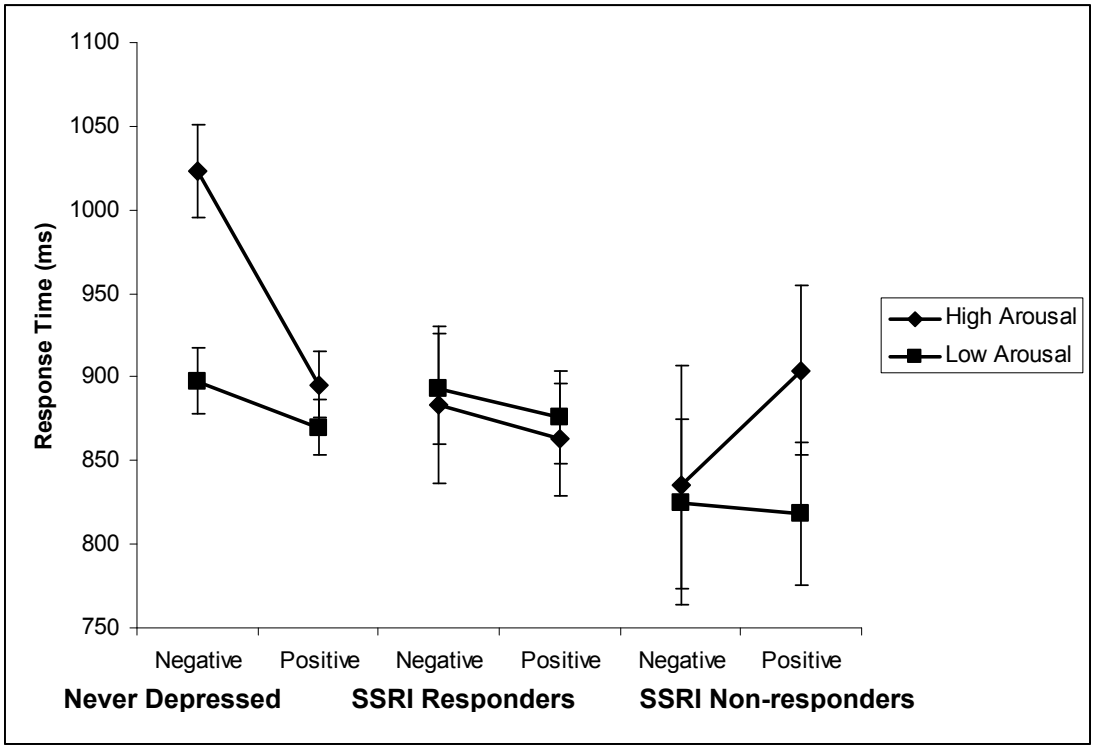

Figure 7. Response times for SSRI Responders, SSRI Non-responders and Never Depressed groups for words of negative and positive valences, and of high and low arousal. The vertical lines are standard error bars.

No effect of VF x Responder Group was found, indicating that the responder groups did not differ in their overall VF advantages for RTs. However, a significant three-way interaction between Valence x VF x Responder Group was found (see Figure 8); $F(2, 105) = 3.36$, $p = .04$.

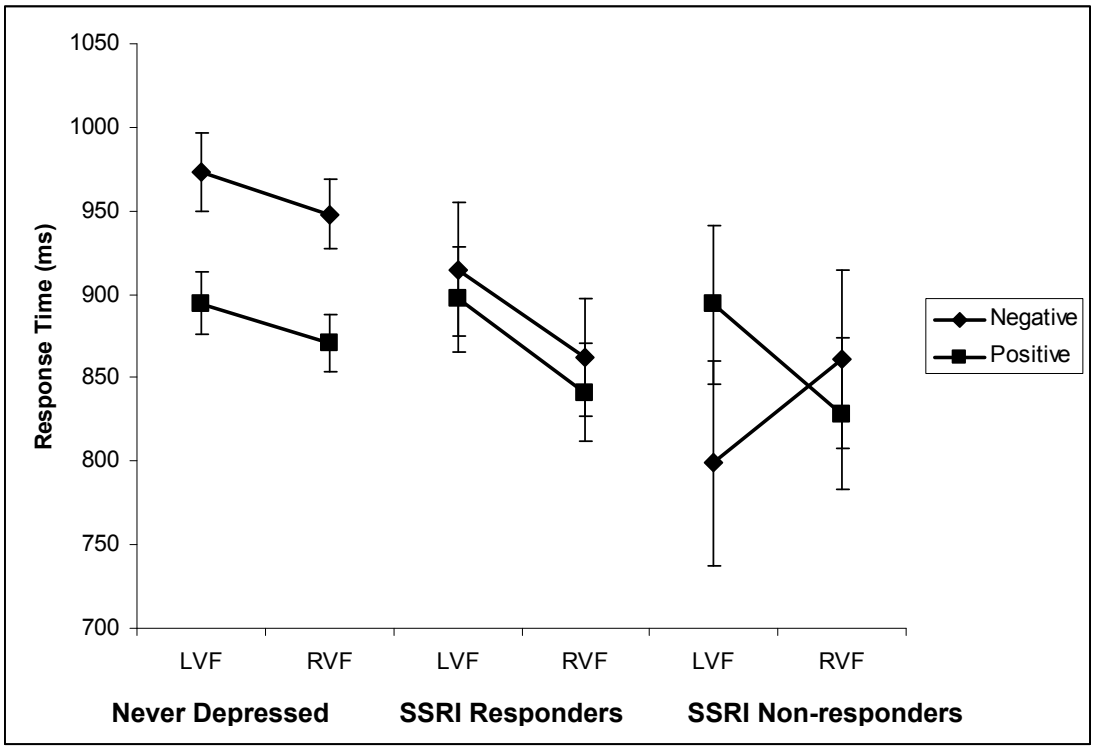

Figure 8. Response times for each visual field, for both positive and negative words, for SSRI Responders, SSRI Non-responders and Never Depressed controls. LVF = left visual field, RVF = right visual field. The vertical lines are standard error bars.

This can be examined as valence differences within each VF: Never Depressed controls had a significant advantage for positive over negative words in the LVF, $t(72) = 3.18$, $p < .01$; and the RVF, $t(72) = 2.89$, $p < .01$. SSRI Responders do not differ in their processing of negative vs. positive words in the LVF, $t(24) = .74$, $p = .47$; or RVF, $t(24) = 1.23$, $p = .23$. SSRI Non-responders had a significant advantage for negative over positive words in the LVF, $t(10) = -2.53$, $p = .03$, but no difference in the RVF, $t(10) = 1.13$, $p = .29$. Alternatively, this interaction can be examined as VF advantages for each valence: Never Depressed controls showed a RVF advantage

for positive words, $t(72) = 1.96$, $p = .05$, and a non-significant RVF advantage for negative words, $t(72) = 1.53$, $p = .13$. SSRI Responders had a RVF advantage for both positive, $t(24) = 3.15$, $p < .01$, and negative words, $t(24) = 2.72$, $p = .01$. SSRI Non-responders showed the interesting pattern of a trend towards a RVF advantage for positive words, $t(10) = 2.00$, $p = .07$, and a LVF advantage for negative words, $t(10) = -2.33$, $p = .04$. This indicates that the Valence x VF x Group interaction effect in the previous analysis was primarily carried by the atypical laterality seen in the SSRI Non-responder group.

d' (Sensitivity).

Previously Depressed vs. Never Depressed groups. See Table 4 for hit rates and accuracy laterality indices for the Previously Depressed and Never Depressed groups. Accuracy laterality indices are calculated with the formula: (RVF hits – LVF hits) / (RVF hits + LVF hits). Hit rates are confounded by the effects of bias, so analyses focussed on measures of sensitivity and bias separately. See Table 5 for the *d'* means and standard deviations for the Previously Depressed and Never Depressed groups. A repeated measures ANOVA was conducted to determine whether there were differences in sensitivity between Previously Depressed ($n = 46$) and Never Depressed ($n = 73$) groups. *d'* measures the ability to discriminate between whether a word is positive or negative, thus valence is no longer a variable in these analyses. The within-subjects factors were arousal and VF, the between-subjects factor was group (Previously Depressed and Never Depressed); anxiety was used as a covariate. It should be noted that the sensitivity (or *d'*) results largely parallel the RT results; indicating that there was no speed-accuracy trade off.

Table 4

Accuracy scores (hits) and accuracy laterality indices for the Never Depressed and Previously Depressed groups.

	Never Depressed (*n* =73)				Previously Depressed (*n* =46)				Never Depressed	Previously Depressed
	LVF	LVF	RVF	RVF	LVF	LVF	RVF	RVF	Laterality	Laterality
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*M*
Negative										
High	10.14	1.67	10.31	1.36	9.54	1.79	10.37	1.53	**0.01**	**0.04**
Low	10.14	1.78	10.50	1.27	9.65	2.31	10.28	1.61	**0.02**	**0.04**
Positive										
High	9.07	1.72	9.46	1.60	9.15	2.26	10.09	1.58	**0.02**	**0.06**
Low	9.68	1.86	10.16	1.54	8.76	2.12	9.91	1.56	**0.03**	**0.07**

Note. LVF = Left visual field. RVF = Right visual field. Laterality scores (in bold) greater than zero indicate relatively better RVF/LH accuracy; while scores less than zero indicate relatively better LVF/RH accuracy. Accuracy scores are out of a possible 12.

Table 5

The d' (sensitivity) means and standard deviations for Previously Depressed and Never Depressed groups, for each visual field and arousal condition.

