Hemispheric specialization for emotional word processing is a function of SSRI responsiveness

Amy Walsh, John McDowall, Gina M. Grimshaw *

Victoria University of Wellington, New Zealand

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ABSTRACT

Vulnerability to depression and non-response to Selective Serotonin Reuptake Inhibitors (SSRIs) are associated with specific neurophysiological characteristics including greater right hemisphere (RH) relative to left hemisphere (LH) activity. The present study investigated the relationship between hemispheric specialization and processing of emotional words using a divided visual field paradigm administered to never-depressed and previously-depressed individuals, who were subdivided into SSRI responders and non-responders. SSRI responders and never-depressed participants were similar in their left hemispheric lateralization for evaluating emotional words. In contrast, SSRI non-responders showed a relative shift towards RH processing of negative words, and a strong bias toward negative evaluation of words presented to the RH. The results are discussed within the context of a biological–cognitive model of vulnerability to depression.

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1. Introduction

Depression is characterized by a distinct neuropsychological profile, involving hypoactivity in left frontal and right posterior areas, and hyperactivity in right frontal areas. Converging evidence for this pattern of activity comes from several lines of evidence including emotional responses associated with brain lesions (Jorge, Robinson, Starkstein, & Arndt, 1993; Robinson, Bolduc, & Price, 1987) electrophysiological (EEG) measures (Coan & Allen, 2004; Henriques & Davidson, 1991; Thibodeau, Jorgensen, & Kim, 2006), and studies of perceptual asymmetries (Bruder, Stewart, McGrath, Deliannides, & Quitkin, 2004; Bruder, Wexler, Stewart, Price, & Quitkin, 1999; Bruder et al., 2002; Heller, Etienne, & Miller, 1995; Pine et al., 2000). The frontal asymmetry is thought to reflect asymmetries in motivational control, with left frontal activity associated with behavioral approach and right frontal activity associated with behavioral withdrawal (Davidson, 1993; Harmon-Jones, 2003). Decreased activity in right hemisphere (RH) tempo-parietal areas is thought to reflect the hypoarousal that is characteristic of depression (Heller, 1993; Heller & Nitschke, 1998).

According to Davidson’s (1998) diathesis-stress hypothesis, this pattern of frontal asymmetry reflects a cognitive and biological predisposition to a negative affective style, which increases emotional reactivity to stressful life events and can lead to depression. Although a large body of research has confirmed relations between patterns of neurophysiological activity and personality (Coan & Allen, 2004; Sutton & Davidson, 1997) or affective variables (Davidson, Ekman, Saron, Senulis, & Friesen, 1990; Jackson et al., 2003; Pine et al., 2000; Tomarken, Davidson, & Henriques, 1990; Tomarken, Davidson, Wheeler, & Doss, 1992), much less is known about the cognitive mechanisms that might mediate the relationship between neurophysiological function and vulnerability to depression (Caccioppo, 2004; Davidson, 2004). The present study examined hemispheric differences in the evaluation of emotional words in never-depressed and previously-depressed individuals, in order to test the hypothesis that vulnerability to depression is associated with a negative processing bias in language that is specifically linked to the RH.

The pattern of asymmetry that is typically observed in depression may reflect vulnerability and not depression per se, as it is also observed in individuals at risk of depression, including previously-depressed individuals (Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1990), adolescents (Tomarken, Dichter, Garber, & Simien, 2004) and infants of depressed mothers (Field & Diego, 2008), as well as individuals with a family history of depression (Bruder et al., 2004, 2005; Bruder, Tenke, Warner, & Weissman, 2007), and children at risk for depression (Hayden et al., 2008; Shankman et al., 2005). Prospective studies show that rightward frontal asymmetry predicts the onset of depression in adolescents (Pössel, Lo, Fritz, & Seemann, 2008), and that rightward frontal asymmetry in infancy predicts stable behavioral inhibition in childhood (Fox, Henderson, Rubini, Calkins, & Schmidt, 2001). Thus, this atypical pattern of hemispheric asymmetry appears to be a stable trait which is present in both those at risk for and in remission from depression.
If previously-depressed individuals share neuropsychological organization with those with current depression, they become an attractive population in which to study vulnerability, as findings are not confounded by current affective and somatic symptoms of depression (such as fatigue or psychomotor slowing), lack of motivation, or current medication regimes. Previously-depressed individuals are themselves at risk of future depression, having a 70% chance of experiencing another depressive episode (Kessler & Walters, 1998). The study of previously-depressed individuals confers another advantage as it is possible to consider individual differences in treatment response as a moderating variable. Recently, neuropsychological organization has been found to vary as a function of responsiveness to Selective Serotonin Reuptake Inhibitor (SSRI) medications. Differences in EEG asymmetries between SSRI responders and non-responders suggest a pattern of overall greater relative left hemisphere (LH) activity in responders, and overall greater relative RH activity in non-responders (Bruder et al., 2001, 2008). In dichotic listening studies a similar pattern is observed, with SSRI responders showing an enhanced right ear advantage (REA) for words and an attenuated left ear advantage (LEA) for complex tones than non-responders, indicating increased LH and reduced RH involvement in the perception of auditory stimuli (Bruder et al., 1996, 2001, 2004). SSRI responsiveness may well account for some of the heterogeneity in the hemispheric asymmetry literature (e.g., Reid, Duke, & Allen, 1998).

