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Review

# Review of brain functioning in depression for semantic processing and verbal fluency

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ABSTRACT

Neurobiological models of depression point to brain regions that are proposed to be involved with both emotion regulation and language processing. This qualitative review focused on neurophysiological evidence for semantic processing and verbal fluency deficits associated with left frontal lobe and dorsolateral prefrontal cortex functioning in depression, respectively. Findings suggest that there are no behavioral or neurophysiological evidence of performance differences between depressed and healthy individuals for semantic processing of neutral information, arguing against generalized left frontal lobe deficits. However, the preponderance of evidence points to enhanced processing of negative information in both left and right frontal lobes and behavior. Studies of verbal fluency were limited to non-emotional information. The majority of studies evaluated phonemic verbal fluency in depression (e.g., producing words that begin with a particular letter) and results generally showed bilateral hypoactivation of the frontal lobe with no concomitant deficits in behavioral performance. Overall, semantic processing and verbal fluency studies did not provide substantive evidence of specific left frontal lobe deficits. Evidence that emotional information may differentially impact brain functioning relative to neutral information in depression suggests that examination of verbal fluency for emotional information may contribute to the elucidation of executive functioning processes associated with the dorsolateral prefrontal cortex in depression.



## 1. Introduction

Major depression is common, disabling, and on the rise in the United States. The prevalence of depression in a given year increased from 3.3% in 1991–1992 to 7.1% in 2001–2002 with concurrent substance use disorder increasing the prevalence of major depression to 15.1% in 2001–2002 (Compton et al., 2006). In addition to potential devastating disability, depression can be fatal due to increased risk for suicide. Most people with depression suffer multiple episodes, with the probability of further episodes increasing with each occurrence of relapse (Solomon et al., 2000). Given the prevalence and gravity of major depressive disorder (MDD), it is essential to elucidate mechanisms of brain functioning that contribute to this emotional disorder in order to provide a comprehensive model that informs treatment and predicts relapse.

Depression is characterized by prolonged, potentially involuntary, emotion processing that may be due to deficits in frontal lobe functioning (Abercrombie et al., 1998; Drevets et al., 1992; Siegle et al., 2002, 2007). Neurobiological models of MDD point to brain regions that are thought to be involved with both emotion regulation and language processing. For example, it has been suggested that activity in the left frontal lobe is generally associated with approach-related goals whereas activity in the right is associated with withdrawal goals (e.g., Davidson, 2000; Davidson and Irwin, 1999; Davidson et al., 2002). Evidence of hypoactivation in the left prefrontal lobe in individuals diagnosed with depression (Gotlib et al., 1998; Henriques and Davidson, 1991, 2000; Holthoff et al., 2004) suggests a deficit in this region, which has been interpreted as being related to reduction in the ability of depressed individuals to experience pleasure or have appetitive goals.

The dorsolateral prefrontal cortex (DLPFC) is thought to be associated with goal-directed behavior. This is because the DLPFC is involved in higher order cognitive abilities characterized as executive functions (e.g., working memory and attentional capacity) that help maintain affective goals and predict future consequences of behavior. Brain imaging studies show evidence of DLPFC dysfunction in depression (e.g., Baxter et al., 1989; Bench et al., 1993; Siegle et al., 2007) and disruption of executive functions may fail to adequately inhibit subcortical brain regions directly involved in emotion processing (e.g., amygdala; Davidson, 2000, 2003; Drevets and Raichle, 1998; Mayberg et al., 1999; Ochsner et al., 2002).

Performance on language processing tasks may provide a window into the study of such neurobiological deficits, as certain language tasks have been shown to activate these brain regions. For example, semantic processing activates the left frontal lobe (Bedny et al., 2007; Binder et al., 2003; D'Arcy, et al., 2004; Seghier et al., 2004) involving

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such regions as the inferior frontal gyrus and prefrontal cortex (Bedny et al., 2007; Seghier et al., 2004), whereas, verbal fluency activates the DLPFC (Elfgren and Risberg, 1998; Gaillard et al., 2000; Ravnkilde et al., 2002).

The purpose of this paper is to review the neurophysiological evidence for semantic processing and verbal fluency in depression in order to help refine neurophysiological models of depression and perhaps shed light on the behavioral inconsistencies that may in turn contribute to the modification of such depression models. The studies reviewed were identified from PsycINFO and Medline databases using terms related to these language tasks (e.g., verbal, semantic) and brain functioning (e.g., EEG, fMRI). The reference sections of relevant articles were also reviewed for additional articles. Inclusion criteria were empirical studies in the English language that comprised individuals with depression and a control group. Excluded from this review are studies in which depression may be comorbid with cognitive impairment (e.g., seizure, alcoholism).

## 2. Semantic processing

Semantic tasks involve the processing of relationships between words or phrases (e.g., whether a word is meaningfully related to a sentence or category; Bedny et al., 2007; D'Arcy, et al., 2004; Seghier et al., 2004) or are based on retrieval of semantic information (discriminating real words from non-words; Binder et al., 2003; Hagoort et al., 1999; Xiao et al., 2005). Semantic processing is based on semantic networks of stored verbal information (Collins and Loftus, 1975). For example, during language production, activation of one network node increases activation of other nodes that represent semantically related concepts (e.g., it is easier to process the word "doctor" after seeing a semantically related prime word such as "nurse"). Individuals with depression have been shown to have difficulty inhibiting negative thoughts and this difficulty may be due, in part, to a disorganized semantic network (Atchley et al., 2003). This disorganization theoretically could generally be reflected in semantic processing deficits or only when emotional information is involved.

### 2.1. Behavioral studies of semantic processing of neutral information

There are two behavioral studies of semantic processing of neutral information that include depressed participants. These studies examined performance in lexical decision tasks in which participants decided whether the word presented to them is a real word. Neither study demonstrated semantic processing deficits in MDD (Besche-Richard et al., 2002; Georgieff et al., 1998). Therefore, these findings suggest that there is no dysregulation of left frontal lobe functioning in depression when neutral material is processed.

### 2.2. Neurobiological studies of semantic processing of neutral information

There are three neurobiological reports of neutral semantic processing in major depressive disorder and all relied on event-related brain potentials (ERPs). In a series of three studies, Deldin et al. (2006) utilized the N400 component of the ERP to examine semantic processing deficits in MDD. N400 is sensitive to the meaningfulness of sentence endings (Kutas and Hillyard, 1980a,b). For example, when the last word of a sentence is semantically incongruent (e.g., "The pizza was too hot to cry" p. 75), the N400 is larger than when the final word is congruent (e.g., "The pizza was too hot to eat" p. 75). Deldin et al. (2006) evaluated semantic processing of congruent and incongruent sentence endings with N400 in three studies of patients diagnosed with MDD and a non-psychiatric control group and in one study that also included patients with dysthymia (a chronic but less severe type of depression). All participants exhibited larger N400 in response to incongruent, but not congruent, stimuli. N400 did not differ between groups. The lack of group differences suggested that individuals with MDD or dysthymia do not exhibit deficits in semantic processing as measured by the N400 to neutral stimuli.

