Abnormal self-schema in semantic memory in major depressive disorder: Evidence from event-related brain potentials

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ABSTRACT

An overly negative self-schema is a proposed cognitive mechanism of major depressive disorder (MDD). Self-schema − one's core conception of self, including how strongly one believes one possesses various characteristics − is part of semantic memory (SM), our knowledge about concepts and their relationships. We used the N400 event-related potential (ERP) − elicited by meaningful stimuli, and reduced by greater association of the stimulus with preceding context − to measure association strength between self-concept and positive, negative, and neutral characteristics in SM. ERPs were recorded from MDD patients ($n = 16$) and controls ($n = 16$) who viewed trials comprising a self-referential phrase followed by a positive, negative, or neutral adjective. Participants' task was to indicate via button-press whether or not they felt each adjective described themselves. Controls endorsed more positive adjectives than did MDD patients, but the opposite was true for negative adjectives. Patients had smaller N400s than controls specifically for negative adjectives, suggesting that MDD is associated with stronger than normal functional neural links between self-concept and negative characteristics in SM.

1. Introduction

A predisposing and perpetuating factor in major depressive disorder (MDD) is thought to be the presence of an overly negative self-schema (Beck, 1967; Dozois & Beck, 2008). Self-schema is a person's core conception of self, including how strongly one believes that one possesses various characteristics (Rogers, Kuiper, & Kirker, 1977). According to Beck and colleagues' cognitive model of MDD, abnormally negative self-schemata − in which the self is associated with traits of helplessness (e.g., "I am inadequate") and unlovability ("I am undesirable") − form during childhood but may remain latent until activated later by stressful life events (Disner, Beevers, Haigh, & Beck, 2011; Dozois & Beck, 2008). In this model, once activated, negative self-schemata predispose to depression by enhancing both automatic and controlled processing of schema-consistent, negative information − thus contributing to negative interpretations of experiences, and in turn leading to core MDD symptoms such as sadness, hopelessness, worthlessness and guilt (American Psychiatric Association, 2013; Shestyuk & Deldin, 2010).

Data from a variety of behavioral studies support the view that negative traits are disproportionately prominent in the self-schemata of persons diagnosed with MDD. For instance, compared to healthy individuals, persons with MDD rate themselves as exhibiting negative traits more strongly, and positive traits less strongly (Brewin, Smith, Power, & Furnham, 1992; Shestyuk & Deldin, 2010). Convergent results come from studies using implicit methods rather than asking participants directly. For example, after rating whether or not different adjectives describe themselves, depressed individuals, compared to healthy controls, exhibit better recall for negative self-referent adjectives, and worse recall for positive ones (Derry & Kuiper, 1981; Shestyuk & Deldin, 2010).

There are also data indicating that successful treatment of MDD may be linked to normalization of negative self-schemata, but that this normalization depends on the modality of treatment. To address this question, Dozois et al. (2009) compared depressed patients treated with both pharmacotherapy and cognitive therapy versus those treated with pharmacotherapy alone. One goal of cognitive therapy is to remedy overly negative self-schemata by challenging their accuracy

(Kovacs & Beck, 1978). While both groups exhibited similar improvements in depressive symptoms, only the combined-treatment group exhibited a decrease in negative characteristics and an increase in positive characteristics of self-schemata, as measured by participants' ratings of self-relevance of person-referent adjectives. The authors concluded that normalization of negative self-schemata may underlie cognitive therapy's greater benefits for preventing relapse of MDD, compared to pharmacotherapy (Dobson et al., 2008).

A person's self-schema, inasmuch as it comprises a network of beliefs about one's characteristics, is thought to be part of semantic long-term memory, our knowledge about concepts and their relationships (Segal & Vella, 1990). In line with this model, we can view concepts of self and of various personal characteristics as nodes in semantic memory (Spitzer, 1997), which may have different connection strengths across individuals, thus determining the functional organization of each individual's self-schema.