Although cognitive factors are proposed to play an important role in the development and maintenance of depression (e.g., Beck, 2008; Bower, 1981; Clark & Beck, in press; Gottlib & Joormann, 2010; Mathews & MacLeod, 2005; Sheppard & Teasdale, 2000), and depression-related changes in hemispheric activation presumably reflect the operation of lateralized cognitive functions (Bruder et al., 2001; Green, Morris, Epstein, West, & Engler, 1992; Heller, 1993; Heller & Nitschke, 1997; Herrington et al., 2010; Levin, Heller, Mohanty, Herrington, & Miller, 2007), researchers have only recently turned their attention to elucidating the cognitive mechanisms through which the relationship between lateralized brain function and depression might be realized. One possibility is that alterations in asymmetry reflect the activity in systems that subserv emotional evaluation, interpretation and regulation (see Browning, Holmes, & Harmer, 2010; de Raedt & Koster, 2010; Heller, 1993; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Mathews & MacLeod, 2005). Within the language domain, depressed individuals have enhanced memory for negative information (Gottlib & Joormann, 2010; Hamilton & Gottlib, 2008; Mathews & MacLeod, 2005), facilitated automatic priming of negative information (Scott, Mogg, & Bradley, 2001), a negative bias in the interpretation of ambiguous information (Lawson, MacLeod, & Hammond, 2002), failure to inhibit and disengage from negative words (Browning et al., 2010; Herrington et al., 2010) and a top-down attentional bias for negative words (de Raedt & Koster, 2010; Mathews, Ridgeway, & Williamson, 1996). To some extent these processing biases are also seen in vulnerability to depression, although as predicted by the diathesis-stress hypothesis they are most likely to emerge under conditions of stress or negative mood (Dearing & Gottlib, 2009; McCabe, Gottlib, & Martin, 2000; Miranda, Gross, Persons, & Hahn, 1998).

Given that vulnerability to depression is associated with atypical patterns of hemispheric asymmetry and with a processing bias toward negative words, it is possible that vulnerability to depression is associated with hemispheric differences in emotional word processing (e.g., Klumpp & Deldin, 2010). However, specific predictions regarding how such relations should manifest themselves are complicated by a lack of consensus on how emotional word processing is lateralized in healthy individuals. Word processing across a number of phonological, lexical, and semantic tasks is strongly lateralized to the LH (Bryden, 1982), however, the RH seems to play a greater role in the processing of emotional than of neutral words (for a review, see Lindell, 2006). The two predominant views are characterized as the RH hypothesis (e.g., Borod, Zgaljardic, Tabert, & Koff, 2001; Borod et al., 1998; Heller, Nitschke, & Miller, 1998; Landis, 2006) which maintains a role for the RH in the processing of all emotional information, and the valence hypothesis (e.g., Adolphs, Jansari, & Tranel, 2001; Ahern & Schwartz, 1979) which lateralizes positive processing to the LH and negative processing to the RH. These competing views are often reconciled by distinguishing between the experience of emotion (which seems to rely heavily on frontal systems that are differentially lateralized for emotional valence or motivation; Davidson et al., 1990; Tomarken et al., 1990) and the perception of emotion, which is thought to rely predominantly on posterior RH networks (Heller et al., 1998). However, neuroimaging studies suggest that even emotional perception tasks in other modalities include both posterior components that are lateralized to the RH, and bilateral anterior components that may be lateralized according to valence (e.g., Killgore and Yurgelun-Todd (2007) for faces; Wildgrubber, Ethofer, Kreifelts, and Grandjean (2008) for prosody). Unfortunately, findings are still equivocal regarding functional imaging of emotional word processing as findings vary greatly as a function of task (e.g., passive vs. active processing; perception, evaluation, or generation), stimuli (self-descriptive adjectives vs. valenced words), and participant characteristics (clinical or healthy) as well as the experimental design. What is clear from the neuroimaging literature is that emotional word processing involves a widespread network of frontal, temporal and subcortical regions (Beauregard et al., 1997; Cato et al., 2004; Herbert et al., 2009; Wager, Phan, Liberzon, & Taylor, 2003).