In a similar study (Iakimova et al., 2009), patients with diagnosed with MDD and a control group viewed semantically congruent and incongruent sentences during ERP recording. ERPs analysis included N400 and late positive component (LPC), which represents continued processing in language comprehension (Coulson and Kutas, 2001; Kuperberg, 2007). Participants were asked to judge whether a sentence made sense or not via button press. Behavioral results showed that patients were less accurate and had longer response latencies relative to the control group regardless of sentence type. Moreover, in patients only, there were significant behavioral correlations with ERP. That is, there was a positive correlation between percentage of correct judgments for congruent sentences and positive N400 peak amplitude, a correlation between greater age and LPC (i.e., reduced amplitude and prolonged latency), and an association between reduced LPC amplitude and longer response latencies regardless of sentence type. Yet, ERP results alone showed that patients exhibited normal N400 amplitude and LPC, which is consistent with Deldin et al. (2006). Taken together, the investigators proposed behavioral and correlational results indicate brain processes involved in language may be impaired in depression and suggest that impairment may be greater in older patients.

In a second ERP study of semantic processing, Abdullaev et al. (2002) studied patients diagnosed with major depression before pharmacotherapy treatment and after responding to treatment. Investigators evaluated the time course of activation in particular brain regions (e.g., left temporo-parietal area, anterior cingulate, insula) during a simple reading task and semantic processing task. In the reading task, the participant read the words out loud after a response cue, which served as a control condition for the semantic generation task to isolate brain activity during semantic processing. For example, the reading task alone is associated with left occipital and right insula activations (Raichle, 1994; Raichle et al., 1994), and this set of activation is referred to as the "automatic, reading pathway" (p. 157). In the semantic processing task, participants saw the same words used in the reading task, but in random order. The goal was to say out loud a use for each word (e.g., pound for hammer) after a question mark appeared serving as a response cue. Different word lists were used for each participant in the pre-treatment and post-treatment sessions. Behavioral results showed that the accuracy did not differ in either task before or after the depressed patients were successfully treated.

ERPs were calculated separately for the reading and semantic processing tasks before and after treatment and differences between these tasks were examined with statistical probability mapping. ERP results suggested cortical dysfunction in depression pre-treatment that normalized following treatment. Specifically, before treatment higher, positive activity in the semantic task compared to the reading task was found in the middle frontal region at around 160 ms. At about 180 ms, this middle frontal activation was coupled by a right prefrontal difference. Additionally, left temporo-parietal activation, usually demonstrated in normal participants from about 540 ms appeared later in the depressed group at about 750 ms after stimulus onset.

After responding to treatment, results include the finding that the frontal difference was eliminated and activity in the left prefrontal and midline frontal regions was similar to normal participants. For the left posterior temporo-parietal region, ERP waveforms showed a trend toward normalization in terms of greater, negative amplitude and earlier onset of task-related difference (reading v. semantic task). Additionally, activity in the right anterior temporal region (greater semantic compared to reading task difference) that investigators presume represents insula activity, was eliminated. Rather, with remission, there was a later right anterior temporal negative difference (reading greater than semantic task difference starting at around

730 ms), which investigators propose is similar to what is exhibited in normal participants.

In conclusion, there is mixed behavioral evidence of non-emotional semantic processing deficits in depression with Iakimova et al. (2009) showing impaired processing in depression (reduced accuracy for semantic judgments) and Abdullaev et al. (2002) showing no behavioral evidence of impairment in depression. Regarding neurophysiological findings, the three studies included in the Deldin et al. (2006) investigation show no evidence of semantic processing deficits for non-emotional stimuli in depression. Iakimova et al. (2009) also show normal ERP effects in depression as well, however, their ERP-behavioral correlations indicate that depression-related behaviors (e.g., motor slowness) may reflect neural abnormalities involved in language processing. With regard to laterality effects, this leaves only one study showing any evidence of left frontal lobe hypoactivation in depression (Abdullaev et al., 2002) and this study evaluated the time course of regional brain activation during semantic processing with statistical probability mapping as opposed to evaluation of a particular ERP component (e.g., N400). Therefore, the preponderance of a very small literature suggests no left frontal lobe dysfunction in depressed subjects to semantically neutral information. However, the Abdullaev et al. (2002) and Iakimova et al. (2009) studies suggest there is some evidence that this processing may be slowed down for neutral words.

### 2.3. Behavioral studies of semantic processing of emotional information

Four behavioral studies of semantic processing for emotionally valenced words have shown some mixed evidence of semantic processing dysregulation. First, in a study by Weisbrod et al. (1999), depressed patients and controls saw sentence stems that were completed with either positive or negative words (e.g., "to fly is fun" v. "to fly is dangerous" p. 20). Participants were asked to indicate whether the final word in the sentence was a real word. Results revealed that depressed patients were faster at identifying negative words than non-words compared to controls. This bias for negative information was partially replicated in a study that evaluated hemispheric lateralization on semantic processing and found that depressed and previously depressed individuals were faster than controls at identifying negative target words and slower than controls in identifying positive words. However, these results only occurred when words were processed in the right hemisphere with no such effects evident in the left hemisphere, suggesting right hemispheric involvement in language processing of emotional words (Atchley et al., 2003).

In a lexical decision task that evaluated "automatic" semantic processing for emotional words (Scott et al., 2001), participants saw trials in which prime words were shown for 28 ms, followed by a mask (random letter string) for 28 ms, followed by a target word. The target word remained until the participant indicated whether the word was real. The prime-target stimulus onset asynchrony (SOA) was 56 ms, and results showed that students who scored high on the Beck Depression Inventory (BDI; Beck et al., 1979), compared to those who scored low on the BDI, exhibited greater priming for depression words (shorter response latencies) compared to neutral words. While results for positive words were not significant, the high BDI group also tended to exhibit more priming for depression words than positive words compared to the low BDI group. In a second experiment, a long prime-target SOA condition (i.e., 2000 ms) was compared to a relatively short SOA condition (i.e., 56 ms). Results for the short condition were similar to that of the first experiment with the high BDI group, compared to the low BDI group, exhibiting significantly more semantic priming for depression words relative to neutral words and positive words. These mood-congruent effects were not found in the long-SOA condition; investigators proposed results provide evidence that mood congruent priming is brief, at least when a lexical decision task is used to evaluate automatic semantic processing for depression-relevant stimuli. In contrast to the above studies, Dannlowski et al. (2006) did not show semantic priming differences for emotional words between depressed and non-depressed individuals.

In summary, behavioral studies of semantic processing of emotional words have been somewhat mixed in depression. Nevertheless, the preponderance of evidence points to enhanced or faster processing of negative information. The fact that the majority of studies showed no group difference in the processing of positive and neutral words in the context of enhanced processing of negative stimuli argues against a general left frontal lobe deficit in depression. Rather, it suggests a facilitation of negative information processing in emotional semantic processing tasks in depression.

### 2.4. Neurobiological studies of semantic processing of emotional information

Nikendei et al. (2005) examined syntactic (noun or not) versus orthographic (capital letters or not) processing of pain related and neutral words utilizing N100, P300, and slow wave ERP components in participants who scored high or low on a screening measure for depression (Allgemine Depressions Skala; Hautzinger and Bailer, 1992). Behavioral results showed that all participants made more correct responses to pain words than to neutral words and more correct responses to syntactically and orthographically processed words than new words in the lexical decision task. There were no group differences in correct responses or in reaction time for syntactic processing, orthographic processing, or lexical decision. However, the high depression group rated both pain and neutral words as more threatening than the low depression group. ERP results showed no group differences for N100. The high depression group exhibited greater P300 amplitudes (bilaterally) for pain-related words than the low depression group. A similar pattern was exhibited for neutral words; however, the difference between groups for P300 amplitudes was not significant compared to pain words. Group differences were exhibited at the parietal region for pain words with the high depression group showing more positive slow waves compared to the low depression group. This group difference was reduced for neutral words. Investigators interpreted results as evidence for enhanced processing of pain-related stimuli in an analogue sample of depressed individuals.