The degree of association between different concepts in semantic long-term memory can be probed using the N400 event-related brain potential (ERP) waveform. The electroencephalographic ERP technique noninvasively measures voltage changes at the scalp associated with specific cognitive events. These voltage changes are thought to reflect the synchronous postsynaptic activity of cortical pyramidal neurons (Luck, 2005). The N400 ERP waveform is a negative voltage deflection which occurs between 200 and 500 ms (peaking around 400 ms) after any potentially meaningful stimulus, such as a word or a picture (Kutas & Federmeier, 2011). It is seen broadly across the scalp, but is largest medially and centroparietally (Duncan et al., 2009; Kutas & Federmeier, 2011). It is thought to reflect activity in inferior and anterior medial temporal neocortical networks (Nobre, Allison, & McCarthy, 1994; Nobre & McCarthy, 1995). Normally, its amplitude is reduced (i.e., made less negative, or even positive, in voltage) by factors that prime or facilitate processing of its eliciting stimulus, including relatedness to preceding context, among other factors that ease the access of information from semantic memory (Kutas & Federmeier, 2011). Thus, after seeing *CAT*, people exhibit a smaller (less negative) N400 in response to *MOUSE* than to *ARROW*. Likewise, following a sentence context, e.g. "*Don't touch the wet…*", N400 is smaller after the most expected ending "*paint*" than after a less expected ending "*dog*" (Kutas & Hillyard, 1984).

Researchers have proposed that these "N400 semantic priming effects" reflect use of context to facilitate processing of related items by pre-activating their neural representations in semantic long-term memory (DeLong, Urbach, & Kutas, 2005; Kutas & Federmeier, 2011). Thus, the N400 has been used as a neurophysiological probe of the functional organization of semantic memory in psychiatric disorders such as schizophrenia (Kiang, Kutas, Light, & Braff, 2008; Kostova, Passerieux, Laurent, & Hardy-Bayle, 2005; Mathalon, Faustman, & Ford, 2002; Salisbury, 2010) and posttraumatic stress disorder (Kimble, Batterink, Marks, Ross, & Fleming, 2012). Advantages of this technique include its ability to provide a non-invasive window on neural processing in semantic memory, without relying on any explicit or overt response from the subject.

In the present study, we aimed to use the N400 to test for abnormal self-schemata in semantic memory in MDD. Specifically, we hypothesized that depressed patients have stronger than normal associations between their self-concept and negative characteristics, and/or weaker than normal associations between self-concept and positive characteristics, in semantic memory. We predicted that these abnormalities would be reflected, respectively, in MDD patients having smaller (less negative in voltage) N400 amplitudes than healthy individuals in response to negative adjectives, and/or larger than normal N400 amplitudes than healthy individuals to positive adjectives, in a self-referential context. We also hypothesized that, consistent with previous research, MDD patients, compared to controls, would endorse more of the negative adjectives, and fewer of the positive adjectives, as referring to themselves. In healthy individuals, the N400 was previously found to

be smaller in response to positive compared to negative personality-trait adjectives in a self-referential context (Chen et al., 2014; Zhou et al., 2013), confirming a typical "self-positivity bias" (Chen et al., 2014), in which self-concept is associated more strongly with positive than with negative traits. Previous N400 studies in MDD did not find any abnormalities (Deldin et al., 2006; Iakimova et al., 2009; Klumpp et al., 2010), but these examined N400 responses to non-self-referent stimuli. To our knowledge, our study is the first to examine N400 responses to positive, negative and neutral adjectives in MDD in a self-referential context.

2. Methods

2.1. Participants

Participants included 16 outpatients with nonpsychotic major depressive disorder (MDD) meeting DSM-IV (American Psychiatric Association, 2000) criteria for a current major depressive episode, and scoring greater than 7 and less than 30 on the 17-item Hamilton Depression Rating Scale (HAMD$_{17}$) (Hamilton, 1980), recruited from the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario, Canada; and 16 healthy control participants (HCPs) from the surrounding community. All participants gave informed written consent. The protocol was approved by the CAMH Research Ethics Board.

Participants were screened diagnostically for DSM-IV disorders with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Exclusion criteria for all participants included: visual or hearing impairment; exposure to a language other than English before age 5; lifetime self-reported neurological disorder; and lifetime substance dependence, or substance abuse in the past six months. HCPs were also excluded if they met criteria for any other Axis I diagnoses, or were taking psychotropic medication. Table 1 shows group demographic characteristics and patients' clinical characteristics. Ten patients met DSM-IV criteria on the MINI for a comorbid anxiety disorder, 3 met criteria for dysthymia, 1 for bulimia nervosa, and 5 did not meet criteria for any comorbid disorder. Twelve patients were prescribed drugs for depression (specific agents shown in Table 1); of these, 7 were prescribed one drug and 5 were prescribed two drugs.

2.2. Stimuli

Stimuli included 141 person-referent target adjectives drawn from the Affective Norms for English Words (ANEW) database (Bradley & Lang, 1999). In this database, words were normed on their affective valence (ranging from pleasant to unpleasant). From these norms, we selected 47 adjectives for each of the following conditions: positive (top tercile; mean affective valence rating = 7.7), negative (bottom tercile; mean affective valence = 2.2) and neutral (middle tercile; mean affective valence = 4.7). Adjectives were matched across conditions on mean word length, number of orthographic neighbors for each word, and word frequency in the English language (Francis & Kucera, 1982). Sample adjectives for each condition are shown in Table 2.

