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The Cerebral Glucose Metabolic Response to Combined Total Sleep Deprivation and Antidepressant Treatment in Geriatric Depression: A Randomized, Placebo Controlled Study

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Abstract

A randomized, placebo controlled study was performed to evaluate whether the onset of the glucose metabolic effects of a selective serotonin reuptake inhibitor (paroxetine) would be accelerated by total sleep deprivation (TSD). Patients were randomly assigned to one of three groups: TSD and paroxetine treatment, TSD and two weeks of placebo followed by paroxetine treatment, or two weeks of paroxetine treatment. Sixteen elderly depressed patients who met DSM-IV criteria for major depressive disorder and nine age-matched comparison subjects underwent Positron Emission Tomography (PET) studies of cerebral glucose metabolism at baseline, post-TSD (or a normal night's sleep for the paroxetine only group), post-recovery sleep and two weeks post-paroxetine or placebo treatment (patients only). TSD was not consistently associated with a decrease in depressive

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symptoms between groups nor with decreases in cerebral metabolism in cortical regions that have been associated with rapid and sustained clinical improvement (e.g. anterior cingulate gyrus). The observation of a synergistic antidepressant effect of combined TSD and paroxetine treatment that was observed in a previous “open label”, pilot study was not observed in the present randomized study, consistent with lack of a cerebral metabolic effect in brains regions previously shown to be associated with improvement of depressive symptoms.

Keywords

geriatric depression; selective serotonin reuptake inhibitors; placebo; sleep deprivation; Positron Emission Tomography(PET); glucose metabolism

1.Introduction

Studies conducted over the past two decades have demonstrated that sleep deprivation is associated with a rapid reduction in depressive symptoms in depressed patients across the lifespan (Reynolds et al., 1987a,b, Post et al., 1987, as reviewed by Wu et al., 1990, Leibenluft and Wehr, 1992, Gillin et al., 2001). Total sleep deprivation (TSD) has been shown consistently to decrease cerebral blood flow and metabolism, the extent to which is correlated with the magnitude of clinical improvement (Ebert et al., 1991, Volk et al., 1997, Wu et al., 1999, 2008). Based on these observations, Gillin et al. (2001) suggested that TSD is an “excellent experimental model of antidepressant treatment” that can be used as an intervention platform in both animal and human subjects to investigate the neurobiological mechanisms underlying the antidepressant response. In fact, an understanding of the neurochemical alterations associated with symptom improvement secondary to TSD may inform pharmacotherapy.

Clinical and neuroimaging studies have evaluated the possibility that the acute antidepressant effect of TSD may be sustained by initiating pharmacotherapy after TSD (Szuba et al., 1994, Bump et al., 1997, Benedetti et al., 1997, Green et al., 1999). Studies in patients with geriatric depression have shown that TSD, when performed before treatment with an selective serotonin reuptake inhibitor (SSRI, paroxetine), did result in a rapid and sustained clinical improvement that persisted after a night of recovery sleep and after two weeks of SSRI treatment (Bump et al., 1997). A comparison of the TSD data with archival medication treatment data showed that the clinical response after two weeks of antidepressant treatment was greater when treatment was preceded by TSD compared to medication only (Green et al., 1999). The improvement in depressive symptoms with TSD was accompanied by reductions in cerebral glucose metabolism in certain brain regions (e.g. anterior cingulate gyrus, precuneus) that persisted after recovery sleep and two weeks of antidepressant treatment (Smith et al., 1999). In fact, the regional decreases in metabolism after TSD were correlated with symptom improvement after a twelve week course of SSRI treatment, suggesting that the acute metabolic response may have some predictive value with respect to treatment outcome (Smith et al., 2002b). These previous studies that demonstrated an accelerated clinical and cerebral metabolic effect did not include placebo controls for either the TSD or the medication aspects of the study.

