SLEEP DEPRIVATION EFFECTS ON MOOD AND BRAIN CHEMISTRY IN UNIPOLAR DEPRESSION

by

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Abstract

Background. Partial or total overnight sleep deprivation has been shown to produce immediate antidepressive effects in about half of patients suffering from depression. This very rapid and robust response creates an opportunity to investigate the neurochemical changes associated with the improvement of depressive symptoms. **Objectives.** Neurochemical correlates of responses to sleep deprivation were assessed in two brain regions of eleven young women with unipolar depression and of healthy controls, using localized proton magnetic resonance spectroscopy (^{1}H-MRS) in a 1.5 tesla magnet. Neurochemical responses to sleep loss were expected to differ between depressed and control participants, and to correlate with the degree of mood improvement shown. **Methods.** Participants were scanned on baseline day and at the same time of day 24 h later after having had the opportunity to sleep for only 2.5 h (22:30-01:00). Two spectroscopic volumes were selected: the left anterior dorsal prefrontal (LADPF) region and the pons. Three neurochemical signals were analysed, in reference to internal water (H_2O): *N*-acetylaspartate (NAA), Choline compounds (Cho), and total creatine-plus-phosphocreatine (tCr). Changes in the severity of depressive symptoms were monitored repeatedly using the Profile of Mood States (POMS) and a short version of the Hamilton Depression Inventory (HDI). **Results.** About half the depressed participants showed at least 30% improvement in HDI mood (Responders), while the remainder showed no change or worsening in mood after sleep restriction (Non-responders). Baseline pontine Cho:H_2O values were abnormally low in subsequent Non-responders but not in subsequent Responders to sleep loss. After sleep restriction, a significant 17.9% increase in mean Cho:H_2O was observed in the LADPF region of the Depressed group, and a 20.1% decrease in pontine tCr:H_2O of Depressed and Control groups combined. At baseline, greater sadness (HDI) in depressed participants was associated with lower prefrontal NAA:H_2O. After sleep restriction, an improvement in Fatigue (POMS) in depressed participants was correlated with the degree of reduction in pontine Cho:H_2O. **Conclusions.** Phospholipid metabolism appears to be implicated in the antidepressant effects of sleep deprivation in both pontine and LADPF regions. Changes in creatine metabolism in the pons after sleep restriction may be found in both healthy and depressed people.

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Chapter 1 Introduction

1.1 The Syndrome of Depression

A systematic review of epidemiological studies of affective disorders reported pooled rates of 4.1% for the one-year prevalence of major depressive disorder (MDD), and 6.7% for lifetime prevalence (see Waraich, Goldner, Somers, & Hsu, 2004). In fact, statistical projections have estimated that by 2030, unipolar depressive disorders will be the second leading cause of disability-adjusted life years for all medical conditions (see Mathers & Loncar, 2006). In addition to the substantial emotional distress experienced by the affected individual and his/her family, the financial burden to society is considerable. Statistics computed for England in 2000 showed that 109.7 million working days were missed, due to incapacity to work as a result of depression (Thomas & Morris, 2003).

Some patients never recover from a first episode of major depression, and the disorder becomes chronic. Even when recovery occurs, recurrences of depressive episodes are frequent, and the probability of further recurrences increases with each successive episode (see Solomon et al., 2000). A 10-year follow-up in a naturalistic, observational study of showed that 318 patients recovered out of an initial sample of 366 patients (age 17 years and more) suffering from a first episode of primary, unipolar depression. Of these 318 individuals who recovered, 202 later experienced a recurrence of the disorder. Over time, the risk of a further recurrence was estimated to increase by 16% at each successive episode (see Solomon et al., 2000).

The clinical expression of major depression encompasses a variety of symptoms (Drevets

& Todd, 1997b). The chief complaint is a physical symptom, anergia, which is accompanied by a lack of motivation. Other neurovegetative manifestations may include sleep disturbances, alterations in appetite, and loss of libido. Depressed people also report the intrusion of negative emotions, irritability and anxiety along with the absence of positive emotions (anhedonia, or absence of pleasure in previously pleasurable activities). Psychological manifestations consist of self-reproach, ruminations on past failures, hopelessness, and sometimes impaired insight and poor judgment. A preoccupation with death or suicide is present in 60% of patients; these thoughts are described as intrusive and difficult to control. Psychosomatic manifestations like headaches, gastrointestinal complaints, and cardiovascular symptoms, as well as psychomotor manifestations like agitation or retardation may be present (Drevets et al., 1997b).

Criteria for diagnosis of depression include two paramount clinical symptoms, depressed mood (sadness) and anhedonia, which are experienced all day (or almost all day) for at least the last two weeks (American Psychiatric Association, 2000). At least three more symptoms from the following list must also be present: weight loss, sleep disturbances, psychomotor agitation or retardation, fatigue, excessive guilt, difficulty concentrating and suicidal ideations. These symptoms represent a significant change from how the patient felt previously; they also create significant distress, and they cannot be attributed to a physiological or medical condition, or to bereavement.

Once the diagnosis has been made according to these clinical criteria, the severity of depressive symptoms can be monitored over time using a validated rating scale. One such

rating scale that has been widely used in research studies is the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), but other validated scales, for example the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1992), have been used as well.

Two main strategies for treating unipolar depression are pharmacological treatments and psychotherapy. The Health Evidence Network has published a summary of the main categories of pharmaceutical and psychological treatments that have demonstrated efficacy in treating depression (see Moller & Henkel, 2005). The types of antidepressant medications traditionally used to treat depression include tricyclic drugs (TCAs), heterocyclic drugs, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). Newer drugs, like noradrenergic reuptake inhibitors and drugs that inhibit both serotonin and noradrenergic reuptake (SNRIs), are also sometimes used.

The main theoretical orientations used for brief psychotherapy include psychodynamic, interpersonal, supportive and cognitive-behavioural models. Compilation of data from several studies has shown that antidepressant medication and psychotherapy are equally effective, at least in the acute period of treatment; furthermore, combining these two forms of treatment has been shown to be beneficial, especially in the reduction of relapse rates (see Moller et al., 2005).

Electroconvulsive therapy (ECT), which is performed under anesthesia, is sometimes used for severe depression. A meta-analysis concluded that short-term benefits of ECT

are probably greater than those of drug therapy; however, relapse rates are high (see Geddes et al., 2003). Neurostimulation therapies also include vagus nerve stimulation, a long-term treatment used concomittantly with pharmacotherapy; repeated transcranial magnetic stimulation applied to the left dorsal lateral prefrontal cortex, an acute treatment that has been mainly used as monotherapy; and deep brain stimulation, which is still considered in the early stages of investigation (see Marangell, Martinez, Jurdi, & Zboyan, 2007).

Other forms of therapeutic intervention have been investigated. For example, antidepressant properties have been described for bright light therapy (Neumeister et al., 1996), and for manipulations of the timing of the normal sleep-wake schedule (Wehr, Wirz-Justice, Duncan, Gillin, & Goodwin, 1979). Sleep deprivation therapy is a widely studied therapeutic intervention for depression, which is discussed in detail below.

1.2 Sleep Deprivation Therapy for Depression

1.2.1 Effects of Sleep Deprivation in Depressed Patients

In 1978, a study of sleep deprivation therapy for depression was published, involving 47 patients divided into a group treated with antidepressant medication as a monotherapy, and a group treated with medication combined with sleep deprivation therapy (Pflug, 1978). Results showed a shorter duration of depressive episodes in the group of patients treated with both medication and sleep deprivation, as compared to the group with antidepressant medication monotherapy. Thereafter, numerous experiments have been conducted with the goal of replicating these findings and identifying the main factors

associated with the antidepressant effects of sleep deprivation therapy.

A typical protocol for sleep deprivation therapy starts with a regular night of sleep (on patients' normal sleep schedule). Patients then stay awake and avoid napping for the following day (baseline day) while repeated measures of the severity of depressive symptoms are collected. Patients maintain wakefulness during the following night and day (sleep deprivation day) under close supervision, while the collection of repeated measures of the severity of depressive symptoms continues. Total duration of the wakefulness period is around 35 to 40 h. At the end of this period of prolonged wakefulness, patients are allowed a full night of recovery sleep on their usual schedule, and repeated measures of depressive symptoms are collected again on the following recovery day. This design is called total sleep deprivation therapy, and it is the standard approach to this form of treatment for depression.

Numerous reviews of sleep deprivation studies conducted with depressed patients have summarized the available evidence for effectiveness (see following: Gillin, 1983; Wehr, 1990; Wu & Bunney, 1990; Kuhs & Tolle, 1991; Leibenluft & Wehr, 1992; Demet, Chicz-Demet, Fallon, & Sokolski, 1999; Wirz-Justice & Van den Hoofdakker, 1999; Ringel & Szuba, 2001; Giedke & Schwarzler, 2002). These reviews reported that amongst several hundreds of patients suffering from different subcategories of depression who have undergone this form of therapy, about half responded with a transient, but substantial alleviation of their depressive symptoms. The nature and time course of sleep deprivation effects on the severity of depressive symptoms were described in detail in

one of the earliest investigations of sleep deprivation therapy (Gerner, Post, Gillin, & Bunney, 1979). Twenty-five depressed patients were selected for total sleep deprivation therapy, while self-report measures of the severity of depressive symptoms were collected every 2 h throughout the protocol. Results showed that following a night of sleep deprivation, patients felt better than they had on the preceding baseline day on three different clusters of symptoms: (1) depressive mood (sad, depressed, hopeless), (2) dysphoria (anxious, restless, angry, difficulty concentrating), and (3) activation (elation and talkativeness).

On the other hand, the same protocol of prolonged wakefulness conducted concurrently with twenty healthy volunteers had either no effect or a detrimental effect on the same measures (Gerner et al., 1979). After a night of total sleep deprivation, healthy participants had worse ratings than on the baseline day for the dysphoria and activation items, whereas ratings did not differ for the depressive mood items. The depressed and control groups differed significantly on all three clusters of symptoms, in terms of the pre-/post-treatment change scores: there was improvement on every scale in the depressed group, while there was worsening of ratings on every scale in the control group. On the recovery day, ratings of symptoms were back to baseline values in both depressed and control groups (Gerner et al., 1979).

Fourteen patients (67%) reported an alleviation of their depressive symptoms during the period of prolonged wakefulness (Responders), whereas seven patients (33%) did not improve (Non-responders). On the baseline day, no significant difference was observed

between these two subgroups on any of the three scales. The between-subgroup divergence in self-reported measures (improvement versus worsening of symptoms) started during the sleep deprivation night at around 03:00 for the activation items, followed by the depressive mood items at 05:00 and finally by the dysphoria items at 09:00. At these time points, self-reported scores started to markedly improve in Responders, while they dropped (or remained low) in Non-responders (Gerner et al., 1979).

During the recovery day (after overnight recovery sleep), the Responder subgroup still reported a statistically significant alleviation of the depressed mood items (as compared to baseline), while self-reports on the two other scales had returned to baseline levels. Surprisingly, on the recovery day the Non-responder subgroup showed a marked and significant elevation of scores on the activation items collected at 09:00 and 11:00. This burst of elation and talkativeness disappeared at 13:00 (Gerner et al., 1979).

Another sleep deprivation study (Szuba, Baxter, Jr., Fairbanks, Guze, & Schwartz, 1991) assessed the change in the severity of different depressive symptoms by collecting self-reports every 2 h during the daytime periods of a two-day sleep deprivation protocol (baseline day and sleep deprivation day). Thirty-seven patients with major depression self-rated their symptoms on the POMS, which included six subscales: Depression, Fatigue, Vigour, Tension, Confusion, and Anger. In Non-responders to sleep deprivation, there was no significant change in the severity of depressive symptoms on any of the six POMS subscales throughout the 2-day protocol. Responders, however, showed a

progressive and sustained alleviation of their depressive symptoms, as compared to baseline measures. On the POMS Depression subscale, Responders reported an alleviation of depressed mood during the post-sleep deprivation day starting at 07:00 or 09:00; the improvement became more pronounced at 11:00 and was maintained until 19:00. Improvement on the Confusion and Anger subscales was observed later in the day. Scores on both subscales showed a trend toward worsening of symptoms at the 07:00 and 09:00 time points; however, starting at 11:00 and maintained until 19:00, there was a clear and sustained improvement of these symptoms in Responders. No more self-ratings were collected after 19:00 on the sleep deprivation day (Szuba et al., 1991).

The differential impact of sleep deprivation on various depressive symptoms was described in another sleep deprivation study involving 30 inpatients with severe endogenous depression, which is a depression occurring without any identifiable psychosocial stressor (Schilgen & Tolle, 1980). Trained clinicians assessed the severity of depressive symptoms twice a day (morning and evening) on the baseline day and on the day following the sleep deprivation night, using a scale derived from the Hamilton Depression Rating Scale. Beneficial effects of sleep deprivation were observed on all symptoms. However, the scores on items targeting the affective components of the depressive syndrome (mood, anhedonia and suicidal ideations) showed a greater reduction after sleep deprivation than the scores on the items targeting the somatic aspects (physical symptoms) of the syndrome (Schilgen et al., 1980).

Summary

Taken together, studies using sleep deprivation therapy for depression reported that it triggered a statistically and clinically significant alleviation in the severity of depressive symptoms in about half of depressed patients. The evolution of changes in the severity of symptoms was described in detail in one study (Gerner et al., 1979): improvement started during the early morning hours and was sustained during the whole day of prolonged wakefulness. The greatest beneficial impact was observed on the affective components (mood and anhedonia) of the depressive syndrome (Gerner et al., 1979; Schilgen et al., 1980). After a full night of recovery sleep, a relapse in depression was typically reported for Responders (Gerner et al., 1979). Non-responders showed no change or a slight worsening in the severity of symptoms during the whole protocol (Gerner et al., 1979).

1.2.2 Detrimental Effects in Healthy Volunteers

Several research studies have assessed the impact of prolonged wakefulness using research designs that included only healthy and well-functioning people. One such study involved 25 young military people 20-35 years of age, who underwent 56 h of continuous wakefulness (Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007). Self-reports were collected using the Personality Assessment Inventory (PAI), a scale assessing personality features (Morey, 1991). Participants completed the PAI at around 15:00 on the baseline and sleep-deprived days. The difference scores showed a significant increase in self-reports of somatic complaints, depressive mood, anhedonia, and physiological symptoms of anxiety, along with some worsening in mistrust and feelings of hostility and persecution during sleep deprivation. Prolonged wakefulness did not affect scores on

manic symptoms, psychotic or antisocial features (Kahn-Greene et al., 2007).

Another study used a naturalistic design to evaluate the impact of sleep deprivation in 20 young physicians (24-35 years of age), using the POMS self-rating questionnaire along with choice reaction time and vigilance reaction time tasks (Orton & Gruzelier, 1989). Measures were collected toward the end of a normal day of work, and again at a similar time on another day of work that was continuous with a night "on duty". On the day following sleep loss, the physicians reported significant worsening on all the POMS subscales (Depression, Fatigue, Vigour, Tension, Confusion, and Anger) relative to baseline scores; they also scored lower in friendliness and positive affect. Moreover, tests of reaction time showed that sleep deprivation had a detrimental effect on central processing and on vigilance tasks, with slower reaction times for both (Orton et al., 1989).

Indeed, normal human functioning is markedly affected by sleep deprivation. A summary of findings from 19 research studies involving 1932 participants provided information about the strength and consistency of sleep deprivation effects in healthy volunteers (see Pilcher & Huffcutt, 1996). Partial sleep deprivation was defined as less than 5 h of sleep in a 24 h period; short-term total sleep deprivation, as less than or equal to 45 h of prolonged wakefulness; long-term total sleep deprivation, as more than 45 h of prolonged wakefulness. This meta-analysis concluded that the performance level of sleep-deprived participants was 1.37 standard deviations below the performance level of non-sleep-deprived participants. Surprisingly, the overall effect was much stronger for partial sleep

deprivation than for either short-term or long-term total sleep deprivation. The authors pointed to this unexpected finding as a target for future research. More precisely, partial sleep deprivation had a markedly more detrimental effect on mood and cognitive performance than either short-term or long-term total sleep deprivation. When data were pooled from participants undergoing the three types of sleep deprivation, they showed more impairment for mood than for cognitive performance, the latter being in turn more affected than motor performance. Effect sizes were -3.16 for mood, -1.55 for cognitive performance, and -0.87 for motor performance (see Pilcher et al., 1996).

Summary

Prolonged wakefulness or some level of sleep deprivation in healthy people has been shown to increase ratings of depressive mood, anhedonia, somatic complaints, mistrust and hostility (Kahn-Greene et al., 2007). Detrimental effects on cognitive abilities were also reported: slower reaction times were observed for central processing and vigilance tasks (Orton et al., 1989). Finally, a meta-analysis of several sleep deprivation studies in healthy participants demonstrated an increase in depressed mood, somatic complaints, anhedonia and physiological symptoms of anxiety, as well as a detrimental effect on vigilance and cognitive performance (see Pilcher et al., 1996). This effect was generally opposite to the improvement of depressive symptoms (more pronounced for mood and anhedonia) that was observed after sleep deprivation therapy in more than 50% of depressed patients (see Wu et al., 1990; see also Giedke et al., 2002).

1.2.3 Alternative Forms of Sleep Deprivation Therapy

Studies have compared the effects of partial and complete overnight sleep deprivation therapy on the symptoms of depression. Based on the fact that the improvement in depressive symptoms was reported to begin late during the usual sleep phase (Gerner et al., 1979), it was hypothesized that sleep deprivation during the second half of the night (called late partial sleep deprivation) would be as effective as a full night of sleep deprivation (Schilgen et al., 1980).

Thirty inpatients with major depression were allowed to sleep from 21:00 until 01:30, at which time they were required to get up and stay awake until the following evening (Schilgen et al., 1980). Results showed that 67% of patients experienced a moderate to considerable alleviation of the severity of their depressive symptoms on the day following this partial sleep deprivation protocol. The authors concluded that the effects of partial sleep deprivation during the second half of the night were as potent as those described previously for a night of total sleep deprivation (Schilgen et al., 1980).

In a later study (Giedke, Klingberg, Schwarzler, & Schweinsberg, 2003), direct comparisons were made between the effects of late partial sleep deprivation and those of total sleep deprivation. Thirty-nine inpatients with major depression underwent both protocols (partial and total sleep deprivation) in a randomized, crossover design a week apart. After the first course of treatment (either total or partial sleep deprivation), and as assessed by the clinicians, the rate of positive response to sleep deprivation was 53% (9/17) in patients who underwent total sleep deprivation, and 27% (6/22) in patients who

underwent late partial sleep deprivation (Giedke et al., 2003). The antidepressant effects of the initial course of sleep deprivation were compared to those of a second course of sleep deprivation during which patients were crossed over to the alternate treatment. Second treatments yielded a smaller response compared to the initial treatment (regardless of sleep deprivation condition); this finding was attributed to the fact that patients were less depressed at the time of second treatment and had less capacity for improvement. Final results showed that total sleep deprivation produced a statistically significant greater improvement over partial deprivation for only one self-report scale, suggesting a slightly greater benefit from total sleep deprivation therapy (Giedke et al., 2003).

The finding that half a night of sleep deprivation might be almost as effective as total sleep deprivation raised the issue of what the ideal timing of partial sleep deprivation should be for the best antidepressant effect. One study compared the effects of late partial sleep deprivation to those of early partial sleep deprivation (Sack, Duncan, Rosenthal, Mendelson, & Wehr, 1988). Sixteen inpatients with major depression underwent both partial sleep deprivation protocols in a randomized, balanced order and crossover design a week apart. Electroencephalographic (EEG) recordings were obtained; total duration of sleep was a maximum of 5 hours in each condition. Results showed that patients improved significantly more after late than after early partial sleep deprivation, as assessed by trained clinicians. With the late sleep deprivation protocol, 10 patients were classified as Responders and six as Non-responders. With the early sleep deprivation protocol, only four patients were classified as Responders, and 12 as Non-responders.

The authors concluded that late partial sleep deprivation was more effective than early partial sleep deprivation (Sack et al., 1988).

One potential limitation was outlined by the authors in regard to the interpretation of these findings (Sack et al., 1988). In the late sleep deprivation condition, the group averaged 3.62 h of sleep, but in the early sleep deprivation condition, they averaged 5.54 h. Thus, although patients spent equal durations in bed in both conditions, EEG recordings showed that they slept less in the late sleep deprivation condition. In addition, in the late sleep deprivation condition, the amount of clinical improvement in Responders was negatively correlated with total sleep obtained. Therefore, it may be that the less potent effects of early sleep deprivation resulted from the less severe sleep loss patients experienced in this condition.

A similar limitation might also account for the findings from another study in which the effects of late and early partial sleep deprivation protocols were compared directly, but EEG was not recorded (Szuba et al., 1994). Sixteen inpatients with major depression were assigned randomly to either early or late partial sleep deprivation. In the late sleep deprivation group, patients were allowed to rest in bed from 22:00 until 02:00 (4 h of rest), whereas in the early sleep deprivation group, patients rested in bed from 02:00 until 07:00 (5 h of rest). They found that the antidepressant effects of the late partial sleep deprivation protocol were statistically superior to those of the early sleep deprivation protocol (Szuba et al., 1994).

The additional hour in bed for the early sleep deprivation patients might have allowed more sleep in this condition. Furthermore, patients going to bed at 02:00 would be more likely to fall asleep quickly than those going to bed at 22:00. Therefore, early sleep deprivation could have permitted longer sleep durations (i.e., less actual sleep loss) than late sleep deprivation in this study, which could contribute to a less potent antidepressant effect for the early deprivation condition.

Another study compared the antidepressant effects of early and late partial sleep deprivation directly (Leibenluft, Moul, Schwartz, Madden, & Wehr, 1993). Twenty-six patients with major depression were randomly assigned to either condition; each patient underwent four cycles of the assigned partial sleep deprivation protocol over a period of two weeks. In the late sleep deprivation group, rest in bed was prescribed from 22:00 until 02:00; in the early sleep deprivation group, rest in bed was from 03:00 until 07:00. Thus, each group spent 4 h in bed, but EEG recordings were not collected so actual sleep durations are not known. Several mood ratings and biological measures were collected repeatedly throughout the protocol. There were no group differences (between early and late partial sleep deprivation conditions) in any measures either acutely in response to the first sleep deprivation cycle or chronically in response to repeated sleep deprivation protocols (Leibenluft et al., 1993).

A single study compared the antidepressant effects of early and late partial sleep deprivation protocols directly, while insuring that total sleep time was kept constant between the two conditions by recording sleep EEG (Giedke, Geilenkirchen, & Hauser,

1992). Twenty-five patients with major depression underwent both sleep deprivation protocols in a crossover design. Twelve patients were randomly assigned to start with early sleep deprivation, while 13 were assigned to start with late sleep deprivation. The two treatments were separated by a period of six days or more. Total sleep time was similar between the two conditions (about 180 min, with the averages differing by only 5 min). There was a marked and significant alleviation of depressive symptoms in both partial sleep deprivation conditions (Giedke et al., 1992). The analyses of variance yielded no significant differences in the mean antidepressant effects between the two sleep deprivation conditions on any measures of the severity of depressive symptoms over time. The authors concluded that antidepressant effects are similar in both sleep deprivation conditions if total sleep time is equated between the two conditions. Based on these findings, they hypothesized that total duration of sleep restriction (i.e., accumulated sleep debt) is the active agent triggering beneficial effects, rather than the specific timing of partial sleep restriction (Giedke et al., 1992).

Summary

Total sleep deprivation may be slightly more potent than partial sleep deprivation (Giedke et al., 2003). In several studies, however, a partial sleep deprivation approach was favoured because it is quite effective and might be easier for patients to accept. Early and late partial sleep deprivation protocols have been shown to be equally potent when total sleep time during the study was equated between the two conditions (Giedke et al., 1992), suggesting that the duration of sleep lost, not its timing, is primarily responsible for improvement of depressive symptoms. Consistent with this idea, the amount of

clinical improvement following a partial sleep deprivation protocol has been shown to be negatively associated with total sleep time during the period of bed rest (Sack et al., 1988).

1.2.4 Effects of Daytime Naps

Brief episodes of sleep during the day of prolonged wakefulness may reverse the beneficial effects of sleep deprivation therapy. A study involving 12 patients with major depressive disorder allowed an early afternoon nap during the day of prolonged wakefulness (Wiegand, Berger, Zulley, Lauer, & Von Zerssen, 1987). Patients were free from antidepressant medication for at least eight days prior to the start of the study. The afternoon nap did not have an impact on the depression scores of those who were Non-responders to sleep deprivation. However, afternoon naps produced two different types of effects in Responders to treatment. After the nap, half of the Responders experienced a reversal of the beneficial effects initiated by sleep deprivation, while the other half reported no change in their depression scores. It was noted that Responders who relapsed after the nap slept longer on average during their afternoon nap (119.7 min.), as compared to Responders who did not relapse (61.8 min.). The authors attributed the differential impact of afternoon naps in patients of the Responder group to the differences in total sleep time during the nap, and they concluded that sleep episodes during the prolonged wakefulness day may have a detrimental impact on the antidepressant effects triggered by sleep deprivation therapy.

Other studies have reported different effects of naps interrupting prolonged wakefulness

among depressed patients who did not benefit from sleep deprivation. In one study, 19 depressed inpatients underwent total sleep deprivation therapy (Gillin, Kripke, Janowsky, & Risch, 1989). Sixteen patients were free from medication from 1 to 14 days or more prior to the start of the study, and three were on stable antidepressant medication. A 10 min nap was permitted during either the morning or afternoon of the extended wakefulness day. Neither nap timing condition affected the mood of those who responded with improvement to sleep deprivation (n = 6). On the other hand and surprisingly, the brief nap triggered a significant alleviation of symptoms in the group of Non-responders (n = 13). This result may be related to the report of a transient increase in activation in Non-responders following a recovery night's sleep (Gerner et al., 1979).

Another study reported a beneficial impact of naps in Non-responders (Reist, Chen, Choeu, Berry, & Bunney, 1994). A 90 min nap was permitted at noon, during the day of prolonged wakefulness. All patients were free from antidepressant medication for at least 14 days prior to the start of the study. Fifteen patients (71%) responded positively to total sleep deprivation, while six patients (29%) did not benefit from the treatment. After the nap, the Responder group experienced a significant relapse of depressive symptoms; the relapse was further accentuated after the following night of recovery sleep. The Non-responder group showed a slight improvement (not statistically significant) in their depression scores during the period of prolonged wakefulness. Surprisingly, a further and significant improvement was observed after the nap. However, after the following night of recovery sleep, a relapse into depression occurred for this group as well.

Even ultra-short periods of sleep (lasting at least 15 seconds and also called micro-sleep periods), which can be observed through continuous EEG recordings, have been postulated to have a detrimental impact on the antidepressant response to sleep deprivation (Hemmeter, Bischof, Hatzinger, Seifritz, & Holsboer-Trachsler, 1998). Twelve medicated inpatients with major depression underwent a partial sleep deprivation protocol (waking at 01:30). The total duration of micro-sleep periods during the prolonged wakefulness day discriminated between Responders and Non-responders to sleep deprivation: Responders had significantly less micro-sleep than Non-responders. In addition, the beneficial response to sleep deprivation was significantly and negatively associated with the duration of micro-sleep observed during the period of prolonged wakefulness.

Summary

Depressed patients who do not benefit from sleep deprivation therapy may respond to a nap interrupting the day of sustained waking with either no benefit or with some mood improvement. On the other hand, in Responders to sleep deprivation, naps and even micro-sleep periods can attenuate the beneficial effects of sleep loss.

1.2.5 Response Rates in Bipolar and Unipolar Depression

One review suggested that patients with bipolar depression might be better Responders to sleep deprivation than those with unipolar depression (Giedke et al., 2002). At least two sleep deprivation studies with reasonable sample sizes have found no statistical differences in the proportion of Responders between patients with bipolar and unipolar

depression (Baumgartner, Graf, Kurten, Meinhold, & Scholz, 1990; Gerner et al., 1979). On the other hand, at least three other sleep deprivation studies with reasonable sample sizes have reported better responses in patients with bipolar than those with unipolar depression.

In one study, 80 medicated patients underwent total sleep deprivation therapy (Fahndrich, 1981). By self-report, 17/22 (77.3%) of bipolar patients and 8/19 (42.1%) of those with involutional depression responded positively. Involutional depression is a marked depression first occurring during middle age; bipolar depression is a form of depression that can be preceded or followed by episodes of mania (extremely elevated mood and energy, and racing thoughts) or hypomania (a less severe form of mania). Of patients having depression during the phase of remission from schizophrenia and those with neurotic depression, 6/10 (60%) and 1/13 (0.07%) responded, respectively. Neurotic depression refers to the absence of psychotic symptoms. Thus, patients with bipolar depression showed the most robust response to total sleep deprivation.

In a study using a late partial sleep deprivation approach, a higher rate of response was also found among patients with bipolar rather than unipolar depression: 89% (8/9) of patients with bipolar I disorder (alternating depression and mania), 38% (9/24) of those with unipolar depression, and 0% (0/4) of those with bipolar II disorder (alternating depression and hypomania – a milder form of illness) responded to the treatment (Szuba et al., 1991).