The 141-trial stimulus list included all target adjectives once, in a fixed pseudorandomized order, in three blocks of 47 trials each.

2.3. Task

Participants were seated 100 cm in front of a video monitor on which stimuli were visually presented, with each letter subtending on average 0.36° of visual angle horizontally, and up to 0.55° vertically. Words were displayed in yellow letters on a black background.

Each participant was presented with the 141-trial stimulus list, with short breaks between blocks. On each trial participants saw: a) a row of preparatory fixation crosses at the center of the screen for 500 ms, followed by a blank screen for 250 ms; b) the prime phrase "*I am…*" for

Table 1
Demographic, neuropsychological and clinical characteristics of the study sample (means ± standard deviations, with range in parentheses given where applicable).

	HCPs ($n = 16$)	MDD patients ($n = 16$)
Age, years	31.0 ± 10.8 (18 − 54)	38.1 ± 10.1 (21 − 55)
Sex	8 female, 8 male	11 female, 5 male
Handedness	16 right, 0 left	16 right, 0 left
Years of Education	15.5 ± 2.2 (12 − 19)	15.5 ± 2.2 (12 − 20)
National Adult Reading Test (Nelson & Willison, 1991) estimated verbal IQ	113.4 ± 7.3 (102.0 − 123.4)	113.6 ± 8.6 (97.6 − 125.1)
HAMD$_{17}$ Score	-	16.1 ± 5.7 (9 − 27)
Drugs for depression (number of patients, mean dose in mg)	-	Amitriptyline (1, 100)
		Bupropion (2, 250)
		Duloxetine (1, 60)
		Escitalopram (3, 15)
		Fluvoxamine (1, 50)
		Mirtazapine (1, 30)
		Moclobemide (1, 300)
		Nortriptyline (2, 67.5)
		Sertraline (2, 125)
		Trazodone (1, 100)
		Venlafaxine (1, 150)
		Vortioxetine (1, 20)

Groups did not differ significantly on any demographic or neuropsychological variable, $p > 0.05$.
HAMD$_{17}$, 17-item Hamilton Rating Scale for Depression; HCPs, healthy control participants; MDD, major depressive disorder.

Table 2
Sample adjective stimuli, by type.

Positive	Negative	Neutral
loyal	helpless	skeptical
friendly	stupid	serious
romantic	useless	modest
joyful	cruel	tidy
fun	toxic	hungry

Fig. 1. Schematic representation of the time course of events in each trial.

175 ms, followed by a blank screen for 825 ms; c) a target adjective for 250 ms, followed by a blank screen for 1250 ms; d) the prompt *Yes or No?* Participants were asked to wait for the prompt to press one of two buttons positioned under the right and left thumbs respectively, to indicate whether or not they felt the target word applied to them. Assignment of buttons was counterbalanced across participants. The delayed-response task helped ensure that participants were attending to the stimuli, while minimizing movement-related potentials that could overlap the N400. After participants pressed a button, the screen was blank for 2000 ms, then the next trial began. Fig. 1 schematically illustrates the sequence of each trial.

2.4. Electroencephalographic data collection and analysis

During the experimental task, the electroencephalogram (EEG) was recorded from 60 Ag/AgCl electrodes embedded in a cap and approximately equally distributed across the scalp according to a modified International 10–20 System (electrode sites shown in Fig. 2), and referenced to the vertex between Cz and CPz. The EEG was recorded through a Synamps2 amplifier (Compumedics Neuroscan, Charlotte, NC) at a bandpass of 0.3–200 Hz and continuously digitized at 1000 Hz. Blinks and eye movements were monitored via electrodes on the supraorbital and infraorbital ridges and on the outer canthi of both eyes. Offline, the EEG was re-referenced to the algebraic mean of the mastoids, and lowpass-filtered at 100 Hz. Continuous data were algorithmically corrected for eyeblink artifact (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997). ERPs for target words were computed for epochs from 100 ms before stimulus onset to 900 ms after stimulus onset. Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected off-line by visual inspection before time-domain averaging; mean percentage of trials lost to such artifacts was 8% for patients and 4% for controls.