Thus, a randomized, placebo-controlled study was undertaken to determine if an acceleration of the onset of antidepressant response would be observed to a greater extent in patients who underwent combined TSD and paroxetine treatment, as compared to combined TSD and placebo treatment or to paroxetine treatment only without TSD (Reynolds et al., 2005). In contrast to the study hypothesis, the results indicated that greater clinical improvement was observed in the paroxetine only and TSD and placebo treatment groups compared to the TSD and paroxetine treatment group. After controlling for baseline depression severity, there were no statistically significant differences in response or remission rates between the three groups.

Some of the patients enrolled in the clinical study also underwent serial positron emission tomography (PET) studies of cerebral glucose metabolism which is the focus of the present report. We hypothesized that reductions in cerebral glucose metabolism would be observed to a greater extent in patients who underwent combined TSD and antidepressant treatment and that the metabolic alterations would correspond to improvement in depressive symptoms. Reductions in metabolism would be observed in areas including the anterior cingulate, precuneus and increases in occipital cortex as shown to be affected by TSD and antidepressant treatment in prior studies in geriatric depression (Smith et al., 2002a,b).

2.Methods

2.1 Study Design

The design of the treatment study from which the PET subjects were recruited has been described in detail and the results of this larger clinical trial reported (Reynolds et al., 2005). Briefly, the depressed patients and age-matched comparison subjects underwent three consecutive nights of electroencephaologaphy (EEG) sleep studies at the Sleep and Chronobiology Laboratory at the Western Psychiatric Institute and Clinic. The patients were randomly assigned to three groups. The TSD + paroxetine group underwent thirty-six hours of TSD and began treatment with paroxetine on the night of recovery sleep. The TSD + placebo group underwent thirty-six hours of TSD and then began treatment with placebo for two weeks. After two weeks of placebo treatment, the patients began treatment with paroxetine. The paroxetine only group spent three nights in the sleep laboratory and began treatment with paroxetine prior to the third night of sleep (at the same time as the TSD/paroxetine group started treatment). To control for potential differences in treatment expectancies between the TSD and paroxetine only groups, the paroxetine only group underwent an educational session regarding good sleep practices and delayed their bedtime by thirty minutes (the other groups did not undergo this session). The EEG recordings were monitored by a sleep technologist and to ensure none to minimal sleep and if stage 1 to 2 sleep was detected, a buzzer would ring to alert the subject to awaken, to minimize the interaction with the study staff. None of the subjects met criteria for sleep onset, defined as ten consecutive minutes of stage 2 sleep.

The patients underwent four PET scans at the same time of day (10–11am). The first three scans were performed on consecutive days: Scan I: at baseline before TSD, Scan II: 24 hours after TSD and Scan III: after the first night of recovery sleep. The depressed patients had been administered the first dose of paroxetine prior to going to bed on the evening of recovery sleep, so that this PET scan represents the effects of recovery sleep, in addition to the first dose of paroxetine. The depressed patients underwent Scan IV two weeks after paroxetine treatment began. The paroxetine treatment regimen was as follows: A 10mg dose of paroxetine was given at bedtime prior to recovery sleep and the following night. The dose was then increased to 20mg once daily and after two weeks of treatment; the dose was increased to 30mg, if clinically indicated. The clinical trial of paroxetine in all three patient groups continued for a total of twelve weeks.

2.2 Subjects

Depressed patients were recruited from the outpatient clinic of the Intervention Research Center for Late-Life Mood Disorders. The inclusion/exclusion criteria for the patients were the same as for the clinical trial (Reynolds et al., 2005). The criteria included DSM-IV diagnosis of current major depressive episode (non-bipolar, non-psychotic), 17-item Hamilton Depression Scale score ≥ 17 and mini-mental status examination score (MMSE, Folstein et al., 1975) ≥ 17. Subjects were medically stable (as evidenced by physical examination and laboratory testing) and were screened for sleep apnea, which was also an exclusion for the study. Sixteen depressed patients were enrolled in the PET study. (TSD + paroxetine n=7, TSD