Regardless of the ultimate resolution on this debate, studies of perceptual asymmetries are in favor of valence-driven effects of depression on lateralization of emotional word evaluation. A series of studies by Atchley and colleagues (Atchley, Iardi, & Enloe, 2003; Atchley, Stringer, Mathias, Iardi, & Minnatre, 2007) suggest that hemispheric differences in emotional word processing are influenced by valence, and furthermore that such differences are modulated by both current and past depression. Atchley et al. (2003) presented a lateralized affective priming task to currently depressed, previously-depressed, and never-depressed participants. Words were affectively-valenced person-descriptive adjectives (e.g., smart, cruel, brave, etc.). Participants saw a centrally-presented prime followed by a lateralized target, and made a valence judgment to both items. Within the right visual field (RVF)/LH, there were no effects of valence or of group, however, within the left visual field (LVF)/RH, never-depressed participants showed a processing advantage (in both accuracy and reaction time, RT) for positive words, whereas currently depressed and previously-depressed showed a processing advantage for negative words. In a follow up study (Atchley et al., 2007), participants made a valence judgment to unilaterally-presented emotional words that varied in valence and arousal. The primary finding was replicated, although only accuracy was analyzed because error rates were very high. Specifically, no effects of word type or group were observed in the RVF/LH. However, in the LVF/RH, never-depressed participants were more accurate for positive than for negative words, but currently- and previously-depressed participants were more accurate for negative than for positive words. In both studies, previously-depressed individuals were indistinguishable from currently depressed individuals.

These findings suggest both that the RH is more sensitive to valence than the LH, and that previous and current depression are both related to a shift in negative processing toward the RH. Atchley and colleagues interpret their findings for previously-depressed participants as reflecting changes in semantic organization for emotional words as a result of depression, a version of the scar
hypothesis (Lewinsohn, Steinmetz, Larson, & Franklin, 1981). However, given prospective and family studies that suggest that atypical hemispheric asymmetry reflects a risk for future depression, their results could implicate altered RH processing of emotional words in vulnerability for depression.

The present study partially replicates and extends that of Atchley et al. (2007). Never-depressed and previously-depressed individuals made valence judgments to unilaterally-presented words that varied in valence and arousal. Previously-depressed participants were further classified as SSRI responders or non-responders. Because sex differences have been observed in hemispheric asymmetry (McGlove, 1980; Voyer, 1996), SSRI responsiveness (Bigos, Pollock, Stankevich, & Bies, 2009) and in the incidence and etiology of depression (Nolen-Hoeksema, 2001; Piccinelli & Wilkinson, 2000), the current study included only women in an effort to keep groups as homogenous as possible in all other respects. Given that SSRI responders tend to show relatively greater LH activity (Bruder et al., 2001, 2008), and LH involvement in dichotic listening tasks (Bruder et al., 1996, 2001, 2004) compared to SSRI non-responders, it is possible that only the SSRI non-responders will show the hypothesized shift toward RH processing of negative words, and the negative processing advantage for words presented to the RH.