For each participant, separate ERP averages were obtained for accepted trials with positive, negative, and neutral target words. The mean voltage over the 100-ms prestimulus period was used for baseline correction. N400 amplitude was measured as mean voltage of the ERP average for each of the above target conditions between 350 and 500 ms, consistent with the literature (Carreiras, Vergara, & Barber, 2005; Van Petten & Kutas, 1990).

2.5. Statistical analysis

To test for differences in percentage of affirmative responses as a function of Group (MDD vs. HCP) and Target (positive vs. negative vs. neutral), all pairwise comparisons of factor-level means were made using Tukey HSD simultaneous comparisons, at a familywise error rate of 0.05, 2-sided (Howell, 2012).

To test for differences in N400 amplitude between MDD patients and HCPs as a function of Group (MDD vs. HCP) and Target (positive vs. negative vs. neutral), N400 amplitude was averaged across 26 contiguous electrode sites (F1-4, Fz, FC1-4, FCz, C1-6, Cz, T7-8, CP1-6, CPz) in the region where N400 effects are most prominent (Duncan et al., 2009). Planned pairwise comparisons were made to compare N400 amplitude, averaged across these sites, between MDD patients and HCPs for each of the positive, negative, and neutral target conditions, at
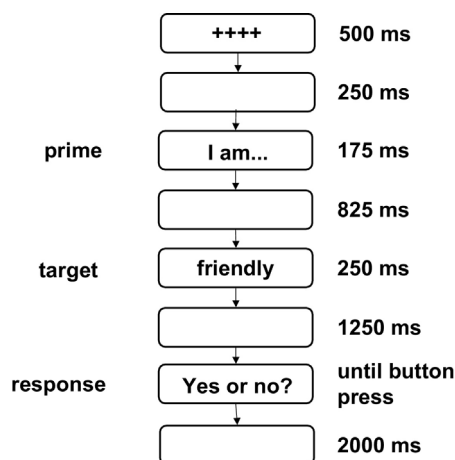
Healthy control participants
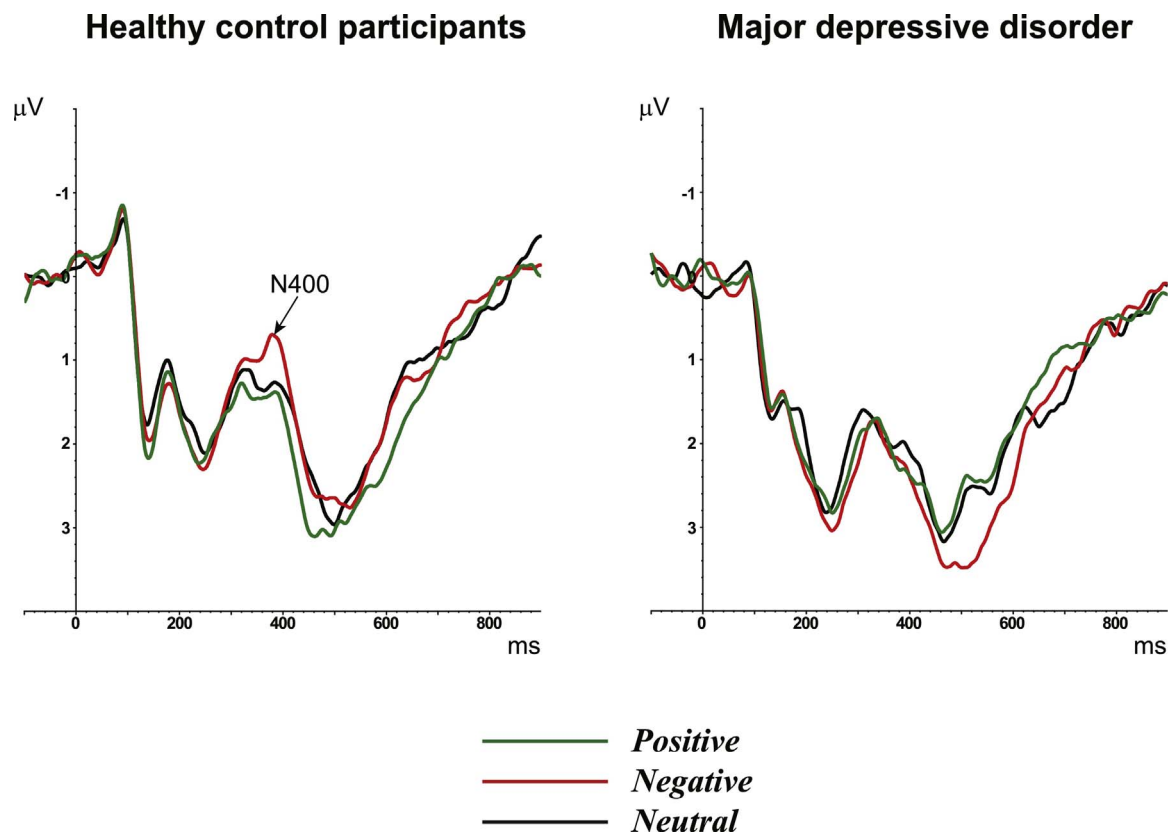
Major depressive disorder