	Never Depressed (*n* =73)		Never Depressed		Previously Depressed (*n* =46)		Previously Depressed	
	LVF	LVF	RVF	RVF	LVF	LVF	RVF	RVF
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Low Arousal	2.07	0.88	2.29	0.71	1.31	1.09	1.85	1.11
High Arousal	1.70	0.85	2.00	0.66	1.71	0.89	1.86	1.02

Note. LVF = Left visual field. RVF = Right visual field. Higher *d'* scores indicate better accuracy/sensitivity to the valence of the word.

A main effect of group was found; $F(1, 116) = 7.94$, $p < .01$. The Never Depressed group was more sensitive to the valence of the words ($M = 2.00$, $SD = 0.81$) than the Previously Depressed group ($M = 1.68$, $SD = 1.04$). The only significant interaction was between Arousal x Group, $F(1, 116) = 18.30$, $p < .01$. The Never Depressed group were more accurate for words of low compared to high arousal, $t(72) = 4.33$, $p < .01$. The Previously Depressed group were more accurate for words of high compared to low arousal, $t(45) = -2.11$, $p = .04$. There was a non-significant trend towards a Arousal x VF x Group interaction; $F(1, 116) = 3.10$, $p = .08$. This can be examined as arousal advantages in each VF: The Never Depressed group was significantly more sensitive to processing low arousal compared to high arousal words in the LVF, $t(72) = 2.84$, $p < .01$; and the RVF, $t(72) = 3.68$, $p < .01$. The Previously Depressed group was significantly more sensitive to processing high

compared to low arousal words in the LVF, $t(45) = -2.25$, $p = .03$, but showed no difference in processing high vs. low arousal words in the RVF, $t(45) = -0.12$, $p = .91$. Alternatively, this interaction can be examined as VF advantages for each arousal type: The Never Depressed group had a significant RVF advantage for low arousal words $t(72) = -2.37$, $p = .02$, and high arousal words $t(72) = -2.70$, $p = .01$. The Previously Depressed group had a significant RVF advantage for low $t(45) = -3.01$, $p < .01$, but not high arousal words, $t(45) = -0.90$, $p = .37$.

SSRI Responders vs. SSRI Non-responder groups. See Table 6 for hit rates and accuracy laterality indices for the SSRI Responder and SSRI Non-responder groups. See Table 7 for the *d'* means and standard deviations for SSRI Responders, SSRI Non-responders and Never Depressed groups. A repeated measures ANOVA was conducted to determine whether there were differences in sensitivity or *d'* between the SSRI Responders, SSRI Non-responders, and the Never Depressed controls. The within-subjects factors were arousal and VF, the between-subjects factor was group (SSRI Responders, SSRI Non-responders, and Never Depressed controls); anxiety was used as a covariate.

Table 6

Accuracy scores (hits) and laterality indices for accuracy scores, for the SSRI Responder and SSRI Non-responder groups.

	SSRI Responders (*n* =25)				SSRI Non-responders (*n* = 11)				Never Depressed	SSRI Responders	SSRI Non-responders
	LVF	LVF	RVF	RVF	LVF	LVF	RVF	RVF	Laterality	Laterality	Laterality
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*M*	*M*
Negative											
High	9.00	1.94	10.24	1.27	10.55	1.44	10.36	2.34	**0.01**	**0.07**	**-0.02**
Low	8.84	2.46	10.56	1.61	10.73	2.24	9.91	1.58	**0.02**	**0.10**	**-0.03**
Positive											
High	9.72	1.72	10.12	1.45	8.09	3.27	10.09	1.87	**0.02**	**0.02**	**0.14**
Low	8.84	1.86	10.12	1.56	8.55	3.01	9.82	1.54	**0.03**	**0.07**	**0.09**

Note. LVF = Left visual field. RVF = Right visual field. Laterality scores (in bold) greater than zero indicate relatively better RVF/LH accuracy; while scores less than zero indicate relatively better LVF/RH accuracy.

Table 7

The d' (sensitivity) means and standard deviations for the Never Depressed, SSRI Responder and SSRI Non-responder groups, for each visual field and arousal condition.

	SSRI Responders (*n* =25)				SSRI Non-responders (*n* =11)			
	LVF	LVF	RVF	RVF	LVF	LVF	RVF	RVF
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Low Arousal	1.14	0.98	2.21	0.83	1.71	1.40	1.57	1.21
High Arousal	1.72	0.84	2.08	0.83	1.73	1.22	1.73	1.22

Note. LVF = Left visual field. RVF = Right visual field. Higher *d'* scores indicate better accuracy/sensitivity to the valence of the word.

A trend towards a main effect of responder group was found; $F(2, 105) = 2.38$, $p = .10$. The Never Depressed group was the most sensitive to the valence of the words ($M = 2.00$, $SD = 0.81$); followed by the SSRI Responders ($M = 1.79$, $SD = 0.95$); and lastly the SSRI Non-responders ($M = 1.67$, $SD = 1.22$). A significant interaction was found between Arousal x Responder Group, $F(2, 105) = 7.13$, $p < .01$, and for VF x Responder Group (see Figure 9), $F(2, 105) = 4.86$, $p = .01$.

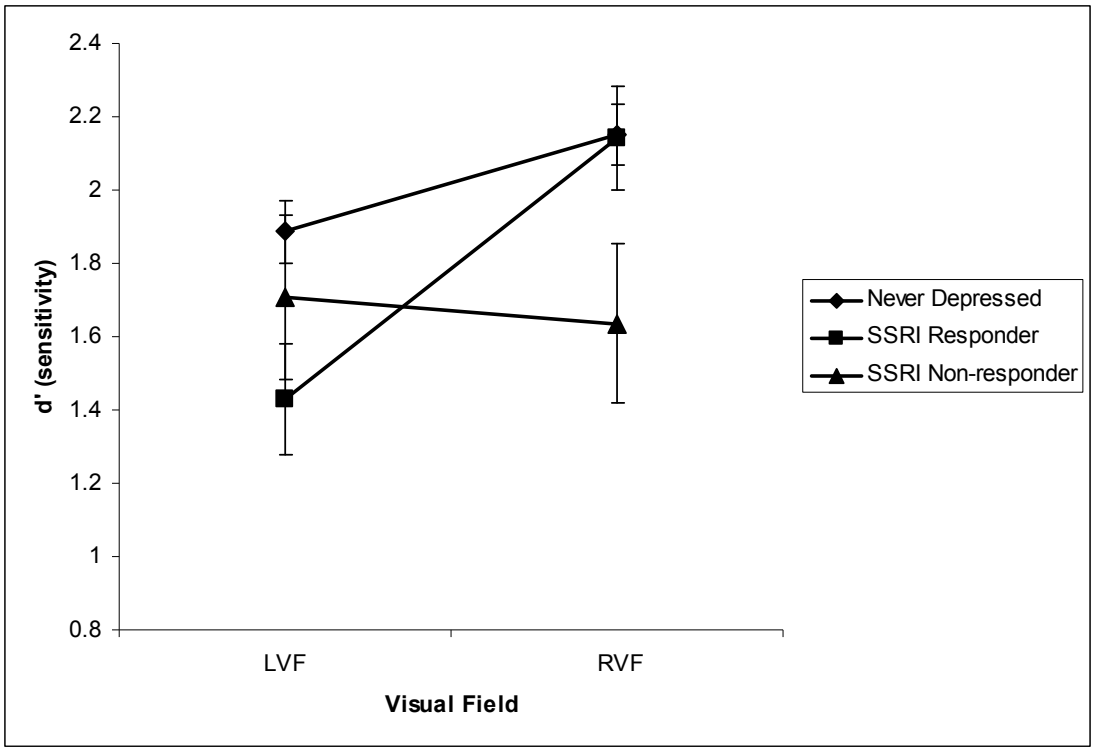

Figure 9. d' (sensitivity) scores for Never Depressed, SSRI Responders and SSRI Non-responders, for each visual field. Greater values indicate better accuracy/sensitivity in identifying the valence of the word. LVF = left visual field, RVF = right visual field. The vertical lines are standard error bars.

These two-way interactions are better explained by a three-way significant interaction for Arousal x VF x Responder Group (See Figure 10) $F(2, 105) = 3.54$, $p = .03$. Further analyses examining words of each arousal type separately showed that this VF x Responder Group interaction was significant only for low arousal words; $F(2, 105) = 8.77$, $p < .01$, but not for high arousal words; $F(2, 105) = 0.40$, $p = .67$. For low arousal words, the Never Depressed controls had a RVF advantage, $t(72) = -2.37$, $p = .02$. The SSRI Responders also had a RVF advantage for low arousal words $t(24) = -4.70$, $p < .01$. The SSRI Non-responders did not show a VF advantage for words of low arousal, $t(10) = 0.44$, $p = .67$ (but showed a non-significant LVF advantage).