Hypothesizing that different concomitant antidepressant medications might account for the unipolar-bipolar differences reported previously, another study addressed this question in 51 medication-free patients with depression (Barbini et al., 1998). After three total sleep deprivation cycles, a significant alleviation of depressive symptoms was observed in each group of patients. The magnitude of improvement was highest for the bipolar II and major depressive episode groups, followed by the bipolar 1 group and finally, by the major depressive disorder group. The antidepressant effects of sleep deprivation appear to vary with type of depression, independently of medication use, and with bipolar disorder patients showing the strongest responses (Barbini et al., 1998).

Summary

Several well-designed studies have reported no difference in response to sleep deprivation between unipolar and bipolar depression (Gerner et al., 1979; Baumgartner et al., 1990), or better response rates in bipolar patients than in other diagnostic categories (Fahndrich, 1981; Szuba et al., 1991; Barbini et al., 1998). It is not clear whether patients with bipolar I or II disorder respond more favourably.

1.2.6 Manic or Hypomanic Responses to Sleep Deprivation Therapy

There are concerns that sleep deprivation therapy might trigger hypomanic or manic episodes, particularly in patients with bipolar depression (non-rapid cycling subtype) as compared to patients with unipolar depression. In one large study, 206 inpatients with bipolar depression (without psychotic features) underwent repeated total sleep deprivation protocols either alone or concurrently with heterogeneous antidepressant

medications (Colombo, Benedetti, Barbini, Campori, & Smeraldi, 1999). Patients who underwent sleep deprivation therapy responded with hypomania in 5.8% of cases, and with mild or moderate mania in 4.9% of cases, yielding a total 'switch rate' of ~11%.

The frequency of such overshooting responses to sleep deprivation therapy can be compared with the natural rate of spontaneous switch into mania reported in untreated patients with bipolar depression, and with the frequency of manic switch reported during antidepressant medication treatment. A retrospective study (see Peet, 1994) pooled and compiled published data to create two groups of patients treated with two different types of antidepressant medications, along with a third group of patients treated with placebo. In the group of bipolar inpatients treated with placebo, the naturalistic rate of switch into mania was found to be 4.2%; this rate was not statistically different from the 3.7% rate of switch found in bipolar patients treated with SSRIs (serotonin re-uptake inhibitors). Bipolar patients treated with TCAs (tricyclic antidepressants) showed a substantially and significantly higher rate of manic switch: 11.2% (see Peet, 1994). On the other hand, in the group of patients diagnosed with unipolar depression, the rate of manic switch was found to be less than 1%, irrespective of drug treatment (SSRIs, TCAs, or placebo).

Summary

The results summarized above indicate that sleep deprivation therapy can trigger manic or hypomanic episodes in patients with bipolar disorder to the same extent as treatment with TCAs (~11%). This rate appears to be higher than what would be expected from the naturalistic course of the illness (4.2%), or from treatment with SSRIs (3.7%), suggesting

a specific tendency for bipolar patients to respond to sleep loss with overly elevated moods.

1.2.7 Diurnal Mood Variations on Baseline Day: A Predictor?

Several authors have discussed the predictive value of the course of mood changes occurring spontaneously during the baseline day prior to sleep deprivation. Three studies reported that patients with a positive diurnal variation of mood (feeling better in the evening) on the baseline day had a significantly better response to a subsequent night of sleep deprivation than did those without such baseline mood variation (Elsenga & Van den Hoofdakker, 1987; Riemann, Wiegand, & Berger, 1990; Haug, 1992). One interpretation of these results is that the spontaneous improvement observed during the late afternoon and evening of the baseline day simply continued on the same trajectory during the following night and day in the absence of the usual nighttime sleep episode (see Wu et al., 1990).

The frequency and nature of diurnal variations in symptom severity was assessed in an older study involving ten inpatients with depression, using a structured interview every evening during their stay on the ward (an average of about two months). Patients were asked to compare the intensity of several symptoms in the evening to how they had felt in the morning of the same day (Stallone, Huba, Lawlor, & Fieve, 1973). Considering either global assessments of their mood or specific items yielded similar results: most days showed no difference between morning and evening (57.2%), while mood improved in the evening on 24.5% of days, and got worse in the evening on 18.4% of days.

Autocorrelation analyses indicated that there was very little predictability across successive days; the direction of mood change, if any, seemed to be random over days. In their discussion, the authors questioned the classical view that spontaneous diurnal variations in intensity of symptoms would be a typical feature of the depressive syndrome.

These findings suggesting that diurnal variations in mood were not typical of depression were replicated by another study using a within-subject design and a larger group of inpatients (n = 72) with endogenous depression (Tolle & Goetze, 1987). Over five days of assessment, the purportedly typical positive diurnal variation in symptoms occurred in only about one third of patients. The authors stressed the very large intra-individual variability in findings observed over the five days of longitudinal assessment.

Another study used a within-subject design and data from 34-39 inpatients with endogenous depression (data were sometimes missing), assessed over an average of 95 days. These data were reported from different perspectives in three separate research reports (Reinink, Bouhuys, Gordijn, & Van den Hoofdakker, 1993; Gordijn, Beersma, Bouhuys, Reinink, & Van den Hoofdakker, 1994; Gordijn, Beersma, Bouhuys, Korte, & Van den Hoofdakker, 1995). Findings from longitudinal assessments of mood during the patients' stay at the hospital showed that no diurnal variation of mood occurred on 72.6% of days, while a positive variation (feeling better in the evening) occurred on 20.8% of days, and a negative diurnal variation on 6.6% of days. The frequency of spontaneous diurnal mood variations did not differ between periods of severe depression and periods

of improvement.

The measure that showed the strongest correlation with a beneficial response to sleep deprivation therapy was the standard deviation of diurnal mood fluctuations (r = .65). This positive association remained statistically significant even when corrected for the other measures of mood fluctuation (e.g., % of positive and negative diurnal variations). On the other hand, the association between positive diurnal variations on baseline day and response to sleep deprivation was initially significant, but did not remain significant when corrected for the other measures of mood fluctuation. The authors concluded that the frequency and the direction of diurnal mood variation on the baseline day were not the best predictors of a beneficial response to a subsequent night of sleep deprivation. The extent of variability in diurnal mood ratings (i.e., the standard deviation of spontaneous mood variations), irrespective of the direction, was the most powerful predictor of a beneficial response to sleep deprivation therapy.

Summary

Data from studies using within-subject designs have demonstrated that the parameter that best predicted a positive response to sleep deprivation was a high degree of spontaneous diurnal variability in severity of depressive symptoms, irrespective of the direction and as assessed in a longitudinal design. The authors hypothesized that instability in diurnal mood fluctuations may be associated with sensitivity to environmental factors and sensitivity to sleep deprivation.

1.2.8 Sleep Deprivation Therapy Combined With Pharmacotherapy

Rates of responding to a single night of sleep deprivation therapy do not appear to be affected by the presence or absence of concurrent, stable antidepressant medication (see Wu et al., 1990). However, relapse rates after the immediate response (during and after recovery day) might be affected by whether patients are medicated or not (see Wu et al., 1990, Table 1; see also Giedke et al., 2002, Table 1). Averaging across the results of 17 sleep deprivation studies, relapse rates on recovery day were 59.3% for patients who were medicated, as opposed to 82.7% for patients who were not medicated at the time of sleep deprivation therapy.

In fact, combining pharmacotherapy with sleep deprivation therapy was shown to enhance and prolong the beneficial effects of sleep deprivation in a sample of 40 inpatients with depression (bipolar type) who were randomly assigned to one of two treatment groups: sleep deprivation combined with pindolol or sleep deprivation combined with placebo (Smeraldi, Benedetti, Barbini, Campori, & Colombo, 1999). In the sleep deprivation plus pindolol group, 75% of patients were defined as Responders; seven days later, 70% of patients in this group still met criteria for a complete response. On the other hand, only 15% of patients in the sleep deprivation plus placebo group met the criteria for Responders; one week later, the response was maintained in only 5% of the patients in this group. The authors speculated that combining pindolol with sleep deprivation therapy created a synergistic interaction between the two forms of treatment, and decreased the rates of early relapse after a full night of sleep.

Ongoing treatment with lithium carbonate was also reported to increase and lengthen the beneficial effects of sleep deprivation in 40 inpatients with bipolar depression (Benedetti, Colombo, Barbini, Campori, & Smeraldi, 1999). One half of patients were under stable, long-term treatment with lithium carbonate; the other half did not receive psychotropic medications. Results showed that 70% (14/20) of patients with lithium had a beneficial effect from sleep deprivation therapy, as opposed to 25% (5/20) of patients in the sleep deprivation monotherapy group. At the end of a three-month follow-up period, 13/20 patients with lithium had maintained the positive response, as opposed to 2/20 patients from the sleep deprivation monotherapy group. Therefore, the combined therapy approach enhanced and prolonged the effects of sleep deprivation therapy in a synergistic way that could be maintained for several months.

The superiority of a combined therapy approach might be evident only some weeks after initiating treatment (Kuhs, Farber, Borgstadt, Mrosek, & Tolle, 1996). Fifty-one patients with major depression were randomly assigned to one of two treatment groups: amitriptyline monotherapy (n = 24) or amitriptyline combined with sleep deprivation therapy (n = 27). Sleep deprivation therapy consisted of six partial late-sleep deprivation protocols (waking at 01:30), conducted at 4 or 5-day intervals. Both groups improved significantly and similarly during the first two weeks of treatment. However, during the third week of treatment, a further improvement was observed in the combined therapy group and not in the monotherapy group. At the end of the four-week experimental period, the overall therapeutic effect was greater and the proportion of Responders was higher in the combined therapy group, as compared to the monotherapy group. The

authors stressed the importance of a long enough follow-up period for the assessment of therapeutic effects.

Summary

Available data support the hypothesis that combining pharmacotherapy with sleep deprivation therapy augments and prolongs the effects of sleep deprivation in patients with bipolar depression (Smeraldi et al., 1999; Benedetti et al., 1999), as well as in patients with unipolar depression (Kuhs et al., 1996).

1.3 Brain Imaging Studies of Sleep Deprivation in Healthy Humans

1.3.1 Functional Imaging Studies

Positron emission tomography (PET) studies and single photon computerized tomography (SPECT) studies use a scanning technique that allows the assessment of brain metabolic activity. Depending on which radiopharmaceutical product is used, these methods can provide information about oxygen metabolism, blood volume or blood flow in the brain.

Three PET studies involving 57 healthy volunteers assessed the effects of a night of total sleep deprivation on cerebral metabolic activity. Sleep deprivation caused a decrease in whole brain global cerebral metabolic activity in one of these studies (Thomas et al., 2000), but not in the other two (Wu et al., 1991; Wu et al., 2006). The most consistent finding pertains to the region of the thalamus where significant decreases in relative regional metabolic activity were observed after sleep loss in all three studies.

Significant decreases in regional metabolic rates were also reported in the caudate (Wu et al., 1991; Wu et al., 2006), putamen and globus pallidus (Wu et al., 1991; Wu et al., 2006; Thomas et al., 2000), in the frontal (Wu et al., 2006) and prefrontal regions (Thomas et al., 2000), in temporal (Wu et al., 2006) and parietal regions (Thomas et al., 2000), in cerebellum (Wu et al., 1991), mesopontine and pontine regions (Thomas et al., 2000).

Conversely, significant increases in regional metabolic rates have been reported after sleep deprivation: the most recent study, which also involved the largest sample size (n = 32), reported significant increases in regional metabolic activity in the occipital region, in addition to the decreases in other brain regions (Wu et al., 2006). In this same group of participants, a full night of recovery sleep increased and normalized regional metabolic rates in frontal regions, but not in subcortical regions (Wu et al., 2006).

1.3.2 Magnetic Resonance Spectroscopy Studies

Magnetic resonance spectroscopy (MRS) is a non-invasive brain imaging technique used to assess concentration levels of some biochemicals in the brain. Single proton magnetic resonance spectroscopy (^{1}H-MRS) and phosphorus magnetic resonance spectroscopy (^{31}P-MRS) are the MRS techniques used most frequently in psychiatric research.

Three MRS studies assessed the effects of sleep deprivation in healthy humans during a 'resting state'; i.e., participants simply remained in a supine posture in the scanner, with

no task to perform other than staying awake. Data were initially reported for a group of 14 healthy volunteers who were scanned during two consecutive mornings, before and after a night of total sleep deprivation (Murashita, Yamada, Kato, Tazaki, & Kato, 1999). Phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) was used with a 1.5T scanner, while selecting the frontal lobes as the volume of interest. The following peaks were measured as a fraction of the total phosphorus signal: phosphomonoester (PME), inorganic phosphate, phosphodiester (PDE), creatine phosphate (PCr) and three peaks from nucleotide triphosphates (see Appendix 1 for a brief summary of the postulated functional roles of these neurochemicals in the brain, and section 1.6 for a more detailed discussion).

In all the neurochemicals assessed, sleep-deprived volunteers displayed one of two different patterns of change after prolonged wakefulness. Some participants responded with increased levels of neurochemical concentrations, while other participants showed decreased values. Therefore, the group mean values in neurochemical concentrations did not change significantly after one night of sleep deprivation. The authors hypothesized that healthy humans may, just like patients with depression, show two different patterns of response to a night of total sleep deprivation.

Non-significant pre/post-treatment changes were also reported in a study involving 11 healthy young volunteers (Dorsey et al., 2003). ^{31}P-MRS was performed with a 1.5T scanner during three consecutive mornings: before and after a night of total sleep deprivation, as well as after a full night of recovery sleep. A large volume of interest was

selected in the medial prefrontal region. On the morning of prolonged wakefulness, there was no change in any % peak area measures of regional brain phosphorus metabolism (concentrations expressed as a fraction of the total phosphorus signal), as compared to the baseline measures acquired on the preceding morning, thus replicating the findings previously reported.

However, measures of ^{31}P-MRS acquired from nine participants after recovery sleep uncovered an overshoot type of phenomenon occurring on that day, relative to baseline measures acquired before sleep deprivation (Dorsey et al., 2003). After recovery sleep, there were elevated concentration levels relative to baseline values for the high-energy nucleoside triphosphate (NTP) compounds beta-NTP and gamma-NTP, as well as for measures of total NTP, while reduced values were observed in concentration levels of GPC (glycerophosphorylcholine: involved in phospholipid metabolism catabolite production). A negative association was also reported between reduced levels of GPC and increases in total NTP. The authors speculated that although adenosine was not measured directly, since it attaches to phosphate groups, increases in concentrations of NTP could reflect increases in levels of adenosine triphosphate (ATP). More precisely, since 80% of the beta-NTP resonance is assumed to represent concentrations of ATP, it is likely that increases in beta-NTP reflect mainly increases in levels of ATP. In this context, recovery sleep might have triggered a rebound phenomenon in concentration levels of ATP in the medial prefrontal region, relative to levels measured at pre-treatment time (Dorsey et al., 2003).

With the authors' interpretation of these findings in mind, the lack of significant differences between baseline day and sleep deprivation day reported with these young healthy men (Dorsey et al., 2003) can be contrasted to findings from a sleep deprivation study that measured changes in adenosine concentrations in several selected brain regions of adult male cats (Porkka-Heiskanen, Strecker, & McCarley, 2000). Measurements were repeatedly obtained at one-hour intervals during the six hours of the sleep deprivation period, as well as during the initial three hours of recovery sleep. Measurements obtained in the cortex region showed a gradual increase in adenosine concentration levels during the first five hours of sleep deprivation. The ANOVA showed an overall statistically significant increase over time; however, follow-up tests revealed that statistical significance was not reached for either of the individual time points relative to baseline measures. Furthermore, the sixth hour of sleep deprivation revealed the beginning of a reversal pattern towards baseline concentration values: a statistically significant decline in concentration levels of adenosine started between the fifth and sith hour of sleep deprivation and continued progressively during the recovery sleep period.

Therefore, the lack of statistical differences reported in young healthy men (Dorsey et al., 2003), comparing neurochemical concentrations between baseline day and sleep deprivation day, could be caused by a lack of power due to the single time point assessment performed on each day. Another potential explanation could be the larger number of sleep deprivation hours involved in the human study, as compared to the animal study. Based on the fact that the rise in adenosine concentrations with sleep deprivation began to reverse between the fifth and sixth hour of sleep deprivation in cats

(Porkka-Heiskanen et al., 2000), it would be reasonable to postulate that after a night of total sleep deprivation, this decline might have started in humans as well (Dorsey at al., 2003).

On the other hand, the elevated concentrations levels found during the recovery day in the young healthy men (relative to their baseline values) for beta-NTP, gamma-NTP and total NTP (Dorsey et al., 2003) are not in line with the findings in the Porkka-Heiskanen et al. (2000) study, which reported a gradual and progressive decline in cortical adenosine concentration levels of cats, as assessed during each of the initial three hours of recovery sleep. One potential interpretation of these discrepant findings on the recovery day would be in terms of the different time point measurements that were involved in each study: cats were assessed during the initial three hours of recovery sleep, while the young healthy mean were assessed after several hours (a full night) of recovery sleep.

A proton magnetic resonance spectroscopy (^{1}H-MRS) study (Urrila et al., 2006) assessed the effects of sleep deprivation in eight healthy participants, using a 1.5T scanner while selecting a large volume of interest in the occipital region. All baseline scans were performed in the morning after a regular night of sleep, while repeated scans were performed during the following evening, after 40 hours of sustained wakefulness. Findings showed that concentration levels of *N*-acetylaspartate (NAA) and choline compounds (Cho) were significantly decreased after the period of prolonged wakefulness, as compared to baseline measures, while levels of total creatine-plus-phosphocreatine (tCr) did not change (concentration levels of neurochemicals were

referenced to internal water in the same volume of interest). The proportion of pre/post-treatment differences was 7% for NAA and 12% for Cho. However, since the two ^{1}H-MRS scans were performed at different times of day, these results might reflect physiological diurnal changes, i.e., normal morning-evening differences in concentration levels of ^{1}H-MRS-detectable neurochemicals, rather than, or in addition to, effects of prolonged wakefulness (Urrila et al., 2006).

Indeed, findings from two different types of brain imaging studies tend to support the 'diurnal-variation' interpretation. A ^{1}H-MRS study conducted with a 3T scanner and involving 10 healthy volunteers assessed concentration levels of neurochemicals during morning and afternoon periods in a crossover design (Soreni et al., 2006). Concentration levels of NAA (institutional units), assessed in the regions of left and right striatum, were found to be significantly lower during the afternoon period. This difference in concentration levels between morning and afternoon periods was interpreted as a normal physiological diurnal variation. Diurnal variations were additionally reported in a PET study involving 13 healthy volunteers who were scanned twice: morning and evening (Buysse et al., 2004). Relative regional glucose metabolism was found to be lower in a large region of the occipital lobes during the evening as compared to the morning scans. These findings were tentatively interpreted as reflecting a normal diurnal variation. The occipital cortical region studied by Buysse (2004) using PET was similar to that studied by Urrila (2006) using spectroscopy, further supporting a possible role for diurnal variation in generating the post-sleep deprivation spectroscopy results.

Summary

Data from functional imaging studies indicate that prolonged wakefulness in healthy volunteers causes decreased regional metabolic rates most consistently in the region of the thalamus, but also in different regions of the basal ganglia, in the frontal and prefrontal regions, temporal and parietal regions, cerebellum, mesopontine and pontine regions. Interestingly, one full night of recovery sleep restored baseline metabolic activity in frontal regions but not in subcortical regions.

Data from ^{31}P-MRS studies indicated no group effect of prolonged wakefulness in frontal (Murashita et al., 1999) and medial prefrontal regions (Dorsey et al., 2003) of healthy humans. However, post-recovery levels of beta and gamma nucleoside triphosphates and of total nucleoside triphosphates were reported to increase above pre-treatment levels, which could reflect increases in levels of adenosine triphosphate (Dorsey et al., 2003). Post-recovery decreases below pre-treatment values were also reported in levels of glycerophosphorylcholine in the same group of subjects; this resonance reflects phospholipid metabolism catabolic production. Post-recovery increases in total NTP were significantly associated with decreased levels of glycerophosphorylcholine.

1.4 Brain Imaging Studies of Sleep Deprivation in Depression

Several functional imaging studies have investigated the effects of sleep deprivation on cerebral metabolic activity in depressed patients: four SPECT studies (Ebert, Feistel, & Barocka, 1991; Ebert, Feistel, Barocka, & Kaschka, 1994; Volk et al., 1992; Volk et al., 1997), three PET studies (Smith et al., 1999; Wu et al., 1992; Wu et al., 1999), and one

functional magnetic resonance imaging (fMRI) study (Clark et al., 2006a; Clark et al., 2006b; these two publications refer to the same group of depressed patients). Functional MRI is a brain imaging technique that does not require radioactive isotopes, and that can map changes in hemodynamics of the brain.

Significant baseline group differences in regional metabolic rates were reported between subsequent Responders to sleep deprivation therapy on the one hand, and subsequent Non-responders and/or healthy volunteers (when a control group was present) on the other hand. Elevated baseline metabolic rates were found in subsequent Responders most consistently in the anterior ventral cingulate region, but also in medial and orbital prefrontal and amygdala/hippocampus regions (Ebert et al., 1991; Ebert et al., 1994; Wu et al., 1992; Wu et al., 1999; Volk et al., 1997; Clark et al., 2006a; Clark et al., 2006b).

Elevated metabolic rates observed regionally before treatment were significantly decreased after sleep deprivation among those who responded to treatment. Decreases in metabolic rates after treatment were reported in the anterior ventral cingulate region (Ebert et al., 1991; Volk et al., 1997; Smith et al., 1999; Wu et al., 1999; Clark et al., 2006a; Clark et al., 2006b), the amygdala/hippocampus (Ebert et al., 1991; Wu et al., 1992), and the orbital frontal region (Ebert et al., 1991; Volk et al., 1997). Regional metabolic activity remained unchanged after sleep deprivation in groups of Non-responders and in healthy controls (Wu et al., 1992; Wu et al., 1999; Smith et al., 1999). A single study reported *increased* regional metabolic rates after sleep deprivation in Responders; this increase was observed in temporal and parietal regions (Volk et al.,

1992).

1.5 Functional Imaging Studies of Unipolar Depression

Functional imaging studies using PET or single photon emission computerized tomography (SPECT) have reported inconsistent differences in regional cerebral metabolic rates between patients with depression and healthy controls, as well as between depressed and remitted states. Differences in methodologies might have contributed to these inconsistencies, including the use of heterogeneous patient groups with different subtypes of depressive illness. Several criteria were applied for inclusion in the summary of results below: studies that included mainly patients with unipolar depression; studies that assessed patients resting in the scanner ('resting-state'); and studies with sample sizes greater than four patients. Another potential contributor to discrepancies in results might be the differential inclusion of drug-free and medicated patients among studies. In this review, studies were included regardless of medication status at baseline scan. Because of inconsistencies in results across studies, the major emphasis is on findings that have been replicated in several studies.

1.5.1 Depressed State Relative to Healthy Controls

Several studies have attempted to identify differences in regional cerebral blood flow and glucose metabolism between patients with unipolar depression and healthy controls. One of the most consistent findings pertains to reduced regional metabolic rates in anterior dorsal brain regions of depressed patients; these areas include the inferior, medial and superior frontal gyri and anterolateral prefrontal region (Baxter et al., 1989; Austin et al.,

1992; Biver et al., 1994; Mayberg, Lewis, Regenold, & Wagner, 1994; Ito et al., 1996; Galynker et al., 1998; Drevets, Bogers, & Raichle, 2002a; Aihara et al., 2007; Kohn et al., 2007), as well as the anterior dorsal cingulate region (Mayberg et al., 1994; Ito et al., 1996; Drevets et al., 1997a; Galynker et al., 1998; Kohn et al., 2007).

Conversely, increased regional metabolic rates were reported in depressed patients in ventral lateral and medial prefrontal regions, in the rostral anterior cingulate region, and in the orbital prefrontal cortex (Drevets et al., 1992; Drevets, Spitznagel, & Raichle, 1995; Drevets et al., 2002a; Biver et al., 1994; Kennedy et al., 2001; Videbech et al., 2002; Konarski et al., 2007). However, opposite findings of lower baseline metabolic rates were also reported in the medial and/or orbitofrontal regions of depressed patients (Galynker et al., 1998; Kohn et al., 2007). Both increased regional metabolic rates (Drevets et al., 1992; Drevets et al., 2002b; Videbech et al., 2002) and lower metabolic activity (Kohn et al., 2007) have been reported in the left amygdala of depressed patients.

Several other brain regions (temporal, parietal, occipital, and insular regions; cerebellum), as well as several subcortical structures (thalamus, brain stem and basal ganglia) were reported to show altered regional metabolic rates in depressed patients. The presence and even direction of patient-control group differences have, however, been quite inconsistent across studies. Finally, at least two studies have reported no between-group differences in global or regional metabolic rates (Silfverskiold & Risberg, 1989; Maes et al., 1993).

Summary

The search for a cerebral metabolic pattern that can discriminate between populations of depressed patients and healthy controls has yielded some findings that are generally reliable: reduced metabolic rates in large sections of the dorsal anterior frontal and prefrontal cortical regions. For the ventral and orbital prefrontal cortex and limbic structures, both elevated and reduced metabolic rates have been reported in patients. Numerous other brain regions have been suggested to show differences, but these results have not been replicated consistently.

1.5.2 Post-treatment Changes Relative to Baseline

Functional imaging studies have investigated whether patterns of regional metabolic changes from before to after antidepressant medication were associated with a positive response to treatment. In dorsal prefrontal regions, significant increases in regional metabolic rates were reported in some groups of patients (Baxter et al., 1989; Mayberg et al., 2000; Kennedy et al., 2001), while decreased metabolism was observed in other patients (Kennedy et al., 2007). In the mid part of the anterior cingulate region, both increases (Kennedy et al., 2001; Vlassenko, Sheline, Fisher, & Mintun, 2004) and decreases (Holthoff et al., 2004) in regional metabolism were reported upon remission, while decreases were observed in the subgenual part (Drevets et al., 2002a; Mayberg et al., 2000). In the ventrolateral, ventral medial and orbital aspects of the prefrontal cortical region, increases in regional metabolic rates occurred upon remission in some group of patients (Kennedy et al., 2001; Vlassenko et al., 2004), while decreases in the same regions were observed in others (Saxena et al., 2002; Kennedy et al., 2007).

Medications were quite diverse across and sometimes within these studies. Some studies involved patients who used a selective serotonin reuptake inhibitor (SSRI): fluoxetine (Mayberg et al., 2000), or paroxetine (Kennedy et al., 2001; Saxena et al., 2002). In another study, subjects used the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (Kennedy et al., 2007). Other studies included patients using two or more different categories of antidepressant medications. These medications included paroxetine, fluoxetine, or amesergide (a selective serotonin antagonist) (Vlassenko et al., 2004); citalopram (SSRI) or mirtazapine (a SNRI) (Holthoff et al., 2004); a tricyclic antidepressant (TCA) or a TCA plus a monoamine oxidase inhibitor (Baxter et al., 1989); sertraline or a TCA (Drevets et al., 2002a).

Regional metabolic changes upon remission have additionally been reported in several other cortical regions, including the temporal, parietal and occipital lobes, in subcortical structures, and in the cerebellum and brain stem. However, these regional changes were less frequently replicated, and the direction of reported changes also sometimes differed among studies.

Based on these empirical data, no typical pattern of post-treatment changes in regional metabolic rates can be associated with remission of depressive symptoms. The heterogeneity of antidepressant medications used across trials might be one of the factors responsible for inconsistent and mixed findings.

1.5.3 Pre-treatment Markers of Subsequent Response to Treatment

Brain regional metabolic rates were studied in patients before treatment to identify characteristics that could discriminate between subsequent Responders and Non-responders to a variety of antidepressant medications. Patients who responded subsequently to drug treatment were found to have elevated baseline regional metabolic rates in the rostral cingulate region, while subsequent Non-responders had lower metabolic rates than controls in this same region (Mayberg et al., 1997). Treatment consisted of a SSRI for some patients (n = 13), or of a TCA or bupropion (a norepinephrine and dopamine reuptake inhibitor and nicotinic antagonist) for other patients (n = 5).

In other studies, subsequent Responders to citalopram had elevated baseline regional metabolic rates (relative to Non-responders) in superior and inferior frontal regions, insula and posterior cingulate regions (Joe et al., 2006). Subsequent Responders to paroxetine displayed elevated pre-treatment metabolism (relative to Non-responders) in regions of medial prefrontal cortex and rostral anterior cingulate gyrus, and reduced metabolic rates in the thalamus and right amygdala (Saxena et al., 2003). Reduced pre-treatment metabolic rates were reported for subsequent Responders (relative to healthy controls) but not for Non-responders in inferior and medial prefrontal regions, in hippocampus/parahippocampus regions and in bilateral insula (Little et al., 2005); antidepressant treatment consisted of either bupropion or venlafaxine.

Based on these empirical data, no general pattern of between group differences in

regional metabolic rates before treatment can be described that discriminates between subsequent Responders and Non-responders to antidepressant medication therapy. As in the previous section, the heterogeneity of antidepressant medications used for treatment across trials might in part be responsible for the variety of findings.