Fig. 2. Grand average event-related potentials for the three target types, averaged across the 26 electrode sites used for analysis, for healthy control participants and major depressive disorder patients ($n = 16$ per group). Time is plotted on the *x*-axis, with 0 ms representing target stimulus onset. Voltage is plotted on the *y*-axis with negative voltage plotted upward.

a Bonferroni-corrected level of significance of $p = 0.05/3 = 0.0167$ (2-tailed) (Howell, 2012; Wilkinson & The Task Force on Statistical Inference, 1999).

3. Results

3.1. Behavioral data

Percentages of affirmative ("Yes") responses for MDD patients and controls for each target condition are shown in Table 3. An ANOVA of percentage of affirmative responses with Group (MDD vs. HCP) as between-subject variable and Target (positive vs. negative vs. neutral) as within-subject variable showed significant effects of Group ($F_{1,30} = 9.58$, $p = 0.004$) and Target ($F_{2,60} = 47.10$, $\varepsilon = 0.64$, $p < 0.0001$), and a significant Group x Target interaction ($F_{2,60} = 40.11$, $\varepsilon = 0.64$, $p < 0.0001$).

The Tukey HSD test (familywise $p < 0.05$) showed that for positive adjectives, the percentage of affirmative responses was smaller for patients than for controls, whereas for negative adjectives, this was larger for patients than for controls. In contrast, there was no significant difference in percentage of affirmative responses between the groups for neutral adjectives. Furthermore, the test showed that in controls the

Table 3
Percentage of affirmative ("Yes") responses, by participant group and target condition.

Target	HCPs ($n = 16$)		MDD patients ($n = 16$)		Tukey HSD
	Mean	SD	Mean	SD	
Positive	75.0	9.9	43.4	18.6	HCP > MDD
Negative	5.1	9.9	40.2	18.2	HCP < MDD
Neutral	29.9	10.1	44.5	12.2	

HCPs, healthy control participants; MDD, major depressive disorder.

percentage of affirmative responses was larger for positive than for neutral adjectives, and larger for neutral than for negative adjectives; whereas there was no significant difference in percentage of affirmative responses across the three target conditions for patients.

3.2. N400 amplitudes

Grand average ERPs averaged across all 26 electrode sites used for analysis are shown for HCPs and MDD patients in Fig. 2. Scalp topographic plots of N400 amplitude (mean voltage from 350 to 500 ms) for each target condition are shown for HCPs and MDD patients in Fig. 3. Mean N400 amplitudes averaged across these electrodes are shown for each group and condition in Table 4.

An ANOVA of mean N400 amplitude with Group (MDD vs. HCP) as between-subject variable and Target (positive vs. negative vs. neutral) as within-subject variable showed that there was no significant effect of Group ($F_{1,30} = 0.45$, $p = 0.51$, $\eta^2_{partial} = 0.015$) or Target ($F_{2,60} = 0.72$, $\varepsilon = 0.99$, $p = 0.49$, $\eta^2_{partial} = 0.024$), or Group x Target interaction ($F_{2,60} = 2.41$, $\varepsilon = 0.99$, $p = 0.099$, $\eta^2_{partial} = 0.074$). Planned contrasts showed that at the Bonferroni-corrected level of significance of $p = 0.0167$, compared to controls, patients had significantly smaller (less negative in voltage) N400 amplitudes for negative adjectives ($F_{1,60} = 17.82$, $p < 0.0001$, Cohen's $d = 0.37$). However, there was no significant difference between groups in N400 amplitude for positive ($F_{1,60} = 1.29$, $p = 0.26$, $d = 0.10$) or neutral ($F_{1,60} = 5.69$, $p = 0.02$, $d = 0.23$) adjectives.