In a study by Shimizu et al. (2006) ERP components at 200 ms (P2) and 400 ms (N2) were evaluated in a modified lexical decision task in right-handed university students who scored high or low on the BDI (Beck et al., 1961). The study comprised presentation of neutral (e.g., ordinary, plan), positive (e.g., kind, bright), and negative (e.g., dark, evil) words, and participants had to decide if the word fit their personality or not (fit/unfit) and if they preferred the word or not (positive/negative) with a button press. Reaction times and ERP recordings were performed sequentially; after ERP recordings, participants made their classification decisions. Behavioral data showed no group differences in reaction time, and there was also no difference in the selection of words for fit/unfit, positive/negative categorizations. ERP results showed that baseline-to-peak P2 amplitude was greater in the high depression group compared to the low depression group regardless of categorization type (i.e., for fit/unfit and positive/negative) in central and parietal regions bilaterally. Investigators interpret these results as evidence that individuals in the high depression group were more attentive to the words because they may have been more sensitive to processing emotionally valenced words. For the N2 component, the amplitude was larger in the high depression group compared to the low depression group regardless of categorization type (i.e., for fit/unfit and positive/negative) in the frontal and parietal regions bilaterally and in the midline central region. The investigators suggest that this

result indicates enhanced and continuous semantic processing for emotionally valenced words.

In another modified lexical decision task, Serfaty et al. (2002) evaluated contingent negative variation (CNV) and postimperative negative variation (PINV) in depressed patients and controls. Whereas CNV represents arousal and attention, prolonged PINV reflects uncertainty, decision-making problems (McCallum and Walter, 1988; Klein, 1997). For the task, participants were presented emotionally valenced words aurally and asked to make a decision about whether neutral (e.g., doors, stars), positive (e.g., capable, gentle), or negative (e.g., clumsy, stupid) words personally applied to them. Behavioral data showed the depressed group took longer to make this decision for all words compared to the control group. Additionally, the depressed group chose more negative than positive words as self-referential compared to the control group. There were no group differences in CNV magnitude. However, compared to the control group, the depressed group exhibited larger PINV wave for non-self-referential positive and non-self-referential negative words. Results regarding laterality differences for words of different emotional valence or reference (self-referential v. non-self-referential) showed no interhemispheric differences between the depressed and control group in CNV or PINV amplitude for processing emotionally valenced words. The investigators proposed PINV results reflect indecision for non-self-referenced emotional words in depression, which they suggest is consistent with a ruminative response style that inhibits processing that might be distracting to an individual's mood (Nolen-Hoeksema, 1991).

In summary, despite certain inconsistent results between data from behavioral studies and behavioral data in neurophysiological studies, there is support that depressed individuals exhibit enhancement in semantic processing for emotional information, particularly negative information, and that this enhancement is also typically seen in ERPs.

### 2.5. General semantic processing summary

There is little behavioral or neurophysiological evidence for decreased left frontal lobe functioning in major depression during semantic processing tasks. Instead, it appears that during these tasks, individuals with depression show enhanced bilateral frontal lobe functioning during the processing of negative information. These findings are consistent with the notion that the frontal lobe fails to inhibit the processing of negative information in depression. To what extent this failure of inhibition is a function of depressed mood as opposed to a premorbid deficiency is not clear as none of the neurophysiological semantic processing studies that used negative stimuli evaluated processing in remitted depression.

## 3. Verbal fluency

Verbal fluency may be used to describe the production of a series of words from a predetermined category. The predetermined category can be phonemic or semantic in nature (Basso et al., 1997; Borkowski et al., 1967; Frith et al., 1991). In phonemic verbal fluency tasks, the goal is to produce as many words as possible in a given time constraint, typically 1 min, beginning with a specific letter. The semantic version is similar with the exception that instead of a letter, individuals name as many words as possible for a particular category (e.g., animals or fruits).

Verbal fluency is related to executive processes such as initiation (Ruff et al., 1997). Evidence that depressed individuals have difficulties with initiation is demonstrated in a study by Lafont et al. (1998) which evaluated initiation in verbal fluency in individuals with depression and schizophrenia. The verbal fluency task comprised generating as many words as possible for animal and fruit categories in 2 min and investigators examined semantic subcategories of the category (i.e., clusters) during fluency. For example, words for the category animal may comprise the subcategory of zoo animals or birds. Clusters were defined as at least three contiguous words belonging to the same semantic subcategory. Inhibition was calculated as the number of subcategorical transitions between clusters. Verbal fluency results showed that depressed and schizophrenic patients produced fewer words than controls. Furthermore, both depressed and schizophrenic patients showed problems switching between one subcategory to another compared to controls suggesting both patient groups had problems with initiation.

Because initiation is involved at the start of a phonemic or semantic trial, verbal fluency performance in depression may be affected by varying time constraint. For example, depressed individuals may have more difficulty on verbal fluency tasks that have short time constraints (e.g., produce as many words as possible in 20 s) compared to relatively long time constraints (e.g., 1 min), as shorter trials require faster switches between categories. This hypothesis becomes relevant when qualitatively comparing verbal fluency results among depression studies with different time constraints.

### 3.1. Behavioral studies of phonemic and semantic verbal fluency

There have been no behavioral studies of emotional verbal fluency and the verbal fluency of neutral words in depression shows mixed results. Regarding phonemic fluency, depressed individuals, compared to controls, have exhibited phonemic fluency deficits in some studies (Lavender and Watkins, 2004; Stordal et al., 2004) but not in others (Airaksinen et al., 2004; Fossati et al., 2003; MacLeod and Salaminiou, 2001). Semantic fluency studies also show inconsistent results. For example, Fossati et al. (2003) and Lafont et al. (1998) showed that depressed patients compared to controls produced fewer words on semantic fluency. Others, however, have failed to find this fluency difference between depressed individuals and controls (e.g., Hartog et al., 2003). Inconsistencies may, of course, be due in part to the heterogeneity of depressed individuals. The data also suggest that depressed individuals may not have a specific DLPFC deficit. For example, authors of a meta-analytic review of phonemic and semantic fluency in depression proposed that both types of fluency are equivalent in their sensitivity of executive functioning (Henry and Crawford, 2005). However, to determine the extent to which verbal fluency performance is related to executive functioning, as opposed to more generalized impairment in depression, verbal fluency deficits were compared to psychomotor speed performance, and data showed that the magnitude of verbal fluency deficits was of a smaller or comparable magnitude to psychomotor speed performance. Henry and Crawford interpret this finding as evidence that the role of executive dysfunction in depression has been overestimated (see also Zarrinpar et al., 2006). Deficits in verbal fluency may reflect a more generalized impairment (e.g., cognitive slowing) rather than executive function deficits (Henry and Crawford, 2005).

Words produced for phonemic verbal fluency measures are typically not analyzed for valence, therefore, it is not known if depressed individuals are likely to generate more negative words for particular letters than non-depressed individuals given their difficulty to inhibit negative thoughts. Additionally, it is not clear if group differences in tasks presumed to activate the DLPFC are more likely to occur during emotion processing. If so, then verbal fluency tasks that pertain to emotionally valenced words (e.g., generate words with positive associations) may be a more sensitive measure of DLPFC dysregulation in depression. Although some non-depression studies have modified these tasks to evaluate fluency for emotionally salient words (e.g., spider phobics name as many words as possible to the category of spider; Mohlman et al., 2004), we were only able to identify traditional neutral verbal fluency tasks in our review of brain functioning during fluency in depression.