1.6 Magnetic Resonance Spectroscopy Studies of Unipolar Depression

Single proton magnetic resonance spectroscopy (^{1}H-MRS) can provide *in vivo* measures of neurochemicals such as the choline compounds glycerophosphorylcholine (GPC) and phosphorycholine (PC), total creatine-plus-phosphocreatine (tCr), and *N*-acetylaspartate (NAA). These three peaks of the ^{1}H-MRS spectral profile have strong signals and low coupling properties. When using a 1.5 tesla (T) scanner, these three signals can be measured individually with good precision.

^{1}H-MRS measures have also been reported for myo-inositol (mI), γ-aminobutyric acid (GABA), and glutamate-plus-glutamine (Glx). GABA and Glx are multiplets with strong coupling properties, which renders the validity of acquisition of their specific signals at 1.5T questionable. However, the validity of acquisition of these individual signals increases using higher field scanners (e.g., Coupland et al., 2005; Hasler et al., 2007) and/or using specific acquisition methods that target a specific neurochemical (e.g., Sanacora et al., 1999; Sanacora et al., 2003; Sanacora et al., 2004).

Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) can provide measures of phosphomonoesters (PME), phosphodiesters (PDE), phosphocreatine (PCr), inorganic

phosphate, and nucleoside triphosphates (α, β, and γ-NTP), which are high-energy phosphates in the brain that include adenosine triphosphate (ATP).

1.6.1 Alterations in Regional Levels of tCr, PCr, and NTP

^{1}H-MRS detects signals from creatine (Cr) and phosphocreatine (PCr), yielding a singlet (tCr) observed at 3.03 ppm (chemical shift scale) on the spectral profile, relative to the standard tetramethylsilane; other peaks can also be observed at 3.91 ppm for Cr and 3.93 ppm for PCr (Govindaraju, Young, & Maudsley, 2000). These two guanidino compounds, along with the creatine kinase (CK) isoenzymes system and the Cr transporter (CrT) protein are the chemical mechanisms involved in creatine metabolism and uptake by tissues (Speer et al., 2004).

Creatine can be provided by food (fish and meat) and by creatine supplementation. It can also be endogenously synthesized via the action of two enzymes: L-arginine:glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT). Creatine is synthesized mainly in the kidney, pancreas and liver (Speer et al., 2004). Inborn errors of creatine synthesis can involve defects of AGAT or GAMT, resulting in brain creatine depletion and, if undetected and untreated, in developmental delay and mental retardation. Oral supplementation of creatine can slowly and progressively elevate brain creatine concentration values towards normal levels. However, inborn defects in CrT will not respond to oral supplementation of creatine (Verhoeven, Salomons, & Jakobs, 2005; Bianchi et al., 2007).

Creatine is transported through the blood into tissues with high energy demands by the specific transporter, CrT. CK isoenzymes in the tissue then produce phosphocreatine from ATP and creatine (Speer et al., 2004). ATP plays a critical role as an energy source and in energy transfer within cells. It is continuously regenerated from the large cellular pools of phosphocreatine via the action of the CK enzymes. This CK/PCr system maintains relatively stable ATP energy levels in the brain (Wallimann, Wyss, Brdiczka, Nicolay, & Eppenberger, 1992). It has been suggested that the CK/PCr system is an essential network connecting sites of ATP production and consumption (Wallimann et al., 1992).

Alterations in brain regional levels of ^{1}H-MRS-detectable tCr and ^{31}P-MRS-detectable phosphocreatine (PCr) have been observed in patients with unipolar depression. Levels of tCr:H_2O (tCr expressed as a ratio to water content within the same volume of interest [VOI]), assessed with a 3T scanner, were reported to be markedly and significantly elevated in a large right and left anterior dorsal frontal region of 17 depressed patients as compared to 17 age- and gender-matched healthy controls (Gruber et al., 2003). This well-designed study provided evidence that regional levels of tCR:H_2O in the brain can be altered during depression in large bilateral sections of the anterior dorsal frontal cortex. Conversely, alterations in levels of tCr:H_2O in the opposite direction were reported in a pediatric study of a smaller, more localized section of the anterior dorsal region: tCr:H_2O assessed with a 1.5T scanner in a small region of the anterior dorsal cingulate gyrus was found to be reduced in a group of 13 pediatric depressed patients, as compared to healthy controls (Mirza et al., 2004; Rosenberg et al., 2004). It is unclear

whether the different results reflect different VOIs or the use of adult versus pediatric populations.

A ^{31}P-MRS study at 1.5T reported a significant association between gradation in levels of % PCr (PCr as a percentage of the total phosphorus signal) and levels of depression severity in a group of 12 depressed patients. Using a surface coil (instead of a standard head coil), significantly lower levels of % PCr were found in a large region of the anterior frontal pole of severely depressed patients as compared to mildly depressed patients (Kato, Takahashi, Shioiri, & Inubushi, 1992). ^{31}P-MRS studies at 1.5T have additionally reported between-group differences in concentration levels of nucleoside high-energy phosphates. The percent fraction of beta-nucleoside triphosphate (% β-NTP) was reduced during depression, relative to healthy controls, in the region of the basal ganglia (Moore, Christensen, Lafer, Fava, & Renshaw, 1997) and in a large section of the prefrontal and frontal brain regions (Volz et al., 1998). Levels of % total NTP were also reduced in depressed patients in prefrontal and frontal regions (Volz et al., 1998).

Summary

^{1}H-MRS studies have provided data indicating that regional levels of tCr:H_2O can be elevated during depression in the anterior dorsal frontal region, and decreased in the anterior dorsal cingulate region. It is unclear whether these differences arose from studying different specific subregions or from studying adult versus pediatric patients. There is also evidence from a ^{31}P-MRS study that levels of % PCr are reduced in the anterior frontal pole in relation to the severity of depression. The prefrontal and frontal

regions have been reported to display reduced % β-NTP and % total NTP; % β-NTP was also reduced in the basal ganglia. Since PCr and nucleoside triphospshate compounds are important donors of free energy in the brain (see Govindaraju et al., 2000), there might be alterations during depression in regional levels of free energy availability in the anterior dorsal frontal and prefrontal regions, and in the basal ganglia.

These results are relevant to the interpretation of many ^{1}H-MRS studies of unipolar depression. Because of a variety of technical issues involved in the acquisition and post-processing of ^{1}H-MRS data, a number of these studies have reported neurochemical concentration levels solely as a ratio to tCr or to NAA levels (obtained in the same VOI and at the same time as the other neurochemicals). Because levels of tCr have been reported to be altered in some depressed groups but not in others, and because the directionality of these alterations may depend on the population or the specific region being studied, it is difficult to determine which part of the neurochemical:tCr ratio actually changed (and in which direction) when results are expressed solely as ratios to tCr.

1.6.2 Alterations in Regional Levels of *N*-acetylaspartate

NAA is a free amino acid that provides the most prominent resonance in ^{1}H-MRS of the human brain: a peak at 2.02 ppm on the spectral profile, relative to the standard tetramethylsilane; other resonances of NAA can be found at 2.49, 2.67 and 4.38 ppm (see Govindaraju et al., 2000). It is synthesized in neurons and catabolized into aspartate and acetate in oligodendrocytes via aspartoacylase. NAA concentration levels tend to

decrease following stroke or brain injury (see Moffet, Ross, Arun, Madhavarao, & Namboodiri, 2007), suggesting that NAA levels may be useful as a marker for neuronal viability.

The inability to synthesize NAA has been reported in a single case study of a child who presented with developmental delay (Martin, Capone, Schneider, Hennig, & Thiel, 2001). Despite the absence of the NAA metabolic cycle in his brain, the anatomical images and myelination in the brain were relatively normal. This case study was published with the declared intention of challenging the assumption that brain NAA concentration levels are a marker for neuronal viability. For that individual, the absence of the NAA metabolic system had not been an impediment to the brain's capacity to develop and function, albeit with some developmental delay.

Several roles have been proposed for NAA in the brain but there is little agreement as to its main function. NAA is important in the myelination process of the brain, providing building blocks for myelin lipid production (see Moffet et al., 2007). NAA has been shown to act as a precursor in the formation of the neurotransmitter *N*-acetylaspartylglutamate (NAAG), which is assumed to be involved in excitatory neurotransmission. Another important role is in osmoregulation; that is, modulating water balance in neurons (see Moffet et al., 2007). Additionally, NAA has been postulated to have a central role in the metabolism of glutamate, an amino acid involved in brain metabolic activity as well as in neurotransmission: A series of equations have been developed indicating that NAA can be converted into glutamate via an energy-efficient

mechanism (Clark et al., 2006c). Finally, decreases in NAA anabolic activity have been associated temporally to decreases in production of ATP, a high-energy phosphate compound, thus linking NAA synthesis to brain energy metabolism (see Moffet et al., 2007).

Some ^{1}H-MRS studies of unipolar depression have reported reduced concentrations of NAA:tCr. As compared to healthy controls, patients with depression had reduced NAA:tCr in the caudate (Vythilingam et al., 2003), right dorsolateral prefrontal cortex (Grachev, Ramachandran, Thomas, Szeverenyi, & Fredrickson, 2003) and left dorsolateral prefrontal cortex (Brambilla et al., 2005). In the latter study, NAA:H_2O and tCr:H_2O were also computed: neither of these values differed between the two groups of participants. Thus, the finding of reduced levels of NAA:tCr in patients becomes very difficult to interpret in terms of which component of this ratio reflected a change in patients relative to controls and in which direction this change occurred. In the two other studies (Grachev et al., 2003; Vythilingam et al., 2003), only ratios to tCr were reported; again, which part of the ratio differed between groups cannot be determined with confidence.

As for changes upon remission of symptoms, a study reported increased NAA:tCr values in the left medial prefrontal region after successful treatment with antidepressant medication (Gonul et al., 2006). Another study involving 28 depressed patients reported post-treatment increases in levels of NAA:H_2O in the left amygdalar region of Responders to therapy (Michael et al., 2003b). However, the treatment was a course of

ECT, which limits the generalizability of these findings to other, probably less invasive, types of treatment.

Summary

The results available so far implicating changes in NAA levels in depression are not compelling. They provide some support for reduced concentrations of NAA in depressed patients relative to healthy controls, specifically in the dorsolateral prefrontal cortex and caudate regions. There is also some evidence that the concentration of NAA increases in the left amygdalar region after successful treatment and remission of symptoms.

1.6.3 Alterations in Regional Levels of Choline Compounds

1.6.3.1 Interpreting the Phospholipid Peak(s): ^{1}H-MRS at 1.5T reveals a Choline (Cho) peak as a singlet at 3.2 ppm on the spectral profile, relative to the standard tetramethylsilane. The two main contributors to this signal, due to their higher concentrations in normal brain tissue, are the choline derivatives phosphorylcholine (PC) and glycerophosphorylcholine (GPC). Free choline, betaine and acetylcholine are among the other molecules that also contribute to the Cho signal, but to a much lesser extent when the brain tissue is healthy (see Boulanger, Labelle, & Khiat, 2000). PC is an anabolic constituent of the phospholipid metabolic cycle, as well as a crucial second messenger for the proliferating activity of several growth factors (see Cuadrado, Carnero, Dolfi, Jimenez, & Lacal, 1993). GPC is a breakdown product of the phospholipid metabolic cycle.

One study compared *in vivo* ^{1}H-MRS Cho (3.2 ppm peak) levels in a region of interest with *in vitro* measures of choline-containing compounds in biopsied tissue from the same region (Miller et al., 1996). There was a significant and positive correlation between *in vivo* Cho concentrations and separate *in vitro* measurements of GPC, PC, free choline, and tissue cellular density. There was no correlation between the *in vivo* Cho peak and *in vitro* measurements of the membrane-bound phospholipid phosphatidylcholine (PtdCho). This report concluded that membrane phospholipids do not contribute significantly to the Cho signal, whereas water-soluble Cho-containing compounds are the main contributors to Cho, which is also affected by tissue density (Miller et al., 1996). It is now recognized that the restricted motion of the membrane-bound PtdCho, plasmalogen-choline and sphingomyelin-choline is a serious impediment to contributing a well-defined signal to the ^{1}H-MRS spectral profile (see Boulanger et al., 2000).

Alterations in concentration levels of the Cho peak (measured by ^{1}H-MRS) are assumed to be caused mainly by changes in PtdCho metabolism, which modulates the concentrations of the two major constituents of the Cho signal, PC and GPC (see Boulanger et al., 2000). Therefore, changes in metabolic activity related to PtdCho should have a major impact on levels of the major constituents of the Cho peak. Activity of the enzyme phospholipase A_2 (PLA_2), which has a central role in the degradation of PtdCho into GPC (and PC), should as a result have a major impact on the strength of the Cho signal measured by ^{1}H-MRS (see Boulanger et al., 2000).

The spectral profile obtained with ^{31}P-MRS shows three principal peaks for

phospholipids (see Boulanger et al., 2000). PC and phosphoethanolamine are the two main choline derivatives that contribute to the phosphomonoester (PME) peak. They are both precursors to membrane synthesis phospholipid metabolism. The phosphodiester (PDE) peak mainly represents GPC and glycerophosphodiesters, which are breakdown products of phospholipid metabolism in the brain.

Phospholipid metabolic activity in the brain has been postulated to consume around 20% of the total available pool of ATP, the brain's primary energy reservoir, thus linking concentrations of MRS-detectable phospholipids to measures of brain energy metabolism (Purdon, Rosenberger, Shetty, & Rapoport, 2002).

1.6.3.2 Baseline Differences Related to Depression: The most frequently reported results in MRS studies of unipolar depression are alterations in ratio levels of choline compounds. Before treatment and relative to healthy controls, patients with unipolar depression have been reported to have either reduced (Renshaw et al., 1997) or elevated (Charles et al., 1994; Renshaw et al., 1994) levels of ^{1}H-MRS Cho:tCr assessed at 1.5T in the basal ganglia. The depressed group also displayed elevated levels of Cho:tCr in orbital (Steingard et al., 2000) and dorsolateral prefrontal (Kumar et al., 2002) regions, and lower levels in the amygdalar region (Kusumakar, MacMaster, Gates, Sparkes, & Khan, 2001). The findings in the basal ganglia are difficult to interpret since Cho:tCr levels were reported to change in different directions in different groups of patients. Ratio changes in the orbital and dorsal prefrontal regions and in the amygdalar region are also difficult to interpret because of other reports of changes in tCr concentrations in unipolar

depression. Thus, ratio differences between depressed and control subjects may reflect either changes in tCr or in Cho or in both.

Pre-treatment regional concentrations of Cho:H_2O have also been reported to be altered in depressed patients relative to healthy controls. In the dorsolateral prefrontal region, levels of Cho:H_2O were reported to be either reduced (Caetano et al., 2005) or elevated (Farchione, Moore, & Rosenberg, 2002) during depression. Additionally, depressed patients displayed elevated levels of Cho:H_2O in the region of the left caudate (Rosenberg et al., 2000), and reduced levels in the hippocampal region (Ende et al., 2007). Although these data suggest that baseline Cho:H_2O concentrations may differ in depressed patients and controls, the results may not be consistent across structures, nor across studies of the same structure.

Between-group differences at baseline have also been reported in ^{31}P-MRS studies. Relative to healthy controls, depressed patients showed a 16% increase in the % PME (PME relative to the total phosphorus signal) and a 12% increase in % PDE, as measured in the region of the bilateral basal ganglia, while the total phosphorus signal was almost identical (a difference of 1%) in the two groups (Christensen, Renshaw, Stoll, Lafer, & Fava, 1994). Elevated levels of % PME have been observed in another depressed group in a large region of the bilateral prefrontal and frontal cortices (Volz et al., 1998). These preliminary findings from two studies indicate that levels of both anabolic (PME) and catabolic constituents (PDE) of regional membrane phospholipid metabolic processes may be elevated in depression in some brain regions.

1.6.3.3 Post-treatment Changes: Repeated assessment of Cho concentrations before and after treatment for depression showed that elevated levels of Cho:tCr observed before treatment in the basal ganglia were significantly decreased toward normal values after treatment with fluoxetine (Renshaw et al., 1994) and with nefazodone (Charles et al., 1994). In the left caudate and putamen, however, Cho:tCr ratios were reported to be significantly increased by 20% in Responders to fluoxetine, while Non-responders had a non-significant decrease of 12% (Sonawalla et al., 1999). Because these measures are ratios to tCr, post-treatment differences could be interpreted as reflecting changes either in Cho and/or in tCr levels.

A significant post-treatment increase of 16% (relative to pre-treatment) has been reported in levels of Cho:H_2O in the bilateral hippocampal region of 17 unmedicated patients, following a course of ECT (Ende, Braus, Walter, Weber-Fahr, & Henn, 2000). Twelve of these patients were additionally re-assessed during a follow-up evaluation conducted after one year of sustained remission of symptoms (Obergriesser, Ende, Braus, & Henn, 2003). After one year of stable remission, the immediate post-treatment increase in levels of Cho:H_2O observed in the hippocampal region was decreased to pre-treatment value. It is not clear whether the implication that ECT effects are mediated via changes in hippocampal Cho:H_2O levels can be generalized to other types of treatment.

Summary

These studies provide some support for the hypothesis that there are alterations in

regional membrane phospholipid metabolism during depression. Differences between controls and patients before treatment have been observed in the basal ganglia and in the orbital, dorsal frontal and prefrontal regions. Changes from baseline to after successful treatment were observed in the basal ganglia and hippocampus. The specific brain regions affected and the direction of reported changes have not been consistent across studies.

1.6.4 Alterations in Regional Levels of Myo-inositol

Myo-inositol (mI) is a sugar alcohol that is the most common of the nine isomers of inositol found in tissue. It can be measured only by using ^{1}H-MRS acquisition sequences that have a short time of echo. The two main resonances of mI can be seen at 3.52 and 3.61 ppm (see Govindaraju et al., 2000). Myo-inositol is a precursor of some phospholipids involved in cell growth and of some polyphosphoinositides involved in signal transduction. It is also involved in osmotic regulation in the brain, particularly under persistent periods of chronic osmotic stress (see Novak, Turner, Agranoff, & Fisher, 1999). Myo-inositol is found in both glial cells and neurons, but it might be more concentrated in glial cells. Uptake and turnover of mI in the brain is assumed to vary regionally (Novak et al., 1999).

Levels of mI have been reported to be altered in depressed patients relative to healthy controls. In the left dorsolateral prefrontal region, the depressed group showed elevated values for the ratio mI:tCr (Kumar et al., 2002) as well as for the ratio mI:H_2O (Caetano et al., 2005). On the other hand, reduced levels of mI:H_2O have been reported in a large

bilateral region of the frontal lobes (Frey et al., 1998), and in the prefrontal anterior cingulate region (Coupland et al., 2005). Thus, there is some evidence suggesting abnormal mI levels in some brain regions in depressed patients, but there is a need for additional studies to confirm these findings.

1.6.5 Alterations in Regional Levels of GABA

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the brain. It has three resonances located at 1.89, 2.28, and 3.01 ppm (see Govindaraju et al., 2000). GABA has strong coupling properties, which renders its specific measurement quite challenging using MR scanners at lower field strengths. However, specific MRS acquisition methods have been devised to more reliably measure regional levels of GABA. A few studies that used these methods with 2.1 and 3 T scanners reported alterations in regional levels of GABA in patients with unipolar depression as compared to healthy controls.

Before treatment, levels of GABA:tCr were reduced in two different groups of patients with depression, relative to healthy controls, in a large posterior section of the brain that included the posterior cingulate gyrus, as well as the parietal and occipital regions (Sanacora et al., 1999; Sanacora et al., 2004). After treatment, levels of GABA:tCr were reported to increase significantly compared to baseline values in the same posterior region of the brain, in both a drug-treatment with an SSRI (Sanacora, Mason, Rothman, & Krystal, 2002) and in an ECT-treatment study (Sanacora et al., 2003), but there were no significant changes after treatment with psychotherapy (Sanacora et al., 2005).

Two longer-term follow-up studies have compared currently untreated, remitted patients who had been depressed with never-depressed healthy controls. One study found no group differences in levels of GABA:tCr in a large section of the anterior cerebrum including the ventromedial and dorsolateral anterior prefrontal regions (Hasler et al., 2005). Another study reported reduced GABA:tCr levels in remitted patients in a large section of the posterior cerebrum (posterior cingulate, parietal and occipital regions) and in a large section of the anterior dorsal prefrontal region (Bhagwagar et al., 2007).

Summary

These studies suggest that levels of GABA are reduced in posterior cerebrum regions during depression; replication of these findings using ratios of GABA to internal water would strengthen this conclusion. After successful treatment, levels of GABA:tCr in the posterior brain regions appear to increase. Drug-free remitted patients may have normal levels of GABA:tCr in anterior prefrontal regions, but there is also evidence for sustained lower levels in the posterior cerebrum, as well as in the anterior dorsal prefrontal region.

1.6.6 Alterations in Regional Levels of Glx

Glutamate is the most abundant amino acid found in the brain, and is also the principal excitatory neurotransmitter. Because of its strong coupling properties, glutamate has several low intensity peaks spread across the ^{1}H-MRS spectral profile. It has been observed at 3.74 ppm, as well as in the range of 2.04 to 2.35 ppm (see Govindaraju et al., 2000). Glutamine is a precursor of glutamate, which shares most of its structural

properties. Glutamine has several resonances located at 2.12 ppm, 2.46 ppm, 3.75 ppm, 6.82 ppm, and 7.53 ppm (see Govindaraju et al., 2000). It is almost impossible to separate *in vivo* resonances of these two neurochemicals with field strengths of less than 3T. Therefore, it is common to report glutamate and glutamine together as Glx when studied at lower field strengths. Interpretation is further complicated by overlap of Glx resonances with those of GABA and NAA (see Govindaraju et al., 2000).

Levels of Glx:H_2O acquired at 1.5T were reported to be reduced in three groups of depressed patients relative to healthy controls, in the anterior cingulate region ([1] Auer et al., 2000; [2] Pfleiderer et al., 2003; [3] Mirza et al., 2004; Rosenberg et al., 2004), and in the left dorsolateral prefrontal and amygdalar regions (Michael et al., 2003a; Michael et al., 2003b). Reductions were also reported in levels of Glx:tCr acquired at 3T in the anterior dorsomedial and ventromedial prefrontal regions (Hasler et al., 2007). Only one study (at 1.5T) reported increased levels of Glx:H_2O in the depressed group, in the region of the left caudate (Rosenberg et al., 2000). These preliminary findings will need to be replicated at higher field strengths that allow reliable discrimination of glutamate, glutamine and GABA resonances.

1.7 Summary of MRS-detectable Neurochemical Changes in Depression

Regional concentration levels of tCr:H_2O measured with ^{1}H-MRS were reported to be altered during depression, specifically in the anterior dorsal frontal region, but the direction of these alterations is not clear. In addition, levels of PCr measured with ^{31}P-MRS were reduced in the anterior frontal pole, in proportion to the severity of depression.

Prefrontal and frontal brain regions were reported to show reduced % β-NTP and % total NTP; % β-NTP was also reduced in the basal ganglia. Thus, there appear to be alterations in regional levels of free energy available during depression in the anterior dorsal frontal and prefrontal regions, and in the basal ganglia.

There is no compelling evidence for changes in regional concentrations of NAA in depression, but there is some support for decreased NAA concentrations in the dorsolateral prefrontal and caudate regions, and for increased levels of NAA in the left amygdalar region upon remission from depression.

A number of studies support the idea of altered membrane phospholipid metabolism in some brain regions during depression. Depressed patients showed differences relative to controls in the basal ganglia, orbital and dorsal frontal and prefrontal cortical regions, and changes in the basal ganglia and hippocampus after successful treatment. It is not possible, however, to reach strong conclusions about the regions affected, nor about the direction of these differences based on available data.

There is also evidence for elevated concentrations of mI in the dorsolateral prefrontal region and reduced concentrations in the frontal lobes and anterior cingulate among depressed patients, relative to controls. These claims, however, will also require replication and confirmation.

Reduced ratios of GABA:tCr have been reported in a large posterior region of the

cerebrum during depression. At immediate post-treatment time, levels of GABA:tCr increased in this region with medication (SSRI) and ECT, but not with successful psychotherapy. Longer-term follow-up studies of unmedicated remitted patients showed normal levels of GABA:tCr (relative to healthy controls) in ventromedial and dorsolateral prefrontal region for one group of remitted patients, but reduced levels in another group of patients. In the posterior cerebrum, reduced levels of GABA:tCr were still present at follow-up. Replication of these findings using ratios to internal water would help to clarify these differences and strengthen these initial results.

Concentrations of Glx:H_2O may be reduced during depression in sections of the anterior dorsal and medial prefrontal cortical regions, in the anterior cingulate and in the amygdalar region. The caudate nuclei have, however, been reported to show increased concentrations. Replication of these studies at higher field strengths would help to interpret these preliminary findings.

In summary, many of the available results provide tentative support for neurochemical changes in selected brain regions during depression and in response to successful treatments for depression. Studies of any one neurochemical may, however, have targeted different brain regions, used different imaging methods and different analytic approaches. It is thus not surprising that there are inconsistent findings across studies. The issues associated with interpreting resonances with strong J-coupling properties acquired at lower field strengths add to the ambiguity of results. Finally, the heterogeneity inherent in the population of patients who may be diagnosed with unipolar major depression

undoubtedly contributes further to the complexity of interpreting the available data.

1.8 Research Goal and Hypotheses

The goal of this project was to use ^{1}H-MRS to identify neurochemical correlates of the clinical response to late partial sleep deprivation in selected brain regions of young women with unipolar depression. Women were chosen for this study because of a larger lifetime prevalence of major depressive disorder in women (7.5%) relative to men (3.8%), reported in epidemiological studies of affective disorders (see Waraich, Goldner, Somers, & Hsu, 2004). Partial sleep deprivation was chosen over total sleep deprivation because this approach was assumed to be easier for research participants to tolerate. Late partial sleep deprivation was chosen over early sleep deprivation because it is the most frequently used approach in studies using partial sleep deprivation.

The three main singlets of the neurochemical spectral profiles ([1] *N*-acetylaspartate, [2] choline compounds, and [3] creatine-plus-phosphocreatine) were targeted in this study because of the limitations of data acquisition using a 1.5T scanner.

Hypotheses

a) That neurochemical responses to sleep loss will differ between depressed women and healthy controls.

b) That the pattern of changes in depressive symptoms after sleep deprivation will differ between the two groups.

c) That depressed participants will have a positive response to sleep deprivation in about

50% of cases.

d) That depressed women who respond and do not respond with mood improvement to sleep deprivation might differ in baseline neurochemical levels and/or in the neurochemical changes shown after sleep deprivation.

Functional changes in depression and reversal of these changes with successful treatment have been studied in a number of different brain regions (see section 1.5). Because of the limited time available for scanning, only two brain regions were targeted in this study: the left anterior dorsal prefrontal region and the pons. The pontine region, which involved a relatively small volume, was assessed bilaterally. The dorsal prefrontal region was assessed on the left side. Early studies suggested that reduced metabolism in the left prefrontal region was characteristic of depression (Cummings, 1993; Hirono et al., 1998). This evidence led to the use of repetitive transcranial magnetic stimulation (rTMS) to selectively activate the left prefrontal region as a therapy for depression (Ridding & Rothwell, 2007). However, two recent functional imaging studies of unipolar depression (Aihara et al., 2007; Kohn et al., 2007) with good sample sizes (24 and 33 depressed patients, respectively) found reduced metabolism bilaterally in the dorsal prefrontal region, with no lateralized differences. It may be that either side of the dorsal prefrontal region would be an appropriate target for an MRS study, but given the uncertainty in the literature, the left side was selected for this project.

The anterior dorsal prefrontal region was chosen based on the fact that the most reliable finding from functional imaging studies of unipolar depression relates to the anterior

dorsal region of the cerebrum, which was reported to show abnormally reduced metabolic rates during depression (Baxter et al., 1989; Austin et al., 1992; Biver et al., 1994; Mayberg et al., 1994; Ito et al., 1996; Galynker et al., 1998; Drevets et al., 2002a; Aihara et al., 2007; Kohn et al., 2007). Although the orbital frontal region also shows changes in depression, exploratory spectroscopic acquisitions performed prior to conducting this study revealed a more consistently good quality of spectral profiles acquired in the dorsal region as compared to the orbital ventral region.

The dorsal prefrontal region has a role in cognitive functioning, and cognitive functions are relevant to depression. Neuropsychological tests of moderately to severely depressed patients show widespread cognitive deficits in this population relative to healthy matched controls (Ravnkilde et al., 2002). Significant impairments were observed on several tasks including tests of attention, speed of cognitive processing, semantic fluency, and executive functioning. A meta-analysis of functional imaging studies including 275 studies of cognition demonstrated that the dorsolateral prefrontal cortex is consistently activated in healthy participants during the performance of a variety of cognitive tasks (Steele & Lawrie, 2004). In addition to its role in cognitive functioning, there is evidence that this brain region may be a site where regulation of cognition and emotion are integrated (see Pessoa, 2008; Gray, Braver, & Raichle, 2002). Altogether, the dorsolateral prefrontal region was a relevant target to study in the analysis of depression.