3.3. Correlations of behavioral data and N400 amplitudes with HAMD$_{17}$ scores

Within the MDD group, the correlation of total HAM-D scores with percentage of negative adjectives receiving a "Yes" response ap-
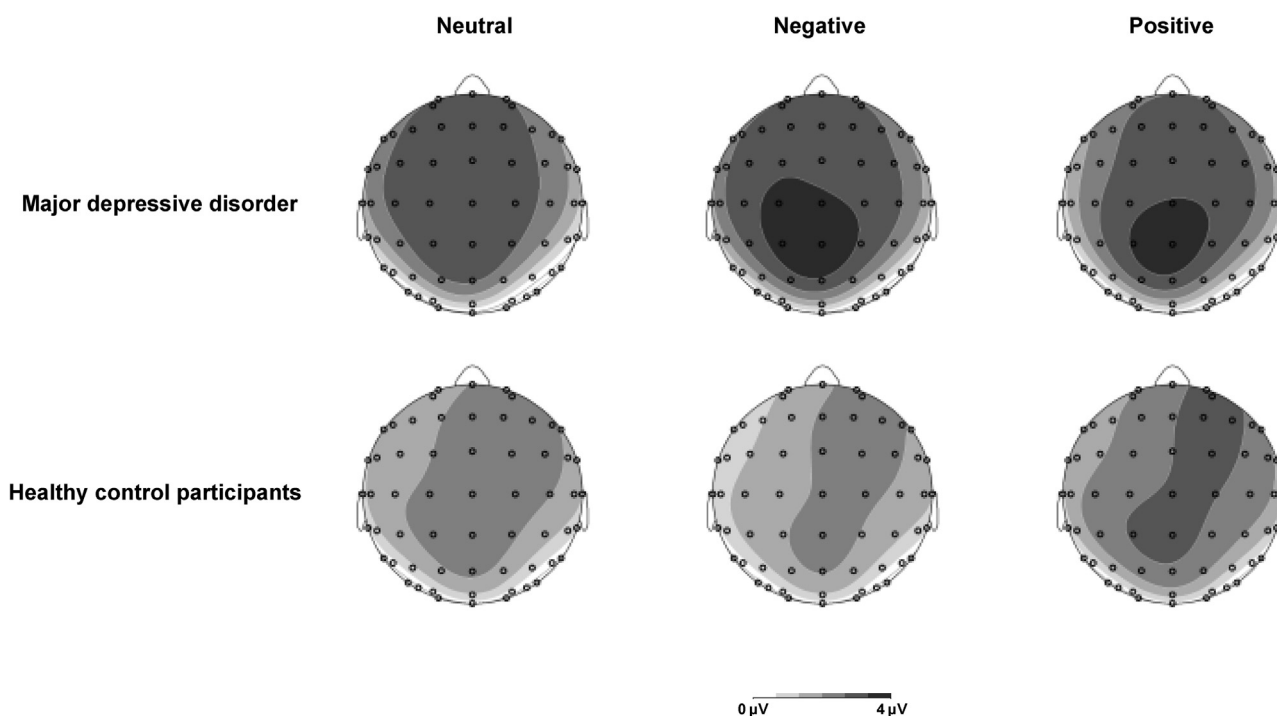
Fig. 3. Topographic map of average ERPs from 350 to 500 ms post-stimulus-onset for the three target types, for healthy control participants and major depressive disorder patients (*n* = 16 per group).

Table 4
Mean N400 amplitude (μV), by participant group and target type.

	HCPs (*n* = 16)		MDD patients (*n* = 16)	
	Mean	SD	Mean	SD
Positive	2.28	2.31	2.58	3.39
Negative	1.70	2.85	2.80	3.15
Neutral	1.91	2.38	2.54	3.12

HCPs, healthy control participants; MDD, major depressive disorder.

proached significance (*r* = 0.48, *p* = 0.06). Correlations of HAM-D scores with percentages of positive (*r* = −0.27, *p* = 0.31) and neutral adjectives (*r* = 0.40, *p* = 0.12) receiving a "Yes" response were not significant.

Within the MDD group, Pearson pairwise correlations between total $HAMD_{17}$ scores and N400 amplitudes (averaged across the above 26 electrodes) for each target condition (positive, negative and neutral) were not significant (all *p*-values > 0.70).

4. Discussion

In this study, we aimed to use the N400 ERP to measure the strength of association of self-concept with positive, negative and neutral characteristics in semantic long-term memory in MDD patients. We measured N400 amplitudes to positive, negative and neutral person-referent adjectives in a self-referential context in MDD patients and healthy controls. Although there was no interaction of group and adjective type on N400 amplitude in an omnibus ANOVA, planned contrasts showed that, compared to controls, MDD patients exhibited significantly smaller (less negative in voltage) N400 amplitudes for negative adjectives in particular. This result suggests that activation of MDD patients' self-schemata is associated with greater than normal activation of concepts representing negative personal traits. These results provide direct, real-time evidence at the neural level for abnormally strong functional links between the concepts of self and of negative traits in semantic memory networks in MDD.