+ placebo n=6, paroxetine only n=3). In addition, patients and comparison subjects with a current diagnosis of diabetes (not controlled by diet) were excluded from the PET sub-study. All patients were free of psychotropic medications for a minimum of ten days (four weeks for fluoxetine due to the half life of nor-fluoxetine).This time interval was chosen to allow for at least three half lives of most SSRI's (except fluoxetine) so that there would be no detectable plasma concentration at the time that the study began. Thus despite treatment, the patients were symptomatic enough to meet the study entry criteria for depression severity. Nine age and gender matched normal comparison subjects were enrolled in the study that had no history or current diagnosis of a psychiatric (including major depression) or neurological illness. The comparison subjects had a current Hamilton Depression Scale Score (HDS-17) of 7 or less and a MMSE score of 27 or greater. The normal comparison subjects were recruited by advertisements in the local media

The subject characteristics for the PET sub-study are shown in Table 1. A comparison of the patients enrolled in the PET sub-study to the larger clinical study sample revealed that the two samples were comparable with respect to age, gender composition, mental status and depression severity. Unlike the larger clinical study, however, the baseline depression severity in the three patient groups enrolled in the PET study was comparable. The patients in the clinical study who did undergo PET scanning did not participate due to issues including claustrophobia, exclusions related to the magnetic resonance scan (e.g. metal implants, weight limitations), and logistics. After complete description of the study to the subjects, written informed consent was obtained according to procedures established by the Biomedical Institutional Review Board and the Radioactive Drug Research Committee/Human Use Subcommittee-Radiation Safety Committee at the University of Pittsburgh Medical Center

2.3 Clinical Assessment

As in the previous studies, the 17-item Hamilton Depression Scale (HDS-17; Hamilton et al., 1960, Green et al., 1999, Smith et al., 2002) was administered on a weekly basis and a modified version (13-items total, without the three sleep items and the one item for weight, HDS-13) was administered daily for the first 17 days of the study. The HDS-13 results were reported for baseline, post-TSD, post-recovery sleep and after two weeks of treatment to correspond to the PET studies.

2.4 Neuroimaging

All subjects underwent magnetic resonance (MR) scanning prior to the first PET study. The MR scans were performed at the University of Pittsburgh Medical Center MR Research Center, using a GE Signa 1.5 Tesla scanner (GE Medical Systems, Milwaukee, WI).

The acquisition procedure for the [18F]-2deoxy-2-fluoro-D-glucose ([18F]-2DG) PET studies was the same as the prior sleep deprivation PET study (Smith et al., 1999). PET scans were performed with the Siemens HR+ ECAT PET scanner (Siemens/CTI, Inc., Knoxville, TN). For the PET studies, 5 mCi of [18F]-2DG was injected as an intravenous bolus to measure glucose metabolism. After injection of the [18F]-2DG, the subject was asked to repeat letters as presented on a computer screen. The task was used to keep the subjects' behavioral state constant and to keep the subjects awake during the uptake interval, across scans. The subjects' were observed during the uptake interval by a PET technologist and the subjects' were awakened by the technologist if they fell asleep during the uptake interval. A static emission scan began at 35 minutes after radiotracer injection and lasted for 40 minutes. The averaged frames for the attenuation corrected emission scans was used for image processing.

The image processing and analysis procedures were similar to the previous study (Smith et al., 1999). The data were analyzed using a voxel-wise method, Statistical Parametric Mapping

(SPM99, MRC Cyclotron Unit, Hammersmith Hospital, London, UK, Friston et al., 1991). Global normalization (to 50ml/dl/min) and proportional scaling were used. The co-registered PET images were smoothed with a Gaussian Filter (8 ×8 × 8mm). The PET data was processed by SPM with ANOVA and post-hoc t-tests to detect regions of significant state-dependent change. For the SPM analysis, contrasts were performed for each group comparing the three scans in the controls and four scans in the patients. The significantly different pixels were output by a normalized Gaussian Z-score and their Talairach atlas coordinates provided (Talairach and Tourneau, 1988). A region was reported as significant if it was greater than or equal to 50 voxels and if the Z score was 3.29 or greater ($p < 0.001$, two-tailed).