The present study also extends the research of Atchley and colleagues by applying a signal detection approach to the analyses. A valence judgment is essentially a signal detection task. As such, measures of accuracy will be influenced by both sensitivity (the ability to discriminate between positive and negative words) and criterion (a bias to respond “positive” or “negative” under conditions of uncertainty). The pattern of results Atchley et al. (2003, 2007) observed in the LVF could result entirely from a response bias if, under uncertainty, never-depressed participants respond “positive” and previously-depressed participants respond “negative”. Furthermore, such uncertainty is more likely to occur with LVF/RH presentation than with RVF/LH presentation because of the LH’s superior word recognition abilities. The signal detection analysis allowed us to determine whether group differences in emotional word processing reflected changes in sensitivity or criterion. Given the high co-morbidity of depression and anxiety (Keller et al., 2000), and the finding that the effects of anxiety on brain activity and cognition are sometimes consistent and sometimes contrary to those of depression (Beuke, Fischer, & McDowall, 2003; Engels et al., 2007; Heller & Nitschke, 1998; Heller, Nitschke, Etiene, & Miller, 1997; Nitschke, Heller, Palmieri, & Miller, 1999), the current study matched groups in terms of both depression and anxiety symptoms.

2. Method

2.1. Participants

The 70 never-depressed participants were female psychology students from an introductory psychology course. None had been treated for depression in the past or currently. The 37 previously-depressed female participants were recruited from the same class, and through advertisements in the university magazine and posters around campus. Criteria for inclusion were a previous diagnosis and pharmacological treatment for depression, no current treatment (through therapy or medication) and a self-report of recovery. All participants completed the Zung Self-Rating Depression Scale (Zung, 1965) to ensure that none were currently depressed. Previously-depressed participants completed a depression history questionnaire asking what medications they had received and whether they thought that medication had helped their depression. Healthcare in New Zealand is universal and standardized, and treatment must fail with two SSRIs before alternative medications can be trialed. Therefore, even if participants could not recall their specific medication, all were guaranteed to have received an SSRI. On the basis of their responses, the previously-depressed group were further divided into a ‘SSRI responders’ group (n = 26) and a ‘SSRI non-responders’ group (n = 11). All participants were self-described right handers, spoke fluent English, and were without vision or hearing impairments. The mean age for the never-depressed group was 19.09 years (SD = 3.53); for the SSRI-responder group was 23.46 years (SD = 5.79); and for the SSRI non-responders was 21.00 years (SD = 3.85).

2.2. Materials

The target words were a mixture of positively and negatively valenced words, of high and low arousal. All participants saw the same 96 words (24 of each valence/arousal combination), selected from the Affective Norms for Emotional Words database (ANEW: Bradley & Lang, 1999). The valence and arousal ratings were taken from the published norms for the ANEW. Valence was rated on a scale from 1 (negative) to 9 (positive), and arousal on a scale from 1 (low) to 9 (high). The positive, low arousal list had an average valence rating of 7.42 and an average arousal rating of 3.71. The positive, high arousal list had an average valence rating of 7.64 and an average arousal rating of 7.15. The negative, low arousal list had an average valence rating of 2.91 and an average arousal rating of 3.81. The negative, high arousal list had an average valence rating of 2.70 and an average arousal rating of 7.02. Independent samples t-tests ensured that the positive and negative lists significantly differed in valence ratings: and that the low and high arousal lists significantly differed in arousal ratings. None of the lists significantly differed from each other in word frequency or word length.

Current depression and anxiety were assessed with the Zung Self-Rating Depression Scale (Zung, 1965) and the Zung Self-Rating Anxiety Scale (Zung, 1971) respectively. Each scale consists of 20 statements (both positively and negatively worded) that participants endorse on a four-point rating scale (a little of the time, some of the time, a good part of the time and most of the time). The Zung scales have good reliability (split-half r = .73, Zung, 1972; Chronbach alpha = .79; Knight, Waal-Manning, & Spears, 1983), and they correlate well with the Hamilton Depression and Anxiety Scales (r = .76 for depression, Biggs, Wylie, & Ziegler, 1978; r = .75 for anxiety, Zung, 1971).

2.3. Procedure

Written informed consent was obtained for all participants. 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 RT and accuracy. Tasks were presented on a Dell PC with a 17” CRT monitor at a refresh rate of 75 Hz. SPSS 16.0 was used to analyze the data.

Participants placed their heads in a chin rest which was positioned 60 cm from the computer screen. A centrally presented fixation cross was presented for 1000 ms, followed by a target word which appeared in either the LVF or RVF for 185 ms. Targets were immediately followed by a pattern mask (##########) in the same location. The degree of visual angle to the inner edge of the lateralized stimuli was 2°. Participants were required to indicate whether the valence of the word was positive or negative by pressing “one” or “two” on the number pad of the keyboard, with the index or middle finger of their right hand as quickly and accurately as possible. Response keys were counterbalanced across participants. Participants were required to respond within 2500 ms after target onset, or an incorrect trial was recorded, and they automatically moved onto 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 lateralized trials. Participants saw each word only once (in either the left or right VF), and the lists were counterbalanced so that each word was presented to the left and to the right VFs an equal number of times across participants. There were 12 trials in each condition. After completion of the divided visual field task, participants 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.