Unlike previous studies which found smaller N400s for positive compared to negative adjectives in a self-referential context in healthy individuals (Chen et al., 2014; Zhou et al., 2013), this comparison was not significant in HCPs in our study. This discrepancy could be due to task differences, as the previous studies required participants to evaluate on different trials whether adjectives applied either to themselves, or an imagined unfamiliar person (Chen et al., 2014); or whether adjectives described themselves either from their own perspective, or from others' perspective (Zhou et al., 2013). In contrast, in our study, participants were asked only to judge whether adjectives applied to themselves. It is possible that the presence of a contrasting condition, in which participants evaluate themselves from another's perspective, or another person from their own perspective, might increase their propensity to prime positive traits when evaluating themselves from a self-perspective.

Although we did not find a statistically significant difference between MDD patients and controls in N400 amplitudes to neutral adjectives, this difference approached significance, with N400 amplitude being numerically more positive in MDD patients than in controls. This may be because, although we defined neutral adjectives as those rated in the middle tercile on a positive/negative valence scale, few adjectives are truly neutral, particularly in the context of characterizing a person (Schindler, Wegrzyn, Steppacher, & Kissler, 2014), and the mean affective valence rating of our neutral adjectives was slightly lower than the midpoint of the scale. Therefore, on average, participants may have been processing neutral adjectives more like negative adjectives than positive ones, resulting in a trend toward MDD patients activating them more than did controls.

Our results provide evidence that, in MDD patients, activation of self-concept in turn primes concepts of negative personal traits to a greater degree than in normal individuals during controlled or conscious semantic processing. However, our study paradigm was not designed to test whether or not this is also true at a more automatic level of processing (Minzenberg, Ober, & Vinogradov, 2002). This is because we used a relatively long time interval (stimulus-onset asynchrony of 1000 ms) between prime and target stimuli, and asked participants to consciously process the semantic relationship between

their self-concept and the target adjectives. Other methods, measuring more rapid and/or unconscious semantic priming, would be required to assess whether or not MDD patients also experience greater than normal automatic priming of negative characteristics in semantic memory after self-concept activation.

A potential confounding factor in our results is that there could be a task-related P300 response overlapping the N400 time window (Roehm, Bornkessel-Schlesweesky, Rösler, & Schlesewsky, 2007), which could vary by group and/or condition and thus affect the N400 results. For example, because CHR patients responded affirmatively more often to negative adjectives than did controls, this could increase the amplitude of a P300 voltage positivity in the same window as the N400, contributing to an apparently smaller (less negative) N400. Because such an effect could fully overlap the N400 time window (Roehm et al., 2007), it is not possible to analyze it separately from the N400. Instead, in order to definitively rule it out, one would have to use a task in which the meaning of the stimuli is not relevant (e.g., making a judgment about physical or lexical characteristics of the stimuli). However, evidence against the presence of a P300 effect in the N400 time window is the fact that even though patients responded "Yes" less often to positive adjectives than did controls, there was no difference in N400 amplitude to positive adjectives between the groups.

Our results fit with a neurocognitive model of MDD in which latent, abnormally negative self-schemata become activated due to stressful life events (Disner et al., 2011; Dozois & Beck, 2008). These self-schemata are characterized by beliefs of oneself as defective and incompetent, leading to sad mood and other cognitive symptoms of MDD such as hopelessness and guilt. The emergence of these schemata is thought to abnormally facilitate processing of emotionally negative stimuli at multiple levels of information processing, including attention (Gotlib, Krasnoperova, Yue, & Joormann, 2004; Kellough, Beevers, Ellis, & Wells, 2008), memory (Koster, De Raedt, Leyman, & De Lissnyder, 2010; Mathews & MacLeod, 2005) and cognitive control (i.e., rumination) (Gotlib & Joormann, 2001), perpetuating depressed mood. Enhanced processing of negative stimuli, in turn, sets in motion a positive feedback loop, in which associations between self-concept and negative characteristics are further strengthened. At the level of semantic long-term memory, the emergence of negative self-schemata presumably corresponds to the induction of abnormally strong functional connections between self-concept and negative features. This would result in greater than normal semantic priming of negatively valenced stimuli in a self-referential context, as we found in the present study.