3.Results

3.1 Clinical Data

The subject demographic characteristics and the mean HDS-13 Scores obtained prior to the PET scans for the baseline, post-TSD, post-recovery sleep and two weeks post-paroxetine treatment conditions for the comparison subjects and patients are shown in Table 1. For each of the treatment groups, the HDS-13 scores are lower for each intervention condition compared to baseline. The groups did not significantly differ on post-hoc testing for the HAMD scores between conditions ($p < 0.1$) The proportion of treatment responders for each group was calculated using a criterion applied in the clinical trial (HDS-13 less than 10). For the TSD + paroxetine group, 2/7 (29%) responded to TSD, 29% (2/7) responded to recovery sleep and 57% (4/7) responded to two weeks of treatment. For the TSD + placebo group, 1/6 (17%) responded to TSD, 50% (3/6) responded to recovery sleep and 33% (2/6) responded to two weeks of treatment. For the paroxetine only group, 67% (2/3) responded after scan 2, 67% (2/3) responded to after scan 3 and 67% (2/3) responded to two weeks of treatment. With respect to the day 2 (recovery sleep) responders, for the TSD+ paroxetine group, 2 patients were responders on Day 2 and one patient on Day 3, for the TSD+ placebo group one patient was a responder on day 2 and 3 patients on day 3 and for the paroxetine only condition the three patients were responders on both day 2 [TSD] and day 3 [recovery sleep];

3.2 Neuroimaging Data

The results of the SPM analysis for the four groups are shown in Table 2. The significant Talairach coordinates, z scores and probability levels are presented. Baseline metabolism was compared between the three patient groups (data not shown). No significant baseline differences between the patient groups were observed.

Non-depressed comparison subjects—After TSD, the subjects showed bilateral decreases in metabolism in the cerebellum that persisted after recovery sleep. Increased metabolism in the right post-central gyrus was observed after both TSD and recovery sleep, while increases in right insula, superior temporal gyrus and inferior occipital gyrus were observed after TSD only.

TSD + Paroxetine—After TSD, metabolism was decreased in the left cerebellum. After recovery sleep, metabolism was decreased bilaterally in the middle temporal gyrus and increased in the left middle frontal gyrus (BA 10). In the comparison of the TSD to the recovery sleep condition, metabolism in the right anterior cingulate and medial frontal gyrus was lower in the TSD compared to the recovery sleep condition, but these areas were not significantly reduced relative to baseline. Glucose metabolism was lower in the recovery sleep compared to the TSD condition in the left inferior frontal gyrus, right cuneus, lefty middle occipital gyrus and right cerebellum (data not shown). After two weeks of treatment, decreased metabolism was observed in the cerebellum (bilaterally) and the right middle frontal gyrus. Increased metabolism was observed in right medial frontal gyrus, left anterior cingulate gyrus, left

inferior temporal gyrus, left post-central-gyrus, right inferior parietal and middle occipital gyri, left putamen and right cerebellum.

TSD + Placebo—After TSD, metabolism was reduced bilaterally in the medial frontal gyrus and cerebellum and in the left precuneus and increased bilaterally in the post-central gyrus and left cuneus. After recovery sleep, metabolism was increased in the right post-central gyrus and left inferior parietal lobule. As was the case for the TSD + Paroxetine group, metabolism was lower after TSD than recovery sleep in the right anterior cingulate, right superior frontal gyrus, right inferior parietal lobule, left precuneus and right cerebellum, but not significant different from baseline, except for the middle frontal gyrus (bilaterally; data not shown). After two weeks of placebo treatment, metabolism was reduced in the right cerebellum and increased in the left middle and inferior temporal gyri, post-central gyrus and posterior cingulate.