### 3.2. Neurobiological studies of verbal fluency

#### 3.2.1. Phonemic verbal fluency

In a study employing near-infrared spectroscopy (NIRS[1]) (Herrmann et al., 2004) depressed patients and controls performed a phonemic fluency task (A, F, S) with each trial 1 min long. Although the patient and control groups did not differ in their fluency performance, the control group showed higher bilateral oxyHb concentration values in the frontal lobe than the depressed group indicating bilateral hypoactivation in depression during verbal fluency. Similar results have been demonstrated in a study of elderly depressed patients (Matsuo et al., 2000) although assessment of bilateral frontal lobe functioning was not possible as recordings were limited to the left hemisphere. In the Matsuo et al. (2000) study depressed elderly patients (mean age 65) exhibited hypofrontal activation during a 1-trial phonemic fluency task (i.e., generate words beginning with "ka" for 1 min). Comparable to the Herrmann et al. (2004) study, there was no difference in fluency performance between the depressed and control groups.

These findings of hypoactive frontal lobe functioning during fluency without performance deficits have also been demonstrated in partial or fully remitted patients. In a study by Matsuo et al. (2002) euthymic individuals with a history of MDD, bipolar disorder, and controls also performed a 1-trial phonemic fluency task (i.e., "ka" for 1 min). Assessment of frontal lobe activity was limited to the left hemisphere. Analogous to the Matsuo et al. (2000) study, no fluency deficits were revealed yet individuals with a history of depressive disorder or bipolar disorder showed hypofrontality during verbal fluency compared to controls. Individuals with remitted bipolar disorder exhibited bilateral hypoactivation compared to controls and performance fluency deficits were not evident (Matsuo et al., 2004).

In a NRIS study that focused on cognitive related brain activity over time, Kameyama et al. (2006) examined patients with depression and bipolar disorder, who were euthymic or subclinically depressed, and a control group. Verbal fluency comprised three trials of letters (a, ka, and sa) each trial 20 s long. Results showed the depressed and control groups performed similarly on fluency; however, time course of activation revealed frontal lobe dysregulation. Specifically, compared to the control group, the oxyHb increases in the bipolar group were smaller during the early part of the fluency task period in the right frontal lobe (e.g., first 20 s) but significantly larger in the right frontal lobe later on. Compared to the depressed group, increase in cortical activity in the bipolar group was greater during the late task period in the frontal lobe bilaterally. In contrast, the depressed group exhibited smaller bilateral frontal lobe oxyHb increases than the control group during the early part of the fluency period without significant increases throughout the task. Results suggest delayed activation patterns in partial or remitted bipolar disorder and reduced frontal lobe activation in partial or remitted depression.

Suto et al. (2004) evaluated verbal fluency during NIRS in individuals with major depressive disorder and schizophrenia, who were in partial or full remission, and controls. The fluency task was similar to the 3-letter trial version used in the Kameyama et al. (2006) study above and results were similar. Namely, all groups performed comparably on fluency; however, time course of oxyHb increases differed among the three groups with the depressed group exhibiting a smaller frontal oxyHb increase in the left lower frontal region than controls during the first half of the fluency task. Throughout the entire task, increases in oxyHb in the frontal lobe bilaterally were less in the depressed group than the control group. This outcome indicates some hypoactivation in these regions in partial or fully remitted depressed individuals during verbal fluency. Taken together, the Suto et al. (2004) and Kameyama et al. (2006) results suggest that the initiation of verbal fluency may be related to frontal lobe deficits. Because both studies comprised depressed or bipolar individuals in partial or full remission, it is not known if this pattern of hypoactivation is related to such characteristics as severity of affective history or duration of remittance.

In an fMRI study conducted by Okada et al. (2003), participants covertly generated words for three trials of phonemes (sa, ta, te; each 30 s long) during brain imaging. Once outside of the fMRI camera, they repeated the task. Results showed that the depressed group generated fewer words than the control group. Further, the control group compared to the depressed group exhibited more activity in the left inferior frontal gyrus indicating hypoactivation of the left prefrontal cortex during verbal fluency in depression. In contrast, during a positron emission tomography (PET) study by Videbech et al. (2003) only performance deficits in depression were evident with no concomitant frontal lobe dysregulation. More specifically, depressed patients and controls participated in a 1-trial letter fluency task (e.g., "t" for 1 min). Results showed the depressed patients produced significantly fewer words than controls. However, both groups exhibited similar activation during fluency in the left anterior cingulate region, left DLPC, left medial prefrontal cortex, and right cerebellum.

In summary, the majority of NIRS studies show bilateral hypoactive frontal lobe functioning during verbal fluency in patients with depression and in individuals with partial or remitted depression despite a relative lack of performance deficits in phonemic verbal fluency. This suggests that verbal fluency may function as a probe for frontal lobe activity. The lack of behavioral deficits may be due to compensation of frontal lobe hypoactivation by other brain regions or relative differences in effort between the depressed and control groups (i.e., depressed individuals exerting more effort on fluency). However, similar to behavioral studies, there is inconsistency in verbal fluency performance when compared to other neurobiological investigations, which have shown phonemic verbal fluency deficits. In conclusion, there is mixed neurophysiological evidence of left frontal lobe hypoactivation associated with phonemic verbal fluency performance deficits in depression though the preponderance of the data suggests bilateral hypoactivation.

These results point to the contribution of neurophysiological methodology in evaluating verbal fluency in depression. Behavioral studies with and without concomitant neurophysiological studies show mixed results for performance deficits for phonemic verbal fluency in depression. Reasons for mixed behavioral results may include level of generalized impairment (e.g., cognitive slowing; Henry and Crawford, 2005) and level of effort to compensate for such impairment in depression. However, neurophysiological results indicate that bilateral frontal lobe hypoactivation occurs in depression despite intact behavioral performance, which suggests that neurophysiological methodology may be a more sensitive measure of verbal fluency in depression than behavioral performance.

#### 3.2.2. Phonemic and semantic verbal fluency

In a single photon emission computed tomography (SPECT) study by Audenaert et al. (2002), participants comprised depressed individuals who recently attempted suicide and controls. Verbal fluency involved both phonemic (N, A, K, B) and semantic (animals, jobs, fruits/veggies, interior and furniture) versions with each trial 1 min in duration. The depressed group performed worse than the controls on both the phonemic and semantic fluency tasks. Among SPECT results

[1] Verbal fluency is technically difficult to study utilizing ERPs and fMRI for two reasons: (1) speaking elicits noise in both environments; (2) ERPs, by nature, are elicited in response to stimuli and verbal fluency is a measure of verbal output. Therefore, most studies of verbal fluency do not use these techniques. Instead, studies that evaluated brain functioning during verbal fluency in depression most often have used near-infrared spectroscopy (NIRS) technology. Compared to fMRI and ERPs, NIRS is a relatively recent brain functioning technology. It is similar to fMRI as functioning is based on alterations in oxygenated hemoglobin (oxyHb) and deoxygenated hemoglobin (deoxyHb) in response to a cognitive task (Hock et al., 1995; Fallgatter and Strik, 1998; Watanabe et al., 2002). However, unlike fMRI, which can be used to evaluate whole brain functioning, NIRS is limited to surface cortical regions.

for phonemic fluency, the depressed group exhibited blunted perfusion in the medial temporal gyrus, right anterior cingulate (BA 24), and hypothalamic region compared to the control group. For semantic fluency, the depressed group compared to the control group exhibited blunted perfusion in the left inferior frontal gyrus, right inferior parietal lobe, and anterior cingulate gyrus. When phonemic fluency was compared to semantic fluency in the depressed group, patients showed hyperactivation in the right prefrontal cortex and left gyrus hippocampus for semantic fluency. There was no hyperactivation of the prefrontal lobe for phonemic fluency. The investigators interpret these differential patterns in brain activation between the depressed and control groups as evidence that the semantic fluency is more sensitive to prefrontal lobe functioning than phonemic fluency. These results were not replicated in a SPECT study of elderly depressed patients over age 65 (Philpot et al., 1993) where neither phonemic (F, A, S) nor semantic (animals, supermarket items) fluency deficits were evident. There was also no evidence of frontal lobe dysregulation during fluency tasks.