3. Results

Median RTs (for correct responses) and accuracies were calculated for each condition. Performance of the three groups as a function of arousal, valence and VF was analyzed in a series of Analyses of Variance (ANOVAs) using RT, accuracy, sensitivity, and criterion as dependent variables. Significant interactions involving VF were followed up using two sets of planned comparisons; first, by examining VF effects for different word types, in order to address questions on differential lateralization of emotional word processing in the two groups, and then by examining performance differences within the left and right VFs. This second approach allowed direct comparisons with the findings of Atchley and colleagues (2003, 2007) who found current and previous depression to be related to emotional word processing only within the LVF.

Accuracy was also converted into signal detection measures of sensitivity (d’) and criterion (c; Macmillan & Creelman, 1991). Because the task involved a valence judgment, measures of accuracy could be confounded by response bias. For example, if a participant responded “negative” on every trial, they would have very high accuracy for negative items and very low accuracy for positive items, but in fact be unable to discriminate between them. Thus, while accuracy analyses are reported below for the purposes of completeness and comparability to other literature, the signal detection analyses provide an important supplement to this analysis. For the purposes of calculating d’ and c, negative words were arbitrarily designated as signal and positive words as noise. Positive values of d’ reflect increasing ability to discriminate between positive and negative words. The criterion measure c varies around zero, with positive values reflecting a bias toward positive responses, and negative values reflecting a bias toward negative responses.

On the basis of signal detection measures, seven participants were removed from all analyses, as their sensitivity scores were considered too low to reflect meaningful task performance. Criterion for removal was having all four d’ scores (high and low arousal words, in left and right VFs) less than one. Consistent 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, and two were from the SSRI-responder group. The following analyses are therefore based on 65 never-depressed participants and 35 previously-depressed participants, 11 of whom were SSRI non-responders and 24 of whom were SSRI responders. Table 1 displays Zung Depression and Anxiety scores for each group. The three groups did not differ in either depression, F(2, 97) = .558, p = .574, or in anxiety, F(2, 97) = .605, p = .548.

Accuracy was analyzed in a mixed ANOVA with valence, arousal, and VF as within-subject variables and responder group as a between subject variable (see Table 2). There were many significant lower order interactions; however all were subsumed under a significant three way Valence × VF × Responder group interaction, F(2, 97) = 3.16, p = .047, ηp2 = .06. The nature of this interaction is apparent in Fig. 1. In follow-up analyses, positive words showed a RVF advantage, F(1, 97) = 14.79, p < .001, ηp2 = .13, which did not interact with responder group, F(2, 97) = 1.44, p = .243, ηp2 = .03. In contrast, negative words produced a VF × Responder group interaction, F(2, 97) = 5.95, p = .004, ηp2 = .11. SSRI responders showed a significant RVF advantage t(23) = −3.62, p = .001, d = 0.77; never-depressed participants showed a non-significant RVF advantage, t(64) = −1.64, p = .106, d = 0.19; and SSRI non-responders showed a non-significant LVF advantage, t(10) = 0.82, p = .432, d = 0.25.

To examine valence differences within each VF, separate ANOVAs were conducted for words shown to the LVF and RVF. Within the RVF, there was no significant effect of valence, F(1, 97) = 2.07, p = .154, ηp2 = .02. and no Valence × Responder group interaction, F(2, 97) = .42, p = .657, ηp2 = .01. However, within the LVF, a significant effect of valence was observed, F(1, 97) = 11.49, p = .001, ηp2 = .11. which interacted with responder group, F(2, 97) = 5.71, p = .005, ηp2 = .11. This suggests that, consistent with Atchley et al. (2003, 2007), the groups do not differ in their processing of negative vs. positive words in their RVF/LH, but they do differ within the LVF/RH. However, the nature of the interaction is different than observed by Atchley and colleagues. For words presented to the LVF, non-responders had a large accuracy advantage for negative words, t(10) = −2.35, p = .040, d = 0.93; never-depressed had a small advantage for negative words, t(64) = −3.21, p = .002, d = 0.40; and responders had no valence effect, t(23) = .69, p = .498, d = 0.35.