Paroxetine—Decreases in metabolism after TSD were observed in the right superior frontal and temporal gyri, left middle frontal gyrus, right middle occipital gyrus, left precuneus and right cerebellum. After recovery sleep, metabolism was decreased in the left inferior frontal gyrus and right cerebellum and increased in the left pre-central gyrus. As shown for the other patient groups, the comparison of the TSD to the recovery sleep conditions, revealed that metabolism in left superior and middle frontal gyri, left precuneus, right middle occipital gyri and right cerebellum was lower after TSD than recovery sleep (data not shown). After two weeks of treatment, metabolism was decreased bilaterally in the inferior frontal gyrus, right middle temporal gyrus and right lingual gyrus and increased in the right pre-central gyrus.

4.Discussion

Consistent with the clinical data in the randomized trial (Reynolds et al., 2005) and the results of the PET sub-study, an acceleration of the metabolic response with combined TSD and paroxetine treatment was not observed compared to TSD and placebo and paroxetine only. The PET results from the present randomized, placebo controlled study differed from the results obtained in the open label pilot study in several respects. First, the patients enrolled in both the clinical randomized pilot study and the PET sub-study demonstrated a lesser degree of acute and chronic clinical improvement in the combination of TSD and antidepressant treatment. With respect to the PET data in the present study compared to the pilot study, reductions in metabolism relative to baseline after TSD, recovery sleep and treatment were not observed in brain regions that have been previously shown to be significantly associated with clinical improvement of depressive symptoms with TSD, recovery sleep and paroxetine treatment (e.g. anterior cingulate and precuneus (Smith et al., 1999). In contrast, in all three patient groups, glucose metabolism was lower in the TSD compared to the recovery sleep condition in all three patient groups in regions shown previously to be affected by TSD (anterior cingulate gyrus, superior frontal gyrus, precuneus). However, relative to baseline, these regions did not show reductions. Thus, the reductions in metabolism after TSD were not observed in the present study that persisted with recovery sleep as we had observed in the prior study.

The lesser magnitude of cerebral metabolic response to TSD, recovery sleep and two weeks of paroxetine treatment in the present study compared to the previous study appears to be consistent with the lesser degree of clinical improvement observed. Some aspects of the metabolic findings that we observed in both comparison subjects and patients were consistent with the previous PET study. These findings include the decrease in cerebellar metabolism after TSD and recovery sleep and the increase in post-central gyrus metabolism after TSD (TSD + placebo) and recovery sleep (comparison subjects, TSD + placebo). Other neuroimaging studies of sleep deprivation effects have also noted changes in functional response in these brain regions (Bell-McGinty et al., 2004, Terney et al., 2005).

With respect to the control subjects, in the pilot study (Smith et al., 1999) the controls demonstrated significant changes in metabolism only in the comparison of the recovery sleep condition to baseline (decreases in frontal and occipital cortices). In the present study, we observed decreases in the cerebellum with TSD and recovery sleep and increases in the post-central gyrus in both condition, as well as increases in temporal and occipital cortices in the TSD condition compared to baseline. In addition to differences in the subject samples, the other possibility that might explain the differences in metabolic response is that perhaps subtle differences in the clinical effects of TSD in the controls between studies may not have been detected by the clinical measures used (e.g. Kahn-Greene et al., 2007).