In summary, there are mixed results regarding left frontal lobe hypoactivation (i.e., left inferior frontal gyrus) and bilateral frontal hypoactivation (i.e., anterior cingulate gyrus) during semantic fluency, which was deficient in depressed patients compared to controls in terms of performance (Audenaert et al., 2002). These data indicate that semantic fluency may be a more sensitive probe of frontal lobe functioning than phonemic fluency. However, given these results were not replicated (Philpot et al., 1993), this interpretation needs to be treated with caution.

### 3.3. Summary of verbal fluency

In conclusion, both the purely behavioral studies and behavioral results in neurophysiological studies of verbal fluency show inconsistent performance deficits in depression. This suggests that verbal fluency at the behavioral level is limited in the conclusions that may be drawn. However, at the neurophysiological level, the majority of phonemic fluency studies showed bilateral frontal lobe hypoactivation indicating that depressed individuals have frontal lobe dysregulation that is not lateralized. The finding that bilateral frontal lobe hypoactivation is also evident in remitted depression indicates a premorbid deficit or the possibility that a single major depressive episode alters frontal lobe functioning. Comparatively fewer studies investigated semantic fluency; among those that did, there is evidence of left frontal lobe hypoactivation (left inferior frontal gyrus) as well as bilateral frontal lobe hypoactivation (anterior cingulate gyrus) during semantic fluency but not phonemic fluency (Audenaert et al., 2002).

In addition to the possibility that frontal lobe functioning may be affected by type of fluency task (i.e., phonemic v. semantic), verbal fluency tasks that require multiple shifts in mind set (e.g., rapidly switching from one phoneme to another) may be more sensitive to left frontal lobe deficits compared to those verbal fluency tasks that require fewer shifts. Evidence in support of this hypothesis include the Okada et al. (2003) and Kameyama et al. (2006) studies. More specifically, in Okada et al. (2003), phonemic fluency trials changed every 30 s as opposed to the more common 1 min time constraint and results showed left frontal lobe hypoactivation in depressed patients compared to controls. In the Kameyama et al. (2006) study, depressed patients with partial or full remittance exhibited a smaller frontal oxyHb increase in the left lower frontal region than controls during the first half of the fluency task with bilateral hypoactivation as the task continued. These data indicate that left frontal lobe functioning may be associated with verbal fluency initiation and perhaps tasks that emphasize the initiation process are more likely to be associated with left frontal lobe deficits in depression.

The hypothesis that verbal fluency tasks that require more switching among phonemes may be more sensitive to left frontal lobe deficits than those demanding less switching is consistent with the proposal that verbal fluency is associated with executive processes such as initiation (Ruff et al., 1997) and results from a behavioral study of verbal fluency indicate that depressed individuals have deficits in initiation (Lafont et al., 1998). In addition to initiation, it may be the case that left frontal lobe deficits in depression are also related to other executive functions. For example, there is evidence that working memory and attention play a role in DLPFC functioning. In an fMRI study by Siegle et al. (2007), DLPFC functioning in depression was evaluated with a digit-sort task that emphasized working memory and attention. Results showed decreased activity in the left DLPFC in depressed patients compared to controls. In summary, neurophysiological models of functioning in depression may be refined by studies that examine DLPFC activation in relation to executive processes such as working memory, attention, and initiation. Rather than global deficits or general impairment in frontal lobe functioning in depression, deficits in particular executive processes that help retrieve information and carry out and organize behavior may be dysregulated in depression.

## 4. Conclusion

Major depressive disorder is a common and disabling illness characterized by prolonged, potentially involuntary, emotion processing that may be due to deficits in frontal lobe functioning (Abercrombie et al., 1998; Drevets et al., 1992; Siegle et al., 2002, 2007). Neurobiological models of depression point to brain regions that are proposed to be involved with both emotion regulation and language processing. To this end, we focused on studies of semantic processing and verbal fluency which are associated with frontal lobe functioning and DLPFC functioning, respectively.

Semantic processing studies either comprised non-emotional information or emotionally valenced information. The majority of non-emotional semantic processing neurophysiological studies did not provide evidence of dysfunction in the ability of depressed subjects to semantically process neutral information though there is some evidence that semantic processing of neutral stimuli may be slowed down in depression (Abdullaev et al., 2002; Iakimova et al., 2009). This is consistent with purely behavioral studies of non-emotional semantic processing (Besche-Richard et al., 2002; Georgieff et al., 1998). Taken together, findings indicate that there is no dysregulation of left frontal lobe functioning in depression when neutral material is processed.

For semantic processing of emotional information, there are inconsistent results between data from behavioral studies and behavioral data from neurobiological studies, with purely behavioral studies showing enhanced processing of negative information in particular. While these behavioral findings have not always been replicated in neurobiological investigations, enhanced or faster processing of negative information has also been demonstrated with event-related potentials. The finding that depressed individuals generally exhibit enhanced processing of negative stimuli, as opposed to positive and neutral stimuli, argues against a gross left frontal lobe deficit in depression. Rather, it suggests a facilitation of negative information processing in depression. This facilitation is consistent with the hypothesis that a depressed individual's difficulty in inhibiting negative thoughts may be due, in part, to a disorganized semantic network, for example, right hemispheric involvement in language processing of emotional words in depression (Atchley et al. 2003), or the failure of executive function processes to adequately inhibit subcortical brain regions directly involved in emotion processing (e.g., amygdala; Davidson, 2000, 2003; Drevets and Raichle, 1998; Mayberg et al., 1999; Ochsner et al., 2002; Siegle et al., 2007).

In summary, there is little behavioral or neurophysiological evidence for decreased left frontal lobe functioning in major depression during semantic processing tasks. Instead, it appears that during these

tasks, individuals with depression show enhanced bilateral frontal lobe functioning during the processing of negative information.

With regard to verbal fluency in depression, there have been no behavioral or neurobiological studies of emotional verbal fluency. Verbal fluency tasks are either phonemic or semantic. Behavioral studies of these verbal fluency tasks have shown mixed results with depressed individuals sometimes exhibiting performance deficits for phonemic and semantic fluency (Fossati et al., 2003; Lafont et al., 1998; Lavender and Watkins, 2004; Stordal et al., 2004) and sometimes not (Airaksinen et al., 2004; Fossati et al., 2003; Hartog et al., 2003; MacLeod and Salaminiou, 2001). It has been proposed that such inconsistencies may be due to a more generalized impairment (e.g., cognitive slowing) in depression rather than executive function deficits (Henry and Crawford, 2005).