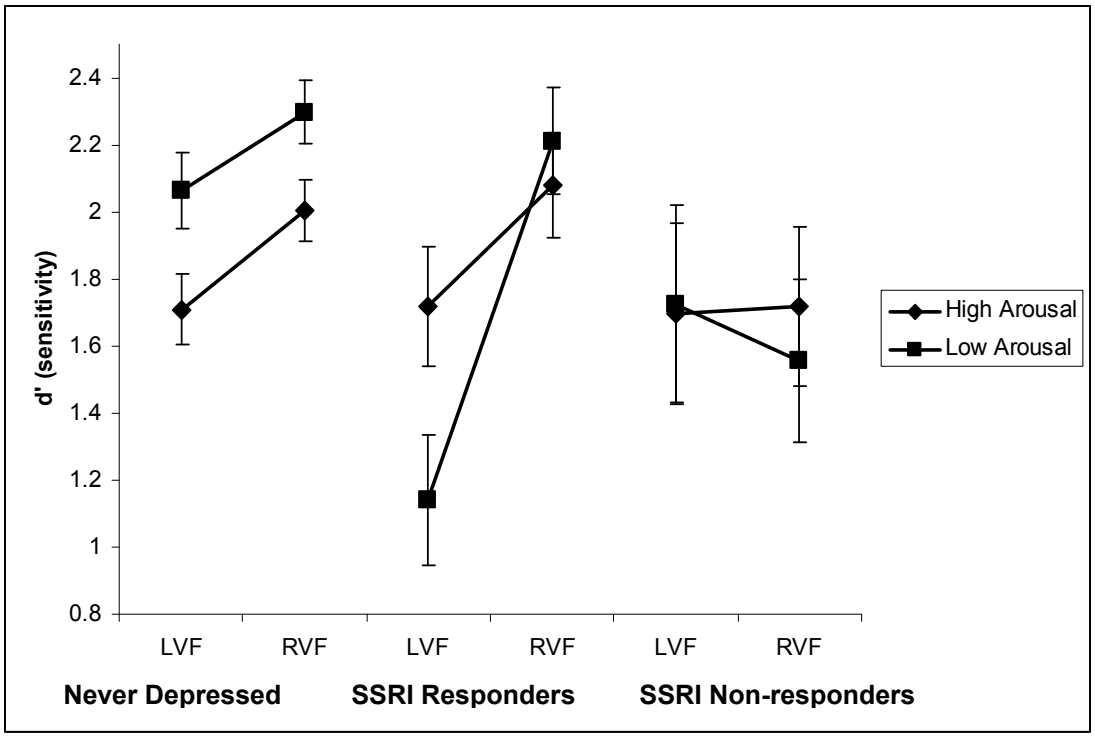

Figure 10. d' (sensitivity) scores for SSRI Responders, SSRI Non-responders and Never Depressed groups for each arousal and visual field condition. Greater values indicate better accuracy/sensitivity in identifying the valence of the word. LVF = left visual field, RVF = right visual field. The vertical lines are standard error bars.

c (Bias). Bias or *c* is a measure of how biased a participant is to responding a certain way, regardless of the actual valence of the word. For example, a participant may tend to respond '*positive*' if they are not sure whether the valence is positive or negative. This would result in a large number of hits (responding that a word is positive, when it is in fact positive), but also a large number of false alarms (responding that a word is positive when it is in fact negative). Bias is a measure of this tendency to respond a certain way, regardless of the actual valence of the word. The formula for calculating *c* is -0.5(z(hit rate) + z(false alarm rate)) (Macmillian & Creelman, 1991). A positive *c* value indicates a bias towards saying that a word is negative; while a negative c value indicates a bias towards saying that a word is positive.

Previously Depressed vs. Never Depressed groups. See Table 8 for the *c* means and standard deviations for the Previously Depressed and Never Depressed groups. An ANOVA was conducted to determine whether there were differences in *c* (bias) between the Previously Depressed (n = 46) and Never Depressed (n = 73) groups. The within-subjects factors were arousal and VF, the between-subjects factor was group (Previously Depressed and Never Depressed) and anxiety was used as a covariate.

Table 8

Means and standard deviations for c (bias) scores for Never Depressed and Previously Depressed groups.

	Never Depressed (n =73)				Previously Depressed (n =46)			
	LVF	LVF	RVF	RVF	LVF	LVF	RVF	RVF
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Low Arousal	0.11	0.37	0.06	0.34	0.39	0.54	0.31	0.55
High Arousal	0.25	0.45	0.14	0.35	0.07	0.42	0.30	0.59

Note. LVF = Left visual field. RVF = Right visual field. Greater values indicate a larger bias towards responding that the word is negative, regardless of the actual valence or the word.

A main effect of group was found; F (1, 116) = 5.14, p = .03. The Previously Depressed group was more negatively biased (M = 0.27, SD = 0.53) than the Never Depressed group (M = 0.14, SD = 0.40). There was a significant interaction between Arousal x Group, F(1, 116) = 27.27, p < .01. There was a trend towards a VF x Group interaction, F(1, 116) = 3.17, p = .08. These two-way interactions are better explained

by the three-way significant interaction between Arousal x VF x Group (see Figure 11), $F(1, 116) = 11.62$, $p < .01$.

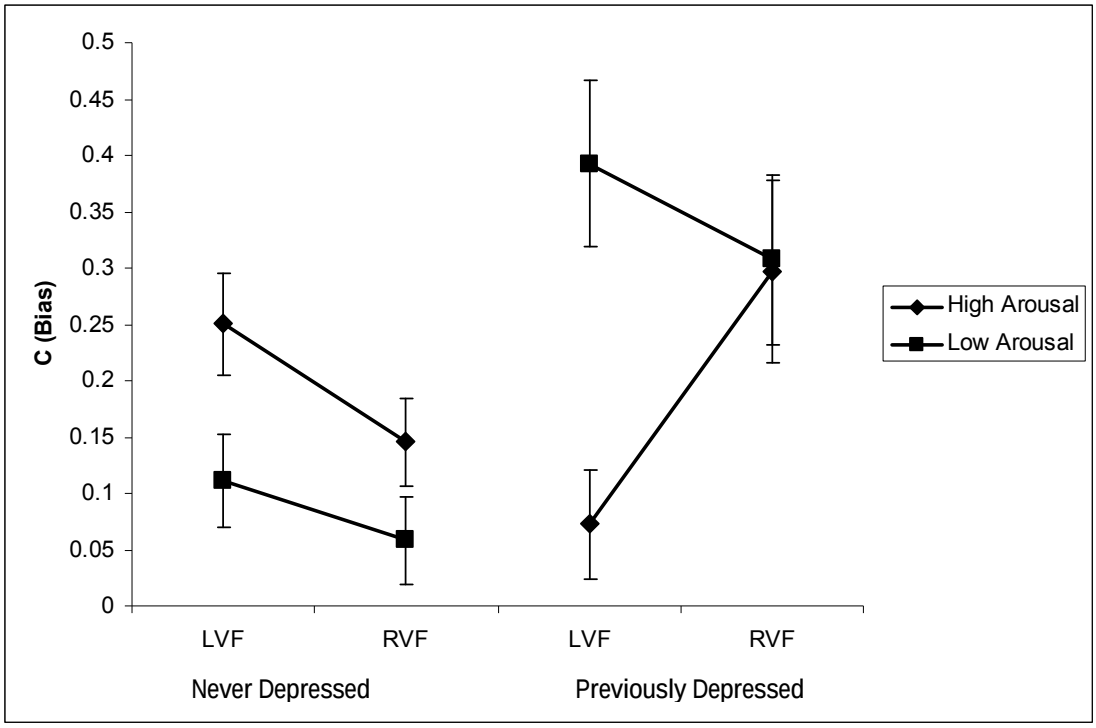

Figure 11. c (bias) scores for Never Depressed and Previously Depressed groups, for low and high arousal conditions in both visual fields. LVF = left visual field, RVF = right visual field. The vertical lines are standard error bars.

Further analyses examining words of low and high arousal separately showed that there was a VF x Group interaction for high arousal words; $F(1, 116) = 9.58$, $p < .01$, but not for low arousal words; $F(1, 116) = 0.19$, $p = .66$. For high arousal words, the Never Depressed group showed a trend towards a larger negative bias when words were presented to their LVF vs. their RVF, $t(72) = 1.70$, $p = .09$. The Previously Depressed group was significantly more negatively biased when words were presented to their RVF vs. their LVF, $t(45) = -2.24$, $p = .03$.

SSRI Responders vs. SSRI Non-responder groups. See Table 9 for the *c* means and standard deviations for the SSRI Responders, SSRI Non-responders, and Never Depressed groups. An ANOVA was conducted to determine whether there were differences in bias (*c*) between the SSRI Responders ($n = 25$), SSRI Non-

responders (n = 11), and Never Depressed controls (n = 73). The within-subjects factors were arousal and VF, the between-subjects factor was group (SSRI Responders, SSRI Non-responders, and Never Depressed controls); anxiety (scores from the Zung Self-Rating Anxiety Scale) was used as a covariate.

Table 9

Means and standard deviations for c scores for the Never Depressed, SSRI Responder and SSRI Non-responder groups.

	SSRI Responders (n =25)				SSRI Non-responders (n =11)			
	LVF	LVF	RVF	RVF	LVF	LVF	RVF	RVF
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Low Arousal	0.18	0.52	0.13	0.43	0.48	0.45	0.22	0.49
High Arousal	-0.08	0.33	0.06	0.37	0.35	0.40	0.34	0.69

Note. LVF = Left visual field. RVF = Right visual field. Greater values indicate a larger bias towards responding that the word is negative, regardless of the actual valence or the word.

A significant main effect of responder group was found, F (2, 116) = 4.35, p = .02. A significant interaction was found for Arousal x Responder Group, F(2, 116) = 8.97, p < .01. Never Depressed participants were significantly more negatively biased for high compared to low arousal words, t(72) = -3.43, p < .01. The SSRI Responders were significantly more negatively biased for low compared to high arousal words, t(24) = 2.57, p = .02. The SSRI Non-responders did not differ in their biases for low compared to high arousal words, t(10) = -.00, p = .99.