While the data must be regarded as preliminary due to the small sample size, the other unexpected observation was the reduction in depressive symptoms and cerebral metabolism observed in the paroxetine only group even though these patients spent three nights in the sleep laboratory and had a regular night's sleep. Changes in cerebral glucose metabolism similar to those observed with antidepressant treatment have been observed in placebo treated patients in pharmacological studies (Mayberg, et al., 2002). In the present study, in addition to clinical improvement, these patients also demonstrated decreases in metabolism in some brain regions (left superior and middle frontal gyri and left precuneus) that have been shown to be altered by both TSD and antidepressant treatment (Smith et al., 1999, 2002, Buchsbaum et al., 1997, Kennedy et al., 2001). The factors that might explain the placebo metabolic effect may include the removal of the patients from a stressful environment and the fact that the placebo subjects enter into a "research relationship" with the investigators, with the expectation that their symptoms might improve. Admittedly, these factors may also have affected response in the other groups. In addition, the session regarding sleep hygiene in the paroxetine only group may have had an effect in these subjects. At the same time, it is important to acknowledge that the session regarding sleep hygiene may not be sufficient to control for the substantial antidepressant effects of citalopram. Because of the small sample size of the paroxetine only group; these results should be regarded as preliminary. Future studies might include a fourth group that did undergo a normal night's sleep and two weeks of placebo treatment to address the placebo response issue more completely.

The factors that should be considered in evaluating the differences between the findings in the pilot study of TSD and paroxetine treatment and the randomized study, include differences in the study samples, clinical and neuroimaging procedures and image processing and analysis methods. Admittedly, the sample size of the pilot and randomized studies are relatively small, but consistent between studies (6 patients in the pilot study and 3–7 patients in the pilot group. With respect to the study samples, variables including demographic (age, gender distribution) and clinical characteristics (diagnosis, depressive symptomatology, global cognitive impairment) were considered. The comparison of these variables across studies (and in the present study between the patients who enrolled in the PET study relative to those who were enrolled in the clinical protocol only) indicated that the samples were comparable in these respects. With respect to the sleep deprivation protocol, the only difference is that in the first study, a sleep technologist would speak to the subjects if there was EEG evidence that the subject was falling asleep. In the second study, a buzzer would ring to alert the subject, to minimize the interaction with the study staff. The other issue regarding the experimental design is that the group that was not sleep deprived did undergo a brief session on sleep hygiene, which may have had a therapeutic effect. The possibility that might explain the differences in metabolic response in the control group is that perhaps subtle differences in the clinical effects of TSD in the controls may not have been detected by the clinical measures used. The technical issues regarding the scan protocol (radiotracer synthesis and administration, conditions during radiotracer uptake, scan acquisition protocol, analysis and scanner resolution) were similar between studies. A different version of the statistical parametric mapping software was used

(SPM95 versus SPM99 in the present study, which should not have significant effect on the results as these versions of the program are similar.

There are neurobiological factors associated with variability in antidepressant treatment response that may have differed between the study samples and produced a differential response across studies. These factors might also explain the observation that the TSD + paroxetine subjects did do worse than the paroxetine only group at all time points which was unexpected, based on the results from the open label study. These variables include the serotonin transporter promoter or 5-HT1A receptor, or other polymorphisms related to antidepressant response (e.g. Pollock et al., 2000, Parsey et al., 2006), structural brain alterations including white matter hyperintensity burden and white matter functional connectivity (decreased fractional anisotropy; Hickie et al., 1995, Alexopoulos et al., 2008). The available functional neuroimaging data, obtained mainly in younger depressed patients) would suggest that variability in treatment outcome may be associated with differences in glucose metabolism (relatively higher cingulate metabolism, e.g. Mayberg et al.,1997) or increased 5-HT1A receptor availability (Parsey et al.,2006).