The majority of neurobiological studies of verbal fluency focused on phonemic fluency. While the preponderance of these studies had failed to find significant performance deficits, the finding of bilateral frontal lobe hypoactivation during verbal fluency in depression has been relatively consistent. This indicates that depressed individuals have frontal lobe dysregulation that is not lateralized. Comparatively fewer studies investigated semantic fluency; among those that did, there is evidence of both left and bilateral frontal lobe hypoactivations during semantic fluency but not phonemic fluency (Audenaert et al., 2002). These results suggest that frontal lobe functioning may be affected by type of fluency task (i.e., phonemic v. semantic).

The contribution of neurobiological studies of verbal fluency is elucidation of bilateral frontal hypoactivation during phonemic fluency without concomitant performance deficits. Additionally, neurophysiological evidence points to dysregulation of executive processes that contribute to DLPFC functioning (e.g., initiation, working memory, attention) (Kameyama et al., 2006; Okada et al., 2003; Siegle et al., 2007).

In conclusion, results from this qualitative review suggest intact semantic processing for neutral information and generally enhanced semantic processing for negative information. This provides evidence of intact left frontal lobe functioning during semantic processing of non-negative information and enhanced bilateral frontal lobe functioning during the processing of negative information. While verbal fluency studies were limited to non-emotional information, results generally point to bilateral frontal lobe hypoactivation (Table 1). In light of evidence that emotional information, compared to neutral information, may differentially impact frontal lobe functioning, future studies may want to examine verbal fluency for emotional material (e.g., list as many negative personal attributes as possible) in depression. This may clarify the degree to which problems inhibiting negative thoughts in depression are due to bilateral disruptions of executive processing in the frontal lobe relative to lateralized disruptions.

Although overall findings for both semantic processing and verbal fluency argue against left frontal lobe deficits, this review has limitations. Namely, compared to semantic processing of emotional information, there were fewer neurophysiological studies of non-emotional semantic processing. Methodological differences such as covert versus overt processing (e.g., passively reading sentences as opposed to producing words out loud) do not allow for direct comparison of these few studies. Regarding verbal fluency, the majority of studies used NRIS technology and focused on phonemic fluency.

**Table 1**
Summary of neurophysiological study findings of semantic processing.

| Study | Participants | Behavioral results | Frontal lobe effects |
|---|---|---|---|
| *Semantic with neutral words* | | | |
| Deldin et al. (2006) | Depressed, dysthymic, controls | Not measured | No between group frontal effects reported |
| Iakimova et al. (2009) | Depressed, controls | Depressed less accurate and had longer response latencies than controls | No between group frontal effects, however, depressed patients showed frontal lobe–behavioral correlations |
| Abdullaev et al. (2002) | Depressed | No differences between pre- and post-treatment | Pre-treatment: left prefrontal hypoactivation; right prefrontal hyperactivation<br>Post-treatment: Relative increase in left prefrontal activity; relative decrease in right prefrontal activity |
| *Semantic with emotional words* | | | |
| Nikendei et al. (2005) | Depressed (analogue sample) controls | Depressed rated negative and neutral words as more negative than controls | No between group frontal effects reported |
| Shimizu et al. (2006) | Depressed (analogue sample), controls | No group differences | Enhanced P2 and N2 amplitude at frontal sites (F3, F4, and Fz) in high depressed vs. low depressed regardless of affective valence of word |
| *Phonemic verbal fluency* | | | |
| Herrmann et al. (2004) | Depressed, controls | No group differences | Bilateral hypoactivation in depressed vs. controls |
| Matsuo et al. (2000) | Elderly depressed, controls | No group differences | Left frontal hypoactivation in depressed vs. controls; right frontal activation not measured |
| Matsuo et al. (2002) | Euthymic with history of depression or bipolar, controls | No group differences | Left frontal hypoactivation in euthymic vs. controls; right frontal activation not measured |
| Matsuo et al. (2004) | Euthymic with history of bipolar, controls | No group differences | Bilateral hypoactivation in euthymic vs. controls |
| Kameyama et al. (2006) | Euthymic with history of depression or bipolar, controls | No group differences | Bilateral hypoactivation in euthymic vs. controls |
| Suto et al. (2004) | Full or partial remission of depression or schizophrenia, controls | No group differences | Bilateral hypoactivation in depressed vs. controls |
| Okada et al. (2003) | Depressed, controls | Depressed produced fewer words vs. controls | Left frontal hypoactivation in depressed vs. controls |
| Audenaert et al. (2002) | Depressed, controls | Depressed produced fewer words vs. controls | No between group frontal effects reported |
| Videbech et al. (2003) | Depressed, controls | Depressed produced fewer words vs. controls | No between group frontal effects reported |
| Philpot et al. (1993) | Elderly depressed, controls | No group differences | No between group frontal effects reported |
| *Semantic verbal fluency* | | | |
| Audenaert et al. (2002) | Depressed, controls | Depressed produced fewer words vs. controls | Hypoactivation in left inferior frontal gyrus and anterior cingulate gyrus in depressed vs. controls |
| Philpot et al. (1993) | Elderly depressed, controls | No group differences | No between group frontal effects reported |

Although there is evidence that NRIS technology is comparable to other brain imaging techniques such as fMRI (e.g., Irani et al., 2007), there are differences in how the techniques are carried out (e.g., restricted inside a magnet v. mobility). This technique and the predominate use of phonemic fluency limit conclusions that may be made on neurobiological models of brain functioning in depression during verbal fluency, particularly semantic fluency.

## References


Abdullaev, Y., Kennedy, B.L., Tasman, A., 2002. Changes in neural circuitry of language before and after treatment of major depression. Human Brain Mapping 17, 156–167.

Abercrombie, H.C., Schaefer, S.M., Larson, C.L., Oakes, T.R., Lindgren, K.A., Holden, J.E., Perlman, S.B., Turski, P.A., Krahn, D.D., Benca, R.M., Davidson, R.J., 1998. Metabolic rate in the right amygdala predicts negative affect in depressed patients. Neuroreport: An International Journal for the Rapid Communication of Research in Neuroscience 9, 3301–3307.

Airaksinen, E., Larsson, M., Lundberg, I., Forsell, Y., 2004. Cognitive functions in depressive disorders: evidence from a population-based study. Psychological Medicine 34, 83–91.

Atchley, R.A., Ilardi, S.S., Enole, A., 2003. Hemispheric asymmetry in the processing of emotional content in word meanings: the effect of current and past depression. Brain and Language 84, 105–119.

Audenaert, K., Goethals, I., Laere, K.V., Lahorte, P., Brans, B., Versijpt, J., Vervaet, M., Beelaert, L., Heeringen, K.V., Dierckx, R., 2002. SPECT neuropsychological activation procedure with the Verbal Fluency Test in attempted suicide patients. Nuclear Medicine Communications 23, 907–916.

Basso, A., Burgio, F., Prandoni, P., 1997. Semantic category and initial letter word fluency in left-brain-damaged patients. European Journal of Neurology 4, 544–550.

Baxter, L.R., Schwartz, J.M., Phelps, M.E., Mazziotta, J.C., Guze, B.H., Selin, C.E., Gerner, R.H., Sumida, R.M., 1989. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Archives of General Psychiatry 46, 243–250.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Archives of General Psychiatry 4, 561–571.

Beck, A.T., Rush, A.J., Shaw, B.F., Emery, G., 1979. Cognitive Therapy of Depression: A Treatment Manual. Guilford Press, New York.

Bedny, M., Hulbert, J.C., Thompson-Schill, S.L., 2007. Understanding words in context: the role of Broca's area in word comprehension. Brain Research 1146, 101–114.

Bench, C.J., Friston, K.J., Brown, R.G., Frackowiak, R.S., et al., 1993. Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. Psychological Medicine 23, 579–590.

