Changes in Neural Circuitry of Language Before and After Treatment of Major Depression

Yalçın Abdullaev,* Barbara L. Kennedy, and Allan Tasman

*Department of Psychiatry and Behavioral Sciences, University of Louisville
Health Sciences Center, Louisville, Kentucky*

Abstract: Language tasks requiring semantic analysis of word meaning activate distinct brain areas including the anterior cingulate gyrus at about 200 msec after the stimulus onset, the left lateral prefrontal cortex at about 250 msec, and the left temporo-parietal (Wernicke's) area at 500–600 msec. Reading the same words activate the insula around 800 msec and left occipital cortex around 200 msec stronger than the semantic analysis in normal subjects. Many of these brain areas also show abnormal activity in resting state in patients with major unipolar depression. We measured 128-channel event-related brain potentials (ERPs) and statistical probability mapping in the use generation task carried out with single visual nouns to explore the topography and time course of these cortical activations related to semantic processing in 11 patients with major unipolar depression before and 8 weeks after treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram. Before treatment in depressed state, the time course for the left prefrontal cortex activation did not show slowing, but was accompanied by the right prefrontal activation with a similar time course. The left posterior temporo-parietal activation appeared later than in normals. Treatment was accompanied by the complete elimination of the right prefrontal activation in the same use generation task. Time course of the posterior left temporo-parietal area showed a trend toward normalization. Insula-related activation in reading task was not seen in depressed state, but was evident in the same patient group after the depression has lifted, presumably as a result of treatment with citalopram. *Hum. Brain Mapping* 17:156–167, 2002. © 2002 Wiley-Liss, Inc.

Key words: major unipolar depression; melancholia; brain mapping; semantic processing; language localization; time course; citalopram; event-related brain potentials

INTRODUCTION

Major unipolar depression is a highly prevalent mood disorder affecting about 5–17% of the general adult population [Blazer et al., 1994; Kessler et al., 1994; Weissman et al., 1996] and increasing risks for

many serious illnesses [Kiecolt-Glaser et al., 2002]. Neuroimaging studies using positron emission tomography (PET) demonstrate that in a passive resting state, patients with unipolar major depression demonstrate abnormal blood flow in a number of brain regions including the prefrontal cortical areas, anterior cingulate gyrus, insula, amygdala, caudate nucleus [Baxter et al., 1989; Drevets et al., 1992; Drevets and Raichle, 1992; Mayberg et al., 1997; Ogura et al., 1998; Tutus et al., 1998; Yazici et al., 1992]. Stroke-related lesions of some of these brain areas also produce depressive syndromes [Kennedy et al., 1997; Robinson et al., 1984].

Many of the same regions are involved in semantic and executive aspects of language in normal subjects

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*Correspondence to: Dr. Yalçın Abdullaev, 3614-B-3 Green Meadows Drive, Louisville, KY 40218. E-mail: yabdullaev@yahoo.com

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[Posner and Raichle, 1997]. Semantic processing of words is often associated in PET studies with activation of the anterior cingulate, the left lateral prefrontal cortex, and the left temporo-parietal (Wernicke) area [Demonet et al., 1994; Petersen et al., 1989; Posner et al., 1988; Posner and Raichle, 1997; Roskies et al., 2001]. Many functional magnetic resonance imaging (fMRI) studies also provide similar results [Buckner et al., 1996b; Demb et al., 1995; Desmond et al., 1995; Poldrack et al., 1999; Spitzer et al., 1996; Xiong et al., 1998]. Anterior cingulate is active in many demanding cognitive tasks and has been linked to the executive attention [Aston-Jones et al., 1999; Bush et al., 1998, 2000; Carter et al., 1999; Posner, 1994; Posner and Rothbart, 1998; Rothbart and Posner, 2001]. ERP studies using semantic and reading tasks provide the time course of these activations and show that the anterior cingulate activation appears first from about 160–180 msec, and is joined by the left prefrontal activation at about 240–260 msec. Activation of the left temporo-parietal area appears later, at about 540–570 msec [Abdullaev and Posner, 1996, 1998; Posner and Pavese, 1998]. When subjects practice the same use generation task many times with the same word list, most of these activations disappear, and the activations in the use generation task become similar to those in reading task [Raichle et al., 1994]. The reading task itself, often used as a control condition for semantic tasks, is associated with activation of the left occipital regions and the right insula [Raichle, 1994; Raichle et al., 1994]. Within this reading-related set of activations referred to as “automatic, reading pathway” [Raichle, 1994; Raichle et al., 1994], the left occipital activity is observed within 170–250 msec [Abdullaev and Posner, 1998; McCandliss et al., 1997; Ziegler et al., 1997], and the right anterior temporal (insula) activity starts at about 700–800 msec and peaks at about 1,100 msec [Snyder et al., 1995] in normal subjects.