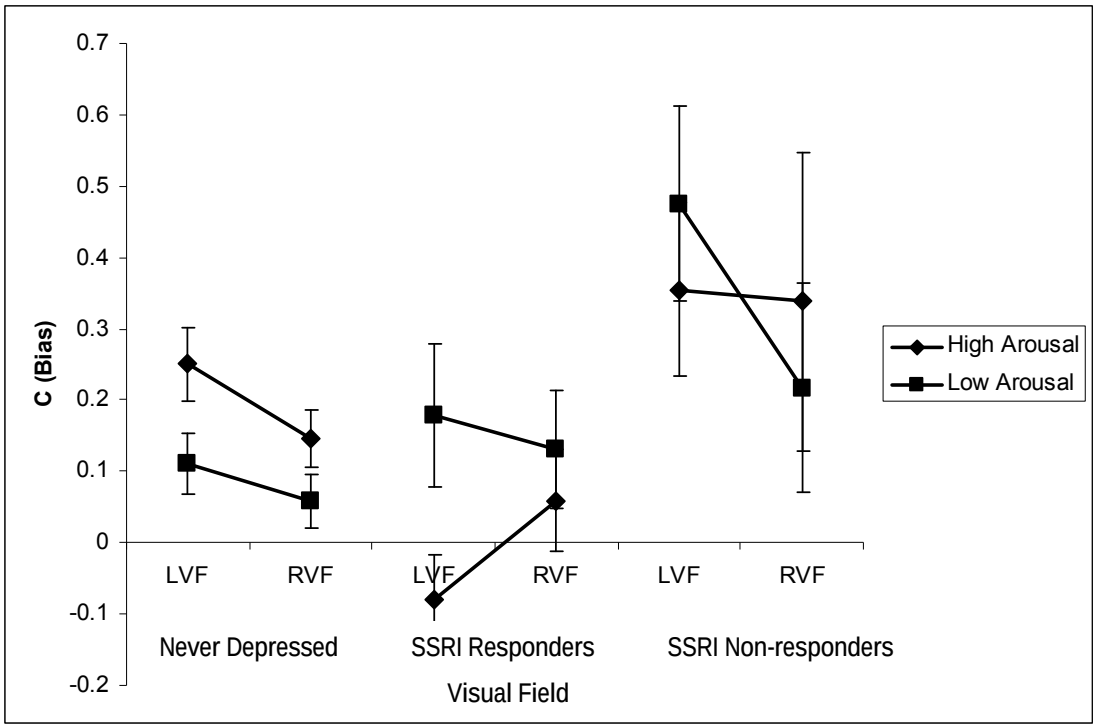

Figure 12. *c* (bias) scores for SSRI Responders, SSRI Non-responders, and Never Depressed controls for each visual field and arousal type. LVF = left visual field, RVF = right visual field. The vertical lines are standard error bars.

Discussion

To date little research has examined hemispheric differences in emotional perception in people vulnerable to depression. Previous research has examined hemispheric asymmetries in brain activity measured with EEG recordings, and found that overall, people vulnerable depression have greater relative frontal RH activity (for a review see Thibodeau et al., 2006). However, there is much heterogeneity in these asymmetries within people vulnerable to depression, and these differences in hemispheric asymmetries may help to predict whether someone is likely to respond to SSRI medication. Specifically, SSRI responders tend to have overall greater relative RH activity, whereas SSRI non-responders tend to have overall greater relative LH activity (Bruder et al., 1996; Bruder et al., 2001; Bruder et al., 2004; Bruder et al., 2008). Additionally, depressed individuals tend to have a negative cognitive processing style (for reviews see Beck, 2008; Mathews & MacLeod, 1994; Mathews

& MacLeod, 2005). However, little is known about how the different patterns of asymmetries in activity relate to this negative cognitive processing style, or to hemispheric differences in the perception of emotional information. The current study investigated asymmetries in the perception of emotional faces and words in a group of Previously Depressed vs. Never Depressed individuals; and in SSRI Responders vs. SSRI Non-responders.

Chimeric Faces

Participants first completed a chimeric faces task, in which photos of faces were presented with half the face smiling, and half the face in a neutral expression (see Figure 1). Two faces were shown simultaneously, one with the smile on the left side, and one with the smile on the right side. Participants chose which of the two faces looked happier in each trial. This was the first study to examine a Previously Depressed sample in this task. Sub-clinical and clinically (melancholic) depressed populations display a relatively smaller left hemispatial bias on this task (Bruder et al., 2002; Heller et al., 1995). However, it has been suggested that this smaller left hemispatial bias is due to suppressed posterior RH activity, which is associated with reduced arousal and the melancholic symptoms of depression (Bruder et al., 1997; Heller et al., 1998). Thus, it was not expected that the Previously Depressed group would display this smaller left hemispatial bias, as they should not currently have reduced arousal and melancholic symptoms. In fact, they showed a larger left hemispatial bias than the Never Depressed group.

All groups showed a left hemispatial bias on this task (see Figures 2 and 3). It has been suggested that the left hemispatial bias in this task is due to an attentional bias to the left side of the face (Levy et al., 1983). The posterior regions of the RH are involved in the processing of emotional facial expressions (Borod et al., 2001; David,

1989; Kucharska-Pietura et al., 2003; Levy et al., 1983), modulating arousal (Borod et al., 2001; Heller, 1993), and directing attention in space (Heller, 1993). When the face initially appears, the left side is projected to the RH and the right side is projected to the LH (Butler et al., 2005). As the RH is specialised for face processing, more attention (and eye fixations) is drawn to the left side of the face than the right (Butler et al., 2005; Butler & Harvey, 2006). A directional scanning bias (due to reading from left to right on the page) combines with this to draw even more attention to the left side (Butler et al., 2005). This has the effect of the left side of the face appearing as more salient than the right side of the face, and thus the face with the smile on the left side of the face appears to be the happier of the two. The greater baseline activity/arousal in the posterior RH, the larger this effect should be (Borod et al., 2001; David, 1989; Heller, 1993; Levy et al., 1983).

Depression is associated with suppressed activity in the posterior RH (Bruder et al., 2004; Bruder et al., 2006; Henriques & Davidson, 1990). This suppressed posterior RH activity has been linked to anhedonic and melancholic symptoms of depression (Bruder et al., 1997; Heller et al., 1998). Higher levels of depression in both sub-clinical and clinical populations have been associated with relatively smaller left hemispatial biases on this task (Bruder et al., 2002; Heller et al., 1995). This is consistent with the notion that the extent of activity in the posterior RH is positively related to the size of the left hemispatial bias in this task. In the current study, the Previously Depressed group had a significantly larger left hemispatial bias than the Never Depressed group (see Figure 2). The results of the current study may at first appear contradictory with previous research, which found depressive symptoms to be associated with smaller left hemispatial biases (Bruder et al., 2002; Heller et al., 1995). However, as the Previously Depressed group were not currently depressed they

should not have the same suppressed posterior RH activity/arousal as currently depressed populations. As the Previously Depressed group do not show the smaller left hemispatial bias seen in currently depressed individuals in other studies, this suggests that this bias is a state-dependent trait, which disappears after remission of symptoms. That is, suppression of posterior RH activity, and the associated decreased left hemispatial bias are dependent on being in a depressed state, consistent with the notion that suppressed posterior RH activity reflects anhedonia.

However, this does not explain why the Previously Depressed group has a significantly larger left hemispatial bias than the Never Depressed group. Anxiety has been associated with larger left hemispatial biases in this task (Heller et al., 1995). However, anxiety is unlikely to be the reason for the Previously Depressed group's relatively larger left hemispatial biases, as the two groups did not differ in anxiety levels, and anxiety was controlled for as a covariate in the analyses. It is possible that the Previously Depressed group experienced more anxious arousal (and thus increased RH posterior activity) in response to the experimental situation compared to the Never Depressed group. This may not be apparent in Zung self-rating anxiety scores, as this is a more general measure of anxiety over the past several days, not specifically at the testing situation. Currently depressed or sub-clinically depressed individuals such as those studied by Heller et al. (1995) and Bruder et al. (2002) may not show this anxiety related increased RH posterior activation in the testing situation, as their current depressive symptoms may have dampened any increase in RH posterior activity. Future studies could manipulate and measure anxious arousal prior to performing the chimeric faces task to determine whether increased anxious arousal does increase the left hemispatial biases in this task, and whether individuals who are vulnerable to depression show greater sensitivity to such a manipulation.

SSRI Responders and Non-responders did not differ in the size of their left hemispatial biases on this task; in fact their mean left hemispatial biases were identical. SSRI Non-responders tend to show relatively more RH activity (measured by EEG) and more RH involvement in perceptual asymmetry tasks (Bruder et al., 1996; Bruder et al., 2001; Bruder et al., 2004; Bruder et al., 2008). It is interesting that they do not show an even larger left hemispatial bias compared to SSRI Responders, as it might be expected that they would have increased RH involvement in the processing of emotional information. However, it may be that this increased RH involvement is only for negative emotional information (which would be predicted by the valence hypothesis of emotional perception; Ahern & Schwartz, 1979), or only for certain types of emotional stimuli (i.e. words). Chimeric faces tasks with sad stimuli could be administered to determine whether this changes the size or direction of an individual's biases.

Divided Visual Field

Participants then completed a divided visual field task, in which emotional words were presented laterally, and participants judged whether each word was emotionally positive or negative, as quickly and accurately as possible. The words were flashed briefly (185ms), which is not enough time to allow for eye movement to the word. Thus, words flashed to the RVF are projected to the LH, and words flashed to the LVF are projected to the RH (Beaumont, 1983). This task has been completed with currently depressed, remitted depressed and non-depressed populations (Atchley et al., 2003; Atchley et al., 2007). However, Atchley et al. used percent correct as their measure of accuracy, which does not separate the effects of sensitivity (how accurate an individual is at discriminating the actual valence of the word) from response bias (how biased the individual is to responding that a word has a certain

valence). Additionally, Atchley et al. (2007) did not examine RT data. Furthermore, differences between SSRI Responders and Non-responders in this task have not been explored. The current study aimed to extend the findings of Atchley et al. (2003; 2007) by using signal detection analysis to examine sensitivity and bias, by analysing RT data, and by investigating hemispheric differences in the perception of emotional words in SSRI Responders and Non-responders.