A second brain structure selected for analysis was in the brainstem, encompassing most of the pontine region. This region was chosen based on its role in sleep-wake regulation

and on the role of neurotransmitter systems originating in the pontine region in mood regulation. The ascending reticular formation is a network of nuclei located in the core of the brainstem including the midbrain, pons, and medulla, which plays a critical role in the regulation of wakefulness and arousal (Boutrel & Koob, 2004). Cell groups in the pontine and midbrain region give rise to noradrenergic and serotoninergic projections to the cortex, and these transmitters have been hypothesized to be involved in expression of depressive symptoms (see Berridge & Waterhouse, 2003; see also Willner, 2002). Therefore, the pontine region may play a role in regulation of both sleep-wake and mood and is thus a good target for investigating how manipulation of sleep affects mood in depressed patients.

Chapter 2 Methods

2.1 Subject Selection

Fifteen healthy women and 12 women with current moderate unipolar depression were recruited to participate in this study. Demographic and clinical characteristics are presented in Table 1. One woman from the Depressed group decided to quit the study during the night of sleep deprivation. The data acquired from her before she left are included where possible.

Diagnosis of depression and screening out of potential comorbid illnesses was performed according to DSM-IV-TR criteria (American Psychiatric Association, 2000), using the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998). Severity of depression symptomatology was assessed with a semi-structured interview using the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960; Williams, 1988). DB performed the initial screening and evaluation. As a second step, a psychiatrist (SD) interviewed all selected participants to confirm that they met inclusion/exclusion criteria. Self-reports of depressive symptoms were obtained using the Profile of Mood States (POMS; McNair et al., 1992) and the Hamilton Depression Inventory (HDI; Reynolds & Kobak, 1995).

A 17-item HDRS score $\geq$18 and a POMS score $\geq$ 30 on the Depression subscale were required at evaluation time for inclusion in the Depressed group. The following exclusion criteria were applied to all participants: a personal or close family history of bipolar disorder (because sleep loss could trigger an episode of hypomania); the presence of

neurological disorders; suicidal ideations (an answer > 2 endorsed on the Suicide item of the HDRS); psychotic symptoms; and usage of prescribed medication (other than regular antidepressant) or street drugs. In the case of previous alcohol or drug dependence or misuse, an abstinence period of one year was required. Participants did not have metal implants, dental braces, pacemakers or any other MR-exclusionary device. Depressed women not currently receiving antidepressant drug therapy were sought preferentially, but current stable pharmacotherapy was permitted (Table 1). Previous studies of sleep deprivation therapy have reported substantial mood improvements in depressed patients whether currently medicated or not (see Giedke et al., 2002, p. 362, Table 1).

2.2 Self-report Measures

Two self-report scales were used to measure changes in the sense of wellbeing throughout the night of sleep deprivation. The HDI was chosen because different forms of the Hamilton interview were the most frequently used depression scales in previous sleep deprivation studies. This self-report scale is a paper-and-pencil form of the Hamilton Depression Rating Scale. It was designed to be consistent with the content and scoring of the HDRS semi-structured interview. The HDI consisted of questions about feelings that were to be answered on a 4-point scale ranking the severity of these feelings as they were experienced at the moment. Seven HDI items were retained for the purpose of repeated measures during the weekend of sleep deprivation (Appendix 2): (1) mood, which was measured with 4 different questions for a composite score on mood; (2) guilt, measuring self-blame with a single question; (3) anhedonia, measuring interest and motivation with two questions; (4) subjective tension, measuring subjective nervousness

or worries with two questions; (5) physical anxiety, measuring the physical symptoms of anxiety with 4 questions; (6) physical energy levels, measured with two questions; and (7) suicidal ideations, measured with one question. Therefore, there were 7 HDI variables plus a summed HDI total score (7 items) for purposes of analyses.

The POMS is the second self-report scale that was repeatedly administered throughout the night of sleep deprivation. It was chosen because its approach to assessing the sense of wellbeing differs from, but complements that of the HDI. This scale comprises 65 statements about current emotional or physical feelings. Participants were requested to select the intensity level that best described their current feeling ("right now") on each item, on a 5-point scale. The POMS has been validated in several different settings, including a university setting using the instruction "right now" as a time frame for feelings to be considered (Pillard, Atkinson, & Fisher, 1967). The sum of scores on all 65 items provided a Total score related to mood disturbance. Six different mood factors were also quantified on six subscales: Tension, Depression, Anger, Vigour, Fatigue and Confusion (Appendix 2). The subscale Tension was defined with 9 items measuring musculoskeletal tension and psychomotor manifestations. The subscale Depression was defined with 15 items representing a sense of personal inadequacy and worthlessness, hopelessness, sadness, guilt, and a sense of emotional isolation. The subscale Anger comprised 12 items using descriptions like grouchy, annoyed, bitter, bad-tempered and resentful. The subscale Vigour comprised 8 items describing the positive affect of energy. The subscale Fatigue included 7 items describing low energy levels. The subscale Confusion was defined by 7 items probing for a sense of cognitive inefficiency.

2.3 Procedures

Selected participants were asked to maintain their usual sleep habits on a Friday night and to come to the Sleep Laboratory (4th floor, Abbie Lane Building, QEII HSC) at 11:00 on Saturday morning. The experimenter (DB) met with them and asked them to fill out the POMS and HDI. The experimenter then brought the participant to the MRI laboratory at the IWK HSC for a brain scan to be performed at ~12:00. Over the several weeks required for data collection from all the participants, the selected participants were consistently scanned within a 2 h time window: their brain scans started at either 12:00 or 13:00, according to the availability of the scanner on each week-end. After the brain scan, participants were instructed to simply go about their usual activities, but avoid napping.

On Saturday evening, participants returned to the Chronobiology Laboratory at the QEII HSC (4th Floor Lane Bldg.) and were met by the experimenter. They were asked to fill in the POMS. They were familiarized with a bedroom in the Laboratory, and they could watch movies or read until ~22:00, at which time they prepared themselves for bed, with lights-out by 22:30. They were allowed to rest or sleep until 01:00 Sunday morning, at which time they were awakened and asked to fill in the POMS again. The experimenter engaged subjects in conversation, short walks within the facility, and interactions, or allowed them to watch movies or read, but not to sleep. Self-reports on the POMS were again obtained at 04:00, 07:30 and 11:30; the HDI was administered at 7:30 and 11:30. Breakfast was provided at 08:00. The experimenter remained with the participant until ~12:00-13:00 on Sunday, when they were brought to the scanner site for a second scan.

In order to discourage participants from falling asleep briefly in the scanner during the second brain scan while they were sleep deprived, participants did not use a blanket while lying in the scanner so that their environment was cooler than usual. They were also prompted to respond to short questions three times during the scanning period.

2.4 MRI and ^{1}H-MRS Acquisition Protocols

2.4.1 MRI Acquisition Parameters

All MR acquisitions were performed with a 1.5 Tesla General Electric Signa scanner and a standard quadrature head coil. After a localizer scan, a T1 weighted 3D SPGR (Spoiled Gradient Recalled) coronal scan was acquired with the following parameters: flip angle = 40 degrees, TE = 5 ms, TR = 25 ms, FOV = 24 cm x 18 cm, matrix = 256 x 160 pixels, NEX = 1, no inter-slice gap, 124 images, each 1.5 mm thick. Anatomical voxel size was 1.5 mm on the coronal plane by .94 mm in the axial and sagittal planes. Subsequent to the T1 weighted MRI acquisition, a T2 weighted FRFSE (Fast Recovery Fast Spin Echo) sequence was prescribed axially with the following parameters: TE = 102 ms, TR = 5150 ms, FOV = 24 cm, matrix = 256 x 192 pixels, no inter-slice gap, 33 slices, each 5 mm thick.

2.4.2 ^{1}H-MRS Acquisition Parameters

Single volume ^{1}H-MRS acquisitions were performed with a Probe PRESS (Point RESolved Spectroscopy) sequence. Parameters were as follows: TE = 30 ms, TR = 2000 ms, 320 acquisitions, 2500 Hz spectral bandwidth, 2048 data points, duration 11.5 min. Two spectroscopic volumes of interest were selected (Appendix 3). A 16 x 16 x 16 mm

volume of interest (VOI) was initially positioned in the left anterior dorsal prefrontal (LADPF) region, encompassing both white matter and gray matter. Positioning of the LADPF VOI was performed according to the following guidelines. In the anterior-posterior direction, the posterior border of the VOI was placed on the slice preceding the most anterior slice of the corpus callosum; in the superior-inferior plane, the inferior border of the VOI was placed two slices below the most superior slice of the corpus callosum; then the VOI was centered within the left hemisphere in the right-left direction. Subsequently, a 13 x 13 x 13 mm VOI was acquired in the pons, with identical ^{1}H-MRS acquisition parameters. Its prescribed volume encompassed most of the pontine region; thus, the location guideline was to place the VOI inside the pontine region in all three planes. Four outer-volume suppression bands were manually placed close to and in line with the VOIs using the coronal view, doubling them with four additional bands placed with an oblique angle at each corner of the VOIs.

2.5 MRI and ^{1}H-MRS Data Processing

2.5.1 Tissue Type Parcellation of the VOIs

The concentrations of ^{1}H-MRS detectable neurochemicals vary significantly with brain tissue type (McLean, Woermann, Barker, & Duncan, 2000). Differences in the fractional content of tissue types within selected VOIs over time and/or between groups could lead to an effect of its own in regard to neurochemical concentrations, which could mask a true effect or yield a false positive effect relative to a research question. Therefore, the estimated concentrations of neurochemicals were adjusted for the fractional content of different tissue types within each VOI. The partial volumes of gray matter, white matter

and CSF were calculated for each VOI using the software package AFNI (Cox, 1996). Each VOI was first placed on the original T1-weighted MR images using the 3D coordinates that were defined during ^{1}H-MRS acquisitions at the scanner. The command line '3dAnhist' was then used, which provided a histogram of tissue types for each VOI along with a counterpart text file from which the volumes of each tissue type were calculated according to published criteria (Gispert et al., 2004).

2.5.2 Spectral Analysis

The focus of this study was on the three dominant peaks of the ^{1}H-MRS spectral profiles: *N*-acetylaspartate (NAA), phosphocreatine-plus-creatine (tCr), and glycerophosphocholine-plus-phosphorylcholine (Cho). Manual peak fitting was performed with fitMAN analysis software (Bartha, Drost, & Williamson, 1999). The GE Probe P files were first converted to fitMAN format. Line-shape correction was performed using QUECC, which consisted of a correction for gradient coil vibration (quality deconvolution) and removal of eddy current distortions, to restore the Lorentzian line shape. Prior to metabolite fitting, the residual water peak was removed using an operator-independent singular value decomposition (SVD) fitting algorithm (van den Boogaart A., van Ormondt D., Pijnappel, de Beer R., & Ala-Korpela, 1994).

Fitting was accomplished by using a 3-peak constraint file (based on prior knowledge) and a 3-peak guess file. In the constraint file, 41 data points (delay time of fit = 16.4 ms) were omitted in the Time domain at the beginning of the FID (free induction decay) curve, in order to minimize the influence of signals coming from short T2 and J-coupled

spectral peaks. These arise from complex overlapping multiplets and from the overlapping peaks of macromolecules, which can obscure assessment of the peaks of interest (Stanley, Panchalingam, Keshavan, Soares, & Pettegrew, 2002). Data points were also omitted at the tail of the FID, the cut-off being performed where the signal was minimal and almost only noise was left; the omission of the tail of the FID improved the signal-to-noise ratio of the neurochemical concentrations. Using the guess file, amplitude, frequency shift and line width were adjusted for each spectrum while visualizing it in the frequency domain, in order to approximate the correct fit prior to applying the automated fitting algorithm. The unsuppressed water signal was fitted similarly. The compilation of estimated neurochemical levels included scaling using the unsuppressed water as an internal standard, as well as an adjustment for the partial volumes of tissue types in each VOI. An adjustment for potential between-group differences in T1 and T2 relaxation times was not performed; therefore, neurochemical levels are reported in institutional units instead of mM/L of wet brain tissue.

Only good quality outputs from manual peak fitting of the spectral profiles were retained for statistical analyses. A number of 3-peak manual fits of spectral profiles are provided in Appendix 4, as examples of the raw data that were included.

Descriptive measures were obtained for the line width of the water peak of the spectral profiles, as an indication of the overall quality of the spectra included for analyses. The line width of the water peaks ranged from 4.52 to 6.86 Hz; the mean (± SD) value was 5.46 (± 0.59).

The signal-to-noise ratio (SNR) of the peaks, which can be calculated by dividing peak amplitude by the standard deviation of the noise (Drost, Riddle, Clarke, & AAPM MR Task Group #9, 2002), was not possible to obtain precisely. This was a consequence of the deletion of a few initial data points in the time domain from the FID curve. This approach was the most appropriate for the current dataset because of its advantage of 'cleaning up' the short TE spectral data by removing the unwanted signals originating from macromolecules or other smaller peaks. However, it meant at the same time that these unwanted signals were left in the residual line, thus inflating the standard deviation of the noise to a level that was not representative of the true noise. In that situation, using the fitMAN compiled values for the standard deviation of the noise would not give accurate SNR. An alternative option was to calculate the SNR individually for each peak, using an available option in fitMAN for manual calculation. However, that option would not allow calculations when data points are omitted from the FID, which was the case for all spectral profiles in this study. An approximation of the SNR could still be developed by visually assessing the images of the fitted spectral profiles. With this approach, the values used for the SNR approximation were the peak height divided by about half the height of the noise from a region where it was regular. Using this approach, it was possible to conclude conservatively that the SNR of the NAA peak was above 10 for all spectral profiles included in the analyses (Appendix 4).

The frequency of good quality spectral data for the raw and difference scores is presented in Appendix 5, for the peaks NAA, Cho and tCr as a function of Group, VOI and

repeated brain scans. From the data acquired in the LADPF region, 14 spectral profiles were retained for statistical analysis at each Scan time for the Control group, while 12 and 10 spectral profiles were retained for the Depressed group at Scan times A and B, respectively. From the data acquired in the pons, 12 and 10 spectral profiles were retained for the Control group for the Cho and tCr peaks at Scan times A and B, respectively, while 13 spectral profiles were retained for the NAA peak at both Scan times. For the Depressed group, 11 and 10 spectral profiles acquired in the pons were retained at Scan times A and B, respectively.

2.6 General Approach to Statistical Analyses

All statistical analyses were performed with the program SPSS for Windows, version 11.5. The threshold for statistical significance was set at .05 unless otherwise specified, and all tests were two tailed.

Box-plot graphs were created for each level of the variables for all the raw scores and difference scores used in the statistical analyses, in order to identify outlier values. Box-plot graphs are useful to display the dispersion of the data for each variable. The middle 50% of the data is contained within the box itself, and the horizontal line inside the box represents the median value. The maximum and minimum values of the data are represented by the ends of the vertical lines on each side of the box. Individual points outside the ends represent outlier values. These outlier values were carefully assessed in order to insure correct data entry and analysis. When the discrepant values were found to be accurate, and no experimental problem was identified in the data acquisition process,

these values were attributed to biological variability and were retained in the statistical analyses.

Transforming the data (square root, logarithmic and inverse procedures) is one approach to dealing with outliers. However, transformations also impact on the associations among the original variables, thus rendering interpretation of findings difficult. Furthermore, transformations of data distributions require that most scores be greater than zero. In the current dataset, the Control group displayed several variables with most of the values being zero, which was another impediment to transforming the data. Given these considerations, the favoured approach was to use statistical tests that are robust in the presence of outliers (non-parametric tests) when assessing variables that were not normally distributed.

The following general approach to statistical analysis was taken. Normality of data distribution was assessed for each level of the analyzed variables. If the assumption of normality of distribution was violated, a non-parametric statistical model was used. Equality of error variances between the two groups was also tested for each level of the analyzed variables prior to conducting between-group comparisons. When this latter assumption was violated, a statistical test with 'equality of variances not assumed' was used.

Despite the small sample size of the Depressed group, an attempt was made to examine the results separately for those who did and did not respond to sleep deprivation therapy.

Previous studies have used a variety of criteria to define a "response", but a threshold of 30% improvement has been used frequently in studies of associations between changes in depression scores and in physiological parameters following sleep deprivation (Baumgartner et al., 1990; Parekh et al., 1998; Kasper et al., 1988; Orth et al., 2001). This criterion was adopted to subdivide the Depressed group in this study.

Chapter 3 Results

3.1 Age of Participants

Age at the time of brain scan was compared between healthy and depressed women using an independent-sample *t*-test. Means (in months) and standard deviations are presented in Appendix 6, as a function of Group. Normality of distribution was tested using the Shapiro-Wilk test for normality (Appendix 6): Age was normally distributed within each group. A Levene test for equality of error variances was conducted to assess between-group differences in variance around the mean (Appendix 6): variances did not differ between the two groups. The *t* test revealed no difference in Age between the two groups, $t(25) = -.435$, $p = .668$ (equal variances assumed).

3.2 Concentration Levels of Brain Neurochemicals

Six 2 x 2 mixed analyses of variance (ANOVAs) were conducted to evaluate the effects of sleep deprivation on the concentration levels of neurochemicals. The six dependent variables were the measured areas (in institutional units) of each of the 3 peaks (NAA:H_2O, Cho:H_2O, and tCr:H_2O) from the spectral profiles acquired in the LADPF region and in the pons. The within-subject factor was Scan time with two levels, A and B (Scan time A was Day 1 at 12:00 and Scan time B was Day 2 at 12:00). The between-subject factor was Group with two levels, Control and Depressed.

Box-plot graphs were created for each level of the variables for the raw and difference scores in order to visualize the data distributions (Appendices 7 - 12). Means, standard deviations and sample sizes for the neurochemical concentrations (raw and difference

scores) are presented in Appendix 13, as a function of brain region, Scan time and Group. Normality of data distribution was tested for each level of the variables, using the Shapiro-Wilk test for normality (Appendix 14). The three following variables did not have normal data distribution: (1) tCr:H_2O at Scan time B acquired in the pons in the Control group, (2) Difference scores for Cho:H_2O acquired in the pons in the Control group, and (3) NAA:H_2O at Scan time A acquired in the LADPF region in the Depressed group. Equality of error variances between the two groups was assessed with the Levene test (Appendix 15). Only one variable displayed inequality of error variances between the two groups: tCr:H_2O acquired at Scan time A in the pons.

ANOVAs revealed a significant main effect of the within-subject factor Scan time for the variable tCr:H_2O acquired in the pons, as well as for the variable Cho:H_2O acquired in the LADPF region (Table 2).

To follow-up the main effect of Scan time for the variable tCr:H_2O acquired in the pons for the Control group, a Wilcoxon test was used (a non-parametric equivalent to a paired-sample *t* test). The choice of a non-parametric test was based on the fact that the tCr:H_2O scores were not normally distributed at Scan time B in the pons for that group (Appendix 14). Results showed that the Control group concentration levels of tCr:H_2O in the pons did not change significantly from Scan time A to Scan time B, $z(7) = -1.023$, $p = .325$ (exact significance). For the Depressed group, a follow-up paired-sample *t* test showed that there was no effect of Scan time on tCr:H_2O concentration levels in the pons, $t(9) = 1.236$, $p = .248$. Therefore, the main effect of Scan time revealed by the ANOVA,

indicating lower concentration levels of tCr:H_2O after sleep deprivation, was attributable to the two groups pooled together (Figures 1 - 2). The post-treatment decrease in tCr:H_2O levels in the pons was 20.1% of baseline values. The standardized effect size *d* was 0.541, which is considered to be a medium effect size.

To follow up the main effect of Scan time on Cho:H_2O acquired in the LADPF region, paired-sample *t* tests were conducted for each group separately, comparing Cho:H_2O concentration levels between Scan time A and Scan time B. Indeed, despite the fact that no significant interaction was revealed by the ANOVA, it could still be the case that only one group would be responsible for the main effect. Paired *t* tests showed that Cho:H_2O concentration levels acquired in the LADPF region for the Depressed group increased significantly after sleep deprivation, as compared to baseline measures, $t(9) = -3.352$, $p = .008$; this paired comparison remained significant after a Bonferroni adjustment that set the alpha value at .025. For the Control group, however, the concentration levels of Cho:H_2O acquired in the LADPF region did not differ between the two times of acquisition, $t(9) = -0.835$, $p = .420$. Thus, the ANOVA main effect of Scan time found for Cho:H_2O in the LADPF region can be attributed to the Depressed subjects, who showed increased Cho:H_2O concentrations in this region after sleep deprivation (Figure 3). The post-treatment increase in Cho:H_2O values was 17.9% of baseline values. The standard effect size *d* was 1.06, which is considered to be a large effect size. The significant main effect of Scan time for the variable Cho:H_2O in the LADPF region is further illustrated in Figure 4, along with the distribution of depressed participants who were medicated or not medicated at the time of the study. No obvious clustering of participants was observed in

relation to medication status.

In previous studies, the positive effects of sleep deprivation have been observed primarily for the affective components of the depressive syndrome (Gerner et al., 1979; Schilgen et al., 1980). Therefore, scores on the item HDI_sad-mood and total HDI_7-item scores were concomitantly used to categorize depressed participants into subgroups. Post-treatment scores (P) were subtracted from baseline values (B) and the difference score was expressed as a percentage change from baseline [(P-B/B)*100]. Criteria for inclusion in the Responder subgroup were (1) a positive percent change score on total HDI_7-item, and (2) at least 30% improvement on HDI_sad-mood (Table 3). These criteria identified 5/11 participants (45%) who were classified as Responders. The other six participants (55%) were considered Non-responders. Mann-Whitney *U* tests showed that subsequent Responders did not differ from subsequent Non-responders in terms of baseline scores on either HDI_sad-mood, $z = -1.792$, $p = .095$ (2 tailed, exact significance), or HDI_7-item, $z = -0.940$, $p = .421$.

Scatterplots were created to illustrate the neurochemical raw and difference scores as a function of Scan time and VOI for Responders and Non-responders (Appendix 17). A visual inspection of the data revealed that the neurochemical raw scores appeared to be randomly distributed (as a function of Responder subgroup) within each factor level of each variable except for Cho:H_2O acquired at Scan time A in the pons (n = 10). Therefore, because of the small sample size involved in each Responder subgroup, only the latter variable was assessed statistically. In fact, Cho:H_2O values in the pons at

baseline were completely segregated between the two subgroups. These values were above 3.5 for all Responders (n = 5) while they were below 3.0 for all Non-responders (n = 5). A Mann-Whitney *U* test revealed that this between-subgroup difference was significant, $z = -2.611$, $p = .008$ (2 tailed, exact significance). This difference remained significant after a Bonferroni correction for multiple comparisons (three neurochemicals in two different VOIs), which set the alpha value at .0083 (.05/6).

This between-subgroup difference in pons levels of Cho:H_2O raised the question of how each subgroup of depressed participants compared to the group of healthy controls at baseline scan. Mann-Whitney *U* tests showed that subsequent Responders did not differ from healthy controls in terms of baseline Cho:H_2O levels in the pons, $z = -0.843$, $p = .442$; on the other hand, subsequent Non-responders to sleep loss showed significantly reduced baseline levels of pons Cho:H_2O relative to healthy controls, $z = -2.951$, $p = .001$.

Further exploration was performed with the difference scores (Scan time A minus Scan time B) for pons Cho:H_2O, in order to assess changes associated with sleep loss as a function of Responder subgroup. Results from a Mann-Whitney *U* test showed that Responders to sleep loss tended to have an opposite pattern of changes in post-treatment levels of Cho:H_2O (29.6% *decrease*) relative to Non-responders (21.8% *increase*), $z = -2.193$, $p = .032$. However, this p value did not meet significance levels required by a Bonferroni correction for multiple comparisons. Means, standard deviations and sample sizes are presented in Appendix 18.

3.3 Depression Raw Scores

The 7-item version of the HDI was administered at three time points: Day 1 at 11:30 prior to the first brain scan, Day 2 at 07:30 on the morning after sleep deprivation, and Day 2 at 11:30 prior to the second brain scan. Self-report scores were obtained for the following variables: mood (HDI_sad-mood), guilt (HDI_guilt), anhedonia (HDI_anhedonia), tension (HDI_subjective-tension), anxiety (HDI_physical-anxiety), energy-loss (HDI_energy-loss) and suicidal ideations (HDI_suicidality). A variable was also created with the summed scores of the seven variables (HDI_7-item), for a total of eight variables for statistical analysis of changes in HDI scores.

Self-report repeated measures were also obtained for the six subscales of the Profile of Mood States: tension (POMS_tension), depression (POMS_depression), anger (POMS_anger), vigour (POMS_vigour; negatively scored), fatigue (POMS_fatigue) and confusion (POMS_confusion). A variable was also created for the composite total score of the six subscales (POMS_total), for a total of seven variables that were analysed statistically. The POMS was administered at six time points over the two days: Day 1 at 11:30 (Time 1) and at 22:00 (Time 2), and Day 2 at 01:00 (Time 3), 04:00 (Time 4), 07:30 (Time 5) and 11:30 (Time 6).

A one-way within-subject ANOVA was planned for each of the Depression variables with the repeated measures factor being Time of self-report, for the purpose of assessing differences in Group mean scores across Time levels for each dependent variable and for

each group separately. This statistical model was favoured over two-way mixed ANOVAs (Group x Time) for two main reasons. (1) The two groups were initially created by the experimenter on the basis of the presence or absence of a clinical diagnosis of unipolar depression. Thus, the assessment of baseline between-group differences in Depression scores was not an objective. (2) In addition, the large discrepancy in error variances observed between the two groups of some Depression variables was a deterrent to running an omnibus test that requires equality of error variances between the two groups being compared. Therefore, the adopted approach was a one-way within-subject ANOVA, with the goal of assessing changes in Depression scores across Time levels for each group separately.

Box-plot graphs were created for each variable of both Depression scales, in order to visualize the distribution of the data at each level (Appendix 19). Means and standard deviations for the Depression self-reports are presented in Appendix 20, as a function of Time and Group.

Appendix 21 reports the statistics from the Shapiro-Wilk tests for normality of distribution that were conducted for the raw scores of each variable acquired at Times 1 and 6, as well as for the difference scores (Time 1 minus Time 6). The Shapiro-Wilk tests for normality revealed that for several variables, Depression scores were not normally distributed for at least one Time point. Therefore, repeated-measures non-parametric tests (Friedman tests) were conducted in addition to the one-way ANOVAs. Supplementary Shapiro tests were also conducted for a few more Time levels, for those variables that

required follow-up analyses (Appendix 22).

Parametric and non-parametric analyses are presented side-by-side in Table 4: the Friedman tests, evaluating differences in group median scores across Time levels, and the one-way ANOVAs, evaluating differences in group mean scores over Time levels. Self-reported scores for the Control group changed significantly over the period of sleep deprivation for the following variables: HDI_anhedonia, HDI_subjective-tension, HDI_energy-loss, POMS_total, POMS_tension, POMS_vigour, POMS_fatigue and POMS_confusion. In the Depressed group, variables that changed over Time were: HDI_sad-mood, POMS_total, POMS_tension, POMS_anger, POMS_vigour, and POMS_confusion.

To follow-up the main effect of Time in the variables mentioned above, paired-sample *t* tests were conducted across Time levels for the variables that displayed normal data distributions. Wilcoxon tests were the non-parametric equivalent used for the other variables, comparing Group mean ranks across Time levels. Table 5 reports the statistical values for both models of follow-up tests.

Follow-up tests for the HDI variables showed that the Control participants reported an increase in their scores on HDI_anhedonia and HDI_energy-loss over the period of sleep deprivation, indicating that they were getting less energetic and less interested and motivated as they became more sleep deprived (Figures 6 - 7). Control participants also reported a decrease in their HDI_subjective-tension scores from Time 1 to Time 5;

however, this significant decrease was not maintained at Time 6 (Figure 8). For the Depressed participants, the self-report scores on the variable HDI_sad-mood decreased over Time: there was a significant decrease in HDI_sad-mood ratings from Day 1 at 11:30 prior to the first brain scan, to Day 2 at 07:30 during the morning of sleep deprivation, which difference was maintained for the last Time of self-report, Day 2 at 11:30. This group of young depressed women reported an improvement in HDI_sad-mood, as they became sleep deprived (Figure 9).

Follow-up tests for the POMS variables showed that the POMS_total score increased steadily across Time levels for the Control group (Figure 10), due mainly to the scores on the subscales POMS_vigour (Figure 11), POMS_fatigue (Figure 12), and POMS_confusion (Figure 13). Therefore, Control participants reported a gradual and marked increase in their feelings of Fatigue and Confusion, and a gradual decrease in Vigour, as they became more sleep deprived. In the Depressed group, the POMS_total score displayed a curvilinear change across Time levels. Severity of total depressive symptoms was alleviated from Day 1 at 11:30 until the mid-point during the night of sleep deprivation (04:00). However, the total scores at Time 6 were back up to baseline levels (Figure 10). This pattern of curvilinear change across Time levels observed in the POMS_total scores was also observed in the subscales POMS_tension (Figure 14), POMS_confusion (Figure 13), and POMS_anger (Figure 15). The variable POMS_vigour did not show this curvilinear trend of changes over Time (Figure 11). Instead, increases in scores of POMS_vigour were observed over the whole sleep deprivation period, indicating a gradual and sustained decrease in feelings of Vigour for this group as well.

Table 10 provides a summary of significant changes in Depression raw scores that occurred for each group during the sleep deprivation procedure.