Such extensive overlap between brain regions showing abnormal activity in patients with major depression during resting state and those associated with semantic and executive aspects of language in normal subjects may indicate that in major unipolar depression these cognitive functions are carried out by a somewhat altered circuitry. The alterations may include recruiting additional, compensatory brain areas as well as changing the time course and temporal relationships of these local brain activations. The latter may contribute to the often cited but somewhat poorly understood clinical attribute of major depression referred to as “mental slowness”, “slowed thinking”, etc. Therefore, we used ERPs to compare the neuroanatomy and time course of brain activations during

semantic processing of single words in patients with major unipolar depression before and after treatment. Guided primarily by previous neuroimaging data, we asked the following five questions in this study: 1) will semantic encoding of written words during depression show “slowed thinking” in the time course of regional brain activations in comparison with normal performance; 2) if so, will the anterior cingulate, the left prefrontal, or the left temporo-parietal (Wernicke) region activations manifest this “slowing”; 3) will any slowing be correctable after remission of the depressed state after antidepressant treatment; 4) will additional brain areas be recruited in depressed patients to perform semantic task; and 5) if new areas are present during the depressed state, will this difference in neuroanatomy be reversible when the depression is relieved after antidepressant treatment? Part of the results have been reported earlier in abstract form [Abdullaev et al., 2002].

SUBJECTS AND METHODS

Subjects were 11 non-medicated patients aged 28–60 years (mean age = 45) diagnosed with major unipolar depression, melancholic type according to the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [American Psychiatric Association, 1994]. An additional three patients did not complete the study. The 14 patients were consecutively recruited through advertisements via outpatient psychiatry service at the University of Louisville Hospital, provided written informed consent approved by the University of Louisville Human Studies Committee for recording ERPs in cognitive tasks, and for a clinical trial of citalopram (Celexa; Forest Laboratories, NY) for the treatment of unipolar major depression. Citalopram is one of the latest SSRIs approved for the treatment of depression [Keller, 2000]. One subject did not respond to the antidepressant treatment. ERPs from 10 subjects (8 females) with significant clinical improvement after treatment are reported here. Admission criteria included age of 18–65 years, DSM-IV diagnosis of major unipolar depression, no significant neurological history, absence of psychotic comorbidity or substance abuse or dependence (except nicotine) determined by both clinical and structured interviews, minimum score of 18 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D) [Hamilton, 1960]. None had electroconvulsive therapy before. In addition to the major unipolar depression, one patient had obsessive-compulsive disorder, and two had social phobia. All patients received free diagnosis and treat-

TABLE I. Clinical and demographic data of patients

Patient No.	Gender	Age (yr)	Education (yr)	Handedness		Dose (mg)	Depression scores	
				LQ	LS		HAM-D	MADRS
1	F	28	12	100	65	20	23/3	23/1
2	F	45	16	-10	-10	20	24/2	34/1
3	F	50	18	100	65	30	18/7	17/4
4	F	35	13	57	40	20	25/6	38/5
5	F	60	10	100	60	30	23/8	31/5
6	F	51	12	83	50	20	21/3	29/9
7	M	50	12	100	100	30	21/8	32/13
8	F	57	14	100	100	20	26/6	38/8
9	F	39	14	83	50	30	28/10	42/12
10	M	32	14	79	75	20	23/1	36/4
11	M	47	15	100	60	20	22/17	31/26