Based on the results of Atchley et al., (2003), it was expected that for words presented to the RVF/LH, both Never Depressed and Previously Depressed participants would have an advantage for positive over negative words. It was predicted that for words presented to the LVF/RH, the Never Depressed group would have an advantage for positive words; whereas the Previously Depressed group would have an advantage for negative words. It was expected that consistent with previously research (Atchley et al., 2003; Atchley et al., 2007; Borod et al., 2001) the Never Depressed group would have a RVF/LH processing advantage for both positive and negative words. Based on EEG and dichotic listening studies (which find increased RH involvement in SSRI Non-responders; Bruder et al., 1996; Bruder et al., 2001; Bruder et al., 2004; Bruder et al., 2008) it was expected that the SSRI Responders would resemble Never Depressed participants, showing a RVF/LH advantage, whereas SSRI Non-responders would show a relatively decreased RVF/LH advantage, or a reversal towards a LVF/RH advantage. These predictions were largely supported. The current results were mostly consistent with Atchley et al.'s (2003; 2007) findings, and extend their findings by showing that SSRI Non-responders process emotional words differently from both SSRI Responders and Never Depressed controls.

Divided visual field tasks using words usually elicit a RVF/LH advantage, due to the LH's dominance for language processing (Borod et al., 2001). There was an overall RVF/LH speed advantage for processing both positive and negative words (see Figure 5). However, this LH advantage was larger for positive words than for negative words. This suggests that the RH may be playing more of a role in processing negative words relative to the LH. That is, valence may play a role in the extent to which the RH is involved in processing emotional words. This is in contrast to the RH hypothesis of emotional perception, which predicts that the RH is involved in the processing of emotional content, regardless of its valence (Borod et al., 1983; Borod et al., 2001). However, this finding is in support of the valence hypothesis (Ahern & Schwartz, 1979); that the LH is more involved in the perception of approach/positive emotions, while the RH is more involved in the perception of withdrawal/negative emotions. This finding supports the proposal that this lateralisation of emotion may not only be related to the *experience* of emotion, but also to the *perception* of emotional information.

For high arousal words, the Never Depressed group had an advantage for positive over negative words, whereas the Previously Depressed group had no advantage for either valence. There were no valence advantages for low arousal words for either group. Examination of Figure 4 shows that the Never Depressed group's speed advantage for high arousal positive words is caused by their relatively slow RTs for high arousal negative words. This suggests that people who are not vulnerable to depression may process high arousal negative words more slowly than other types of words, while remitted depressed individuals may process high arousal negative words more efficiently than people who have not been depressed. This is consistent with

findings of a positive interpretational bias in healthy controls (Hirsch and Mathews, 2000).

Further research could investigate whether the Previously Depressed groups' relative advantage (compared to the Never Depressed group) for processing high arousal, negative words is apparent in processing other emotional stimuli, such as faces and prosody. Highly arousing negative stimuli are stress inducing, and so the ability to process these types of stimuli more effectively could potentially increase a person's stress responsiveness, which is consistent with Davidson's diathesis-stress hypothesis (Davidson, 1992). Perhaps a contributing factor to developing a 'negative affective style' is this efficiency for processing highly arousing negative stimuli. This is also consistent with the idea that negative cognitive style is the mediating variable between a genetic predisposition and increased stress reactivity in the development of depression. Alternatively, perhaps repeated exposure to stressors and the experience of negative affect can reshape a person's processing style such that they become better at processing highly arousing negative stimuli.

Future research should determine whether this processing advantage is a negative affective style which predisposes someone to developing depression, or whether it is the product of the depressed state which lingers after remission. People at risk of depression (who have not yet experienced a depressive episode) could be selected based on family history of depression, and their hemispheric differences for processing different types of emotional information could be examined to determine whether this relative advantage for highly arousing negative stimuli is present before the onset of depression.

When the Previously Depressed group is divided into SSRI Responder and SSRI Non-responder groups, neither group has a significant advantage for processing

high arousal words of either valence. However, the SSRI Non-responders show a trend towards processing highly arousing negative words more efficiently than highly arousing positive words (see Figure 7). Perhaps during periods of depression, SSRI Responders shared this advantage for highly arousing negative stimuli, which disappeared after successful treatment and remission. Or perhaps SSRI Responders never had this advantage, which could potentially contribute to why they might respond to SSRI treatment more effectively than people with this advantage for processing highly arousing negative stimuli. Further studies could follow a group of currently depressed participants through SSRI treatment, to determine the extent to which this relative advantage for highly arousing negative words is predictive of SSRI response.

For words presented to the RVF/LH, both the Never Depressed and Previously Depressed groups had an advantage for positive over negative words. For words presented to the LVF/RH, the Never Depressed group again had an advantage for positive over negative words, but the Previously Depressed group showed no advantage for either valence (and show a slight trend towards an advantage for negative words; see Figure 6). This effect in the Previously Depressed group was mainly carried by SSRI Non-responders. SSRI Non-responders have a distinctive pattern of asymmetry for the processing of emotional, particularly negative, words. That is, SSRI Responders do not differ in their processing of negative vs. positive words presented to the LVF. However, SSRI Non-responders had a significant advantage for negative over positive words presented to the LVF/RH (see Figure 8). In terms of VF advantages, for positive words the Never Depressed, SSRI Responder and SSRI Non-responder groups all showed a pattern of a RVF/LH advantage. However, the groups differed in their lateralisation of negative words. The Never

Depressed group did not have a VF advantage for negative words. SSRI Responders had a RVF/LH advantage for negative words; whereas the SSRI Non-responders had a LVF/RH advantage for negative words (see Figure 8). The lack of a RVF/LH advantage for negative words in the Never Depressed group suggests that even in healthy participants, the RH may be more involved in processing negative than positive words. This is consistent with the valence hypothesis (Ahern & Schwartz, 1979), and contradicts the RH hypothesis (Borod et al., 1983; Borod et al., 2001) of emotional perception.

These results suggest that SSRI Non-responders may have a distinctive pattern of asymmetry for the processing of emotional words, depending on the word's valence. SSRI Non-responders have the opposite asymmetry for processing negative words to those who do respond to SSRIs. This suggests that for a subset of people vulnerable to depression (SSRI Non-responders) the RH is relatively more involved in the processing of negative words (and potentially other emotional stimuli). This is not consistent with the RH hypothesis of emotion processing, as the RH hypothesis does not predict asymmetry differences in processing words of different valences (Borod et al., 2001). This finding lends support to the valence hypothesis of emotional perception (Ahern & Schwartz, 1979). This finding suggests an interaction between stimulus variables (e.g. valence) and subject variables (e.g. responsiveness to SSRIs) in explaining hemispheric differences in emotional word processing.

In addition, SSRI Non-responders were more sensitive to discriminating the valence of a word presented to their LVF/RH than to their RVF/LHs (see Figure 9). This was the opposite pattern to both SSRI Responders and Never Depressed controls, who were both more sensitive to discriminating the valence of a word presented to their RVF/LH than their LVF/RH. The analysis of *d'* scores demonstrates that it was

an actual perceptual advantage for the RH, and not just a bias towards responding that a word is negative when unsure of the actual valence of the word. This suggests that rather than a negative response bias, The SSRI Non-responders may have a unique structure to their semantic networks and/or a difference in their ability to attend to information in the LVF.

The pattern that emerges from the data is that SSRI Non-responders process emotional words differently from both Never Depressed controls and SSRI Responders. These results are largely consistent with Atchley et al.'s (2003; 2007) findings that for words presented to the LVF/RH, both Currently and Previously Depressed participants had an advantage for identifying the valence of negative compared to positive words; while Never Depressed controls had an advantage for identifying the valence of positive compared to negative words. The present study extended their findings by showing that for words presented to the LVF/RH, Previously Depressed participants as a whole did not have an advantage for negative over positive words, but that SSRI Non-responders did. This suggests that SSRI Non-responders may have been driving this effect in the Previously Depressed group in Atchley's studies. This highlights a potential problem of using Currently Depressed or Previously Depressed groups without differentiating between SSRI Responders and SSRI Non-responders.

It has previously been shown that depressed patients have a processing style which favours the processing of negative information, and may have a tendency to interpret ambiguous information as negative (Beck, 2008; Gotlib & Neubauer, 2000; Mathews & MacLeod, 1994; Mathews & MacLeod; 2005). It is not clear whether this negative cognitive style disappears during remission, or it remains only under certain conditions (e.g. negative mood induction; Mathews & MacLeod, 2005). The negative

cognitive processing style in people vulnerable to depression may depend on the extent of the processing involvement of each hemisphere. Thus, the negative processing style may be more robustly demonstrated by the use of perceptual asymmetry tasks. Atchley et al. (2003; 2007) demonstrated that negative word processing advantages in the RH can be found in remitted depressed individuals when using a divided visual field paradigm to isolate effects in the two hemispheres. The current study shows that this negative processing style may be exclusive to those vulnerable to depression who do not respond to SSRI medication. Atchley's findings along with the current results highlight the importance of using lateralised presentation when looking at the processing of emotional information, as potential effects of negative processing advantages specific to the RH could be disguised when looking at processing of centrally presented stimuli.

As this study examined remitted depressed participants, it cannot be determined whether during periods of depression SSRI Responders and Non-responders differed in their hemispheric differences in processing emotional words. Changes in the RH semantic network may have occurred as a result of the depressive episode. Thus, while experiencing a depressive episode, the SSRI Responders and Non-responders may both have had a speed of processing advantage for negative over positive words. The SSRI Responders' RH semantic networks may have then been reorganised during treatment and subsequent recovery, such that they developed an advantage for positive over negative words. Alternatively, the SSRI Responders may have processed emotional words differently from SSRI Non-responders, even during (or prior to) periods of depression. Either of these possibilities could play a role in why SSRI Responders improve with SSRI treatment, while SSRI Non-responders do not. Either the SSRI Responders' RH semantic networks are more malleable and able

to change with treatment; or SSRI Responders RHs' may have always processed positive stimuli more effectively than negative stimuli, which could give potentially give them an advantage for recovery. Such hypotheses point to the importance of longitudinal studies with groups of currently depressed participants, that could examine asymmetries in the processing of emotional information, and then follow their treatment response to determine whether SSRI responders and non-responders differ in how they process emotional stimuli during periods of depression, and how this changes during treatment and recovery.