3.4 Depression Difference Scores

Independent-sample *t* tests were conducted in order to evaluate between-group differences in the Depression difference scores computed between Time 1 (Day 1 at 11:30) and Time 6 (Day 2 at 11:30).

Box-plots were created to visualize the distributions of each variable (Appendix 23). Means and standard deviations for the Depression difference scores were previously reported in Appendix 20. Normality of distributions was tested for each variable using the Shapiro-Wilk test (previously reported in Appendix 21). Several variables did not display normal data distributions. For the Control group, these variables were: HDI_sad-mood, HDI_guilt, HDI_energy-loss, POMS_depression, POMS_anger, and POMS_vigour. For the Depressed group, variables that did not approximate normal data distributions were: HDI_guilt, HDI_energy-loss, HDI_suicidality and POMS_tension. Mann-Whitney *U* tests were used for the variables that were not normally distributed.

Equality of error variances between the two groups was tested with the Levene test (Appendix 24). Variances differed significantly between the two groups for the variables: HDI_sad-mood, HDI_suicidality, POMS_total, POMS_depression, and POMS_anger. For these variables, the independent-sample *t* test statistic and *p* value for "equal variances not assumed" was retained.

Independent-sample *t* tests and Mann-Whitney *U* tests for the Depression difference scores are reported side-by-side in Table 6. These tests revealed between-group differences in the pattern of change in feelings over Time of sleep deprivation for the variables HDI_7-item (Figure 16), HDI_sad-mood (Figure 17), HDI_anhedonia (Figure 18), and HDI_energy-loss (Figure 19). The difference scores for the variable POMS_total also differed between groups (Figure 20), along with the difference scores on the subscales POMS_depression (Figure 21), POMS_vigour (Figure 22), POMS_fatigue (Figure 23) and POMS_confusion (Figure 24). For all these significant between-group comparisons, the Group mean difference score was consistently smaller in the Control group relative to the Depressed group. The more negative difference scores observed in the Control group were an indication that the severity of depression symptoms tended to increase with sleep deprivation in this group significantly more than in the Depressed group. Table 11 provides a summary of significant between-group differences in Depression score schanges from Day 1 to Day 2.

3.5 Association Between Depression Scores and ^{1}H-MRS Concentrations

Bivariate correlations were computed between the Neurochemical concentration levels observed at Scan time A and at Scan time B on the one hand, and the self-report scores on the 15 Depression variables acquired prior to each brain scan on the other hand. These correlations were conducted for each group separately and for both groups pooled. In addition, difference scores derived from the Neurochemical concentration levels (Scan time A minus Scan time B) were correlated with the Depression difference scores (Time

1 minus Time 6). Pearson correlations were used when scores from both variables being assessed were approximately normally distributed. Spearman correlations were used with ranked scores when data for one or both variables were not normally distributed.

Means and standard deviations for the Depression raw and difference scores used for the correlations with the Neurochemical concentrations are presented in Appendix 25, for each group separately and for both groups pooled. Means and standard deviations for the Neurochemical raw and difference scores used for correlations with the Depression scores are presented in Appendix 26 as a function of VOI, for each group separately and for both groups pooled.

The Shapiro-Wilk test was used to assess univariate normality of distribution for the raw and difference scores of Depression variables and of Neurochemical concentrations (Appendices 27 - 28).

Correlations are presented in Table 7 for Scan time A, in Table 8 for Scan time B, and in Table 9 for the difference scores. The threshold of significance was adjusted to .01, with the goal of decreasing the probability of false positive findings while still permitting some exploration of the data. In addition, correlations were not considered valid when one or both of the variables being assessed had fewer than five data points different from zero.

The correlations showed that at Scan time A in the Depressed group, the scores of

HDI_sad-mood were negatively associated with the concentration levels of NAA:H_2O acquired in the LADPF region (Figure 25). Thus, NAA:H_2O concentration levels in the LADPF region were lower for depressed subjects when their mood ratings indicated greater sadness. The index r^2 was .514, indicating that 51.4% of the variance in levels of NAA:H_2O was accounted for by its relationship with scores on HDI_sad-mood. Figure 25 also illustrates the distribution of depressed participants who were on stable antidepressant medication at the time of the study. No obvious clustering of Medicated or Non-medicated participants was observed to potentially contribute to this significant correlation, with respect to either variable.

At Scan time B (after sleep deprivation), no correlation reached the adjusted threshold of significance.

With respect to the Difference scores, there were two significant correlations. In the Control group, the variable HDI_7-item was positively associated with NAA:H_2O concentration levels acquired in the pons (Figure 26). The index r^2 was .508, indicating that 50.8% of the variance in levels of NAA:H_2O in the pons could be accounted for by changes in total HDI_7-item scores. Therefore, for healthy volunteers who rated the HDI items higher than baseline as they became more sleep deprived (thus yielding negative Depression difference scores), the concentration levels of NAA:H_2O in the pons also increased at Scan time B, giving negative difference scores as well. It is interesting to note in Figure 26 that five healthy participants reported some decrease in their total scores on the HDI scale with sleep deprivation (yielding positive difference scores),

while seven healthy participants reported some degree of increase in their total HDI scores occurring with sleep deprivation (negative difference scores).

In the Depressed group, a significant positive association was found between the Difference scores on the subscale POMS_fatigue and the Difference scores of Cho:H_2O acquired in the pons (Figure 27). The index r^2 was .629, indicating that 62.9% of the variance in levels of Cho:H_2O was accounted for by its relationship with scores on POMS_fatigue. A decrease in POMS_fatigue at Time 6 was associated with a decrease in concentration levels of Cho:H_2O at Scan time B. Figure 27 also illustrates the distribution of depressed participants who were on stable antidepressant medication at the time of the study. No obvious clustering of Medicated or Non-medicated participants was observed to potentially contribute to this significant correlation, with respect to either variable.

Chapter 4 Discussion

4.1 Neurochemical Concentrations

It was hypothesized that the pattern of changes in neurochemical concentrations following sleep deprivation would differ between the two groups. This hypothesis was supported by the finding that depressed participants responded to treatment with a significant 17.9% increase in concentration levels of Cho:H_2O in the left anterior dorsal prefrontal region, while levels of Cho:H_2O did not change in the Control group. Another finding was observed for both groups combined: a significant 20.1% decrease in concentration levels of tCr:H_2O in the pons following sleep deprivation (Figure 28).

Post-treatment changes in neurochemical concentrations of the dorsal prefrontal region have not been reported previously in the literature. The elevated post-treatment levels of Cho:H_2O found in the left anterior dorsal prefrontal region of the Depressed group are suggestive of alterations in the metabolic activity of phosphorylcholine (PC) and/or glycerophosphorylcholine (GPC), which are the two major constituents of the ^{1}H-MRS Cho signal. Additionally, this finding is suggestive of changes in metabolic activity of the membrane-bound phospholipid phosphatidylcholine, which is assumed to modulate concentration levels of PC and GPC (see Boulanger et al., 2000). And finally, considering that phospholipid metabolic activity has been estimated to consume about 20% of total adenosine triphosphate (ATP, the principal source of metabolic energy) in the brain (Purdon et al., 2002), this post-treatment increase in Cho:H_2O might be reflective, in part, of changes in ATP metabolic activity in this brain region. Consistent with this line of reasoning, previous functional imaging studies have reported that

remission of depressive symptoms, following a course of antidepressant medication, was associated with increased regional metabolic rates in the anterior dorsal prefrontal region (Baxter et al., 1989; Buchsbaum et al., 1997; Mayberg et al., 2000; Kennedy et al., 2001).

Reduced post-treatment levels of tCr:H_2O observed in the pontine region are reflective of a change in creatine and/or phosphocreatine metabolic activity in the pons during sleep deprivation, in both healthy and depressed individuals. This brain region has not been examined previously in spectroscopic studies of depression. Since the creatine kinase/phosphocreatine network is known to be involved in connecting sites of ATP production and consumption (Wallimann et al., 1992), decreased levels of tCr:H_2O are suggestive of altered ATP metabolic activity. Consistent with this interpretation, a PET study of sleep deprivation effects in healthy people reported lower metabolic rates in the mesopontine and pontine regions after sleep deprivation (Thomas et al., 2000).

The observation that there were no significant changes in neurochemical concentrations in the left anterior dorsal prefrontal region of the Control group after sleep deprivation is consistent with two previous ^{31}P-MRS studies of sleep deprivation in healthy participants. These reported no immediate neurochemical effects of prolonged wakefulness in a large section of the frontal lobes (Murashita et al., 1999) and in the ventral prefrontal region (Dorsey et al., 2003).

Another finding was unexpected. Within the Depressed group at baseline scan, subsequent Responders to sleep loss showed Cho:H_2O values in the pons that did not

overlap the distribution of values for subsequent Non-responders. The significant baseline difference between subgroups in Cho:H_2O remained so after Bonferroni correction. Non-responders to sleep deprivation showed abnormally reduced levels of Cho:H_2O in the pons, relative to either Responders or Controls. Furthermore, difference scores (Scan time A minus Scan time B) revealed a trend ($p = .032$) differentiating the two subgroups: Responders to sleep loss had a post-treatment decrease in pontine levels of Cho:H_2O, while Non-responders showed a slight increase from their abnormally low baseline. Replication of these findings with a larger sample size would suggest that pontine phospholipid metabolism may be a marker for, and be involved in, the beneficial effects of sleep deprivation on mood.

4.2 Depression Scores

Applying a measure of 30% improvement in Mood (HDI), 5/11 (45.5%) in the Depressed group responded positively to sleep deprivation therapy. This result is consistent with reviews of the literature that have reported an average positive response rate of about 50% for various kinds of sleep deprivation therapy.

Control and Depressed participants differed in their responses to partial sleep deprivation with respect to several symptoms of depression (Table 10). In the Depressed group, raw scores for HDI_sad-mood were markedly improved on Day 2 at 07:30, and improvement was maintained at 11:30 prior to the second brain scan. A gradual improvement in feelings of Tension, Anger and Confusion (POMS) started early and peaked during the night of sleep deprivation; however, a significant reversal toward baseline values was

observed prior to the second brain scan. A detrimental effect of sleep deprivation was observed in POMS_vigour, which showed gradual worsening throughout the experimental period. At the time of the second brain scan, only two variables had maintained significant changes: improvement in HDI_sad-mood and deterioration in POMS_vigour.

The pattern of mood improvement is consistent with previous studies using a total sleep deprivation approach which reported an improvement of mood in depressed patients starting during the sleep deprivation night as the most substantial effect on depressive symptoms (Gerner et al., 1979; Schilgen et al., 1980). Reduced feelings of Anger and Confusion (POMS) have also been reported for depressed subjects, starting later during the period of prolonged wakefulness and being maintained until recovery sleep during the following evening (Gerner et al., 1979; Szuba et al., 1991). In this study, collection of self-reports ended at noon after sleep deprivation, so the subsequent course of symptom change cannot be compared to these earlier reports.

In the Control group, sleep deprivation had detrimental effects on several variables (Table 10). Healthy subjects became less energetic, interested and motivated (HDI). They also reported a marked worsening in feelings of Fatigue, Confusion and Vigour (POMS). Deterioration started on Day 1 at 22:00 for Vigour, and on Day 2 at 01:00 for Fatigue and Confusion, progressing steadily until the last assessment on Day 2 at 11:30. The only beneficial effect of sleep deprivation was observed on HDI_subjective-tension and POMS_tension, for which variables the improvement was already significant on Day 1 at

22:00; however, these self-report scores reverted to baseline values by Day 2 at 07:30. In sum, a significant and sustained worsening was observed for the Control group in Anhedonia and Energy-loss (HDI), and in Fatigue, Confusion and Vigour (POMS).

These findings are consistent with previous studies that have reported detrimental effects of sleep deprivation in healthy subjects. Deterioration in self-report scores has been observed in healthy controls for somatic complaints and anhedonia (Kahn-Greene et al., 2007), and for scores on all six POMS subscales: Depression, Fatigue, Vigour, Tension, Anger and Confusion (Orton et al., 1989).

Measures that were not significantly altered in either group included Depression (POMS), Guilt and Physical-anxiety (HDI). Depressed participants reported no significant changes over time in Fatigue (POMS), and Anhedonia, Subjective-tension and Energy-loss (HDI), while Controls did not report significant changes in Sad-mood (HDI) and Anger (POMS).

A meta-analysis of studies conducted with healthy participants found that the most substantial effect of sleep deprivation in healthy people is a deterioration of mood, with a very strong effect size of -3.16 (see Pilcher et al., 1996). In this study, mood in Controls did not change significantly after sleep loss, which is consistent with one early study (Gerner et al., 1979). This discrepancy between the present results and most previous sleep deprivation studies of normal controls may be related to the types of scales used for mood assessment. The variables Mood and Anhedonia were well discriminated using the Hamilton scale in this study: healthy controls showed a marked and sustained

deterioration in their scores on HDI_anhedonia but not on HDI_sad_mood during sleep loss. It is possible that earlier studies did not assess effects on analogous subscales separately and reported deterioration on combined measures of mood that obscure these possible differences.

The lack of improvement in mood in the Depressed group, as assessed using the POMS_depression subscale (Table 10), contrasts to previous reports of mood improvement using this measure for Responders to treatment (Szuba et al., 1991). Because of the small sample size in the present study, subscale scores for Responders and Non-responders were not analysed separately, as in the Szuba et al. (1991) study. It is likely that scores from Non-responders obscured the changes in mood scores seen in Responders.

Significant between-group disparities in Difference scores (Time 1 minus Time 6) are summarized in Table 11. Group mean total scores changed in opposite directions, as previously reported (Gerner et al., 1979): mean HDI scores improved for Depressed participants, but deteriorated for Controls. The differential impact of sleep deprivation between the two groups was observed on variables of Sad-mood (HDI) and Depression (POMS), as only Depressed participants showed mood improvement as assessed by these subscales. Additionally, Fatigue, Confusion (POMS), Anhedonia and Energy-loss (HDI) deteriorated only in the Control group, while Vigour (POMS) deteriorated for both groups, but significantly more so for the Control group.

4.3 Association Between Depression Scores and ^{1}H-MRS Concentrations

Significant correlations were found between depression scores and neurochemical concentrations. A pre-treatment correlation was found in the Depressed group between concentration levels of NAA:H_2O in the left anterior dorsal prefrontal region and scores for Sad-mood (HDI). Lower levels of NAA:H_2O were associated with greater sadness (Figure 29).

Reduced levels of NAA:tCr have previously been reported in the dorsal prefrontal region during the depressed state (Grachev et al., 2003). However, reduced levels of % PCr in the anterior frontal pole have also been linked to greater severity of depression (Kato et al., 1992), and the denominator in the NAA:tCr ratio would include % PCr. It is difficult to interpret the reported alterations in levels of NAA:tCr (Grachev et al., 2003), since changes in both measures have been reported in depression.

One potential interpretation of the pre-treatment association found in the present study is based on the significant correlation observed between decreases in NAA anabolic activity and decreases in production of ATP (Moffet et al., 2007). Considering previous findings of reduced levels of total % nucleoside triphosphates in the frontal and prefrontal regions of depressed patients (Volz et al., 1998), the pre-treatment association found in this study might, in part, reflect reduced levels of ATP. This interpretation would align with the consistent observation in functional imaging studies of hypometabolism in this brain region during depression.

At post-treatment time in the Depressed group, a decrease in Fatigue (POMS), which can be considered a positive response to sleep deprivation, was associated with reduced levels of Cho:H_2O in the pons (Figure 30). Three subjects from the Depressed group showed an alleviation in Fatigue with sleep deprivation, three subjects reported no change, while four reported some degree of worsening.

In the Control group, post-treatment worsening (increase) in total scores of the HDI scale, a typical response to sleep deprivation in healthy subjects, was associated with increased concentration levels of NAA:H_2O in the pons (Figure 30). Based on the HDI total scores, seven healthy participants experienced a worsening of symptoms, while five of them experienced a slight degree of improvement with prolonged wakefulness. These different responses to partial sleep deprivation are consistent with a previous ^{31}P-MRS study of sleep deprivation effects in healthy subjects (Murashita et al., 1999), which reported two different types of neurochemical responses to prolonged wakefulness. The authors hypothesized that healthy people may, like depressed patients, show two different patterns of responses to sleep deprivation.

An important limitation to the interpretation of associations between severity of specific symptoms and levels of specific neurochemicals in each VOI pertains to the large number of comparisons that were computed. These reported associations should, therefore, be considered tentative and as likely targets for future experimental assessment.

4.4 Summary and Conclusion

The main findings with respect to ^{1}H-MRS-visible neurochemicals were: 1) a significant 17.9% increase in Cho:H_2O observed in the LADPF region of the Depressed group following sleep deprivation; 2) a significant 20.1% post-treatment decrease in tCr:H_2O observed in the pons for both groups pooled together; and 3) a clear segregation at baseline between subsequent Responders and Non-responders to sleep deprivation, of Cho:H_2O values in the pons (with baseline values abnormally reduced in subsequent Non-responders).

In terms of responses of depression scores and their association with neurochemical changes after partial sleep deprivation, the main findings were: 1) the Depressed group responded to sleep deprivation with an improvement in Mood (HDI) and a deterioration in Vigour (POMS); 2) the Control group reported a gradual and sustained deterioration in Anhedonia and Energy-loss (HDI), and in Fatigue, Confusion and Vigour (POMS); 3) there was a pre-treatment association in the Depressed group, with lower baseline levels of NAA:H_2O in LADPF being significantly correlated with greater sadness (HDI); 4) at post-treatment time, an improvement in Fatigue (POMS) in the Depressed group was associated with reduced levels of Cho:H_2O in the pons; and 5) in the Control group, a worsening in HDI total scores was associated with increased levels of NAA:H_2O in the pons.

A consistent theme emerging from these findings is the relation of the levels of choline compounds to depressive symptoms. One striking observation was the abnormally

reduced concentration levels of choline compounds in the pons before treatment in subsequent Non-responders but not in subsequent Responders to sleep loss. If confirmed in future studies, this observation suggests a way of predicting responsiveness to sleep deprivation therapy. It also opens the door for analysis of other correlates of low pontine choline levels, which may provide additional insights into the biological basis for responsiveness to sleep deprivation.

Another finding involving choline compounds was the significant increase in their concentration in the LADPF region after sleep loss among depressed participants but not among healthy controls. In addition, the pre-/post-treatment change in LADPF choline compounds was related to the extent of decrease in Fatigue scores for Depressed patients but not for Controls.

These findings imply that changes in choline compounds in some brain regions may be critical correlates of changes in mood and other features of the depressive syndrome, and that their levels may even be predictive of responsiveness to some treatments. This observation suggests that pontine Cho levels should be explored as a potential endophenotype linking genetic and physiological characteristics to treatments for mood disorders. One limitation of this study, however, is that at 1.5T, the different neurochemical components contributing to the Cho peak cannot be resolved.

Another important limitation of the present findings relates to the relatively small sample size in this study, which can restrict the generalizability of the findings. In addition to

planning for a larger sample size, future research protocols could schedule a longer experimental period in order to assess changes in depression scores and neurochemical concentrations occurring during the afternoon and evening parts of the day following sleep deprivation, and following a full night of recovery sleep. Another point to mention is the possibility that, despite the precautions taken, participants might have inadvertently slept during the second brain scan, conducted in a state of sleep deprivation. With respect to ^{1}H-MRS data acquisition, future studies conducted with a 1.5T scanner (thus focusing on the three main singlets of the spectral profiles) would likely benefit from using a long TE sequence rather than the short TE sequence that was used in this study. (Our scanner could not accommodate a long TE sequence at the time this study was conducted.)

This study employed a partial sleep deprivation approach, which some participants may find less stressful than total sleep deprivation. A previous study reported substantial effects of partial sleep deprivation, with 67% of patients responding to this treatment (Schilgen et al., 1980); however, another study reported that total sleep deprivation might have slightly more potent effects (Giedke et al., 2003). It is thus possible that a total sleep deprivation intervention would yield more robust findings in terms of neurochemical responses to sleep loss. Additionally, repeated cycles of sleep deprivation therapy, as has been used in previous studies, might allow assessment of the reliability of the neurochemical changes observed and the degree to which their magnitude is affected by repetition.

Sleep deprivation is the only known therapy for depression that typically produces an

antidepressant response within a period of 24 h in about half of depressed patients. This unique advantage makes it an excellent tool for exploring the neural substrates accompanying alleviation of depression and those associated with the typical relapse observed after recovery sleep. This research tool also allows for the inclusion of a healthy control group, which is not always ethically possible with other types of treatment approaches. One should keep in mind, however, that a short-term elevation of mood might be driven by different physiological mechanisms than the more delayed but longer-term improvement of depressive symptoms that may result from other treatment modalities. Furthermore, it is not known whether Responders to sleep deprivation therapy are a biologically distinct subgroup of depressed patients, as compared to those who respond to medications, psychotherapy or ECT treatments and as compared to treatment-resistant patients. Nevertheless, understanding the physiological mechanisms associated with an acute alleviation of depressive symptoms could complement and broaden existing hypotheses about the mechanisms underlying major depressive disorder (see Belmaker & Agam, 2008).

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Table 1

Demographic and Clinical Information for Depressed and Control Participants

	Control group (n = 15)	Depressed group[1] (n = 12)
Age range (year;month)	19;07 to 30;05	21;03 to 31;02
HDRS[2] score at screening [M (SD)]	04.00 (2.20)	23.90 (2.90)
Education level	undergraduate: n = 7	undergraduate: n = 8
	graduate: n = 8	graduate: n = 4
Handedness	right: n = 15	right: n = 11
	left: n = 0	left: n = 1
Current antidepressant medication	Non-medicated: n = 15	Non-medicated: n = 5
		Medicated: n = 7
		Paroxetine n = 1
		Venlafaxine n = 2
		Bupropion n = 1
		Citalopram n = 3

Note. [1] One depressed participant quit the study before the sleep deprivation night.
[2] 17-item Hamilton Depression Rating Scale (clinical cut off score for inclusion was 18).

Table 2

Analyses of Variance for Neurochemical Concentrations

Brain region	Neurochemical	Factor	*F*	*p*	*df1*	*df2*
Pons	Cho:H_2O	Scan time[(S, D)]	1.555	.230	1	16
		Scan time x Group	0.058	.813	1	16
		Group	3.966	.064	1	16
	tCr:H_2O	Scan time	5.070*	.039	1	16
		Scan time x Group	0.090	.768	1	16
		Group[(S, R) L]	3.804	.069	1	16
	NAA:H_2O	Scan time	0.028	.868	1	20
		Scan time x Group	0.108	.746	1	20
		Group	0.134	.718	1	20
LADPF[1]	Cho:H_2O	Scan time	5.242*	.033	1	21
		Scan time x Group	0.942	.343	1	21
		Group	0.116	.737	1	21
	tCr:H_2O	Scan time	0.063	.805	1	21
		Scan time x Group	0.746	.398	1	21
		Group	0.849	.367	1	21
	NAA:H_2O	Scan time	0.196	.662	1	21
		Scan time x Group	0.795	.383	1	21
		Group[(S, R)]	0.121	.731	1	21

Note. [(S, D)] Shapiro-Wilk test for normality of distribution is significant for the difference

Table 2 continued

Analyses of Variance for Neurochemical Concentrations

Brain region	Neurochemical	Factor	*F*	*p*	*df1*	*df2*

scores. [S, R] Shapiro-Wilk test for normality of distribution is significant for the raw scores. [L] Levene test of equality of error variances between the two groups is significant.

[1] Left anterior dorsal prefrontal.

* $p < .05$.

Table 3

Categories for Responders and Non-responders Within the Depressed group

		Depression scores		Category	
Research code	Time of self-report[1]	Sad-mood (HDI)[2]	7-item (HDI)	Responders	Non responders
D01	1	2.30	12.47		
	6	2.30	11.10		
	(%Difference)	0.00%	10.99%		X
D02	1	2.86	16.36		
	6	0.86	12.86		
	(%Difference)	69.93%	21.39%	X	
D03	1	2.00	09.67		
	6	0.86	03.53		
	(%Difference)	57.00%	63.50%	X	
D05	1	2.29	09.96		
	6	1.14	05.81		
	(%Difference)	50.22%	41.67%	X	
D06	1	2.57	12.07		
	6	2.00	11.33		
	(%Difference)	22.18%	06.13%		X
D07	1	2.57	10.23		
	6	1.43	08.26		
	(%Difference)	44.36%	19.26%	X	
D08	1	1.43	10.59		

Table 3 continued

Categories for Responders and Non-responders Within the Depressed group

		Depression scores		Category	
Research code	Time of self-report[1]	Sad-mood (HDI)[2]	7-item (HDI)	Responders	Non responders
	6	1.14	08.97		
	(%Difference)	20.28%	15.30%		X
D09	1	1.14	08.30		
	6	1.71	10.21		
	(%Difference)	-50.00%	-23.01%		X
D10	1	1.71	08.87		
	6	0.00	06.83		
	(%Difference)	100.00%	23.00%	X	
D11	1	1.14	07.30		
	6	1.71	08.37		
	(%Difference)	-50.00%	-14.66%		X
D12	1	1.71	07.97		
	6	1.43	06.76		
	(%Difference)	16.37%	15.18%		X
n				5	6

Note. [1] Time 1 was Saturday at 11:30 (baseline); Time 6 was Sunday at 11:30 (post-treatment); %Difference: the difference score between Time 1 and Time 6, divided by score at Time 1 and multiplied by 100. [2] HDI: Hamilton Depression Inventory.

Table 4

Parametric and Non-parametric Statistical Analyses for Depression Raw Scores

Scale[1]_variable[P/NP]	ANOVA[P]					Friedman test[NP]		
	$\Lambda^{\#}$	F	p	$df1$	$df2$	x^2	p^a	df
Control group (n = 15)								
HDI_7-item[NP]	.780	1.830	.199	2	13	3.321	.190	2
HDI_sad-mood[NP]	.878	0.905	.428	2	13	0.400	.819	2
HDI_guilt[NP]	.715	2.588	.113	2	13	3.364	.186	2
HDI_anhedonia[NP]	.505	6.372	.012	2	13	11.056**	.004	2
HDI_subjective-tension[NP]	.458	7.684	.006	2	13	11.643**	.003	2
HDI_physical-anxiety[NP]	.887	0.831	.457	2	13	1.407	.495	2
HDI_energy-loss[NP]	.249	19.620	.000	2	13	18.558**	.000	2
POMS_total[NP]	.156	10.827	.001	2	10	46.596**	.000	5
POMS_tension[NP]	.602	1.321	.330	2	10	22.319**	.000	5
POMS_depression[NP]	.615	1.255	.354	2	10	6.458	.264	5
POMS_anger[NP]	.533	1.753	.210	2	10	9.220	.101	5
POMS_vigour[NP]	.092	19.777	.000	2	10	50.692**	.000	5
POMS_fatigue[NP]	.129	13.520	.000	2	10	47.276**	.000	5
POMS_confusion[NP]	.150	11.331	.001	2	10	41.821**	.000	5
Depressed group (n = 11)								
HDI_7-item[P]	.535	3.916	.060	2	9	7.091	.029	2
HDI_sad-mood[P]	.250	13.470**	.002	2	9	11.842	.003	2

Table 4 continued

Parametric and Non-parametric Statistical Analyses for Depression Raw Scores

Scale[1]_variable[P/NP]	ANOVA[P]					Friedman test[NP]		
	$\Lambda^{\#}$	F	p	$df1$	$df2$	x^2	p^a	df
HDI_guilt[NP]	.818	1.000	.405	2	9	2.800	.247	2
HDI_anhedonia[NP]	.757	1.444	.286	2	9	3.062	.216	2
HDI_subjective-tension[NP]	.653	2.389	.147	2	9	4.345	.114	2
HDI_physical-anxiety[NP]	.847	0.812	.474	2	9	2.971	.226	2
HDI_energy-loss[NP]	.980	0.093	.912	2	9	0.333	.846	2
HDI_suicidality[NP]	.802	1.110	.371	2	9	1.600	.449	2
POMS_total[NP]	.112	9.489	.008	5	6	20.961**	.001	5
POMS_tension[P]	.160	6.292*	.022	5	6	20.416	.001	5
POMS_depression[P]	.360	2.135	.191	5	6	12.493	.029	5
POMS_anger[NP]	.179	5.517	.030	5	6	16.618**	.005	5
POMS_vigour[NP]	.125	8.402	.011	5	6	14.724*	.012	5
POMS_fatigue[P]	.294	2.888	.115	5	6	18.183	.003	5
POMS_confusion[P]	.034	34.365**	.000	5	6	12.052	.034	5

Note. [1] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [P/NP] Parametric or non parametric test retained on the basis of normality of distribution assessed with the Shapiro-Wilk test. [#] Wilk's Lambda. [a] Asymptotic.

* $p < .05$; ** $p < .01$.