ment for 4 months, and were paid to participate in two identical ERP recording sessions; before, and after 8 weeks of treatment with citalopram (Celexa). One patient received 9 weeks of treatment before the post-treatment ERP session. Dosage was titrated until optimal clinical improvement with minimal side effects (Table I). Citalopram (20–30 mg/day) was administered once a day at bedtime. No other medication was administered during this period. Handedness of patients was defined by the Edinburgh Handedness Questionnaire [Oldfield, 1971], and both the laterality quotient (LQ) and the laterality scale (LS) were calculated [Schachter, 1993]. Nine subjects were right-handed, one reported equal preference of both hands. All subjects were native speakers of English. Subjects were assessed by both the HAM-D [Hamilton, 1960] and the Montgomery-Asberg Depression Rating Scale (MADRS) [Montgomery and Asperg, 1979] immediately before each of the two ERP recording sessions: at baseline before any treatment and at 8-week follow-up. The assessments were done by two trained raters independently and the consensus was reached on the final score.

The stimulus material consisted of two lists of 100 single nouns. In each trial, a word from one list was displayed visually on a computer monitor for 150 msec. After 1,200 msec, a question mark was presented for 150 msec and served as a response cue to externally pace the subject's response. Each word was presented once within a block. This stimulus set was presented twice in two separate blocks. In the first block, the subject's task was to read the words aloud after the response cue (the reading task). In the second block, the subjects saw the same words (in a different random order) and their task was to say aloud a use for each word (e.g., hammer, pound; broom, sweep)

after the response cue. All subjects received the same task instruction in a written form, and carried out 10 practice trials before each block with a different set of words. In each block and for each patient, the words were presented in a new random order. One list of words was described earlier [Abdullaev and Posner, 1998], the second list of words is presented in the Appendix. Different word lists were used for each subject in the pretreatment and posttreatment sessions, and these two lists were counterbalanced across subjects. This is the same use generation task used in earlier PET and ERP studies [Abdullaev and Posner, 1998; Petersen et al., 1989; Posner et al., 1988; Raichle et al., 1994].

ERPs were recorded using 128-channel recording montage as described in details earlier [Abdullaev and Posner, 1998]. Two frontal (supraorbital) and two infraorbital electrodes were monitored for eye movements. The recorded ERPs were digitized at 250 Hz and automatically edited for exclusion of eye and motion artifacts. Remaining trials were averaged for each task condition separately, referenced to the re-computed average reference, baseline corrected, digitally filtered with 0.1–30 Hz bandpass and grand-averaged across subjects [Abdullaev and Posner, 1998]. Reaction times (RTs) were measured from the onset of the response cue till the subject's voice onset via a microphone channel. Each trial consisted of 200 msec prestimulus and 800 msec poststimulus ERP fragments. The response cue and subject's motor output were outside of the recorded ERP. Intertrial intervals were randomized within 2–5 sec.

The reading aloud task was used as a control condition for the use generation task to isolate brain activity related to the semantic processing. ERPs grand-averaged across the same group of 10 subjects were

Figure 1.

Grand average ERPs from the group of 10 patients with major depression in the use generation and reading aloud tasks before treatment. The figure roughly represents the view of the head from top; subject's front is on the top and subject's left is on the left with each graph approximately illustrating the location of the

recording electrode. Each graph represents ERPs for the reading task (thin line) and the use generation task (thick line). Small vertical line segment on each graph corresponds to the stimulus onset. Positivity is up. The voice onset cue and subjects' verbal responses are outside of recorded ERPs.

computed separately for the reading aloud and the use generation conditions, and separately for the before- and after-treatment sessions. The differences between the reading aloud and use generation tasks were evaluated across all single-subject averaged ERPs using the parametric *t* test. These *t*-test values were computed for every 4 msec sample of every channel, and were interpolated using the same methods as ERPs [T-test software; Hartry, 1994]. The difference waves and the *t*-test waves were interpolated onto the head surface for each 4 msec time sample using spherical splines [Perrin et al., 1989]. Behavioral and clinical data were analyzed by paired *t* test, and analysis of variance (ANOVA) was applied to selected locations (STATVIEW; Abacus Concepts, Berkeley, CA).