An accuracy advantage for negative words in the LVF could reflect a negative processing advantage, but it could also reflect a negative response bias, which would inflate accuracy for negative words and deflate accuracy for positive words. Such a bias could emerge as a “guessing” strategy when sensitivity is very low (e.g., in response to stimuli presented to the LVF), but it could also reflect hemispheric differences in emotional decision-making processes. In order to tease apart these possible explanations, the signal detection measures (d’ and c; see Table 3) were analyzed in a mixed ANOVA with arousal and VF as within-subject variables and responder group as a between subject variable. Note that the signal detection measures combine positive and negative responses into a single metric, and so valence is no longer a variable. Analyses of criterion revealed a VF × Responder Group interaction, F(2, 97) = 3.12, p = .048, ηp2 = .06. As Fig. 2, demonstrates, responders had no significant bias in either VF. Never-depressed participants had a small but significant negative bias in both the LVF, t(64) = −3.42, p = .001, and the RVF, t(64) = −2.79, p = .007. However, non-responders had no significant bias in the RVF, t(10) = −.28, ns., but a large and significant negative bias in the LVF, t(10) = −2.49, p = .032.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Never depressed</th>
<th>SSRI responders</th>
<th>SSRI non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>35.50</td>
<td>34.92</td>
<td>38.18</td>
</tr>
<tr>
<td>SD</td>
<td>8.43</td>
<td>9.49</td>
<td>8.78</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>33.11</td>
<td>33.38</td>
<td>35.82</td>
</tr>
<tr>
<td>SD</td>
<td>7.79</td>
<td>7.37</td>
<td>6.51</td>
</tr>
</tbody>
</table>

Note: Scores are out of a possible 80.
Thus, the criterion results argue in favor of a negative response bias in the LVF for non-responders. However, the analysis of d’ scores argues against this response bias reflecting a simple guessing strategy when sensitivity falls (when in doubt, say negative). Specifically, a VF × Arousal × Responder group ANOVA on d’ values revealed an overall RVF advantage, F(1, 97) = 19.26, p < .001, ηp² = .17 that further interacted with responder group, F(2, 97) = 3.55, p = .033, ηp² = .07. The nature of this interaction is apparent in Fig. 3. Although the groups did not differ significantly from each other in sensitivity in either VF, F(2, 97) = 2.06, p = .133, ηp² = .04, and F(2, 97) = −.17, p = .844, ηp² = .00 for left and right VFs respectively, the figure shows that the groups have similar sensitivity in the RVF, but the non-responders and never-depressed tend to have better sensitivity than responders in the LVF. Thus the bias of both groups toward negative responding (compared to the responders) is not a strategic response to their low sensitivity, but likely reflects a negative shift in criterion specifically associated with L VF presentation. Note that this interaction can also be described in terms of differing VF effects across groups. Specifically, the responders had a greater RVF advantage than either of the other groups.

Finally, RTs were analyzed to determine if results were largely consistent with those revealed by the accuracy analysis, or suggested a speed–accuracy trade-off (see Table 4). Note that the SSRI non-responder group has an n of 10 for the RT analysis, as one participant did not have any correct scores for positive, high arousal words presented to the LVF, therefore did not have any correct RTs to analyze for that condition. Again several lower order interactions were observed, and the critical Valence × VF × Responder interaction was observed.

Table 2
Proportion correct (hits/12) for each valence, arousal and visual field condition.

<table>
<thead>
<tr>
<th></th>
<th>Never depressed</th>
<th>SSRI responders</th>
<th>SSRI non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVF</td>
<td>RVF</td>
<td>LVF</td>
</tr>
<tr>
<td>Valence arousal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative high</td>
<td>0.84(0.14)</td>
<td>0.86(0.12)</td>
<td>0.75(0.16)</td>
</tr>
<tr>
<td>Negative low</td>
<td>0.84(0.15)</td>
<td>0.87(0.11)</td>
<td>0.74(0.21)</td>
</tr>
<tr>
<td>Positive high</td>
<td>0.76(0.14)</td>
<td>0.79(0.13)</td>
<td>0.81(0.15)</td>
</tr>
<tr>
<td>Positive low</td>
<td>0.80(0.16)</td>
<td>0.85(0.12)</td>
<td>0.74(0.16)</td>
</tr>
</tbody>
</table>

Note: Standard deviations are in parentheses.