It also cannot be determined from the current study whether the SSRI Non-responders' RH processing advantage for negative over positive words is a product of the previously depressed state; or whether it is part of a negative processing style which contributes to a predisposition to depression. To investigate this, at-risk adolescents (who have not yet been depressed) could be selected on the basis of family history of depression, and followed over the course of several years. This could show whether this RH advantage for processing negative words (and potentially other kinds of emotional stimuli) is present before the onset of depression, which would indicate that it is a predisposing factor for depression; or whether it develops during the experience of depression, which would indicate that it is a product of the depressed state. Either possibility is interesting, as this suggests that either semantic networks can be reorganized as a consequence of emotional experience (i.e. depression); or that the organization of semantic networks influences peoples' emotional experience and susceptibility to depression.

Hemispheric Differences in Semantic Processing

Although the LH is the dominant hemisphere for language comprehension in almost all right handed people, this does not mean that the RH is incapable of

language comprehension (Lindell, 2006). The LH and RH semantic systems differ in their activation of word meanings. The LH system uses a fine-grained, controlled, attention-driven process of activating and selecting the meaning of a word (Atchley et al., 2003; Borod et al., 2001; Lindell, 2006; Rotenberg, 2004). In contrast, the RH engages in 'coarse semantic coding' (Beeman, 1998; Borod et al., 2001; Lindell, 2006), resulting in widespread, passive activation of many possible word meanings (Atchley et al., 2003; Beeman, 1998; Borod et al., 2001; Lindell, 2006; Rotenberg, 2004). It seems that it is only the RH semantic system which differs between groups, such that SSRI Non-responders have an advantage for negative over positive words that are presented to the RH; and an advantage for negative words presented to the RH compared to the LH. Additionally, they are more sensitive to the valence of a word presented to the RH.

The RH system integrates the emotional content of words as salient semantic features (Atchley et al., 2003), and has qualities which make it more equipped to process emotional information (for a review see Borod et al., 2001). These include greater neuronal interconnectivity within the RH which allows for the organization and integration of relationships between multiple elements of information (Borod et al., 2001; Rotenberg, 2004). Atchley et al. (2003; 2007) suggest that both Currently Depressed and Previously Depressed individuals have a more efficient spread of activation for negative words in the RH, as the neighbouring and related negative words are more densely represented in these individuals compared to those who have never been depressed. Thus, even if negative words were more densely represented in the LH semantic network, this automatic spread of activation would not occur, as the LH semantic network is limited to controlled, localised activation. Results from the current study suggest that after remission, this may be true for a subset of Previously

Depressed individuals (those who do not respond to SSRIs), but not for others (those who do respond to SSRIs).

If semantic networks can be rearranged through emotional experience, for example through exposure to multiple stressors and the experience of sustained negative affect, then it may be possible to purposefully reorganise people's semantic networks to improve processing of positive material. The negative cognitive processing style in depression appears mainly when conscious processing strategies are possible (for reviews see Mathews & MacLeod, 1994; Mathews & MacLeod, 2005). These conscious strategies may be more conducive to change than if they were automatic processing strategies. If this RH involvement in processing negative information is a factor in why SSRI Non-responders do not respond to treatment, perhaps this could be a target of therapies to change negative biases. For example, repeated exposure to positive stimuli presented to the RH may enhance the RH's ability to process positive stimuli.

The ability to direct attention in space may also be a factor in these group differences in asymmetries in this task. The Stroop task can be administered using lateralised presentation of emotional words. As word meaning is a distraction from the task of naming the colour of the word, relatively more errors for words presented to the RVF/LH would indicate that the LH has an advantage for processing the meaning of the word; and relatively more errors for words presented to the LVF/RH would indicate that the RH has an advantage for processing the meaning of the word. Borkenau and Mauer (2006) administered a lateralised emotional Stroop task to healthy participants and found that they had worse RVF/LH accuracy for positive words; and worse LVF/RH accuracy for negative words. This suggests that the LH was more distracted by positive valence, and the RH was more distracted by negative

valence. That is, the LH attends more to positive valence, and the RH attends more to negative valence, which is consistent with the valence hypothesis of emotional perception. This is inconsistent with the RH hypothesis, which would predict that emotional words presented to the LVF/RH should be more distracting, regardless of valence. Anxiety can affect asymmetries in performance on emotional Stroop tasks (Richards et al., 1995). Thus, it seems plausible that other trait differences such as depressed mood, vulnerability to depression and SSRI responsiveness may also affect asymmetries in attention. Differences in the allocation of attention in space may be a factor underlying group differences in asymmetries in the processing of emotional words in this study. For example, SSRI non-responders may have an enhanced ability to attend selectively to negative information shown to the LVF/RH, and/or a deficit in the ability to attend to information shown to the RVF/LH.

SSRI Responsiveness

Previous research has also shown that SSRI non-responders have relatively greater RH activity, and greater RH involvement in dichotic listening tasks compared to SSRI Responders (Bruder et al., 1996; Bruder et al., 2001; Bruder et al., 2004; Bruder et al., 2008). The current study found that SSRI Non-responders have increased RH involvement in the processing of emotional words, especially negative words. The SSRI Non-responders showed an advantage for negative over positive words that were presented to the RH; and an advantage for negative words presented to the RH compared to the LH. Additionally, they were more sensitive to the valence of a word presented to the RH. This suggests that their RH semantic systems differ from that of SSRI Responders. It is interesting to consider what other factors (e.g. genetic, cognitive and hormonal) determine whether someone responds to SSRIs, and how do these factors relate to one another, and to SSRI non-responders' pattern of

hemispheric and perceptual asymmetries? Little is known about hemispheric asymmetries in serotonin systems, or how serotonergic activity relates to cognitive function. However, considering the unique pattern of hemispheric asymmetry in SSRI Non-responders, and that SSRI medication acts on serotonergic systems, it seems possible that SSRI non-responders may have a distinctive pattern of serotonergic asymmetry which affects both their responsiveness to SSRIs and their processing of negative words.

As the name suggests, SSRIs selectively inhibit the reuptake of serotonin, increasing the amount available to bind to postsynaptic receptors. Serotonin levels are increased immediately from the onset of treatment with SSRIs, however depressive symptoms do not improve for several weeks (Jongsma et al., 2005). In acute doses, SSRIs act on both 5HT (serotonin) 1a and 1b autoreceptors, which act as a feedback mechanism modulating synthesis and release of serotonin (Jongsma et al., 2005). After chronic treatment, there is a reduction in 5HT1a autoreceptor functionality; further increasing serotonin levels (Jongsma et al., 2005). Additional long term adaptations involving the serotonin system are likely to be involved in SSRI response (Murphy et al., 2008).

One factor which appears to be important in predicting responsiveness to SSRIs is the functioning of the Hypothalamic Pituitary Adrenal (HPA) axis. The HPA axis is involved in stress response: Corticotropin-releasing hormone (CRH) is released from the hypothalamus, which is sent to the anterior pituitary, stimulating the release of adrenocorticotropic hormone (ACTH) from the adrenal glands into the bloodstream. ACTH in turn stimulates the synthesis and release of cortisol by cells in the adrenal cortex (for a review see Pariante & Lightman, 2008; Tafet & Bernardini, 2003). Activity of the HPA axis is controlled by negative feedback from cortisol (for

a review see Pariante & Lightman, 2008; Tafet & Bernardini, 2003). Many people with depression show HPA hyperactivity (Pariate & Lightman, 2008; Tafet & Bernardini, 2003), which is consistent with the diathesis-stress hypothesis of depression (Davidson, 1992); that people vulnerable to depression have greater reactivity to stressful events. This may be caused by chronic stress exposure, resulting in alterations in the regulation of the HPA axis and of serotonin systems (Tafet & Bernardini, 2003). Serotonin is involved in activation and feedback control of the HPA axis (Gotlib, Joormann, Minor, & Hallmayer, 2008; Tafet & Bernardini, 2003), and HPA functioning in turn affects serotonin systems (Tafet & Bernardini, 2003). There is a direct correlation between increased cortisol levels and increased serotonin uptake (Tafet & Bernardini, 2003), which results in less available serotonin in the synapse. Cortisol release is also regulated by activation of 5HT1a receptors, which are desensitized after chronic SSRI treatment, decreasing cortisol release and the subsequent HPA stress response (Jongsma et al., 2005). Thus, SSRIs may help to restore normal HPA functioning (Jongsma et al., 2005; Zobel et al., 2001).

Recovery from depression can result in a reduction of this HPA hyperactivity (Binder et al., 2008), but not in all patients (Young et al., 2004). Persistent hyperactivity is a risk factor for relapse (Brouwer et al., 2006; Reppermund et al., 2006; Zobel et al., 2001). SSRI response can be predicted by pre-treatment HPA functioning. Young et al. (2004) found that prior to treatment SSRI Non-responders showed increased HPA axis activation compared to healthy controls, whereas SSRI Responders did not significantly differ from controls. Thus, it may be that these Non-responders need alternative treatment to specifically address this HPA abnormality.