As measures of cerebral glucose metabolism represent a final common pathway of neurochemical activity, the data are extremely useful with respect to informing the design of mechanismtic studies designed to elucidate the neurochemical mechanisms underlying the cerebral metabolic effects. Studies in two independent samples of patients have demonstrated increased cerebral glucose metabolism in geriatric depression in the untreated state in such regions as the superior and middle frontal gyrus, middle temporal gyrus, precuneus and posterior cingulate (Smith et al., 2004). These regions have been implicated in attention processes and comprise the “default network” that is active in the resting state in normal controls and hyperactive in depressed patients (Greicius et al., 2007). Studies of acute and chronic antidepressant (citalopram) treatment, as well as sleep deprivation, in geriatric depression show decreases in these regions with treatment that are correlated with the improvement of depressive symptoms (Smith et al., 2002a,b). The primary neurotransmitter within these cortico-cortico networks is glutamate (Fagg and Foster, 1983). TSD has been associated with increased neurotransmission and gene expression for a number of neurochemical systems functionally linked to glutamate (serotonin, dopamine, acetylcholine), as well as genes related to energy metabolism, trophic factors, synaptic related proteins and hormones (Maudhuit et al., 1996, Weseman et al., 1983, Fadda et al., 1992, Tsai et al., 1994, Cirelli and Tononi et al., 2000). Thus, the neurochemical effect that may underlie the changes in cerebral metabolism with TSD in geriatric depression may involve a secondary effect of the increase in monoamine and/or acetylcholine on the glutamate system that may occur to a greater extent in patients who demonstrate an antidepressant effect of TSD. Given the similarity between the functional neuroanatomic changes that occur with citalopram and TSD, a serotonergic mechanism is likely to be involved.

The results of this randomized, placebo controlled study do not provide support for an acceleration of the onset of the cerebral metabolic effects of paroxetine by TSD and are consistent with the lack of clinical effects observed. Metabolic reductions in certain brain regions (e.g. anterior cingulate and precuneus) were not observed in the present study that have been previously associated with clinical improvement secondary to TSD (Smith et al., 1999, 2002). The results should be considered as preliminary due to the small sample size and the possibility of subject sampling issues. The use of TSD as a safe, non-pharmacologic intervention to induce a antidepressant effect remains a potentially important experimental strategy that can be applied, in combination with neurochemical imaging and genetics methods, to investigate the neurobiological mechanisms associated with changes in the depressive state and to identify the factors that might explain the heterogeneity of the acute antidepressant response and the potential relationship to long-term clinical outcome.

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Table 1

Subject Demographic Characteristics and Hamilton Depression Scale Score (13-item)

	Age	Gender (M/F)	MMSE Score	Hamilton Depression Scale Score (13-item)			
				Baseline	Post TSD	Post-Recovery	Post-Treatment (2week)
Healthy Controls	67.8 ± 4.9	3/6	29.7 ± 0.5	0.75 ± .9	0.87 ± 1.0	0.13 ±0.35	
Paroxetine	71.4 ± 6.0	0/3	29.7 ± 0.6	15.7 ± 3.4	9.7 ± 2.9	6.3 ± 5.5	5.3 ± 5.5
TSD/Paroxetine	69.0 ± 4.6	0/7	28.8 ± 0.7	15.7 ± 3.6	13.6 ± 4.2	14.4 ± 5.0	9.4 ± 3.7
TSD/Placebo	68.6 ± 4.9	3/3	30.0 ± 0.0	16.3 ± 4.8	13.0 ± 5.4	10.2 ± 5.4	12.5 ± 7.9

Table 2

The Cerebral Metabolic Effects of Sleep Deprivation Recovery Sleep and Two Weeks of Treatment (paroxetine/placebo) in comparison subjects and patients with geriatric depression