RESULTS

Figure 1 displays the grand-averaged ERPs for the use generation and reading aloud tasks from the group of 10 patients before treatment. Similar ERPs recorded from the same group of patients after treatment are illustrated in Figure 2. Main task-related differences are highlighted in *t*-test maps in Figure 3.

In a depressed state before treatment, the middle frontal site showed task-related difference around 160 msec (Fig. 3A) indicating higher activity in the use generation condition in comparison to the reading task. This difference was significant in 13 successive samples within 156–208 msec. Around 180 msec, this midline activation was joined by a right prefrontal

Figure 2.

Grand average ERPs from the same group of 10 patients with major depression in the use generation and reading aloud tasks after the treatment. The format is the same as described in the legend to Figure 1.

difference (Fig. 3A) from 164–200 msec. These right and midline frontal activations were joined by the anterior midline and left prefrontal activations at about 220 msec after the stimulus onset, and this set of left, middle and right prefrontal and slightly posterior midline frontal locations demonstrated (50 successive samples from 248–440 msec) task-related differences until about 400 msec (Fig. 3A). From about 520 msec after the stimulus onset, main activations included the posterior frontal midline site joined by two right-sided activations; one at the right prefrontal location, and the other at the right posterior frontal–anterior temporal location, corresponding to the insula location (in 13 successive samples within 508–556 msec) (Fig. 3A). All these frontal sites were accompanied by a bilateral occipital negativity. The left temporo-parietal activation that we usually see in normal subjects from about 540 msec occurred later in the depressed group, at

about 750 msec after the stimulus onset (in 5 successive samples within 640–656 msec, and in 6 successive samples within 740–760 msec) (Fig. 3A). Another point of interest from studies of normal subjects was the negative (reading greater than use generation) difference in the right (and smaller left) anterior temporal location with onset around 700–800 msec. This negativity, presumably reflecting activation of insula, was not present in depressed group, but its analog occurred as a positive activation (use generation greater than reading task) at an earlier time window around 540 msec (Fig. 3A) (in 13 successive samples from 508–556 msec). Absence of the right anterior temporal difference within 700–800 msec is not explained by an insufficient statistical power as can be seen in the ERP waveforms in Figure 1. Channels 109–110 and 114–117 do not show higher amplitude in the reading task in the later part of the trial.

Figure 3.

Topographic maps of statistical t -test values for the use generation vs. reading aloud between-task comparison before (**A**) and after (**B**) treatment. In color scale, four colors from yellow to red represent four levels of significance (from $P < 0.05$ to $P < 0.001$) of differences for initial positivity in ERPs, four colors from light

blue to dark blue represent the same four levels of significance for negativity in ERPs, and three intermediate colors around white represent nonsignificant values. Poststimulus latency in milliseconds is indicated on each map.

Similarly computed t -test statistical maps of the same subjects after the 8-week treatment course are illustrated in Figure 3B. As can be seen in Figure 3B, successful treatment of depression completely eliminated the right frontal difference. The main task-related differences after treatment were increases in the left prefrontal and midline frontal locations similar to those of normal subjects. Moreover, this task-related difference in the left prefrontal activity was somewhat more sustained over time lasting until about 400 msec (in 33 successive samples within 152–280 msec and again in 33 successive samples within 332–460 msec), and was stronger in amplitude after treatment (Fig. 5A). Disappearance of the right frontal activations in post-treatment images cannot be explained by a lack of statistical power because we compare data for exact same group of subjects before and after treatment, and more importantly, because the difference in the right frontal ERP waveforms has actually reversed, with reading task being more positive than use generation task (Figs. 1,2). This reversed difference in right frontal sites strongly demonstrates the treatment-related change and excludes the possibility of Type II error. Strikingly, the right anterior temporal positive difference (reflecting generation-greater-than-reading difference) presumably representing insula activity has completely disappeared with the remission of depression (520 msec in Fig. 3A,B), and switched to the later right anterior temporal negative difference (reading > generation difference; from 730 msec to the end of recorded trial) similar to what we usually see in nor-

mal subjects (see 756 msec in Fig. 3B). The left posterior temporo-parietal activation didn't seem to show change from the pretreatment state on the statistical t -test maps (Fig. 3B). The ERP waveforms, however, demonstrated a trend toward normalization with both stronger amplitude (Fig. 4A,B) and earlier onset of the task-related difference (Fig. 4A), but these treatment-

Figure 4.