Table 5

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
		Control group					
HDI_anhedonia	Day 1, 11:30 / Day 2, 07:30[NP]	-1.581	.136	14	-1.476	.188	15
	Day 1, 11:30 / Day 2, 11:30[NP]	-3.568	.003	14	-2.701 **	.006	15
	Day 2, 07:30 / Day 2, 11:30[NP]	-2.000	.065	14	-1.777	.102	15
HDI_subjective-tension	Day 1, 11:30 / Day 2, 07:30[NP]	3.756	.002	14	-2.636 **	.008	15
	Day 1, 11:30 / Day 2, 11:30[NP]	2.219	.044	14	-1.869	.070	15
	Day 2, 07:30 / Day 2, 11:30[NP]	-1.784	.096	14	-1.633	.250	15
HDI_energy-loss	Day 1, 11:30 / Day 2, 07:30[NP]	-5.137	.000	14	-3.071 **	.001	15
	Day 1, 11:30 / Day 2, 11:30[NP]	-5.916	.000	14	-3.217 **	.000	15
	Day 2, 07:30 / Day 2, 11:30[NP]	-0.367	.719	14	-0.378	.999	15

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
POMS_total	Day 1, 11:30 / Day 1, 22:00[NP]	-0.430	.673	14	-0.691	.511	15
	Day 1, 11:30 / Day 2, 01:00[NP]	-2.047	.060	14	-1.761	.081	15
	Day 1, 11:30 / Day 2, 04:00[NP]	-1.653	.121	14	-1.761	.081	15
	Day 1, 11:30 / Day 2, 07:30[NP]	-6.125	.000	14	-3.327 **	.000	15
	Day 1, 11:30 / Day 2, 11:30[NP]	-6.846	.000	14	-3.408 **	.000	15
	Day 1, 22:00 / Day 2, 01:00[P]	-2.728 *	.016	14	-2.308	.018	15
	Day 1, 22:00 / Day 2, 04:00[P]	-2.425 *	.029	14	-2.308	.018	15
	Day 1, 22:00 / Day 2, 07:30[P]	-5.801 **	.000	14	-3.327	.000	15
	Day 1, 22:00 / Day 2, 11:30[P]	-7.195 **	.000	14	-3.409	.000	15
	Day 2, 01:00 / Day 2, 04:00[P]	0.592	.563	14	0.000	.999	15
	Day 2, 01:00 / Day 2, 07:30[P]	-4.657 **	.000	14	-3.040	.001	15

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 2, 01:00 / Day 2, 11:30[P]	-5.890 **	.000	14	-3.409	.000	15
	Day 2, 04:00 / Day 2, 07:30[P]	-4.863 **	.000	14	-3.040	.000	15
	Day 2, 04:00 / Day 2, 11:30[P]	-5.739 **	.000	14	-3.409	.000	15
	Day 2, 07:30 / Day 2, 11:30[P]	-0.979	.344	14	-0.754	.472	15
POMS_tension	Day 1, 11:30 / Day 1, 22:00[NP]	2.736	.016	14	-2.354 *	.015	15
	Day 1, 11:30 / Day 2, 01:00[NP]	2.525	.024	14	-2.324 *	.018	15
	Day 1, 11:30 / Day 2, 04:00[NP]	2.525	.024	14	-2.324 *	.018	15
	Day 1, 11:30 / Day 2, 07:30[NP]	1.277	.222	14	-1.301	.233	15
	Day 1, 11:30 / Day 2, 11:30[NP]	0.670	.513	14	-0.671	.532	15
	Day 1, 22:00 / Day 2, 01:00[NP]	-0.174	.865	14	-0.530	.656	15
	Day 1, 22:00 / Day 2, 04:00[NP]	-0.174	.865	14	-0.530	.656	15

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 1, 22:00 / Day 2, 07:30[NP]	-2.175	.047	14	-2.229 *	.023	15
	Day 1, 22:00 / Day 2, 11:30[NP]	-2.467	.027	14	-2.829 **	.002	15
	Day 2, 01:00 / Day 2, 04:00[0]			14			15
	Day 2, 01:00 / Day 2, 07:30[NP]	-2.182	.047	14	-2.388 *	.016	15
	Day 2, 01:00 / Day 2, 11:30[NP]	-2.305	.037	14	-2.672 **	.007	15
	Day 2, 04:00 / Day 2, 07:30[NP]	-2.182	.047	14	-2.388 *	.016	15
	Day 2, 04:00 / Day 2, 11:30[NP]	-2.305	.037	14	-2.672 **	.007	15
	Day 2, 07:30 / Day 2, 11:30[NP]	-0.924	.371	14	-0.844	.473	15
POMS_vigour	Day 1, 11:30 / Day 1, 22:00[P]	-3.967 **	.001	14	-2.762	.003	15
	Day 1, 11:30 / Day 2, 01:00[NP]	-4.854	.000	14	-3.155 **	.001	15
	Day 1, 11:30 / Day 2, 04:00[NP]	-4.138	.001	14	-3.155 **	.001	15

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 1, 11:30 / Day 2, 07:30[P]	-10.126 **	.000	14	-3.413	.000	15
	Day 1, 11:30 / Day 2, 11:30[NP]	-9.032	.000	14	-3.411 **	.000	15
	Day 1, 22:00 / Day 2, 01:00[NP]	-2.977	.010	14	-2.361 *	.017	15
	Day 1, 22:00 / Day 2, 04:00[NP]	-3.082	.008	14	-2.361 *	.017	15
	Day 1, 22:00 / Day 2, 07:30[P]	-7.936 **	.000	14	-3.414	.000	15
	Day 1, 22:00 / Day 2, 11:30[NP]	-5.976	.000	14	-3.189 **	.000	15
	Day 2, 01:00 / Day 2, 04:00[NP]	0.052	.959	14	-0.000	.999	15
	Day 2, 01:00 / Day 2, 07:30[NP]	-3.829	.002	14	-2.878 **	.002	15
	Day 2, 01:00 / Day 2, 11:30[NP]	-3.176	.007	14	-2.979 **	.001	15
	Day 2, 04:00 / Day 2, 07:30[NP]	-3.829	.002	14	-2.878 **	.002	15
	Day 2, 04:00 / Day 2, 11:30[NP]	-3.176	.007	14	-2.979 **	.001	15

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	*p*[e]	*n*
	Day 2, 07:30 / Day 2, 11:30[NP]	-0.206	.840	14	-0.045	.996	15
POMS_fatigue	Day 1, 11:30 / Day 1, 22:00[NP]	0.798	.438	14	-1.104	.285	15
	Day 1, 11:30 / Day 2, 01:00[NP]	-2.131	.051	14	-1.627	.109	15
	Day 1, 11:30 / Day 2, 04:00[NP]	-1.679	.115	14	-1.627	.109	15
	Day 1, 11:30 / Day 2, 07:30[NP]	-3.773	.002	14	-3.300 **	.000	15
	Day 1, 11:30 / Day 2, 11:30[NP]	-5.061	.000	14	-3.409 **	.000	15
	Day 1, 22:00 / Day 2, 01:00[P]	-3.855 **	.002	14	-1.339	.207	15
	Day 1, 22:00 / Day 2, 04:00[P]	-3.003 **	.009	14	-1.339	.207	15
	Day 1, 22:00 / Day 2, 07:30[P]	-6.278 **	.000	14	-3.272	.000	15
	Day 1, 22:00 / Day 2, 11:30[P]	-7.794 **	.000	14	-3.411	.000	15
	Day 2, 01:00 / Day 2, 04:00[P]	0.929	.369	14	-0.000	.999	15

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 2, 01:00 / Day 2, 07:30[P]	-1.686	.114	14	-3.018	.001	15
	Day 2, 01:00 / Day 2, 11:30[P]	-2.869 *	.012	14	-3.413	.000	15
	Day 2, 04:00 / Day 2, 07:30[P]	-2.774 *	.015	14	-3.018	.001	15
	Day 2, 04:00 / Day 2, 11:30[P]	-4.394 **	.001	14	-3.413	.000	15
	Day 2, 07:30 / Day 2, 11:30[P]	-1.424	.176	14	-1.674	.101	15
POMS_confusion	Day 1, 11:30 / Day 1, 22:00[P]	0.798	.438	14	-0.877	.396	15
	Day 1, 11:30 / Day 2, 01:00[P]	-2.131	.051	14	-2.022	.043	15
	Day 1, 11:30 / Day 2, 04:00[P]	-2.131	.051	14	-2.022	.043	15
	Day 1, 11:30 / Day 2, 07:30[P]	-3.773 **	.002	14	-3.016	.001	15
	Day 1, 11:30 / Day 2, 11:30[NP]	-5.061	.000	14	-3.207 **	.000	15
	Day 1, 22:00 / Day 2, 01:00[P]	-3.855 **	.002	14	-3.007	.001	15

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 1, 22:00 / Day 2, 04:00[P]	-3.855 **	.002	14	-3.007	.001	15
	Day 1, 22:00 / Day 2, 07:30[P]	-6.278 **	.000	14	-3.303	.000	15
	Day 1, 22:00 / Day 2, 11:30[NP]	-7.794	.000	14	-3.421 **	.000	15
	Day 2, 01:00 / Day 2, 04:00[0]			14			15
	Day 2, 01:00 / Day 2, 07:30[P]	-1.686	.114	14	-2.021	.041	15
	Day 2, 01:00 / Day 2, 11:30[P]	-2.869	.012	14	-2.422 *	.011	15
	Day 2, 04:00 / Day 2, 07:30[P]	-1.686	.114	14	-2.021	.041	15
	Day 2, 04:00 / Day 2, 11:30[NP]	-2.869	.012	14	-2.422 *	.011	15
	Day 2, 07:30 / Day 2, 11:30[NP]	-1.424	.176	14	-1.170	.279	15
	Depressed group						
HDI_sad-mood	Day 1, 11:30 / Day 2, 07:30[P]	4.961 **	.001	10	-2.670	.004	11

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 1, 11:30 / Day 2, 11:30[P]	2.511 *	.031	10	-1.994	.047	11
	Day 2, 07:30 / Day 2, 11:30[P]	-1.807	.101	10	-1.616	.125	11
POMS_total	Day 1, 11:30 / Day 1, 22:00[P]	1.708	.116	10	-1.780	.077	12
	Day 1, 11:30 / Day 2, 01:00[NP]	3.502	.006	10	-2.601 **	.006	11
	Day 1, 11:30 / Day 2, 04:00[NP]	3.024	.013	10	-2.601 **	.006	11
	Day 1, 11:30 / Day 2, 07:30[P]	2.054	.067	10	-1.867	.067	11
	Day 1, 11:30 / Day 2, 11:30[P]	0.696	.502	10	-0.800	.465	11
	Day 1, 22:00 / Day 2, 01:00[NP]	2.036	.069	10	-1.735	.092	11
	Day 1, 22:00 / Day 2, 04:00[NP]	2.323	.043	10	-1.735	.092	11
	Day 1, 22:00 / Day 2, 07:30[P]	0.909	.385	10	-1.023	.332	11
	Day 1, 22:00 / Day 2, 11:30[P]	-1.637	.133	10	-1.423	.168	11

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 2, 01:00 / Day 2, 04:00[NP]	0.412	.689	10	0.000	.999	11
	Day 2, 01:00 / Day 2, 07:30[NP]	-0.897	.391	10	-0.667	.534	11
	Day 2, 01:00 / Day 2, 11:30[NP]	-3.481	.006	10	-2.402 *	.013	11
	Day 2, 04:00 / Day 2, 07:30[NP]	-2.097	.062	10	-0.667	.534	11
	Day 2, 04:00 / Day 2, 11:30[NP]	-5.070	.000	10	-2.402 *	.013	11
	Day 2, 07:30 / Day 2, 11:30[P]	-4.807 **	.001	10	-2.807	.002	11
POMS_tension	Day 1, 11:30 / Day 1, 22:00[P]	1.120	.287	11	-1.026	.332	12
	Day 1, 11:30 / Day 2, 01:00[P]	2.924 *	.015	10	-2.203	.027	11
	Day 1, 11:30 / Day 2, 04:00[P]	2.924 *	.015	10	-2.203	.027	11
	Day 1, 11:30 / Day 2, 07:30[P]	2.675 *	.023	10	-2.097	.035	11
	Day 1, 11:30 / Day 2, 11:30[P]	1.907	.086	10	-1.727	.102	11

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 1, 22:00 / Day 2, 01:00[P]	2.568 *	.028	10	-2.145	.027	11
	Day 1, 22:00 / Day 2, 04:00[P]	2.568 *	.028	10	-2.145	.027	11
	Day 1, 22:00 / Day 2, 07:30[P]	1.373	.200	10	-1.328	.213	11
	Day 1, 22:00 / Day 2, 11:30[P]	0.399	.698	10	-0.563	.611	11
	Day 2, 01:00 / Day 2, 04:00[0]			10			11
	Day 2, 01:00 / Day 2, 07:30[P]	-0.992	.345	10	-1.021	.332	11
	Day 2, 01:00 / Day 2, 11:30[P]	-2.710 *	.022	10	-2.142	.031	11
	Day 2, 04:00 / Day 2, 07:30[P]	-0.992	.345	10	-1.021	.332	11
	Day 2, 04:00 / Day 2, 11:30[P]	-2.710 *	.022	10	-2.142	.031	11
	Day 2, 07:30 / Day 2, 11:30[P]	-1.459	.175	10	-1.382	.190	11
POMS_anger	Day 1, 11:30 / Day 1, 22:00[NP]	-0.041	.968	11	-0.562	.619	12

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 1, 11:30 / Day 2, 01:00[NP]	1.768	.108	10	-1.481	.156	11
	Day 1, 11:30 / Day 2, 04:00[NP]	2.378	.039	10	-1.481	.156	11
	Day 1, 11:30 / Day 2, 07:30[NP]	2.412	.037	10	-2.148 *	.029	11
	Day 1, 11:30 / Day 2, 11:30[NP]	1.256	.238	10	-1.203	.249	11
	Day 1, 22:00 / Day 2, 01:00[NP]	1.762	.109	10	-1.730	.109	11
	Day 1, 22:00 / Day 2, 04:00[NP]	2.991	.014	10	-1.730	.109	11
	Day 1, 22:00 / Day 2, 07:30[NP]	2.572	.028	10	-2.136 *	.031	11
	Day 1, 22:00 / Day 2, 11:30[NP]	1.150	.277	10	-1.014	.355	11
	Day 2, 01:00 / Day 2, 04:00[NP]	1.366	.202	10	0.000	.999	11
	Day 2, 01:00 / Day 2, 07:30[NP]	1.236	.245	10	-1.256	.238	11
	Day 2, 01:00 / Day 2, 11:30[NP]	-0.607	.557	10	-0.582	.616	11

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 2, 04:00 / Day 2, 07:30[NP]	-0.788	.449	10	-1.256	.238	11
	Day 2, 04:00 / Day 2, 11:30[NP]	-2.765	.020	10	-0.582	.616	11
	Day 2, 07:30 / Day 2, 11:30[NP]	-3.135	.011	10	-2.392 *	.016	11
POMS_vigour	Day 1, 11:30 / Day 1, 22:00[NP]	0.467	.649	11	-0.461	.648	12
	Day 1, 11:30 / Day 2, 01:00[P]	-4.227 **	.002	10	-2.676	.006	11
	Day 1, 11:30 / Day 2, 04:00[P]	-0.391	.704	10	-2.676	.006	11
	Day 1, 11:30 / Day 2, 07:30[P]	-0.742	.475	10	-1.132	.285	11
	Day 1, 11:30 / Day 2, 11:30[P]	-2.609 *	.026	10	-2.051	.040	11
	Day 1, 22:00 / Day 2, 01:00[NP]	-2.731	.021	10	-2.390 *	.020	11
	Day 1, 22:00 / Day 2, 04:00[NP]	-0.844	.418	10	-2.390 *	.020	11
	Day 1, 22:00 / Day 2, 07:30[SP]	-0.982	.349	10	-0.898	.387	11

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*
	Day 1, 22:00 / Day 2, 11:30[NP]	-3.008	.013	10	-2.553 **	.008	11
	Day 2, 01:00 / Day 2, 04:00[P]	1.563	.149	10	0.000	.999	11
	Day 2, 01:00 / Day 2, 07:30[P]	1.334	.212	10	-1.309	.223	11
	Day 2, 01:00 / Day 2, 11:30[P]	-0.701	.499	10	-0.762	.500	11
	Day 2, 04:00 / Day 2, 07:30[P]	-0.442	.668	10	-1.309	.223	11
	Day 2, 04:00 / Day 2, 11:30[P]	-2.358 *	.040	10	-0.762	.500	11
	Day 2, 07:30 / Day 2, 11:30[P]	-2.702 *	.022	10	-2.201	.031	11
POMS_confusion	Day 1, 11:30 / Day 1, 22:00[P]	0.875	.400	11	-1.550	.141	12
	Day 1, 11:30 / Day 2, 01:00[P]	2.343 *	.041	10	-1.901	.063	11
	Day 1, 11:30 / Day 2, 04:00[P]	2.201	.052	10	-1.901	.063	11
	Day 1, 11:30 / Day 2, 07:30[P]	1.475	.171	10	-1.483	.152	11

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	*p*[e]	*n*
	Day 1, 11:30 / Day 2, 11:30[P]	0.000	.999	10	-0.059	.984	11
	Day 1, 22:00 / Day 2, 01:00[P]	1.392	.194	10	-1.344	.199	11
	Day 1, 22:00 / Day 2, 04:00[P]	1.850	.094	10	-1.344	.199	11
	Day 1, 22:00 / Day 2, 07:30[P]	0.734	.480	10	-0.498	.636	11
	Day 1, 22:00 / Day 2, 11:30[P]	-1.386	.196	10	-1.284	.236	11
	Day 2, 01:00 / Day 2, 04:00[P]	0.635	.540	10	0.000	.999	11
	Day 2, 01:00 / Day 2, 07:30[P]	-0.326	.751	10	-0.461	.705	11
	Day 2, 01:00 / Day 2, 11:30[P]	-2.018	.071	10	-1.739	.092	11
	Day 2, 04:00 / Day 2, 07:30[P]	-1.188	.262	10	-0.461	.705	11
	Day 2, 04:00 / Day 2, 11:30[P]	-3.328 **	.008	10	-1.739	.092	11
	Day 2, 07:30 / Day 2, 11:30[P]	-3.136 *	.011	10	-2.401	.020	11

Table 5 continued

Parametric and Non-parametric Follow-up Tests for Depression Raw Scores

Scale[1]_variable	Time paired comparison[P/NP]	Paired-sample *t* test[P]			Wilcoxon test[NP]		
		t	*p*	*df*	*Z*	p^e	*n*

Note. [1] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [e] Exact statistic. [P/NP] Parametric / non-parametric test retained on the basis of normality of distribution assessed with the Shapiro-Wilk test. [0] Statistic not computed because the standard error of the difference was 0.

* $p < .05$; ** $p < .01$.

Table 6

Independent-sample and Mann-Whitney Tests for Depression Difference Scores

	t test[P]				Mann-Whitney[NP]	
Scale[1]_variable_Time[2, P/NP]	*t*	*p*	*df* 1	*df* 2	*Z*	p^e
HDI_7-item_D[P]	-3.253**	.003	1	24	-2.777	.004
HDI_sad-mood_D[NP]	-2.236	.047	1	24	-2.193*	.026
HDI_guilt_D[NP]	0.429	.672	1	24	-0.307	.759
HDI_anhedonia_D[P]	-3.141**	.004	1	24	-2.666	.007
HDI_subjective-tension_D[P]	0.378	.709	1	24	-0.162	.875
HDI_physical-anxiety_D[P]	-1.095	.284	1	24	-1.472	.141
HDI_energy-loss_D[NP]	-3.397	.002	1	24	-2.855**	.004
HDI_suicidality_D[NP]	-1.305	.221	1	24	-1.240	.212
POMS_total_D[P, L]	-3.425**	.004	1	24	-2.985	.002
POMS_tension_D[NP]	-1.388	.178	1	24	-1.098	.283
POMS_depression_D[P, L]	-2.670*	.020	1	24	-2.269	.022
POMS_anger_D[NP]	-0.732	.478	1	24	-0.770	.456
POMS_vigour_D[NP]	-5.423	.000	1	24	-3.746**	.000
POMS_fatigue_D[P]	-2.770*	.011	1	24	-2.367	.017
POMS_confusion_D[P]	-2.084*	.048	1	24	-1.980	.048

Note. [1] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [2] D refers to the difference scores between Day 1 at 11:30 and Day 2 at 11:30. [P/NP] Parametric or non parametric statistics were chosen on the basis of normality of distributions,

Table 6 continued

Independent-sample and Mann-Whitney Tests for Depression Difference Scores

	t test[P]				Mann-Whitney[NP]	
Scale[1]_variable_Time[2, P/NP]	*t*	*p*	*df* 1	*df* 2	*Z*	*p*[e]

previously tested with the Shapiro-Wilk test. [e] Exact significance. [L] Levene test was significant; therefore, the statistic implies "equal variances not assumed".

* $p < .05$; ** $p < .01$.

Table 7

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time A[1]

VOI	Scale[2]_variable_Time[3]	Cho:H_2O_A			tCr:H_2O_A			NAA:H_2O_A		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
				Control group						
Pons	HDI_7-item_1	-.183[P]	.569	12	.228[P]	.477	12	.208[P]	.559	13
	HDI_sad-mood_1	.529[S]	.077	12	.198[S]	.537	12	-.302[S]	.316	13
	HDI_guilt_1	-.367[S]	.241	12	.144[S]	.656	12	.166[S]	.588	13
	HDI_anhedonia_1	.393[S]	.206	12	-.218[S]	.495	12	-.077[S]	.802	13
	HDI_subjective-tension_1	-.171[S]	.595	12	.245[S]	.443	12	.148[S]	.629	13
	HDI_physical-anxiety_1	.134[S]	.678	12	.376[S]	.228	12	-.082[S]	.790	13
	HDI_energy-loss_1	-.480[S]	.114	12	.306[S]	.334	12	.000[S]	.999	13
	HDI_suicidality_1[0]			12			12			13
	POMS_total_1	.153[P]	.635	12	.288[P]	.365	12	-.213[P]	.484	13

Table 7 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time A[1]

VOI	Scale[2]_variable_Time[3]	Cho:H_2O_A			tCr:H_2O_A			NAA:H_2O_A		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_tension_1	.155[S]	.631	12	.123[S]	.703	12	.075[S]	.808	13
	POMS_depression_1	.273[S]	.391	12	.257[S]	.419	12	-.401[S]	.175	13
	POMS_anger_1	.038[S]	.908	12	.173[S]	.591	12	.180[S]	.555	13
	POMS_vigour_1	.170[P]	.596	12	.359[P]	.252	12	-.365[P]	.220	13
	POMS_fatigue_1	.108[S]	.737	12	.198[S]	.537	12	-.133[S]	.665	13
	POMS_confusion_1	.006[P]	.985	12	.303[P]	.339	12	-.291[P]	.336	13
LADPF[5]	HDI_7-item_1	.223[S]	.443	14	-.234[S]	.420	14	.336[S]	.241	14
	HDI_sad-mood_1	-.144[S]	.623	14	-.383[S]	.176	14	-.095[S]	.747	14
	HDI_guilt_1	.390[S]	.168	14	.059[S]	.840	14	.578[S]	.030	14
	HDI_anhedonia_1	-.378[S]	.182	14	-.241[S]	.407	14	-.378[S]	.182	14

Table 7 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time A[1]

VOI	Scale[2]_variable_Time[3]	Cho:H_2O_A			tCr:H_2O_A			NAA:H_2O_A		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_subjective-tension_1	.134[S]	.648	14	-.418[S]	.137	14	.117[S]	.690	14
	HDI_physical-anxiety_1	-.188[S]	.520	14	-.387[S]	.172	14	.166[S]	.571	14
	HDI_energy-loss_1	-.103[S]	.726	14	-.103[S]	.726	14	.378[S]	.182	14
	HDI_suicidality_1[0]			14			14			14
	POMS_total_1	-.062[P]	.832	14	-.427[P]	.128	14	.181[P]	.535	14
	POMS_tension_1	-.078[S]	.791	14	-.305[S]	.288	14	-.038[S]	.898	14
	POMS_depression_1	-.115[S]	.695	14	-.525[S]	.054	14	-.033[S]	.910	14
	POMS_anger_1	.399[S]	.158	14	-.108[S]	.714	14	.093[S]	.752	14
	POMS_vigour_1	-.148[P]	.614	14	-.463[P]	.096	14	.170[P]	.560	14
	POMS_fatigue_1	.080[S]	.785	14	-.053[S]	.858	14	.188[S]	.520	14

Table 7 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time A[1]

VOI	Scale[2]_variable_Time[3]	Cho:H_2O_A			tCr:H_2O_A			NAA:H_2O_A		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_confusion_1	-.017[P]	.954	14	-.405[P]	.151	14	.239[P]	.411	14
					Depressed group					
Pons	HDI_7-item_1	.121[P]	.724	11	-.255[P]	.448	11	-.012[P]	.972	11
	HDI_sad-mood_1	.294[P]	.380	11	-.147[P]	.666	11	.087[P]	.800	11
	HDI_guilt_1	-.311[S]	.352	11	-.270[S]	.422	11	-.051[S]	.882	11
	HDI_anhedonia_1	.095[S]	.782	11	.478[S]	.137	11	-.264[S]	.433	11
	HDI_subjective-tension_1	.066[S]	.846	11	.038[S]	.912	11	.237[S]	.483	11
	HDI_physical-anxiety_1	.193[S]	.570	11	-.568[S]	.068	11	-.202[S]	.551	11
	HDI_energy-loss_1	-.058[S]	.866	11	-.058[S]	.866	11	.000[S]	.999	11
	HDI_suicidality_1	.400[S]	.222	11	.000[S]	.999	11	-.226[S]	.503	11

Table 7 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time A[1]

VOI	Scale[2]_variable_Time[3]	Cho:H_2O_A			tCr:H_2O_A			NAA:H_2O_A		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_total_1	.220[P]	.516	11	-.074[P]	.829	11	.048[P]	.889	11
	POMS_tension_1	.196[S]	.564	11	-.232[S]	.492	11	.241[S]	.474	11
	POMS_depression_1	.238[P]	.480	11	-.119[P]	.727	11	-.009[P]	.980	11
	POMS_anger_1	.197[S]	.561	11	-.234[S]	.489	11	-.271[S]	.421	11
	POMS_vigour_1	-.132[P]	.699	11	.336[P]	.312	11	-.091[P]	.789	11
	POMS_fatigue_1	.632[P]*	.037	11	.433[P]	.183	11	-.019[P]	.956	11
	POMS_confusion_1	.116[P]	.733	11	-.095[P]	.781	11	.009[P]	.979	11
LADPF	HDI_7-item_1	.295[P]	.353	12	-.031[P]	.925	12	-.322[S]	.308	12
	HDI_sad-mood_1	-.153[P]	.635	12	-.453[P]	.139	12	-.717[S]**	.009	12
	HDI_guilt_1	.175[S]	.586	12	.175[S]	.586	12	.191[S]	.551	12

Table 7 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time A[1]

VOI	Scale[2]_variable_Time[3]	Cho:H_2O_A			tCr:H_2O_A			NAA:H_2O_A		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_anhedonia_1	.345[S]	.271	12	.060[S]	.853	12	-.210[S]	.512	12
	HDI_subjective-tension_1	.282[S]	.374	12	-.123[S]	.703	12	-.069[S]	.832	12
	HDI_physical-anxiety_1	.399[S]	.199	12	.399[S]	.199	12	.045[S]	.889	12
	HDI_energy-loss_1	.579[S]	.048	12	.338[S]	.283	12	.483[S]	.112	12
	HDI_suicidality_1	-.256[S]	.421	12	-.261[S]	.413	12	-.614[S]*@	.034	12
	POMS_total_1	.007[P]	.982	12	-.364[P]	.245	12	-.399[S]	.199	12
	POMS_tension_1	-.039[S]	.905	12	-.256[S]	.422	12	-.287[S]	.365	12
	POMS_depression_1	-.100[P]	.758	12	-.374[P]	.231	12	-.524[S]	.080	12
	POMS_anger_1	.335[P]	.287	12	.002[P]	.996	12	-.292[S]	.357	12
	POMS_vigour_1	-.108[P]	.737	12	-.205[P]	.523	12	.168[S]	.601	12

Table 7 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time A[1]

VOI	Scale[2]_variable_Time[3]	Cho:H_2O_A			tCr:H_2O_A			NAA:H_2O_A		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_fatigue_1	-.123[P]	.702	12	-.525[P]	.080	12	-.425[S]	.169	12
	POMS_confusion_1	-.038[P]	.980	12	-.410[P]	.186	12	-.496[S]	.101	12
				Both groups						
Pons	HDI_7-item_1	-.246[P]	.259	23	-.067[P]	.763	23	.097[P]	.654	24
	HDI_sad-mood_1	-.016[S]	.943	23	-.086[S]	.696	23	.071[S]	.740	24
	HDI_guilt_1	-.442[S]	.035	23	-.107[S]	.626	23	.180[S]	.401	24
	HDI_anhedonia_1	-.151[S]	.492	23	-.026[S]	.907	23	.085[S]	.693	24
	HDI_subjective-tension_1	-.210[S]	.335	23	-.036[S]	.869	23	.250[S]	.240	24
	HDI_physical-anxiety_1	-.122[S]	.581	23	-.163[S]	.457	23	.007[S]	.975	24
	HDI_energy-loss_1	-.319[S]	.138	23	-.091[S]	.679	23	.139[S]	.517	24

Table 7 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time A[1]

VOI	Scale[2]_variable_Time[3]	Cho:H_2O_A			tCr:H_2O_A			NAA:H_2O_A		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_suicidality_1	.162[S]	.460	23	-.033[S]	.881	23	-.058[S]	.789	24
	POMS_total_1	-.044[S]	.840	23	-.037[S]	.867	23	.010[S]	.961	24
	POMS_tension_1	-.026[S]	.905	23	-.112[S]	.611	23	.164[S]	.443	24
	POMS_depression_1	-.058[S]	.794	23	-.055[S]	.803	23	.003[S]	.990	24
	POMS_anger_1	-.059[S]	.790	23	-.152[S]	.489	23	-.001[S]	.997	24
	POMS_vigour_1	-.185[P]	.399	23	.168[P]	.443	23	-.128[P]	.550	24
	POMS_fatigue_1	.012[S]	.955	23	.057[S]	.795	23	.005[S]	.981	24
	POMS_confusion_1	-.060[S]	.787	23	-.010[S]	.964	23	-.050[S]	.817	24
LADPF	HDI_7-item_1	.017[S]	.934	26	-.139[S]	.497	26	-.165[S]	.420	26
	HDI_sad-mood_1	-.151[S]	.462	26	-.254[S]	.211	26	-.366[S]	.066	26

Table 7 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time A[1]

VOI	Scale[2]_variable_Time[3]	Cho:H_2O_A			tCr:H_2O_A			NAA:H_2O_A		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_guilt_1	.182[S]	.374	26	.071[S]	.729	26	.241[S]	.235	26
	HDI_anhedonia_1	-.039[S]	.850	26	-.098[S]	.635	26	-.331[S]	.098	26
	HDI_subjective-tension_1	.054[S]	.795	26	-.252[S]	.214	26	-.164[S]	.424	26
	HDI_physical-anxiety_1	-.053[S]	.796	26	-.073[S]	.723	26	-.105[S]	.611	26
	HDI_energy-loss_1	.031[S]	.882	26	-.027[S]	.895	26	-.081[S]	.694	26
	HDI_suicidality_1	-.158[S]	.442	26	-.170[S]	.408	26	-.398[S]*@	.044	26
	POMS_total_1	-.106[S]	.605	26	-.288[S]	.154	26	-.241[S]	.236	26
	POMS_tension_1	-.116[S]	.574	26	-.251[S]	.216	26	-.228[S]	.262	26
	POMS_depression_1	-.139[S]	.498	26	-.298[S]	.140	26	-.323[S]	.108	26
	POMS_anger_1	.166[S]	.418	26	-.045[S]	.826	26	-.124[S]	.547	26

Table 7 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time A[1]

VOI	Scale[2]_variable_Time[3]	Cho:H_2O_A			tCr:H_2O_A			NAA:H_2O_A		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_vigour_1	-.212[P]	.299	26	-.265[P]	.191	26	-.101[P]	.625	26
	POMS_fatigue_1	-.071[S]	.731	26	-.216[S]	.289	26	-.249[S]	.219	26
	POMS_confusion_1	-.113[S]	.581	26	-.307[S]	.127	26	-.246[S]	.226	26

Note. [1] Scan time A was Day 1 at 12:00. [2] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [3] Time 1 was Day 1 at 11:30. [4] Left anterior dorsal prefrontal. [P] Pearson correlation. [S] Spearman correlation. [0] Variable not assessed when all scores were 0. [@] Variable has fewer than five data points that are different from zero.