Talairach Coordinates (x,y,z; mm)	Name of Region	z score	Cluster Size
Comparison Subjects			
Decrease with Sleep Deprivation			
28 −68 −36	Right Cerebellum	5.20	1686
−22 −76 −36	Left Cerebellum	4.56	1863
Increase with Sleep Deprivation			
46 −30 20	Right Insula	4.15	2805
40 12 −16	Right Superior Temporal Gyrus	3.89	2805
50 −26 36	Right Post-Central Gyrus	3.85	2805
22 −94 −10	Right Inferior Occipital Gyrus (BA 17)	3.38	684
Decrease with Recovery Sleep			
−30 −74 −34	Left Cerebellum	3.84	685
22 −78 −38	Right Cerebellum	3.75	508
Increase with Recovery Sleep			
50 −26 36	Right Post-Central Gyrus	3.33	73
TSD + Paroxetine			
Decrease with Sleep Deprivation			
−44 −76 −36	Left Cerebellum	3.32	333
Decrease with Recovery Sleep			
−54 −50 0	Left Middle Temporal Gyrus	3.70	2034
52 −42 8	Right Middle Temporal Gyrus (BA 21)	3.63	190
Increase with Recovery Sleep			
−4 54 0	Left Middle Frontal Gyrus (BA 10)	3.84	191
Decrease after Two Weeks of Paroxetine Treatment			
36 62 6	Right Middle Frontal Gyrus (BA 10)	3.67	171
40 −48 −42	Right Cerebellum	4.35	223
−50 −44 −26	Left Cerebellum	3.37	327
After Two Weeks of Paroxetine Treatment			
−6 54 −2	Anterior Cingulate	4.10	361
8 38 −18	Right Medial Frontal Gyrus	3.97	815
−52 −14 −22	Left Inferior Temporal Gyrus	3.29	171
−48 −26 44	Left Post-Central-Gyrus	4.60	1356
−26 −2 4	Left Putamen	4.25	668
46 −34 46	Right Inferior Parietal Lobule (BA 40)	3.79	605
34 −76 −8	Right Middle Occipital Gyrus	3.29	244
TSD + Placebo			
Decrease with Sleep Deprivation			
−4 42 −10	Left Medial Frontal Gyrus (BA 10)	4.50	1377
2 26 −18	Right Medial Frontal Gyrus (BA 25)	4.18	1377

Talairach	Name of Region	z score	Cluster Size
Coordinates (x,y,z; mm)			
−6 −46 46	Left Precuneus	3.67	279
24 −78 −34	Right Cerebellum	3.63	447
−30 −76 −38	Left Cerebellum	3.59	1002
Increase with Sleep Deprivation			
−30 −36 58	Left Post-Central Gyrus (BA 02)	4.13	419
44 −24 44	Right Post-Central Gyrus (BA 02)	3.67	307
−8 −64 8	Left Occipital (Cuneus)	3.47	609
Increase with Recovery Sleep			
44 −24 46	Right Post-Central Gyrus (BA 02)	4.37	1417
−38 −48 56	Left Inferior Parietal Lobule	4.08	458
Decrease Two Weeks of Paroxetine Treatment			
2 −54 −10	Right Cerebellum	3.64	1252
Increase after Two Weeks of Paroxetine Treatment			
−66 −12 −10	Left Middle Temporal Gyrus (BA 21)	3.43	342
−42 −14 −28	Left Inferior Temporal Gyrus	3.39	97
−40 −32 48	Left Post-Central Gyrus	3.79	1055
−10 −60 14	Left Posterior Cingulate	4.07	408
Paroxetine Only			
Decrease with Scan 2			
24 48 40	Right Superior Frontal Gyrus (BA 08)	3.50	81
−30 40 42	Left Middle Frontal Gyrus	3.84	174
36 14 −20	Right Superior Temporal Gyrus (BA 38)	3.62	107
−36 −80 34	Left Precuneus (BA 19)	3.61	136
38 −82 10	Right Middle Occipital Gyrus (BA 19)	4.08	175
8 −66 −28	Right Cerebellum	3.43	128
Decrease with Scan 3			
−48 26 −4	Left Inferior Frontal Gyrus	3.35	404
8 −66 −28	Right Cerebellum (Posterior)	3.67	252
Increase with Scan 3			
−54 4 34	Left Pre-Central Gyrus (BA 06)	3.50	259
Decrease after Two Weeks of Paroxetine Treatment			
56 6 16	Right Inferior Frontal Gyrus (BA 44)	3.44	75
−48 26 −4	Left Inferior Frontal Gyrus	3.82	504
48 6 −18	Right Middle Temporal Gyrus (BA 38)	3.86	5334
4 −72 2	Right Occipital (Lingual Gyrus)	4.80	1617
Increase after Two Weeks of Paroxetine Treatment			
−54 2 36	Left Pre-Central Gyrus (BA 06)	3.32	87