Left temporo-parietal (Wernicke area) ERPs grand-averaged across 10 subjects recorded from channel 58 (**A**) and channel 60 (**B**) before (upper graphs) and after (lower graphs) treatment. Vertical axis represents the amplitude of ERPs and marks stimulus onset (200 msec), each mark corresponds to one μ V, positivity is up. Horizontal axis marks 0 msec, represents time, and each mark corresponds to 100 msec. Thick line represents the use generation task, and thin line represents the reading aloud task.

related differences did not reach statistical significance. It is possible that with more subjects these changes may reach statistical significance.

The left prefrontal activation level has most often been linked to the depressed state as well as to semantic processing in previous studies. We conducted a 2×2 repeated measures analysis of variance with task (use generation, reading) and treatment (before, after) factors. The ANOVA of the left prefrontal site (channel 33) within the time window 160–240 msec showed a significant effect of task (use generation greater than reading, $F(1,18) = 8.15$, $P = 0.01$) and treatment (after treatment greater than before, $F(1,18) = 7.9$, $P = 0.01$), but no significant interaction (Fig. 5A).

To assess possible compensatory treatment-related changes in the insula-related activity, we conducted a similar repeated measures ANOVA for the right insula location. ANOVA of the right anterior temporal (insula) site within the time window 500–560 msec showed significant treatment by task interaction ($F(1,18) = 8.26$, $P = 0.01$), but the main effects of task ($F < 1$) and treatment ($F(1,18) = 3.6$, $P = 0.07$) were not significant (Fig. 5B). This was because task related difference was significant in both before and after treatment sessions but in opposite directions. Before treatment, the use generation task was significantly more positive than reading task ($t = 2.23$, $df = 9$, $P < 0.05$), and this difference reversed after treatment (Fig. 5B). Later, within 610–800 msec, the right insula location demonstrated a significant treatment effect ($F(1,18) = 4.9$, $P = 0.04$) and treatment by task interaction ($F(1,18) = 4.9$, $P = 0.04$), but not significant task effect (Fig. 5C). That was because there were no task-related differences before treatment, and treatment resulted in normalization of activity leading to the task-related difference after treatment ($P = 0.05$).

Table I shows demographic and clinical data of patients before and after treatment. One subject who did not show clinical improvement is included in the table and all clinical (HAM-D and MADRS scores) data reported below, but is not included in the ERP data shown above. Over 90% of patients (10 of 11) reached remission (defined as HAM-D score of 10 or less) at the 8-week follow-up. Each of these 10 patients also satisfied another frequently used remission criterion of reduction of the HAM-D score by 50% or more (Table I). For the whole group of 11 patients, the HAM-D scores showed significant improvement from baseline (23 ± 2.7) to follow-up (6.5 ± 4.5) measurement ($t = 10.569$; $df = 10$; $P < 0.0001$) with an average 72% reduction. The MADRS scores also showed significant improvement from baseline (31.9 ± 7.1) to

Figure 5.

Average ERP amplitudes (in μV) for the left prefrontal site at 150–290 msec (**A**) and the right insula site at 500–560 msec (**B**) and 610–800 msec (**C**) during the use generation and reading tasks before and after treatment. The cross-over interaction in the middle graph indicates that the treatment was effective in reversing the task-related difference in the right insula activity toward normalization.

8-week follow-up (8 ± 7.2) measurement ($t = 8.71$; $df = 10$; $P < 0.0001$) with an average 75% decline. Reaction times are not presented because we used the delayed response design of the task, and subjects responded not after the word but after the response cue (question mark) appearing with a 1,200-msec delay period. The reaction times did not show task-related difference because subjects generated words with above 90% accuracy, and were probably completed the task by the time the cue was presented.