How does the unique pattern of SSRI Non-responders' hemispheric and perceptual asymmetries relate to their hyperactivity of the HPA axis? High levels of

cortisol have a causal influence on increasing relative RH frontal activity (Tops et al., 2005). Tops et al. (2005) administered cortisol to healthy male volunteers and found that this increased their relative RH frontal activity (as measured by EEG alpha power). Thus, increased cortisol levels increased relative RH frontal activity. Gadea et al. (2005) showed that inducing negative affect prior to a dichotic listening task increased participants' left ear (RH) advantages and decreased their right ear (LH) advantages. The negative mood induction was also associated with an increase in cortisol levels. This suggests that hemispheric differences in the perception of information may be related to increased cortisol levels (though whether this is a causal relationship cannot be determined from Gadea et al's., 2005 study). Thus, it is possible that the findings of the current study (that SSRI Non-responders have increased RH involvement in the processing of negative information) could be related to increased cortisol levels. In future studies, cortisol could be administered, followed by completion of emotional perceptual asymmetry tasks, to determine how this affects hemispheric differences in the processing of emotional stimuli.

In addition to hyperactivity of the HPA axis, genetic factors have also been linked to SSRI response. Due to SSRIs' direct action on the serotonin transporter (SERT), the SERT gene has been the target of investigation into differences in peoples' responsiveness to SSRIs. A functional polymorphism in the promoter region of the SERT gene (SLC6A4) is involved in the expression of SERT in the brain (Caspi, Sugden, Moffitt, & Taylor, 2003). The promoter activity of the gene depends on the combination of the alleles within the gene-linked polymorphic region; 5HTTLPR (Caspi et al., 2003). There are three possible combinations of alleles at this region; two short (*s*) alleles, two long (*l*) alleles, or a long and a short allele. The *s*

allele is associated with reduced transcription efficiency of the SERT compared to the *l* allele (Caspi et al., 2003).

The combination of alleles in this region is related to vulnerability to depression, but only when this interacts with life stress. The *s/s* combination may be a candidate for a predisposition for increased stress responsiveness (and HPA response), which increases risk for depression. In a longitudinal study, Caspi et al. (2003) found that individuals with one or two copies of the *s* allele reacted to stress with more depressive symptoms, clinical depression, suicidal ideation, and suicide attempts compared to individuals with two copies of the *l* allele. Gotlib et al. (2008) examined effects of a stressor on adolescent girls' cortisol responses. They found that girls who were homozygous for the *s* allele produced higher and more prolonged levels of cortisol in response to stress than girls with one or two copies of the *l* allele. The *s/s* allele combination is also associated with greater amygdala activity. *S/s* carriers show increased activation of the amygdala and hippocampus in response to life stress (as shown by fMRI studies), compared to non-carriers of the *s* allele (Canli & Lesch, 2007). This gene-stress interaction is consistent with Davidson's (1992) diathesis-stress hypothesis of depression; in which a genetic predisposition interacts with life stress to increase risk for depression.

Atypical RH processing of negative material in SSRI non-responders may be related to the negative cognitive processing style (Beck, 2008; Davidson, 1992) which contributes to the development of depression. This negative processing style may bridge the gap between a genetic predisposition and increased stress reactivity in vulnerability to depression. Hayden et al. (2008) examined the combined effect of the 5HTTLPR genotype and induced negative mood on negative and positive schematic processing in seven year old children. Children with the *s/s* allele combination

showed greater negative schematic processing following negative mood induction compared to those with *s/l* and *l/l* combinations. This indicates that the *s/s* allele variant is related to an increase in negative schematic processing, and that this is a predisposition which is present in childhood, before the onset of depression. Thus, the *s/s* allele combination is related to both increased stress reactivity and negative cognitive processing.

Allele variants of the 5HTTLPR polymorphism can predict SSRI response. The *s/s* variant is associated with the worst response rate to SSRIs; and the *l/l* variant is associated with the best response rate (Murphy et al., 2008; Serretti, Kato, De Ronchi, & Kinoshita, 2007; Smits et al., 2004). Additionally, the *s/s* variant is associated with slower response to SSRIs compared to those with an *l* allele (Pollock et al., 2000; Serretti et al., 2007). *S* carriers have lower 5HT1a receptor binding potential than non-carriers (Canli & Lesch, 2007); which could potentially contribute to their reduced responsiveness to SSRIs. Furthermore, patients with the *s/l* and *s/s* genotype experience more adverse effects of SSRIs than those homozygous for the *l* allele (Murphy et al., 2008; Smits et al., 2007).

How does the unique pattern of SSRI Non-responders' hemispheric and perceptual asymmetries relate to allele variants in 5HTTLPR? SSRI non-response is associated with carriers of the *s* allele variant (Murphy et al., 2008; Serretti et al., 2007; Smits et al., 2004). The current study has shown that SSRI non-response is also related to increased RH involvement in the processing of negative words. It seems possible that expression of the SERT gene may be related to serotonergic asymmetries, which in turn may be related to asymmetries in brain activity, and asymmetries in the processing of emotional information. Very little research has been conducted on serotonin asymmetries in the brain. Further research should investigate

how peoples' allele variants in 5HTTLPR can predict their patterns of hemispheric and perceptual asymmetries, and how these relate to SSRI responsiveness.

Cognitive factors may also predict whether someone will respond to SSRIs. The PFC, which is involved in executive function, is hypoactive in depression (Levin et al., 2007; Rogers et al., 2004). Thus it is not surprising that people with depression often have deficits in executive function (Dunkin et al., 2000). Depressed patients frequently perform poorly on tests of cognitive flexibility, problem-solving, semantic retrieval, working memory, and response inhibition (Dunkin et al., 2000). Beck (2008) suggests that for people who have an negative processing style, executive dysfunction impairs their ability to exert cognitive control over their negative processing style. If cognitive control can be improved through training, they may be able to override their negative cognitive biases. This may point to the importance of cognitive behavioural therapy in the treatment of depression in these SSRI non-responders.

The executive function deficits in depression seem to be related to both HPA functioning and stress responsiveness (McCormick, Lewis, Somley, & Kahan et al., 2007). There are an abundance of glucocorticoid receptors in the PFC (McCormick et al., 2007); and the PFC has inhibitory connections with limbic structures involved in the stress response (Levin et al., 2007). McCormick et al. (2007) found that higher cortisol levels were associated with more errors on the Wisconsin Card Sorting Test (WCST) in women. The WCST is a measure of PFC executive function, which involves 'set shifting', or having to adjust to new sets of rules. This involves cognitive flexibility and the ability to initiate strategies, processes which are often impaired in depression, and may be specifically left PFC functions (Dunkin et al., 2000; Levin et

al., 2007). This is consistent with the fact that in depression, the left PFC is more hypoactive than the right PFC (Levin et al., 2007).

HPA functioning seems to be more related to executive dysfunction in depression than to symptom severity. Egeland et al. (2005) found that hypercortisolism was related to executive dysfunction (as measured by the WCST and Stroop task) and memory impairment, but not with symptom severity. Similarly, Reppermund et al. (2006) found that improvement in HPA functioning was more related to improvement in executive function and memory impairments than it was to improvement of symptom severity. Zobel et al. (2004) found a strong relationship between improvement in working memory performance and normalisation of HPA functioning during SSRI treatment, but no relationship between improvement of symptoms and normalisation of HPA functioning. Thus, hyperactivity of the HPA system seems to be more related to cognitive deficits in depression, than to severity of depression itself (Zobel et al., 2004). This suggests that cognitive deficits may be a mediating factor between HPA hyperactivity and depressive symptoms.

Low levels of serotonin may impair cognitive flexibility (Schmitt et al., 2006). Acute tryptophan depletion (ATD) involves administration of an amino acid drink which reduces tryptophan, and consequently serotonin levels (Evers, van der Veen, Fekkes, & Jolles, 2007). ATD changes brain activation (as measured by fMRI) during tasks which require cognitive flexibility (Evers et al., 2007). It has been suggested that lowered serotonin levels impair the negative feedback process necessary for cognitive flexibility. This is specifically the executive function skill that is most consistently impaired in depression (Dunkin et al., 2000; Levin et al., 2007; McCormick et al., 2007). Thus, lowered levels of serotonin in depressed patients may be related to their executive function deficits, specially deficits in cognitive flexibility.

As executive dysfunction is related to both HPA functioning and serotonin levels, it follows that executive dysfunction may also be related to responsiveness to SSRIs. Indeed, relatively larger executive function deficits may predict reduced responsiveness to SSRIs. Dunkin et al. (2000) found that SSRI Non-responders performed significantly worse than SSRI Responders on pre-treatment executive function tasks (the WCST and Stroop task). Specifically, they had trouble utilizing feedback from the experimenter, learning new rules and strategies, and inhibiting rules they had been told are wrong. There are many ways in which these types of skills would be useful in recovering from depression. For example, the learning of new coping strategies, inhibiting negative patterns of thinking and behaving, and utilizing feedback from others (e.g. therapists) all require executive functions.

It has not yet been examined how executive dysfunction relates to patterns of hemispheric asymmetries in depression. Higher levels of cortisol are associated with both relative RH activity, and executive function deficits. Thus, it seems likely that executive dysfunction would be related to patterns of hemispheric asymmetry. SSRI responsiveness is predicted by hormonal (HPA axis hyperactivity), cognitive (executive dysfunction), and genetic (allele variants of the SERT gene) factors. SSRI responsiveness is also predicted by patterns of hemispheric and perceptual asymmetries (Bruder et al., 1996; Bruder et al., 2001; Bruder et al., 2004; Bruder et al., 2008). The relationship between HPA functioning and hemispheric asymmetry has been established (Tops et al., 2005). However, the relationships between the SERT gene and hemispheric asymmetry, and executive function and hemispheric asymmetry have not yet been explored.