* $p < .05$; ** $p < .01$.

Table 8

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time B[1]

VOI	Sacle[2]_variable_Time[3]	Cho:H_2O_B			tCr:H_2O_B			NAA:H_2O_B		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
				Control group						
Pons	HDI_7-item_6	.162[P]	.656	10	-.103[S]	.776	10	.308[P]	.305	13
	HDI_sad-mood_6	.058[S]	.873	10	.174[S]	.631	10	.000[S]	.999	13
	HDI_guilt_6	-.087[S]	.811	10	.174[S]	.631	10	.228[S]	.454	13
	HDI_anhedonia_6	.062[P]	.865	10	.100[S]	.784	10	.432[S]	.140	13
	HDI_subjective-tension_6	.348[S]	.324	10	.087[S]	.811	10	-.227[S]	.455	13
	HDI_physical-anxiety_6	.392[S]	.263	10	-.135[S]	.710	10	-.434[S]	.139	13
	HDI_energy-loss_6	.055[S]	.880	10	-.385[S]	.271	10	.212[S]	.487	13
	HDI_suicidality_6[0]			10			10			13
	POMS_total_6	.273[P]	.445	10	-.394[S]	.260	10	.237[P]	.435	13

Table 8 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time B[1]

VOI	Sacle[2]_variable_Time[3]	Cho:H_2O_B			tCr:H_2O_B			NAA:H_2O_B		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_tension_6	.704[S] *	.023	10	-.337[S]	.342	10	-.034[S]	.913	13
	POMS_depression_6	.428[S]	.217	10	-.052[S]	.887	10	.339[S]	.257	13
	POMS_anger_6	-.090[S]	.805	10	.067[S]	.853	10	-.514[S]	.072	13
	POMS_vigour_6	.130[P]	.720	10	-.104[S]	.776	10	-.391[S]	.187	13
	POMS_fatigue_6	.396[P]	.258	10	-.532[S]	.113	10	.525[P]	.065	13
	POMS_confusion_6	.532[P]	.114	10	-.235[S]	.513	10	.086[P]	.780	13
LADPF[5]	HDI_7-item_6	-.141[P]	.629	14	-.059[P]	.841	14	-.505[P]	.066	14
	HDI_sad-mood_6	-.447[S]	.109	14	-.103[S]	.726	14	-.378[S]	.182	14
	HDI_guilt_6	-.354[S]	.214	14	-.101[S]	.730	14	-.051[S]	.864	14
	HDI_anhedonia_6	.188[P]	.519	14	-.139[P]	.636	14	-.278[P]	.337	14

Table 8 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time B[1]

VOI	Sacle[2]_variable_Time[3]	Cho:H_2O_B			tCr:H_2O_B			NAA:H_2O_B		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_subjective-tension_6	-.097[S]	.741	14	-.094[S]	.749	14	-.366[S]	.198	14
	HDI_physical-anxiety_6	.261[S]	.367	14	-.086[S]	.771	14	-.076[S]	.795	14
	HDI_energy-loss_6	.096[S]	.745	14	.275[S]	.342	14	-.139[S]	.637	14
	HDI_suicidality_6[0]			14			14			14
	POMS_total_6	-.413[P]	.142	14	.223[P]	.444	14	-.370[P]	.193	14
	POMS_tension_6	-.310[S]	.281	14	-.454[S]	.103	14	-.020[S]	.945	14
	POMS_depression_6	.115[S]	.694	14	-.241[S]	.406	14	-.067[S]	.821	14
	POMS_anger_6	.075[S]	.800	14	.049[S]	.868	14	-.229[S]	.430	14
	POMS_vigour_6	-.049[S]	.869	14	-.033[S]	.910	14	.027[S]	.928	14
	POMS_fatigue_6	-.255[P]	.378	14	.003[P]	.993	14	-.130[P]	.658	14

Table 8 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time B[1]

VOI	Sacle[2]_variable_Time[3]	Cho:H_2O_B			tCr:H_2O_B			NAA:H_2O_B		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_confusion_6	-.029[P]	.923	14	-.210[P]	.471	14	-.045[P]	.879	14
					Depressed group					
Pons	HDI_7-item_6	.343[P]	.332	10	.514[P]	.128	10	-.025[P]	.945	10
	HDI_sad-mood_6	-.344[P]	.330	10	-.095[P]	.793	10	-.246[P]	.494	10
	HDI_guilt_6	.066[P]	.856	10	.329[P]	.354	10	.175[P]	.629	10
	HDI_anhedonia_6	.606[P]	.063	10	.698[P]*	.025	10	.280[P]	.434	10
	HDI_subjective-tension_6	-.195[S]	.590	10	-.331[S]	.350	10	.259[S]	.469	10
	HDI_physical-anxiety_6	.425[P]	.221	10	.223[P]	.535	10	-.179[P]	.620	10
	HDI_energy-loss_6	.375[S]	.286	10	.437[S]	.207	10	-.139[S]	.702	10
	HDI_suicidality_6	.174[S]	.631	10	.406[S]	.244	10	-.522[S]	.122	10

Table 8 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time B[1]

VOI	Sacle[2]_variable_Time[3]	Cho:H_2O_B			tCr:H_2O_B			NAA:H_2O_B		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_total_6	.028[P]	.940	10	.136[P]	.709	10	.118[P]	.745	10
	POMS_tension_6	-.156[P]	.668	10	-.152[P]	.675	10	-.099[P]	.786	10
	POMS_depression_6	-.316[P]	.374	10	-.243[P]	.499	10	-.225[P]	.532	10
	POMS_anger_6	.106[S]	.770	10	.138[S]	.705	10	-.144[S]	.692	10
	POMS_vigour_6	-.236[P]	.511	10	.042[P]	.908	10	.081[P]	.825	10
	POMS_fatigue_6	.470[P]	.170	10	.435[P]	.209	10	.561[P]	.091	10
	POMS_confusion_6	.145[P]	.690	10	.341[P]	.335	10	.242[P]	.500	10
LADPF	HDI_7-item_6	.671[P]*	.034	10	.222[P]	.538	10	.293[P]	.411	10
	HDI_sad-mood_6	-.220[P]	.542	10	-.336[P]	.342	10	-.037[P]	.920	10
	HDI_guilt_6	.054[S]	.883	10	-.315[S]	.375	10	-.107[S]	.768	10

Table 8 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time B[1]

VOI	Sacle[2]_variable_Time[3]	Cho:H_2O_B			tCr:H_2O_B			NAA:H_2O_B		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_anhedonia_6	.741[P]*	.014	10	.385[P]	.272	10	.176[P]	.627	10
	HDI_subjective-tension_6	-.062[S]	.866	10	-.247[S]	.492	10	.192[S]	.595	10
	HDI_physical-anxiety_6	.458[P]	.183	10	.277[P]	.439	10	.177[P]	.624	10
	HDI_energy-loss_6	.569[S]	.086	10	.638[S]	.047	10	.236[S]	.512	10
	HDI_suicidality_6	.355[S]	.315	10	-.121[S]	.739	10	.156[S]	.668	10
	POMS_total_6	.448[P]	.194	10	.225[P]	.533	10	.661[P]*	.037	10
	POMS_tension_6	.158[P]	.664	10	-.197[P]	.585	10	.164[P]	.651	10
	POMS_depression_6	.301[P]	.398	10	-.028[P]	.939	10	.657[P]*	.039	10
	POMS_anger_6	.269[S]	.453	10	-.050[S]	.891	10	.469[S]	.172	10
	POMS_vigour_6	-.258[P]	.471	10	.323[P]	.363	10	-.298[P]	.402	10

Table 8 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time B[1]

VOI	Sacle[2]_variable_Time[3]	Cho:H_2O_B			tCr:H_2O_B			NAA:H_2O_B		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_fatigue_6	.521[P]	.123	10	.538[P]	.108	10	.516[P]	.127	10
	POMS_confusion_6	.422[P]	.225	10	.386[P]	.270	10	.520[P]	.124	10
				Both groups						
Pons	HDI_7-item_6	.010[P]	.966	20	.079[P]	.739	20	.085[P]	.701	23
	HDI_sad-mood_6	-.324[S]	.164	20	.135[S]	.569	20	.011[S]	.959	23
	HDI_guilt_6	-.107[S]	.654	20	.041[S]	.864	20	.220[S]	.313	23
	HDI_anhedonia_6	.309[P]	.184	20	.456[P]*	.043	20	.345[S]	.107	23
	HDI_subjective-tension_6	-.173[S]	.467	20	-.245[S]	.298	20	.081[S]	.713	23
	HDI_physical-anxiety_6	.167[S]	.481	20	.020[S]	.934	20	-.147[S]	.504	23
	HDI_energy-loss_6	.111[S]	.640	20	.095[S]	.690	20	.105[S]	.633	23

Table 8 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time B[1]

VOI	Sacle[2]_variable_Time[3]	Cho:H_2O_B			tCr:H_2O_B			NAA:H_2O_B		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_suicidality_6	.139[S]	.558	20	.219[S]	.354	20	-.354[S]	.098	23
	POMS_total_6	-.053[P]	.826	20	-.099[P]	.677	20	.146[P]	.507	23
	POMS_tension_6	-.094[S]	.692	20	-.314[S]	.178	20	.069[S]	.754	23
	POMS_depression_6	-.214[S]	.365	20	-.198[S]	.403	20	.147[S]	.503	23
	POMS_anger_6	-.196[S]	.409	20	-.009[S]	.971	20	-.115[S]	.602	23
	POMS_vigour_6	-.126[P]	.597	20	-.051[P]	.831	20	-.142[S]	.519	23
	POMS_fatigue_6	.350[P]	.131	20	.112[P]	.638	20	.520[P]*	.011	23
	POMS_confusion_6	.134[P]	.573	20	.074[P]	.755	20	.165[P]	.451	23
LADPF	HDI_7-item_6	.280[P]	.186	24	-.152[P]	.478	24	-.036[P]	.867	24
	HDI_sad-mood_6	-.123[S]	.567	24	-.389[S]	.061	24	-.217[S]	.308	24

Table 8 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time B[1]

VOI	Sacle[2]_variable_Time[3]	Cho:H_2O_B			tCr:H_2O_B			NAA:H_2O_B		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_guilt_6	-.027[S]	.899	24	-.254[S]	.231	24	-.060[S]	.780	24
	HDI_anhedonia_6	.483[P]*	.017	24	.035[P]	.872	24	-.061[P]	.777	24
	HDI_subjective-tension_6	-.013[S]	.954	24	-.270[S]	.201	24	-.109[S]	.611	24
	HDI_physical-anxiety_6	.165[S]	.441	24	-.147[S]	.492	24	-.081[S]	.705	24
	HDI_energy-loss_6	.329[S]	.117	24	.336[S]	.108	24	.062[S]	.773	24
	HDI_suicidality_6	.328[S]	.117	24	-.182[S]	.394	24	-.083[S]	.698	24
	POMS_total_6	.140[P]	.514	24	-.140[P]	.513	24	.131[P]	.542	24
	POMS_tension_6	-.169[S]	.429	24	-.495[S]*	.014	24	-.116[S]	.588	24
	POMS_depression_6	.050[S]	.818	24	-.319[S]	.129	24	-.002[S]	.993	24
	POMS_anger_6	.143[S]	.504	24	-.172[S]	.423	24	-.017[S]	.938	24

Table 8 continued

Correlations of Depression Raw Scores with Neurochemical Concentrations Raw Scores As a Function of Group and Brain Volume of Interest (VOI) at Scan Time B[1]

VOI	Sacle[2]_variable_Time[3]	Cho:H_2O_B			tCr:H_2O_B			NAA:H_2O_B		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_vigour_6	-.079[S]	.715	24	.055[S]	.798	24	-.105[S]	.626	24
	POMS_fatigue_6	.215[P]	.314	24	.209[P]	.327	24	.175[P]	.413	24
	POMS_confusion_6	.254[S]	.230	24	-.067[S]	.755	24	.184[S]	.391	24

Note. [1] Scan time A was Day 1 at 12:00. [2] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [3] Time 1 was Day 1 at 11:30. [4] Left anterior dorsal prefrontal. [P] Pearson correlation. [S] Spearman correlation. [0] Variable not assessed when all scores were 0. [@] Variable has fewer than five data points that are different from zero.

* $p < .05$; ** $p < .01$.

Table 9

Correlations of Depression Difference Scores with Neurochemical Concentration Difference Scores As a Function of Group and Brain Volume of Interest (VOI)

VOI	Scale[1]_variable_Time[2]	Cho:H_2O_D[3]			tCr:H2O_D			NAA:H_2O_D		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
				Control group						
Pons	HDI_7-item_D	-.500[S]	.207	8	.178[P]	.672	8	.713[P]**	.009	12
	HDI_sad-mood_D	-.436[S]	.280	8	.109[S]	.797	8	.226[S]	.481	12
	HDI_guilt_D	-.536[S]	.171	8	.082[P]	.846	8	.498[S]	.101	12
	HDI_anhedonia_D	.110[S]	.795	8	-.057[P]	.893	8	.429[P]	.164	12
	HDI_subjective-tension_D	-.289[S]	.488	8	.151[S]	.721	8	.179[S]	.578	12
	HDI_physical-anxiety_D	-.190[S]	.652	8	.238[P]	.571	8	-.363[P]	.246	12
	HDI_energy-loss_D	.082[S]	.846	8	-.082[S]	.846	8	.311[S]	.325	12
	HDI_suicidality_D[0]			8			8			12
	POMS_total_D	.048[S]	.911	8	-.328[P]	.427	8	.371[P]	.236	12

Table 9 continued

Correlations of Depression Difference Scores with Neurochemical Concentration Difference Scores As a Function of Group and Brain Volume of Interest (VOI)

VOI	Scale[1]_variable_Time[2]	Cho:H_2O_D[3]			tCr:H2O_D			NAA:H_2O_D		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_tension_D	-.258[S]	.538	8	-.162[P]	.701	8	.317[P]	.315	12
	POMS_depression_D	-.292[S]	.483	8	.091[P]	.831	8	.145[P]	.653	12
	POMS_anger_D	-.279[S]	.503	8	-.038[P]	.930	8	.359[S]	.252	12
	POMS_vigour_D	.145[S]	.733	8	.147[P]	.728	8	-.025[S]	.939	12
	POMS_fatigue_D	.515[S]	.192	8	-.603[P]	.114	8	.420[P]	.174	12
	POMS_confusion_D	.494[S]	.213	8	-.551[P]	.157	8	.001[P]	.998	12
LADPF[5]	HDI_7-item_D	-.092[P]	.766	13	-.098[P]	.749	13	-.084[P]	.784	13
	HDI_sad-mood_D	-.168[S]	.584	13	-.004[S]	.990	13	-.294[S]	.329	13
	HDI_guilt_D	-.375[S]	.206	13	-.028[S]	.927	13	.142[S]	.644	13
	HDI_anhedonia_D	-.115[P]	.708	13	-.268[P]	.375	13	-.308[P]	.306	13

Table 9 continued

Correlations of Depression Difference Scores with Neurochemical Concentration Difference Scores As a Function of Group and Brain Volume of Interest (VOI)

VOI	Scale[1]_variable_Time[2]	Cho:H_2O_D[3]			tCr:H2O_D			NAA:H_2O_D		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_subjective-tension_D	-.084[P]	.785	13	-.158[P]	.607	13	-.174[P]	.569	13
	HDI_physical-anxiety_D	.201[P]	.510	13	-.096[P]	.755	13	.230[P]	.450	13
	HDI_energy-loss_D	.382[S]	.197	13	.085[S]	.782	13	.063[S]	.837	13
	HDI_suicidality_D[0]			13			13			13
	POMS_total_D	-.021[P]	.947	13	.008[P]	.980	13	-.214[P]	.482	13
	POMS_tension_D	-.495[P]	.085	13	-.220[P]	.470	13	-.138[P]	.652	13
	POMS_depression_D	-.072[S]	.815	13	-.003[S]	.992	13	-.439[S]	.134	13
	POMS_anger_D	.113[S]	.712	13	.155[S]	.612	13	.054[S]	.862	13
	POMS_vigour_D	.351[S]	.240	13	-.163[S]	.595	13	.036[S]	.907	13
	POMS_fatigue_D	.147[P]	.632	13	.350[P]	.241	13	-.012[P]	.970	13

Table 9 continued

Correlations of Depression Difference Scores with Neurochemical Concentration Difference Scores As a Function of Group and Brain Volume of Interest (VOI)

VOI	Scale[1]_variable_Time[2]	Cho:H_2O_D[3]			tCr:H2O_D			NAA:H_2O_D		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_confusion_D	.010[P]	.973	13	-.081[P]	.792	13	-.096[P]	.756	13
					Depressed group					
Pons	HDI_7-item_D	.624[P]	.054	10	.508[P]	.134	10	-.297[P]	.405	10
	HDI_sad-mood_D	.504[P]	.137	10	.272[P]	.447	10	-.140[P]	.701	10
	HDI_guilt_D	.277[S]	.438	10	.257[S]	.474	10	-.090[S]	.804	10
	HDI_anhedonia_D	.566[P]	.088	10	.643[P*]	.045	10	.182[P]	.615	10
	HDI_subjective-tension_D	-.086[P]	.813	10	.032[P]	.930	10	.041[P]	.910	10
	HDI_physical-anxiety_D	-.234[P]	.516	10	-.449[P]	.193	10	-.347[P]	.327	10
	HDI_energy-loss_D	.165[S]	.648	10	-.165[S]	.648	10	-.275[S]	.441	10
	HDI_suicidality_D	.507[S]	.135	10	.322[S]	.364	10	-.281[S]	.432	10

Table 9 continued

Correlations of Depression Difference Scores with Neurochemical Concentration Difference Scores As a Function of Group and Brain Volume of Interest (VOI)

VOI	Scale[1]_variable_Time[2]	Cho:H_2O_D[3]			tCr:H2O_D			NAA:H_2O_D		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_total_D	.564[P]	.090	10	.326[P]	.359	10	-.147[P]	.685	10
	POMS_tension_D	.343[S]	.333	10	.214[S]	.553	10	-.104[S]	.775	10
	POMS_depression_D	.330[P]	.352	10	.195[P]	.589	10	-.605[P]	.064	10
	POMS_anger_D	-.050[P]	.891	10	-.134[P]	.712	10	-.243[P]	.499	10
	POMS_vigour_D	.254[P]	.479	10	.319[P]	.369	10	.062[P]	.864	10
	POMS_fatigue_D	.793[P]**	.006	10	.498[P]	.143	10	.157[P]	.665	10
	POMS_confusion_D	.626[P]	.053	10	.372[P]	.290	10	.040[P]	.913	10
LADPF	HDI_7-item_D	-.414[P]	.234	10	-.100[P]	.783	10	-.428[P]	.217	10
	HDI_sad-mood_D	-.329[P]	.354	10	-.248[P]	.489	10	-.474[P]	.166	10
	HDI_guilt_D	-.277[S]	.438	10	-.444[S]	.199	10	-.277[S]	.438	10

Table 9 continued

Correlations of Depression Difference Scores with Neurochemical Concentration Difference Scores As a Function of Group and Brain Volume of Interest (VOI)

VOI	Scale[1]_variable_Time[2]	Cho:H_2O_D[3]			tCr:H2O_D			NAA:H_2O_D		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_anhedonia_D	-.637[P]*	.047	10	-.443[P]	.200	10	-.529[P]	.116	10
	HDI_subjective-tension_D	-.065[P]	.857	10	-.197[P]	.586	10	.008[P]	.983	10
	HDI_physical-anxiety_D	.619[P]	.056	10	.715[P]*	.020	10	.133[P]	.714	10
	HDI_energy-loss_D	-.184[S]	.610	10	.178[S]	.623	10	.125[S]	.731	10
	HDI_suicidality_D	-.322[S]	.364	10	-.192[S]	.595	10	-.130[S]	.720	10
	POMS_total_D	-.465[P]	.176	10	-.067[P]	.855	10	-.161[P]	.657	10
	POMS_tension_D	-.372[P]	.290	10	-.375[P]	.286	10	-.356[P]	.313	10
	POMS_depression_D	-.136[P]	.708	10	.234[P]	.514	10	-.099[P]	.785	10
	POMS_anger_D	.012[P]	.974	10	.195[P]	.589	10	-.025[P]	.944	10
	POMS_vigour_D	.058[P]	.872	10	-.215[P]	.551	10	-.003[P]	.993	10

Table 9 continued

Correlations of Depression Difference Scores with Neurochemical Concentration Difference Scores As a Function of Group and Brain Volume of Interest (VOI)

VOI	Scale[1]_variable_Time[2]	Cho:H_2O_D[3]			tCr:H2O_D			NAA:H_2O_D		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_fatigue_D	-.568[P]	.087	10	-.249[P]	.489	10	-.061[P]	.868	10
	POMS_confusion_D	-.544[P]	.104	10	-.084[P]	.818	10	-.175[P]	.628	10
				Both groups						
Pons	HDI_7-item_D	.132[P]	.602	18	.300[P]	.226	18	.229[P]	.305	22
	HDI_sad-mood_D	.252[P]	.313	18	.194[P]	.441	18	-.050[S]	.826	22
	HDI_guilt_D	-.113[S]	.655	18	.197[S]	.432	18	.250[S]	.263	22
	HDI_anhedonia_D	.206[P]	.411	18	.286[P]	.249	18	.320[P]	.146	22
	HDI_subjective-tension_D	-.244[P]	.329	18	.073[P]	.773	18	.148[P]	.510	22
	HDI_physical-anxiety_D	-.186[P]	.460	18	-.292[P]	.240	18	-.320[P]	.147	22
	HDI_energy-loss_D	.072[S]	.777	18	-.174[S]	.491	18	.128[S]	.571	22

Table 9 continued

Correlations of Depression Difference Scores with Neurochemical Concentration Difference Scores As a Function of Group and Brain Volume of Interest (VOI)

VOI	Scale[1]_variable_Time[2]	Cho:H_2O_D[3]			tCr:H2O_D			NAA:H_2O_D		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_suicidality_D	.323[S]	.191	18	.196[S]	.436	18	-.119[S]	.597	22
	POMS_total_D	.210[P]	.403	18	.118[P]	.642	18	.108[P]	.633	22
	POMS_tension_D	.116[S]	.647	18	.046[S]	.856	18	.077[P]	.735	22
	POMS_depression_D	.125[P]	.622	18	.099[P]	.695	18	-.185[P]	.410	22
	POMS_anger_D	-.124[P]	.625	18	-.123[P]	.626	18	-.045[S]	.841	22
	POMS_vigour_D	-.049[P]	.846	18	.107[P]	.673	18	-.089[S]	.694	22
	POMS_fatigue_D	.400[P]	.100	18	.187[P]	.456	18	.288[P]	.194	22
	POMS_confusion_D	.385[P]	.114	18	.154[P]	.541	18	.046[P]	.840	22
LADPF	HDI_7-item_D	-.266[P]	.220	23	.030[P]	.891	23	-.321[P]	.135	23
	HDI_sad-mood_D	-.233[S]	.285	23	-.034[S]	.879	23	-.444[S]*	.034	23

Table 9 continued

Correlations of Depression Difference Scores with Neurochemical Concentration Difference Scores As a Function of Group and Brain Volume of Interest (VOI)

VOI	Scale[1]_variable_Time[2]	Cho:H_2O_D[3]			tCr:H2O_D			NAA:H_2O_D		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	HDI_guilt_D	-.267[S]	.218	23	-.196[S]	.371	23	-.057[S]	.794	23
	HDI_anhedonia_D	-.327[P]	.127	23	-.160[P]	.467	23	-.440[P]*	.036	23
	HDI_subjective-tension_D	-.065[P]	.768	23	-.179[P]	.412	23	-.076[P]	.732	23
	HDI_physical-anxiety_D	.273[P]	.208	23	.400[P]	.059	23	.138[P]	.530	23
	HDI_energy-loss_D	.087[S]	.694	23	.138[S]	.530	23	-.092[S]	.676	23
	HDI_suicidality_D	-.153[S]	.487	23	-.070[S]	.750	23	-.218[S]	.318	23
	POMS_total_D	-.259[P]	.233	23	.073[P]	.742	23	-.252[P]	.245	23
	POMS_tension_D	-.433[P]*	.039	23	-.280[P]	.196	23	-.270[P]	.213	23
	POMS_depression_D	-.159[S]	.467	23	.101[S]	.646	23	-.309[S]	.152	23
	POMS_anger_D	.058[S]	.794	23	.275[S]	.204	23	.074[S]	.736	23

Table 9 continued

Correlations of Depression Difference Scores with Neurochemical Concentration Difference Scores As a Function of Group and Brain Volume of Interest (VOI)

VOI	Scale[1]_variable_Time[2]	Cho:H_2O_D[3]			tCr:H2O_D			NAA:H_2O_D		
		Statistic	*p*	*n*	Statistic	*p*	*n*	Statistic	*p*	*n*
	POMS_vigour_D	.068[S]	.757	23	.049[S]	.824	23	-.137[S]	.533	23
	POMS_fatigue_D	-.186[P]	.396	23	.083[P]	.705	23	-.126[P]	.567	23
	POMS_confusion_D	-.257[P]	.236	23	-.008[P]	.971	23	-.202[P]	.356	23

Note. [1] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [2] Time 6: Day 2 at 11:30. [3] D: the difference scores between Scan time A (Day 1 at 12:00) and Scan time B (Day 2 at 12:00). [5] Left anterior dorsal prefrontal. [P] Pearson correlation. [S] Spearman correlation. [0] Variable not assessed when all scores were 0. [@] Variable has fewer than five data points that are different from zero.

* $p < .05$; ** $p < .01$.

Table 10

Depression Raw Scores: Summary of Significant Changes[1] During Sleep Deprivation

Scale_Item	Control group	Depressed group
HDI_7-item	=	=
HDI_sad-mood (Figure 9)	=	▲
HDI_guilt	=	=
HDI_anhedonia (Figure 6)	▼	=
HDI_subjective-tension (Figure 8)	▲ ↓	=
HDI_physical-anxiety	=	=
HDI_energy-loss (Figure 7)	▼	=
POMS_total (Figure 10)	▼	▲ ↓
POMS_tension (Figure 14)	▲ ↓	▲ ↓
POMS_depression	=	=
POMS_anger (Figure 15)	=	▲ ↓
POMS_vigour (Figure 11)	▼	▼
POMS_fatigue (Figure 12)	▼	=
POMS_confusion (Figure 13)	▼	▲ ↓

Note. [1] ▲ Alleviation over Time; ▼ worsening over Time; = no change over Time;

↓ group mean raw scores had reverted to baseline values prior to second brain scan.