DISCUSSION

Our results show that patients with major depression show both altered neuroanatomy and the prolonged time course of semantic processing. In the first study in depressed-state, early frontal activations of the use-generation task included the anterior midline and left lateral prefrontal regions similar to normal subjects both in location and time course and presumably reflecting activations of the anterior cingulate and left lateral prefrontal cortex. In addition to these, the depressed patients also showed greater activations in the right lateral prefrontal cortex and in the midline posterior frontal location. This set of bilateral prefrontal and bifocal midline frontal activations occurred within 200–400 msec. Later, at approximately 500–600 msec, the expected left temporo-parietal activation was absent in depressed patients and was replaced by a significantly higher activation in the use generation condition in two loci in the right posterior frontal and anterior temporal (insula) locations. The left temporo-parietal activation, usually seen in normal subjects at about 540 msec, appeared later in depressed patients around 750 msec. In summary, semantic processing in depressed state was characterized by diminished and delayed left temporo-parietal activity, inverted anterior temporal (insula) activity (stronger in the use generation task than in reading task), somewhat smaller left prefrontal and anterior midline activity, and also additional strong activation of the right prefrontal cortex.

Successful antidepressant treatment eliminates most of these differences, and we see the same anterior midline, left prefrontal and the left temporo-parietal activations, and negative difference (greater in reading task) in the insula-related right anterior temporal locations, usually observed in normals (Fig. 3B). The late time course of the left temporo-parietal cortex showed a trend toward normalization with the remission of depression (Fig. 4A). Magnitude of the left temporo-parietal difference also showed a trend toward higher amplitude (not significant) after treatment (Fig. 4). We observed also that even though the depressed patients after treatment demonstrated the anterior cingulate and the left prefrontal activation within the early time window, the ratio of these two activations was slightly different from normals. In normals, the anterior cingulate activation appeared earlier, lasted longer, and was stronger than the left lateral prefrontal activation [Abdullaev and Posner, 1998]. In depressed patients after treatment however, the left lateral prefrontal activation had earlier onset, longer duration and stronger amplitude. Somewhat

similar tendency was observed also by George et al. [1997] in depressed patients during the executive attention (Stroop) task, when reduction of PET activation in the anterior cingulate and increase in the left prefrontal cortex was described relative to normal controls.

Changes of brain activations between the baseline and follow-up studies could arguably be related to either remission of depression or practice effect (i.e., performing the same task twice). Earlier PET studies demonstrated that when normal subjects perform the use generation task several times with the same word list, the anterior cingulate, left prefrontal, and left temporo-parietal activations disappear, and the activation of insula (usually seen in reading task) becomes prominent. Replacing the old word list with a new one eliminates this practice effect and restores the initial set of activations [Raichle et al., 1994]. This effect is replicated also with the use of ERPs [Abdullaev and Posner, 1997]. Based on these results, it is unlikely that the ERP differences between the baseline and follow-up visits in our present data are related to practice effect. To avoid the practice effect we used two different word lists for the pretreatment and posttreatment visits, and counterbalanced the lists across subjects. Moreover, practice effect would lead to the weaker midline and left prefrontal and left temporo-parietal activations, and stronger right anterior temporal (insula) activity in the follow-up visit. We see the reverse in our data with insula-related anterior temporal difference being positive and most prominent in the baseline visit, and reversing to the negative (reading > generation) difference in the follow-up visit (Fig. 4B). The left prefrontal difference also shows the reverse of what would have been expected from the practice effect, being more prominent in the follow-up visit (Fig. 4A).