Table 3
The sensitivity (d’) and bias (c) scores for each visual field and arousal condition.

<table>
<thead>
<tr>
<th></th>
<th>Never depressed</th>
<th>SSRI responders</th>
<th>SSRI non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVF</td>
<td>RVF</td>
<td>LVF</td>
</tr>
<tr>
<td>Arousal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d’ low</td>
<td>2.03(0.93)</td>
<td>2.30(0.67)</td>
<td>1.46(0.92)</td>
</tr>
<tr>
<td>d’ high</td>
<td>1.96(0.73)</td>
<td>2.03(0.62)</td>
<td>1.73(0.86)</td>
</tr>
<tr>
<td>c low</td>
<td>−0.09(0.35)</td>
<td>−0.04(0.30)</td>
<td>−0.03(0.38)</td>
</tr>
<tr>
<td>c high</td>
<td>−0.15(0.34)</td>
<td>−0.14(0.32)</td>
<td>0.09(0.34)</td>
</tr>
</tbody>
</table>

Note: Standard deviations are in parentheses.
Group interaction approached significance, visual field, RVF = right visual field. The vertical lines are standard error bars. for SSRI responders, SSRI non-responders and never-depressed controls. LVF = left accuracy for negative words. SSRI non-responders showed an advantage in both RT and negative words, but no difference in accuracy for positive vs. negative words. SSRI responders showed a slight RT advantage for positive words, and a shift toward a LVH/RH advantage for negative words seen in these two groups. These LVF negative advantages are not simply due to guessing ”negative” as a result of poor sensitivity, as never-depressed and non-responder participants were in fact more sensitive to the valence of words presented to the LVF than responders (who showed no bias). The fact that a bias was much greater in non-responders than in never-depressed participants was much smaller than that observed in non-responders, and was not replicated in the RT data. Our findings are therefore consistent with a relative enhancement of RH processing of negative words in non-responders relative to never-depressed controls.

Our findings further suggest that the hemispheric differences related to valence observed in SSRI non-responders may be linked to a biological vulnerability to depression, rather than being a ‘scar’ left by the depressive episode. Support for this conclusion comes from the fact that responders (who have had similar depressive experiences to the non-responders) show the strongest lateralization to the LH of all three groups, and showed a significant advantage for processing positive words with RVF presentation. This strong LH lateralization in responders is consistent with similar effects observed with dichotic listening (Bruder et al., 1996, 2004) and in electrophysiological studies that show greater relative left hemisphere activity in responders than in non-responders (Bruder et al., 2001, 2008). Thus the atypical pattern of lateralization seen in non-responders more likely reflects their biological vulnerability, and not their experience with depression. Of course, prospective longitudinal studies are needed to determine whether SSRI responders and non-responders differ in RH emotional processing prior to the onset of depression and prior to treatment; or whether differences emerge as a result of the depressive episode or in response to treatment.

Signal detection analyses showed that never-depressed and non-responder participants both demonstrated negatively-biased responding for stimuli presented to the LVF/RH, although again the bias was much greater in non-responders than in never-depressed controls. These biases partially explain the higher accuracy for negative words seen in these two groups. These LVF negative advantages are not simply due to guessing ”negative” as a result of poor sensitivity, as never-depressed and non-responder participants were in fact more sensitive to the valence of words presented to the LVF than responders (who showed no bias). The fact that a negative processing advantage in the RH of non-responders is linked primarily to bias does not make the finding uninteresting. Bias measures reflect decision-making processes that play an important role in emotional evaluation. Signal detection studies of emotional processing in anxiety suggest that it too is related to a negative interpretive bias as opposed to a heightened sensitivity to fear-relevant stimuli (Magnuso-Mire, Constans, & Geer, 2005; Winton, Clark, & Edelmann, 1995).