The presence in MDD of aberrantly active functional connections between self-concept and negative concepts in semantic memory networks could, in turn, perpetuate biases toward processing of negative information at other cognitive levels. Neurophysiological evidence from previous N400 studies suggests that, in healthy individuals, self-referential contexts generate greater expectancies for positive versus negative information (Chen et al., 2014; Fields & Kuperberg, 2015; Zhou et al., 2013). Thus, self-referential contexts facilitate the processing of incoming information that is positive in nature, and this bias extends not only to information that is directly related to the self, but to positively valenced information in general (Fields & Kuperberg, 2015). Conversely, in a reversal of this bias, as suggested by our findings in MDD, self-referential thinking could specifically activate concepts representing negative personal characteristics, and this heightened activation could in turn spread to other associates of these concepts in the semantic network, facilitating retrieval of negative information in general, further perpetuating depressogenic cognition.

A limitation of this study was its small sample size, and larger studies are needed to confirm the generalizability of our results. Moreover, although we excluded MDD patients with substance use disorders, neurological disorders, and psychotic symptoms, other psychiatric comorbidities were not excluded. Thus, it cannot be ruled out that comorbid disorders may have affected the results. However,

given that comorbid psychiatric diagnoses (primarily anxiety disorders) are present in the majority of patients with MDD (Melartin et al., 2002), as they were in our sample, our results may be more representative of a naturalistic population than had they been from a pure MDD sample. In future studies, inclusion of more specific questionnaires measuring specific types of negative emotionality associated with MDD − e.g., anxiety, anhedonia or rumination − could help elucidate whether any of these in particular mediate N400 abnormalities found in the present study.

By identifying an ERP index of aberrant neural activity associated with MDD, our findings point to a potential neurophysiological biomarker of this disorder. If replicable, this N400 measure would be a direct, brain-based, non-invasive biomarker of abnormal self-schema in semantic memory in MDD. As an ERP biomarker of MDD, it would offer the advantages of being relatively inexpensive and non-invasive (Luck, 2005). Moreover, it would not be derived from any behavioral response, which could introduce confounds such as social desirability bias, in which participants respond to self-assessment questions in a manner reflecting how they wish to present themselves to others, rather than their true beliefs (Streiner & Norman, 1995). This N400 ERP biomarker could be investigated for its diagnostic or prognostic utility, alone or combined algorithmically with other recently reported candidate ERP biomarkers of MDD. These include larger late (600–800 msec) positive potentials to negative adjectives in self-referential contexts (Shestyuk & Deldin, 2010), blunted ERP responses to rewards (Nelson, Perlman, Klein, Kotov, & Hajcak, 2016), and reduced late positive potentials to rewarding visual stimuli (Weinberg, Perlman, Kotov, & Hajcak, 2016).

A potential limitation of the present study was that it only cross-sectionally examined MDD patients, the majority of whom were prescribed antidepressant medication. Thus, we were unable to ascertain whether or not antidepressant treatment affects our primary N400 measure. Further, longitudinal studies are warranted to examine whether this is the case, and if so, whether such effects predict antidepressant treatment response. If so, then it could complement the use of cognitive (Tranter et al., 2009) and neuroimaging (Fu, Steiner, & Costafreda, 2013) markers that have shown promise as early predictors of subsequent symptomatic response to pharmacotherapy for depression. Neurophysiological biomarkers of MDD that can predict treatment response are urgently needed in order to reduce the duration of ineffective treatment trials (Breitenstein, Scheuer, & Holsboer, 2014; Olbrich & Arns, 2013; Rush et al., 2006). Therapies for MDD could plausibly normalize N400 abnormalities by reducing aberrant biases toward cognitive processing of negatively valenced stimuli (Pringle, Browning, Cowen, & Harmer, 2011). This would, in turn, reduce the frequency and depth of processing of associations between self-referential stimuli and negative concepts. These changes could result in a diminution of abnormal N400 priming of negative features in a self-referential context, given that N400 effects have been shown to exhibit plasticity in response to the degree of exposure to associations over time (Besson, Kutas, & Van Petten, 1992).

In addition, future studies could examine whether more abnormal N400 priming of negative features in a self-referential context distinguishes a subpopulation of MDD patients that is more likely to respond to particular treatments. For instance, it is plausible that MDD patients who demonstrate this abnormality to a greater degree might be more responsive to cognitive-behavioral therapy, which has as one of its goals the correction of overly negative self-schemata (Kovacs & Beck, 1978). Taken together, such information about the possible predictive value of this N400 ERP biomarker could aid in efforts to develop more personalized and rapid therapeutic strategies for patients with MDD.

Acknowledgments

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