Limitations

A limitation of the present study was that only 11 SSRI Non-responders were able to be recruited for the study. Replication with larger samples of SSRI Responders and Non-responders should determine the reliability of the effects found in this study. However, the fact that significant group differences were found with such a small sample size may be an indication of the strength of this effect. Another limitation was that this study relied on self-report of the nature and severity of past depression and treatment, and response to the treatment, as medical records were unable to be obtained. However, responsiveness to treatment should be able to be assessed subjectively by the patient, as they should know if their symptoms have improved subsequent to SSRI treatment or not. It would have been preferable to have a clinical evaluation of response to treatment. Additionally, if a larger pool of participants could be obtained, it would be ideal to split participants into groups of those who only had SSRI treatment (many in the current study were also treated with therapy); those who were only treated with therapy; and a group who were treated with both SSRIs and therapy.

Theoretical Implications and Future Directions

The current study found that Previously Depressed individuals had a larger left hemispatial bias in the chimeric faces task than Never Depressed individuals. It has been suggested that the size of the left hemispatial bias reflects the extent of activity or arousal in the posterior RH. Future research should measure baseline RH posterior activity prior to the task, and during the task, to determine whether this increased activity predicts larger left hemispatial biases. Arousal should be measured and manipulated prior to completion of the task, to determine whether increased arousal increases the left hemispatial bias, and whether certain people (e.g. those vulnerable to depression) are particularly susceptible to such a manipulation. Faces of

expressions other than happy (e.g. sad, angry) should be used to determine whether different emotional expressions elicit different sized biases (and by implication affect the extent of involvement of the posterior RH).

The divided visual field task found that compared to Never Depressed controls and SSRI Responders, SSRI Non-responders have increased RH involvement in the processing of emotional words, especially negative words. The SSRI Non-responders showed an advantage for negative over positive words that were presented to the RH; and an advantage for negative words presented to the RH compared to the LH. Additionally, they were more sensitive to identifying the valence of a word presented to the RH. These effects in SSRI Non-responders provide evidence against the RH hypothesis of emotional perception. In contrast the current findings, the RH hypothesis would predict that the RH would be equally effective at processing words of both positive and negative valence. The current findings provide support for the valence hypothesis of emotional perception, which predicts that the RH is more involved than the LH in processing negative or withdrawal-motivated stimuli.

The current findings contribute knowledge about what the characteristic patterns of hemispheric asymmetries seen in depression actually mean in terms of cognition. Not only are there hemispheric differences in neural activity, there are hemispheric differences in the processing of emotional words, which differ depending on the valence of the word. This suggests that hemispheric asymmetries in activity do affect the processing of emotional information in the environment, consistent with Davidson's (1992) diathesis-stress hypothesis; that greater relative RH activity influences people's emotional responsiveness to emotional stimuli, increasing their risk of developing depression. Future studies should examine both hemispheric asymmetries (measured with EEG) and emotional perceptual asymmetries in the same

population, to determine the precise relationship between asymmetries in neural activity and asymmetries in the perception of emotional information.

The current results point to the importance of using lateralised presentation of stimuli when examining emotional perception. Centralised presentation does not examine hemispheric differences in perception, which may be where these differences in emotional perception emerge. Additionally, the use of lateralised presentation may help to iron out inconsistencies in previous research on the negative processing style in depression. The current findings show that a subset of people vulnerable to depression (SSRI Non-responders) have a processing style favouring the perception of negative stimuli, but only when the words are presented to their LVF/RH. Thus, perhaps the negative processing style is only present for information presented to the RH. Future studies could examine lateralised presentation of other types of emotional stimuli (e.g. faces, images, prosody) to determine whether these effects are specific to emotional words.

As this study used remitted depressed individuals, the effects found must reflect state-independent characteristics, which are not dependent on experiencing depressed mood. However, it cannot be determined whether these effects are a predisposition which was present before the onset of depression, or whether they developed during a depressive episode and remain after remission. Longitudinal studies with at risk individuals would be necessary to determine which is the case. Longitudinal studies could also examine whether SSRI responders and non-responders differ in their hemispheric differences in emotional perception prior to treatment, or whether they emerge as a result of different responses to treatment. If the differences are present prior to treatment, they may contribute to why some people respond to SSRI medication and some do not; as SSRI responders may be better

equipped with a processing style which favours the processing of positive stimuli, whereas SSRI non-responders may have a processing style which favours the processing of negative stimuli. If the differences emerge post-treatment, this would suggest that SSRI medication can affect the organization of an individual's semantic network, and this may be key in treatment response. If this is the case, alternative methods of reorganising semantic networks (e.g. training with positive stimuli) could potentially help SSRI non-responders change their negative processing style.

Differences between SSRI Responders and Non-responders in this study may explain some of the inconsistencies in previous research on depression. If, as it appears from the current results, SSRI non-responders have been carrying previous findings in depressed populations (on negative cognitive processing style, and hemispheric and perceptual asymmetries), then different numbers of SSRI non-responders in each study would affect the strength of these effects. Future research should examine groups of SSRI responders and non-responders separately. It would be interesting to determine whether these characteristic differences which predict responsiveness to SSRI treatment also predict responsiveness to cognitive behavioural therapy. Cognitive behavioural therapy may be essential for those who do not respond to SSRIs, to improve cognitive flexibility and control in order to override their negative cognitive processing style. Future research will benefit from integrating data on executive function, HPA activity, hemispheric and perceptual asymmetries, and allele variants of the SERT gene to build a coherent picture of both the neuropsychology of depression, and of SSRI non-responders' unique neuropsychological profile. By using a combination of these predictor variables, it may be possible to predict with a reasonable level of accuracy whether it is likely that someone will respond to SSRIs or not.

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Appendix A

Zung Self-Rating Depression Scale

For each item below, please place a check mark (□) in the column which best describes how often you felt or behaved this way during the past several days.

Place check mark (□) in correct column.

	A little of the time	**Some of the time**	**A good part of the time**	**Most of the time**
1 I feel downhearted and blue.	□	□	□	□
2 Morning is when I feel the best.	□	□	□	□
3 I have crying spells or feel like it.	□	□	□	□
4 I have trouble sleeping at night.	□	□	□	□
5 I eat as much as I used to.	□	□	□	□
6 I still enjoy sex	□	□	□	□
7 I notice that I am losing weight	□	□	□	□
8 I have trouble with constipation.	□	□	□	□
9 My heart beats faster than usual.	□	□	□	□
10 I get tired for no reason.	□	□	□	□
11 My mind is as clear as it used to be.	□	□	□	□
12 I find it is easy to do the things I used to.	□	□	□	□
13 I am restless and can’t keep still.	□	□	□	□
14 I feel hopeful about the future.	□	□	□	□
15 I am more irritable than usual.	□	□	□	□
16 I find it easy to make decisions.	□	□	□	□
17 I feel that I am useful and needed.	□	□	□	□
18 My life is pretty full.	□	□	□	□
19 I feel that others would be better off if I were dead.	□	□	□	□
20 I still enjoy the things I used to.	□	□	□	□

Appendix B

Zung Self-Rating Anxiety Scale (SAS)

For each item below, please place a check mark (□) in the column which best describes how often you felt or behaved this way during the past several days.

Place check mark (□) in correct column.

	A little of the time	**Some of the time**	**A good part of the time**	**Most of the time**
1 I feel more nervous and anxious than usual.	□	□	□	□
2 I feel afraid for no reason at all.	□	□	□	□
3 I get upset easily or feel panicky.	□	□	□	□
4 I feel like I'm falling apart and going to pieces.	□	□	□	□
5 I feel that everything is all right and nothing bad will happen.	□	□	□	□
6 My arms and legs shake and tremble.	□	□	□	□
7 I am bothered by headaches neck and back pain.	□	□	□	□
8 I feel weak and get tired easily.	□	□	□	□
9 I feel calm and can sit still easily.	□	□	□	□
10 I can feel my heart beating fast.	□	□	□	□
11 I am bothered by dizzy spells.	□	□	□	□
12 I have fainting spells or feel like it.	□	□	□	□
13 I can breathe in and out easily.	□	□	□	□
14 I get feelings of numbness and tingling in my fingers & toes.	□	□	□	□
15 I am bothered by stomach aches or indigestion.	□	□	□	□
16 I have to empty my bladder often.	□	□	□	□
17 My hands are usually dry and warm.	□	□	□	□
18 My face gets hot and blushes.	□	□	□	□
19 I fall asleep easily and get a good night's rest.	□	□	□	□
20 I have nightmares.	□	□	□	□

Appendix C

Questionnaire

Student ID Number:

Age:

Treatment History:

1. **When you were treated for depression, what type of treatment did you receive?**

   SSRI medication Other medication Therapy

If you received SSRI treatment, continue on with the next questions.

2. **Did you experience any side effects from the SSRI treatment?**

   If so, what were they?

3. **In your opinion, did the SSRI treatment help your depression?**

   Yes No

4. **Any additional comments on your treatment or depression history?**

Appendix D

Word Lists:

Low Arousal Negative Words:

unhappy	blister	messy	pity
sad	waste	idiot	feeble
gloom	bored	fault	false
discomfort	dreary	impair	fatigued
obesity	inferior	moody	handicap
coward	manure	dump	mucus

Low Arousal Positive Words:

home	bless	bath	secure
comfort	sleep	cosy	untroubled
safe	bunny	warmth	sunset
dignified	bird	bed	peace
butterfly	protected	wise	pillow
politeness	gentle	carefree	snuggle

High Arousal Negative Words:

hostage	enraged	scared	snake
violent	ambulance	angry	hurricane
crash	tornado	assault	bees
anger	destroy	demon	tense
rage	horror	panic	nervous
mad	intruder	thief	outrag

High Arousal Positive Words:

infatuate	surprise	engaged	graduate
ski-jump	excitement	orgasm	kiss
lust	flirt	sexy	casino
exercise	adventure	passion	astonish
fun	intimate	thrill	treasure
erotic	ecstasy	sex	festive