Even though the ERP differences between the baseline and follow-up visits are likely to be related to the remission of depression, these still could arguably be explained by either spontaneous remission (including psychotherapeutic/social/placebo effects) or the antidepressant treatment with citalopram, or the combination of the two. Even though we did not use the placebo control, citalopram has been studied in multiple placebo-controlled clinical trials and has been proven to be a highly effective antidepressant drug [Keller, 2000]. Typically, it has about 70–90% response rate (compared to about 40% for placebo) depending on whether severely depressed inpatients or moderately depressed outpatients are studied, lowering the HAM-D and MARDS scores by about 50–60% (compared to 30–40% of placebo) [Keller, 2000; Mendels et

al., 1999; Stahl, 2000]. The fact that about 90% of our patients responded to treatment with lowering the HAM-D and MADRS scores by about 70% suggests that most of the effects seem to be related to citalopram with relatively smaller contribution of the placebo effect. However questionable this assumption may seem, the main conclusions of the present study are based on the comparison of the depressed and remission states. They primarily demonstrate changes in the neural circuitry of semantic processing during depression and its reorganization after the depression has lifted (for any reason).

The right prefrontal activation is one of the major differences seen in depressed patients during semantic task. This kind of right prefrontal activity is usually seen in normal subjects in tasks that require memory retrieval [Abdullaev and Posner, 1997; Badgaiyan and Posner, 1997; Badgaiyan et al., 1999; Buckner and Koustaal, 1998; Buckner and Wheeler, 2001; Kiefer et al., 1998; Ranganath and Paller, 1999]. Many lines of research in both animals and humans suggest that depression may be maintained by affectively negative memories [Gold and Chrousos, 1999]. Constant ruminations of depressed patients involve memory associations and are likely to be accompanied by the right prefrontal activity. This may explain the right prefrontal activity in a resting state during depression, but is somewhat harder to account for the right prefrontal activity seen within a well-controlled semantic task. Another likely explanation of the functional significance of the right prefrontal activation may be its compensatory role of “filling in” for the insufficient involvement of the left prefrontal cortex. Patients with lesions of the left prefrontal cortex show compensatory activations on the right side in semantic tasks [Buckner et al., 1996a; Muller et al., 1998; 1999; Neville and Bavelier, 1998]. Because of high prevalence of major unipolar depression in general population, it is possible that part of the right prefrontal activations sometimes seen in normal subjects during high-level semantic tasks may have their origin in subjects’ mood state.

According to our results, another likely candidate for compensatory “filling in” for the inefficient semantic circuitry in depressed state may be the insula as a part of the “automatic, reading” pathway [Raichle, 1994; Raichle et al., 1994]. This may explain our results in depressed state when the left temporo-parietal activation seen in normals around 500 msec is absent during depression, and instead we see the right anterior insula-related activation within the same time window. Perhaps because of this “filling in,” we do not see the normal reading > generation difference in

insular activity around 700–800 msec until after the elimination of depression.

Many PET studies of depression show involvement of these same regions in the depression and their changes during treatment. The left prefrontal and anterior cingulate areas often show differences from normals in a passive resting state [Drevets and Raichle, 1992, 1998; Mayberg et al., 1997]. Glucose metabolism in depression is significantly lower in both left and right prefrontal regions including Brodmann areas 9, 44, 45, 46 (areas known to participate in language tasks), anterior insula, and anterior cingulate [Mayberg et al., 1997]. Some of these changes may even predict treatment response. The glucose metabolism rate of the anterior cingulate was predictive of antidepressant treatment outcome when future responders had significantly higher level of glucose metabolism than nonresponders [Mayberg et al., 1997; Wu et al., 1999]. Responders and nonresponders to treatment also showed differences in the lateral prefrontal and insula metabolism [Mayberg et al., 1997]. Normal subjects, when asked to think sad thoughts, also showed activation of these regions [Drevets and Raichle, 1998; Mayberg et al., 1999]. Sadness was accompanied by increased activity in subgenual cingulate and anterior insula and decreased activity in the right dorsolateral prefrontal cortex. Recovery from depression showed a reversed pattern with a decrease in cingulate and insula, and increase in the frontal cortex [Mayberg et al., 1999]. Serotonergic drugs produce metabolic rate increases in the left prefrontal and temporo-parietal areas and decreases in the right prefrontal cortex and insula [Kennedy et al., 2001; Mann et al., 1996]. These changes of regional brain activation levels were shown either in depressed patients in a passive resting state, or in normal controls during induced mood states. It is not known how these cortical regions function in depression during performance of high-level semantic tasks. Our results show that changes of the semantic network during the task involve most of these regions; part of them normalize with treatment of depression, and part of them do not change with treatment. The right prefrontal and anterior insula-related activations were completely eliminated by clinically successful treatment in our data suggesting that these changes reflect the state of being depressed. PET data obtained in a passive resting condition before and after treatment of major depression also suggest that the anterior frontal and insula changes are mood state-dependent [Drevets and Raichle, 1995]. Changes in the left temporo-parietal area also showed change toward earlier onset and higher amplitude, but these changes did not reach significance to appear in the *t*-test map in