Besche-Richard, C., Passerieux, C., Hardy-Baylé, 2002. Lexical decision tasks in depressive patients: semantic priming before and after clinical improvement. European Psychiatry 17, 69–74.

Binder, J.R., McKiernan, K.A., Parsons, M.E., Westbury, C.F., Possing, E.T., Kaufman, J.N., Buchanan, L., 2003. Neural correlates of lexical access during visual word recognition. Journal of Cognitive Neuroscience 15, 372–393.

Borkowski, J.G., Benton, A.L., Spreen, O., 1967. Word fluency and brain damage. Neuropsychologia 5, 135–140.

Collins, A.M., Loftus, E.F., 1975. A spreading activation theory of semantic processing. Psychological Review 82, 407–428.

Compton, W.M., Conway, K.P., Stinson, F.S., Grant, B.F., 2006. Changes in the prevalence of major depression and comorbid substance use disorders in the United States between 1991–1992 and 2001–2002. American Journal of Psychiatry 163, 2141–2147.

Coulson, S., Kutas, M., 2001. Getting it: human event-related brain response to jokes in good and poor comprehenders. Neuroscience Letters 316, 71–74.

D'Arcy, R.C.N., Connolly, J.F., Service, E., Hawco, C.S., Houlihan, M.E., 2004. Separating phonological and semantic processing in auditory sentence processing: a high-resolution event-related brain potential study. Human Brain Mapping 22, 40–51.

Dannlowski, U., Kersting, A., Arolt, V., Lalee-Mentzel, J., Donges, U.S., Suslow, T., 2006. Unimpaired automatic processing of verbal information in the course of clinical depression. Depression and Anxiety 23, 325–330.

Davidson, R.J., 2000. Affective style, psychopathology, and resilience: brain mechanisms and plasticity. American Psychologist 55, 1196–1214.

Davidson, R.J., 2003. Affective neuroscience and psychophysiology: toward a synthesis. Psychophysiology 40, 655–665.

Davidson, R.J., Irwin, W., 1999. The functional neuroanatomy of emotion and affective style. Trends in Cognitive Sciences 3, 11–21.

Davidson, R.J., Pizzagalli, D., Nitschke, J.B., Putnam, K., 2002. Depression: perspectives from affective neuroscience. Annual Review of Psychology 53, 545–574.

Deldin, P., Keller, J., Casas, B.R., Best, J., Gergen, J., Miller, G.A., 2006. Normal N400 in mood disorders. Biological Psychology 71, 74–79.

Drevets, W.C., Raichle, M., 1998. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions between emotion and cognition. Cognition and Emotion 12, 353–385.

Drevets, W.C., Videen, T.O., Price, J.L., Preskorn, S.H., Carmichael, T., Raichle, M.E., 1992. A functional anatomical study of unipolar depression. Journal of Neuroscience 12, 3628–3641.

Elfgren, C.I., Risberg, J., 1998. Lateralized frontal blood flow increases during fluency tasks: influence of cognitive strategy. Neuropsychologia 36, 505–512.

Fallgatter, A.J., Strik, W.K., 1998. Frontal brain activation during the Wisconsin Card Sorting Test assessed with two-channel near-infrared spectroscopy. European Archives of Psychiatry and Clinical Neuroscience 248, 245–249.

Fossati, P., Guillaume, L.B., Ergis, A.M., Allialaire, J.F., 2003. Qualitative analysis of verbal fluency in depression. Psychiatry Research 117, 17–24.

Frith, C.D., Friston, K.J., Liddle, P.F., Frackowiak, R.S., 1991. A PET study of word finding. Neuropsychologia 29, 1137–1148.

Gaillard, W.D., Hertz-Pannier, L., Mott, S.H., Barnett, A.S., LeBihan, D., Theodore, W.H., 2000. Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. Neurology 54, 180–185.

Georgieff, N., Dominey, P.F., Michel, F., Marie-cardine, M., Dalery, J., 1998. Semantic priming in major depressive state. Psychiatry Research 78, 29–44.

Gotlib, I.H., Ranganath, C., Rosenfeld, J.P., 1998. Frontal EEG alpha asymmetry, depression, and cognitive functioning. Cognition and Emotion 12, 449–478.

Hagoort, P., Indefrey, P., Brown, C., Herzog, H., Steinmetz, H., Seitz, R., 1999. The neural circuitry involved in the reading of German word and pseudowords: a PET study. Journal of Cognitive Neuroscience 11, 383–398.

Hartog, H.M., Derix, M.M.A., Bemmel, A.L., Kremer, B., Jolles, J., 2003. Cognitive functioning in young and middle-aged unmedicated out-patients with major depression: testing the effort and cognitive speed hypotheses. Psychological Medicine 33, 1443–1451.

Hautzinger, M., Bailer, M., 1992. Allgemeine Depressions Skala (ADS). Manual. Beltz Test GmbH, Weinheim.

Henriques, J.B., Davidson, R.J., 1991. Left frontal hypoactivation in depression. Journal of Abnormal Psychology 100, 22–31.

Henriques, J.B., Davidson, R.J., 2000. Decreased responsiveness to reward in depression. Cognition and Emotion 14, 711–724.

Henry, J.D., Crawford, J.R., 2005. A meta-analytic review of verbal fluency deficits in depression. Journal of Clinical and Experimental Neuropsychology 27, 78–101.

Herrmann, M.J., Ehlis, A.C., Fallgatter, A.J., 2004. Bilaterally reduced frontal activation during a verbal fluency task in depressed patients as measured by near-infrared spectroscopy. Journal of Neuropsychiatry and Clinical Neurosciences 16, 170–175.

Hock, C., Muller-Spahn, F., Schuh-Hofer, F., Hofmann, M., Dirnagl, U., Villringer, A., 1995. Age dependency of changes in cerebral hemoglobin oxygenation during brain activation: a near-infrared spectroscopy study. Journal of Cerebral Blood Flow and Metabolism 15, 1103–1108.

Holthoff, V.A., Beuthien-Baumann, B., Zündorf, G., Triemer, A., Lüdecke, A., Winiecki, P., Koch, R., Füchtner, F., Herholz, K., 2004. Changes in brain metabolism associated with remission in unipolar major depression. Acta Psychiatrica Scandinavica 110, 184–194.

Iakimova, G., Passerieux, C., Foynard, M., Fiori, N., Besche, C., Laurent, J.P., Hardy-Baylé, M.C., 2009. Behavioral measures and event-related potentials reveal different aspects of sentence processing and comprehension in patients with major depression. Journal of Affective Disorders 113, 188–194.

Irani, F., Platek, S.M., Bunce, S., Ruocco, A.C., Chute, D., 2007. Functional near infrared spectroscopy (fNIRS): an emerging neuroimaging technology with important applications for the study of brain disorders. Clinical Neuropsychologist 21, 9–37.

Kameyama, M., Fukuda, M., Yamagishi, Y., Sato, T., Uehara, T., Ito, M., Suto, T., Mikuni, M., 2006. Frontal lobe function in bipolar disorder: a multichannel near-infrared spectroscopy study. NeuroImage 29, 172–184.

Klein, C., 1997. The Post-imperative Negative Variation in Schizophrenic Patients and Healthy Subjects. P. Lang, Frankfurt am Main, NY.

Kuperberg, G.R., 2007. Neural mechanisms of language comprehension: challenges to syntax. Brain Research 18, 23–49.

Kutas, M., Hillyard, S.A., 1980a. Reading senseless sentences: brain potential reflects semantic incongruity. Science 207, 204–206.