The differential effects for SSRI responders and non-responders point to the need for a comprehensive model of vulnerability that incorporates neurochemical, neurological, and cognitive risk factors.
factors. In a recent tour-de-force, de Raedt and Koster (2010) proposed an ambitious framework for depression research that describes a biological and a cognitive pathway that interact to produce vulnerability to depression. This vulnerability is a product of the breakdown of frontal regulation of the negative emotional response to stress. The biological pathway does this via a series of mechanisms which increase the subcortical emotional response; while the cognitive pathway does this via a series of mechanisms which decrease attentional control over negative elaborative processes. This biological–cognitive vulnerability may be specifically linked to SSRI non-response, which has been associated with several components of de Raedt and Koster’s (2010) model. These include a risk variant of the serotonin transporter gene (Murphy et al., 2008; Pollock et al., 2000; Serretti, Kato, De Ronchi, & Kinoshita, 2007; Smits, Smits, Schouten, Peeters, & Prins, 2007; Smits et al., 2004); hyperactivity of the hypothalamic pituitary adrenal axis (Pariante & Lightman, 2008; Young et al., 2004); and executive dysfunction (Dunkin et al., 2000). Although de Raedt and Koster (2010) do not specifically address hemispheric asymmetry in their model, these predictors of SSRI non-response have also been associated with greater relative RH frontal asymmetry (Bisnark et al., 2010; Tops et al., 2005). Thus, it is possible that serotoninergic dysregulation affects asymmetries in frontal activity. Experimental manipulation of serotonin levels through tryptophan depletion will in future help to determine serotonin’s effects on frontal asymmetries (e.g. see Allen, McKnight, Moreno, Demaree, & Delgado, 2009).

The cognitive pathway of this model begins with negatively-biased schemas or semantic representations. In fact, several cognitive theories of depression point to a role for negatively-biased semantic representations in the generation and maintenance of depression (Beck, 2008; Bower, 1981). For example, Sheppard and Teasdale (2000) suggest that people with depression have highly elaborated negative schemas, and a decreased ability to monitor the thoughts and emotions that they generate. Further, they suggest that during remission, monitoring processes are normalized, but the negative schemas remain (Sheppard & Teasdale, 2004). Under conditions of stress, monitoring processes fail, and negative cognitive schemas are reactivated, leading to relapse. Negative processing advantages in vulnerable individuals are often observed only under conditions of negative mood induction (e.g., McCabe et al., 2000), a finding that is often cited as consistent with the hypothesis that negative processing biases are a diathesis that only emerges under emotional stress (e.g., Gottlib & Joormann, 2010).

However, in this study, a negative processing bias related to vulnerability was observed without mood induction. The findings from Atchley and colleagues (2003, 2007) and the current study show that negative processing biases can be elicited in biologically vulnerable individuals (SSRI non-responders) without negative mood induction, but only when stimuli are presented to the RH. This suggests that negative schemas (which result in negative processing biases) may be specifically linked to the RH. We concur with Atchley et al. (2007) that latent negative processing biases might be revealed with divided visual field presentations that tap RH affective–semantic processing. One of the effects of negative mood induction is to specifically activate the RH (Asbjornsen, Hugdahl, & Bryden, 1992; Gadea, Gomez, Gonzalez-Bono, Expert, & Salvador, 2005; Van Strien & Boon, 1997). Thus RH arousal in response to emotional stressors may provide the mechanism through which latent negative processing biases become manifest.

Two important limitations of this study should be noted. First, only 11 SSRI non-responders were able to be recruited for the study, reducing power in some of the follow-up comparisons, although the theoretically-important three-way interaction of valence, VF, and responder group was significant (see Figs. 1 and 4). Replication with larger samples of SSRI responders and non-responders should determine the reliability of the effects found in this study. Secondly medical records were not available for participants, and thus we relied on self-report of depression history and SSRI responsiveness. This means we have no indication of whether the two groups were matched on severity of depressive symptoms, dosage, or length of treatment during their depression. Thus, any of these treatment variables are potential mediators of the effects seen here. However, our findings are consistent with current theories of vulnerability to depression, and point to the need for prospective studies with objective measures of treatment variables that will be better able to control for between-group differences in severity of depression symptoms and treatment history.

Depression is a complex and heterogeneous disorder, and integrative attempts to understand its etiology across genetic, neurochemical, neuropsychological, cognitive, and affective domains are yet in early days. However, it is through the integration of such diverse perspectives and research methodologies that we are most likely to make meaningful progress. The findings of the present study point to the importance of considering individual differences in pharmacological responsiveness, which presumably reflect genetic and neurochemical effects, in clarifying the relationship between hemispheric specialization and depression.

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References