Figure 3. It is tempting to interpret this temporo-parietal activation as reflecting the depression trait. However, as the ERP waveforms show (Fig. 4), it is possible that this region activity also changes toward normalization, but more statistical power (e.g., more sample size, i.e. more patients) is needed to uncover it.

Main advantage of the ERPs is high temporal resolution and the ability to measure the time course of local brain activations with a millisecond precision. As such this technique is especially useful for studying major unipolar depression [Spitzer and Kammer, 1996]. Several ERP studies noted delayed ERP components in depression. Vandoollaeghe et al. [1998] found longer latency of the P300 component of ERPs generated in the auditory "odd-ball" target detection task in depressed patients that did not change with antidepressant treatment. The SSRIs have been linked to topographic changes of the P300 in the auditory detection task in normal subjects [d'Ardhuy et al., 1999], with reduction of the P300 amplitude over central and right hemisphere locations.

Cognitive components of language and attention have been relatively well studied in terms of their neuroanatomy and time course [Caplan et al., 1999; Indefrey and Levelt, 2000; Neville and Bavelier, 1998; Posner and Raichle, 1997], but there is very little known about their neurochemical and pharmacological aspects. We believe combining the cognitive neuroscience research with clinical trials employing drugs selective for various neuromediator systems has a potential of uncovering these aspects of cognition. Even the use of highly selective drugs do not guarantee the selective engagement of the target mediator (in our case serotonergic) system because of endogenous interactions between different neuromediator systems [Dewey et al., 1995; Vahabzade and Fillenz, 1994]. For example, it was shown that the SSRIs may increase the dopamine receptor binding in the anterior cingulate and striatum of patients with major depression who respond to treatment, but not in treatment-resistant patients [Larisch et al., 1997]. Thus the question of which changes may be related to the selective serotonergic medication effects, and which may be related to other neuromediator systems, or to a successful antidepressant treatment in general (including psychotherapeutic and placebo effects) can not be addressed in one study. The present study is part of our ongoing studies targeting different neuromediator systems with their selective drugs in an effort to characterize the neurochemical and pharmacological aspects of the brain activations that have been well studied in terms of their cognitive meaning, neural location and time course. With accumulation of more data, these studies

can also provide new insights into cognitive, neural and therapeutic mechanisms of psychopharmacological drugs.

CONCLUSIONS

Semantic encoding of words during major unipolar depression shows "slowed thinking" in the delayed time course of the left temporo-parietal (Wernicke) area activation. During major depression, semantic processing is executed by recruitment of additional brain areas including the right lateral prefrontal cortex at about 250 msec and right insula at about 550 msec. This altered neuroanatomy seems to reflect the depression state and is reversible by the successful antidepressant treatment that employed SSRI citalopram in the present study.

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APPENDIX

Word list 2: arm, army, award,awl, badge, bag, ball, bath, bell, belt, bike, book, box, button, car, carpet, cash, cask, cat, chain, clock, club, coat, coil, college, comb, crew, crib, diaper, dock, doll, door, drug, dust, ear, estate, eye, farm, film, fire, firm, flag, fork, fuel, fur, game, gift, guitar, hair, hall, home, ink, kettle, key, lamp, mall, map, market, match, menu, nail, nest, net, page, pear, pen, pillow, pliers, poem, rail, road, room, ruler, sea, ship, shop, sofa, song, sponge, stream, super, tape, taxi, tea, tent, test, tile, track, trowel, violet, wall, weapon, wheat, wine, wiper, wire, wood, wool, wrench, yacht.