Kutas, M., Hillyard, S.A., 1980b. Reading between the lines: event-related brain potentials during natural sentence processing. Brain and Language 11, 354–373.

Lafont, V., Medecin, I., Robert, P.H., Beaulieu, F.E., Kazes, M., Danion, J.M., Pringuey, D., Darcourt, G., 1998. Initiation and supervisory processes in schizophrenia and depression. Schizophrenia Research 34, 49–57.

Lavender, A., Watkins, E., 2004. Rumination and future thinking in depression. British Journal of Clinical Psychology 43, 129–142.

MacLeod, A.K., Salaminiou, E., 2001. Reduced positive future-thinking in depression: cognitive and affective factors. Cognition and Emotion 15, 99–107.

Matsuo, K., Kato, T., Fukuda, M., Kato, N., 2000. Alteration of hemoglobin oxygenation in the frontal region in elderly depressed patients as measured by near-infrared spectroscopy. Journal of Neuropsychiatry and Clinical Neurosciences 12, 465–471.

Matsuo, K., Kato, N., Kato, T., 2002. Decreased cerebral haemodynamic response to cognitive and physiological tasks in mood disorders as shown by near-infrared spectroscopy. Psychological Medicine 32, 1029–1037.

Matsuo, K., Watanabe, A., Onodera, Y., Kato, N., Kato, T., 2004. Prefrontal hemodynamic response to verbal-fluency task and hyperventilation in bipolar disorder measured by multi-channel near-infrared spectroscopy. Journal of Affective Disorders 82, 85–92.

Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., Silva, J.A., Tekell, J.L., Martin, C.C., Lancaster, J.L., Fox, P.T., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. American Journal of Psychiatry 156, 675–682.

McCallum, W.C., Walter, W.G., 1988. Potentials Related to Expectance, Preparation and Motor Activity. In: Picton, T.W. (Ed.), Human Event-related Potentials. Handbook of Electroencephalography and Clinical Neurophysiology, vol. 3. Elsevier, Amsterdam, pp. 427–534.

Mohlman, J., Mangels, J., Craske, M.G., 2004. The Spider Phobia Card Sorting Test: an investigation of phobic fear and executive functioning. Cognition and Emotion 18, 939–960.

Nikendei, C., Dengler, W., Wiedemann, G., Pauli, P., 2005. Selective processing of pain-related word stimuli in subclinical depression as indicated by event-related brain potentials. Biological Psychology 70, 52–60.

Nolen-Hoeksema, S., 1991. Responses to depression and their effects on the duration of depressive episodes. Journal of Abnormal Psychology 100, 569–582.
Ochsner, K.N., Bunge, S.A., Gross, J.J., Gabrieli, J.D.E., 2002. Rethinking feelings: an fMRI study of cognitive regulation of emotion. Journal of Cognitive Neuroscience 14, 1215–1229.
Okada, G., Okamoto, Y., Morinobu, S., Yamawaki, S., Yokota, N., 2003. Attenuated left prefrontal activation during a verbal fluency task in patients with depression. Neuropsychobiology 47, 21–26.
Philpot, M.P., Banerjee, S., Needham-Bennett, H., Costa, D.C., Ell, P.J., 1993. $^{99m}$Tc-HMPAO single photon emission tomography in late life depression: a pilot study of regional cerebral blood flow at rest and during a verbal fluency task. Journal of Affective Disorders 28, 233–240.
Raichle, M.E., 1994. Images of the mind: studies with modern imaging techniques. Annual Review of Psychology 45, 333–356.
Raichle, M.E., Fiez, J.A., Videen, T.O., MacLeod, A.M.K., Pardo, J.V., Petersen, S.E., 1994. Practice-related changes in human brain functional anatomy during nonmotor learning. Cerebral Cortex 4, 8–26.
Ravnkilde, B., Videbech, P., Rosenberg, R., Gjedde, A., Gade, A., 2002. Putative tests of frontal lobe function: a PET-study of brain activation during Stroop's test and verbal fluency. Journal of Clinical and Experimental Neuropsychology 24, 534–547.
Ruff, R.M., Light, R.H., Parker, S.B., Levin, H.S., 1997. The psychological construct of word fluency. Brain and Language 57, 394–405.
Scott, K.M., Mogg, K., Bradley, B.P., 2001. Masked semantic priming of emotional information in subclinical depression. Cognitive Therapy and Research 25, 505–524.
Seghier, M.L., Lazeyras, F., Pegna, A.J., Annoni, J.M., Zimine, I., Mayer, E., Michel, C.M., Khateb, A., 2004. Variability of fMRI activation during a phonological and semantic language task in healthy subjects. Human Brain Mapping 23, 140–155.
Serfaty, M.A., Bothwell, R., Marsh, R., Ashton, H., Blizard, R., Scott, J., 2002. Event-related potentials and cognitive processing of affectively toned words in depression. Journal of Psychophysiology 16, 56–66.
Shimizu, H., Saito, H., Hoshiyama, M., 2006. Cognitive mechanism for meaning of emotive words in depressed personality: an event-related potential study. Nagoya Journal of Medical Science 68, 35–44.
Siegle, G.J., Steinhauer, S.R., Thase, M.E., Stenger, V.A., Carter, C.S., 2002. Can't shake that feeling: fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. Biological Psychiatry 51, 693–707.
Siegle, G.J., Thompson, W., Carter, C.S., Steinhauer, S.R., Thase, M.E., 2007. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. Biological Psychiatry 61, 198–209.
Solomon, D.A., Keller, M.B., Leon, A.C., Mueller, T.I., Lavori, P.W., Shea, M.T., Coryell, W., Warshaw, M., Turvey, C., Maser, J.D., Endicott, J., 2000. Multiple recurrences of major depressive disorder. American Journal of Psychiatry 157, 229–233.
Stordal, K.I., Lundervold, A.J., Egeland, J., Mykletun, A., Asbjornsen, A., Landro, N.I., Roness, A., Rund, B.R., Sundet, K., Oedegaard, K.J., Lund, A., 2004. Impairment across executive functions in recurrent major depression. Nordic Journal of Psychiatry 58, 41–47.
Suto, T., Fukuda, M., Ito, M., Uehara, T., Mikuni, M., 2004. Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. Biological Psychiatry 55, 501–511.
Videbech, P., Ravnkilde, B., Kristensen, S., Egander, A., Clemmensen, K., Rasmussen, N.A., Gjedde, A., Rosenberg, R., 2003. The Danish PET/depression project: poor verbal fluency performance despite normal prefrontal activation in patients with major depression. Psychiatry Research: Neuroimaging 123, 49–63.
Watanabe, A., Kato, N., Tadafumi, K., 2002. Effects of creatine on mental fatigue and cerebral hemoglobin oxygenation. Neuroscience Research 42, 279–285.
Weisbrod, M., Trage, J., Hill, H., Sattler, H.D., Maier, S., Kiefer, M., Grothe, J., Spitzer, M., 1999. Emotional priming in depressed patients. German Journal of Psychiatry 2, 19–47.
Xiao, Z., Zhang, J.X., Wang, X., Wu, R., Hu, X., Weng, X., Tan, L.H., 2005. Differential activity in left inferior frontal gyrus for pseudowords and real words: an event-related fMRI study on auditory lexical decision. Human Brain Mapping 25, 212–221.
Zarrinpar, A., Deldin, P.J., Kosslyn, S., 2006. Effects of depression on sensory/motor versus central processing in visual mental imagery. Cognition and Emotion 20, 737–758.