Table 11

Depression Difference[1] Scores: Direction of Significant Between-group Discrepancies

Scale_Item	Control group	Depressed group
HDI_7-item (Figure 16)	▼=	▲=
HDI_sad-mood (Figure 17)	=	▲
HDI_guilt		
HDI_anhedonia (Figure 18)	▼	=
HDI_subjective-tension		
HDI_physical-anxiety		
HDI_energy-loss (Figure 19)	▼	=
POMS_total (Figure 20)	▼	=
POMS_tension		
POMS_depression (Figure 21)	=	▲=
POMS_anger		
POMS_vigour (Figure 22)	▼▼	▼
POMS_fatigue (Figure 23)	▼	=
POMS_confusion (Figure 24)	▼	=

Note. [1] Difference: Time 1 minus Time 6; ▲ alleviation over Time; ▼ worsening over Time; = analysis of variances of the raw scores over Time was not statistically significant, or significance was not maintained until the end of the experimental period.

Figure 1

Concentration Levels of Creatine-plus-phosphocreatine Acquired in the Pons As a Function of Group and Scan Time

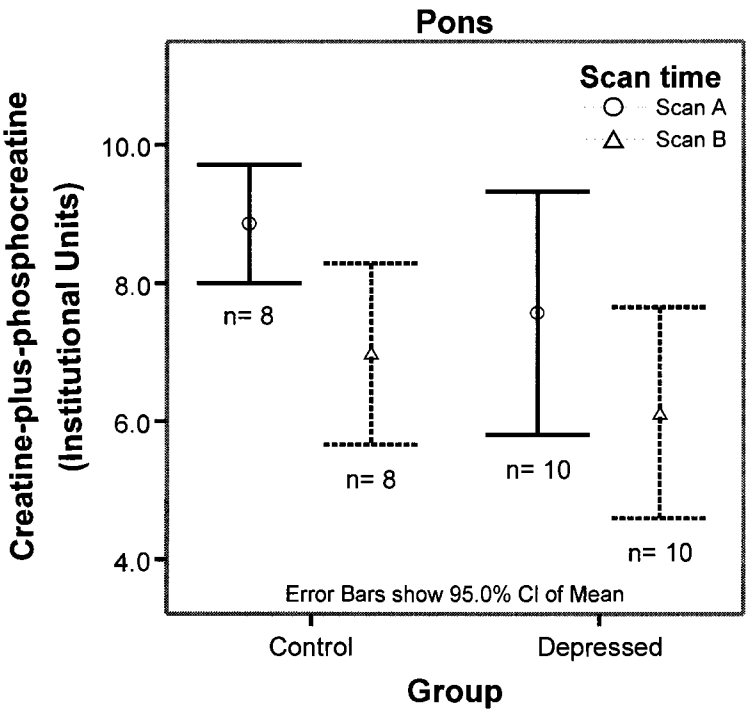


Figure 2

Concentration Levels of Creatine-plus-phosphocreatine Acquired in the Pons As a Function of Scan Time, for Both Groups Pooled

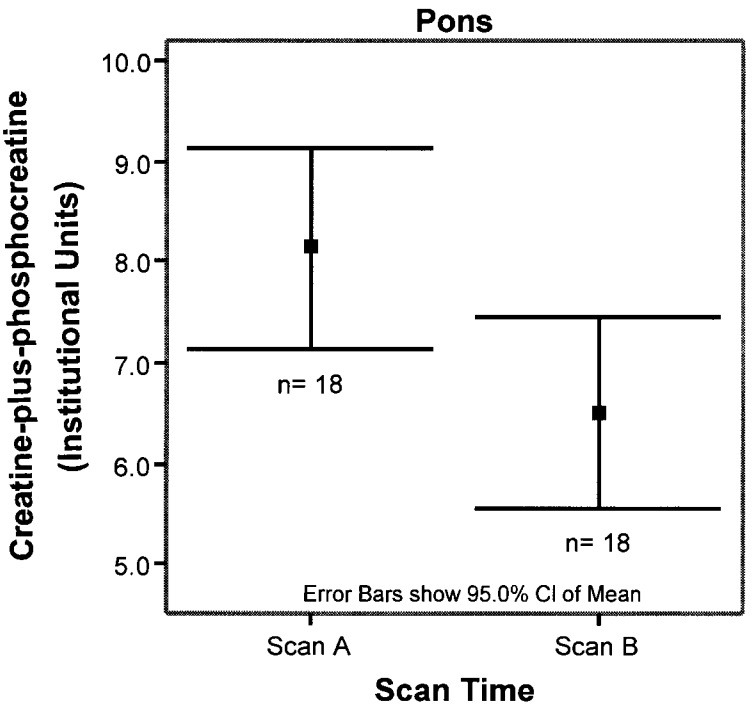


Figure 3

Concentration Levels of Choline Compounds Acquired in the Left Anterior Dorsal Prefrontal Region As a Function of Group and Scan Time

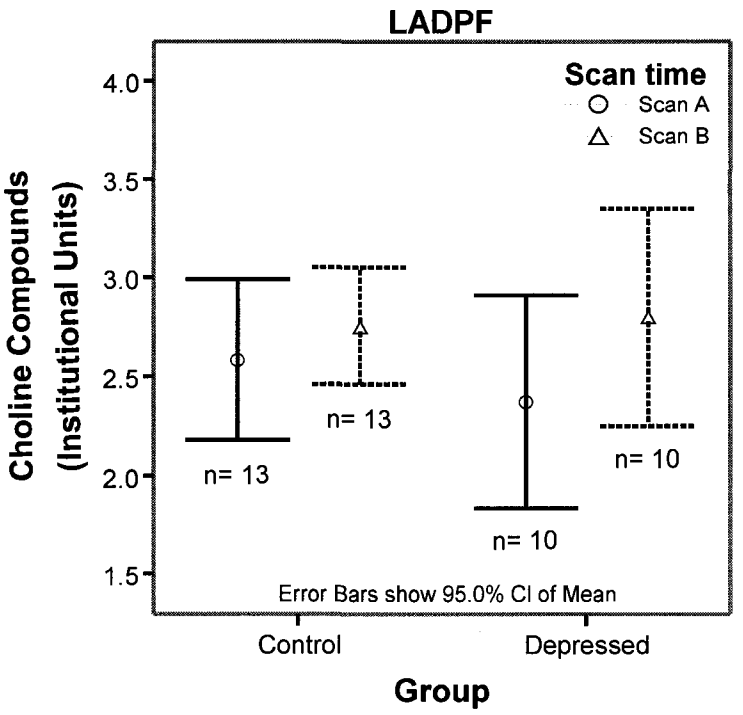


Figure 4

Concentration Levels of Choline Compounds Acquired in the Left Anterior Dorsal Prefrontal Region of the Depressed Group As a Function of Scan Time and Medication Status

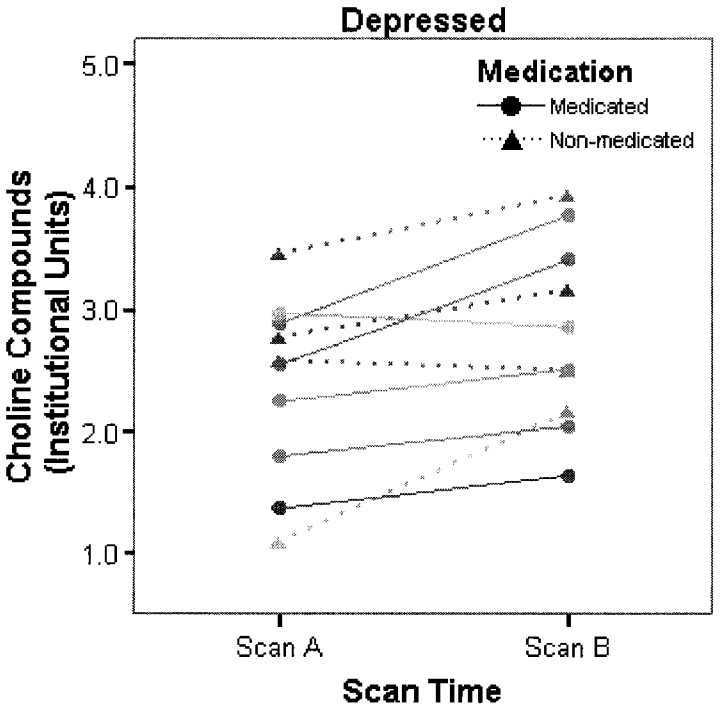


Figure 5

Choline Compounds for the Responder and Non-responder Subgroups

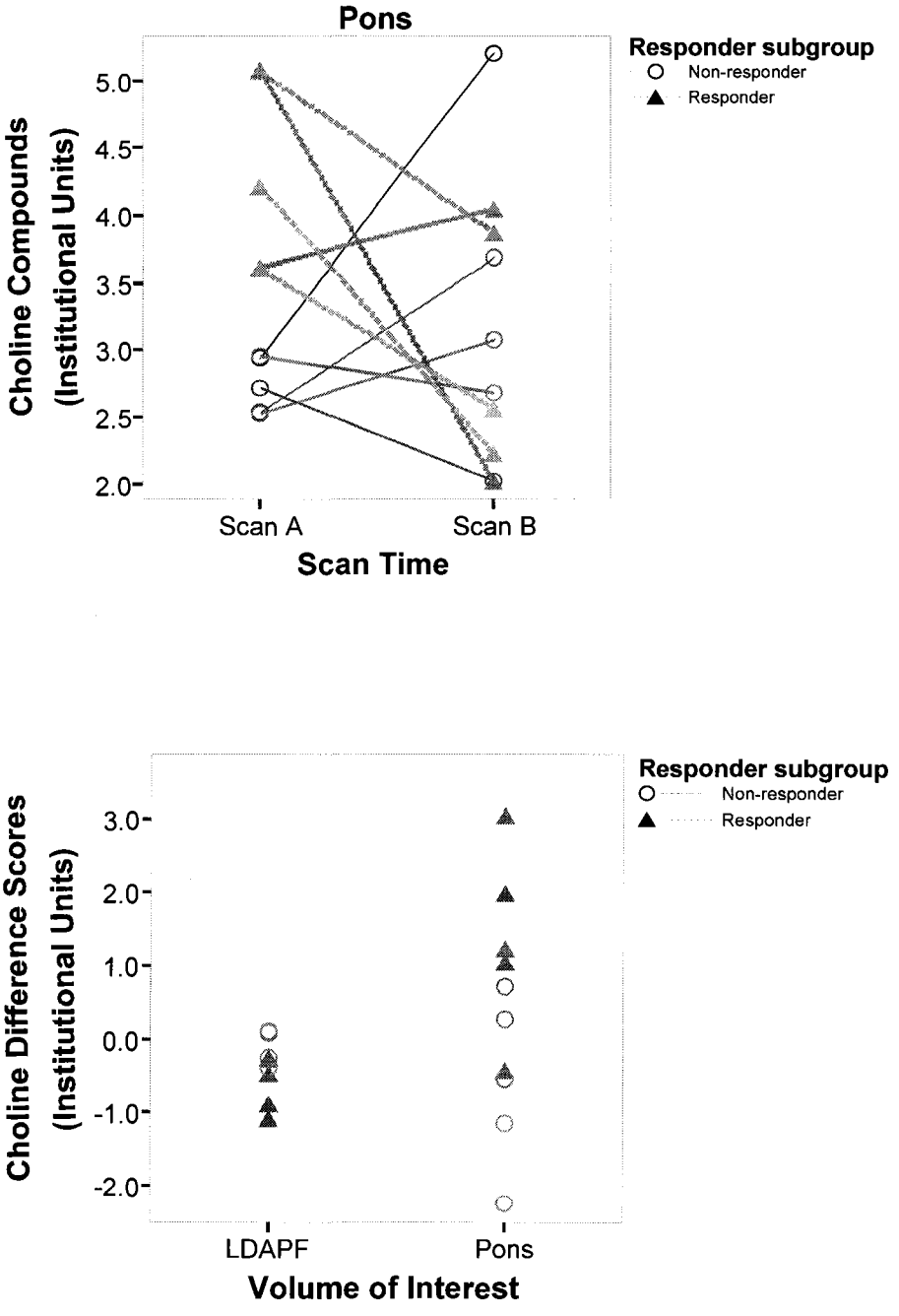
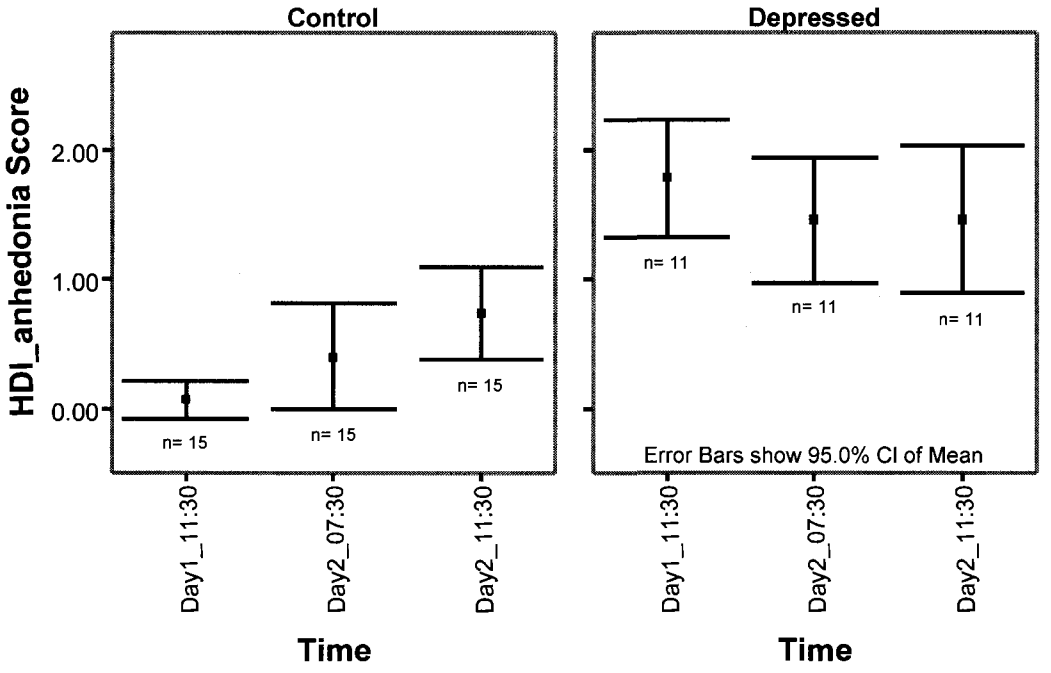


Figure 6

HDI_anhedonia Self-report Scores Over Time



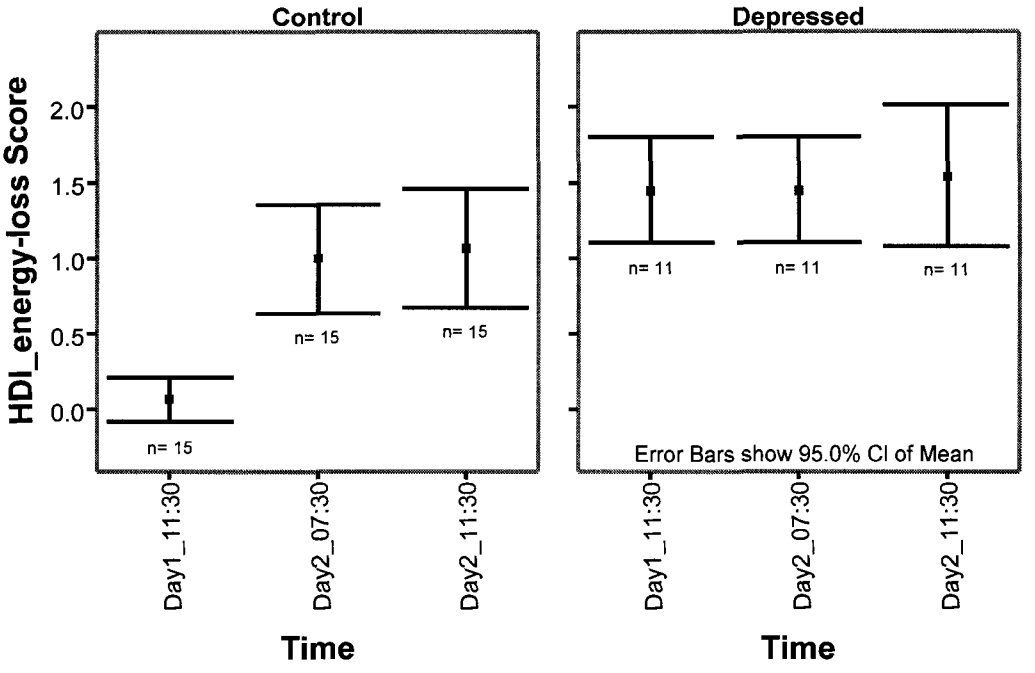
Significant Follow-up Paired Comparisons for HDI_anhedonia Raw Scores

Control group	Depressed group
Day1_11:30 < Day2_11:30**	

** $p < .01$.

Figure 7

HDI_energy-loss Self-report Scores Over Time



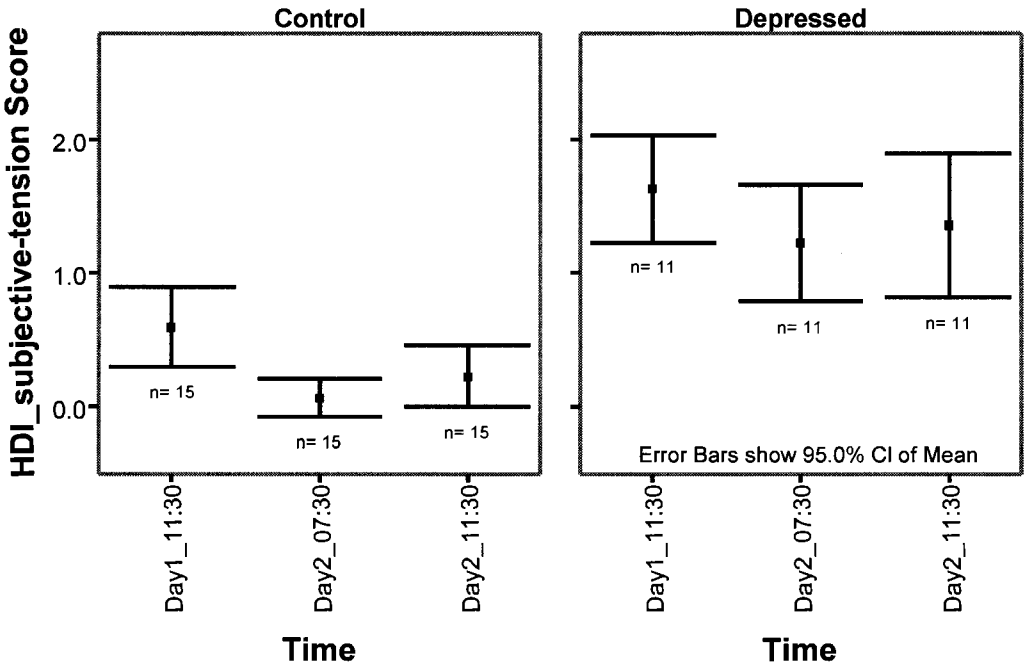
Significant Follow-up Paired Comparisons for HDI_energy-loss Raw Scores

Control group	Depressed group
Day1_11:30 < Day2_07:30**	
Day1_11:30 < Day2_11:30**	

** $p < .01$.

Figure 8

HDI_subjective-tension Self-report Scores Over Time



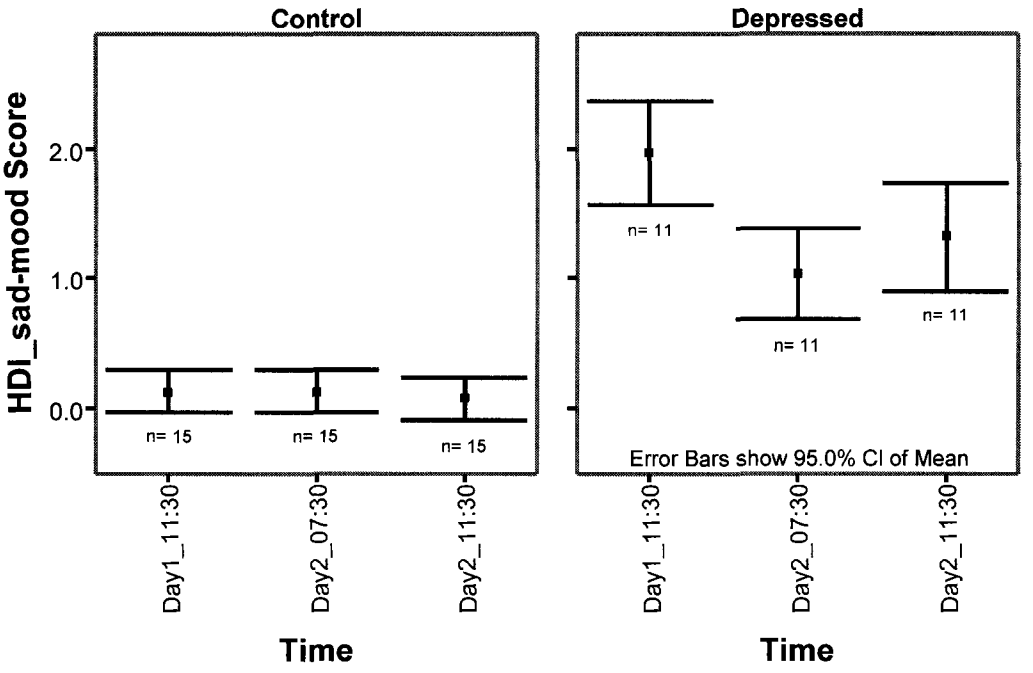
Significant Follow-up Paired Comparisons for HDI_subjective-tension Raw Scores

Control group	Depressed group
Day1_11:30 > Day2_07:30**	

** $p < .01$.

Figure 9

HDI_sad-mood Self-report Scores Over Time



Significant Follow-up Paired Comparisons for HDI_sad-mood Raw Scores

Control group	Depressed group
	Day1_11:30 > Day2_07:30**
	Day1_11:30 > Day2_11:30*

* $p < .05$; ** $p < .01$.

Figure 10

POMS_total Self-report Scores Over Time

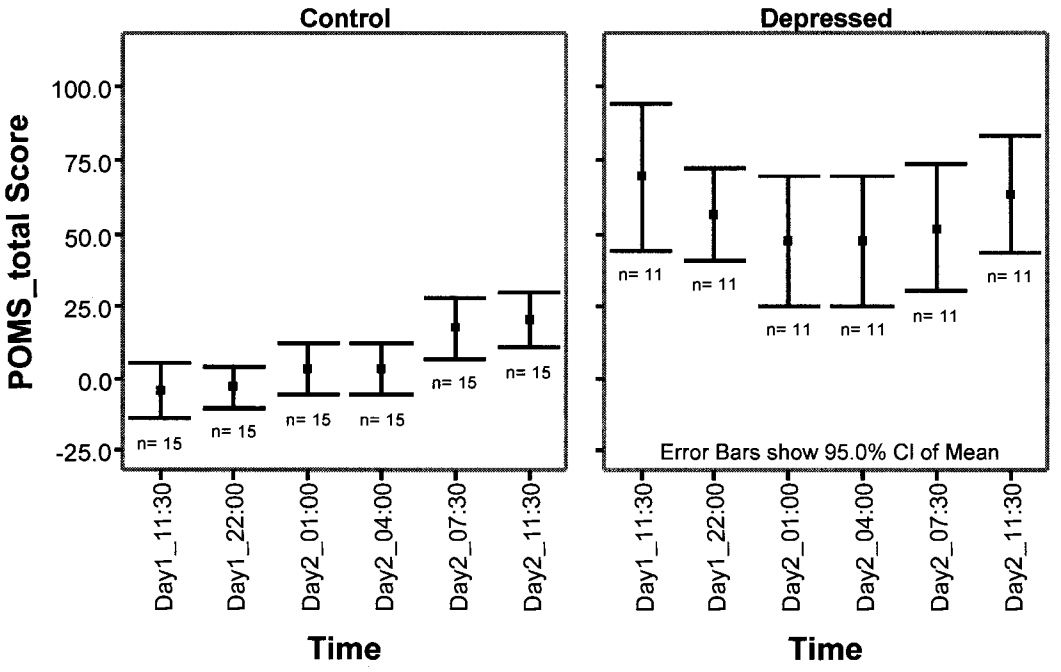


Figure 10 continued

POMS_total Self-report Scores Over Time

Significant Follow-up Paired Comparisons for POMS_total Raw Scores

Control group	Depressed group
Day1_11:30 < Day2_07:30**	Day1_11:30 > Day2_01:00**
Day1_11:30 < Day2_11:30**	Day1_11:30 > Day2_04:00**
Day1_22:00 < Day2_01:00*	Day2_01:00 < Day2_11:30*
Day1_22:00 < Day2_04:00*	Day2_04:00 < Day2_11:30*
Day1_22:00 < Day2_07:30**	Day2_07:30 < Day2_11:30**
Day1_22:00 < Day2_11:30**	
Day2_01:00 < Day2_07:30**	
Day2_01:00 < Day2_11:30**	
Day2_04:00 < Day2_07:30**	
Day2_04:00 < Day2_11:30**	

* $p < .05$; ** $p < .01$.

Figure 11

POMS_vigour Self-report Scores Over Time

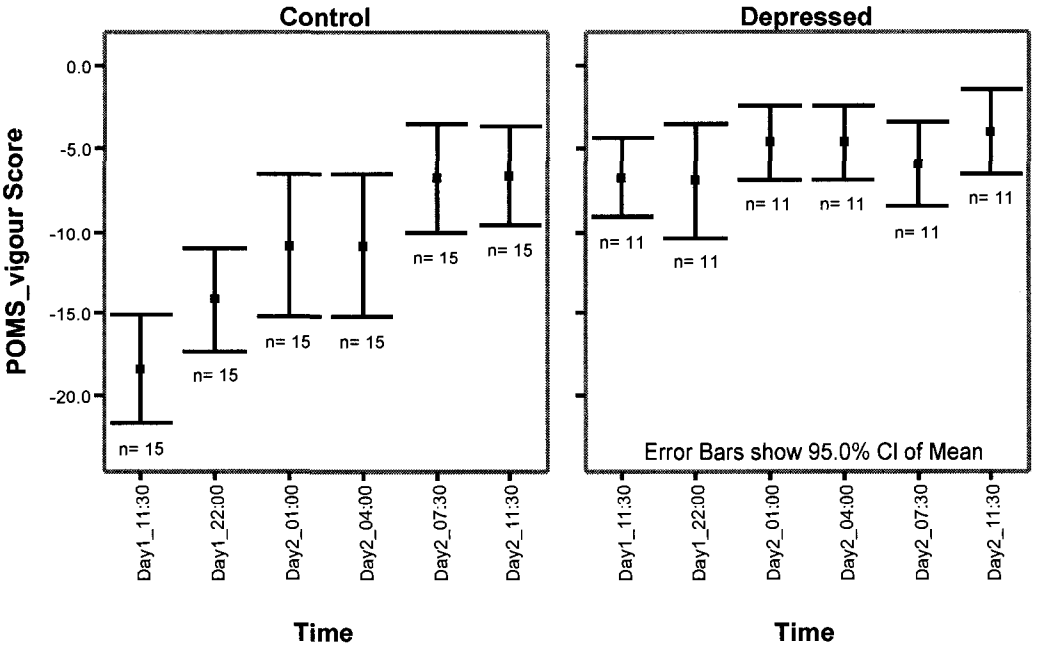


Figure 11 continued

POMS_vigour Self-report Scores Over Time

Significant Follow-up Paired Comparisons for POMS_vigour Raw Scores

Control group	Depressed group
Day1_11:30 < Day1_22:00**	Day1_11:30 < Day2_01:00**
Day1_11:30 < Day2_01:00**	Day1_11:30 < Day2_11:30*
Day1_11:30 < Day2_04:00**	Day1_22:00 < Day2_01:00*
Day1_11:30 < Day2_07:30**	Day1_22:00 < Day2_04:00*
Day1_11:30 < Day2_11:30**	Day1_22:00 < Day2_11:30**
Day1_22:00 < Day2_01:00*	Day2_04:00 < Day2_11:30*
Day1_22:00 < Day2_04:00*	Day2_07:30 < Day2_11:30*
Day1_22:00 < Day2_07:30**	
Day1_22:00 < Day2_11:30**	
Day2_01:00 < Day2_07:30**	
Day2_01:00 < Day2_11:30**	
Day2_04:00 < Day2_07:30**	
Day2_04:00 < Day2_11:30**	

* $p < .05$; ** $p < .01$.

Figure 12

POMS_fatigue Self-report Scores Over Time

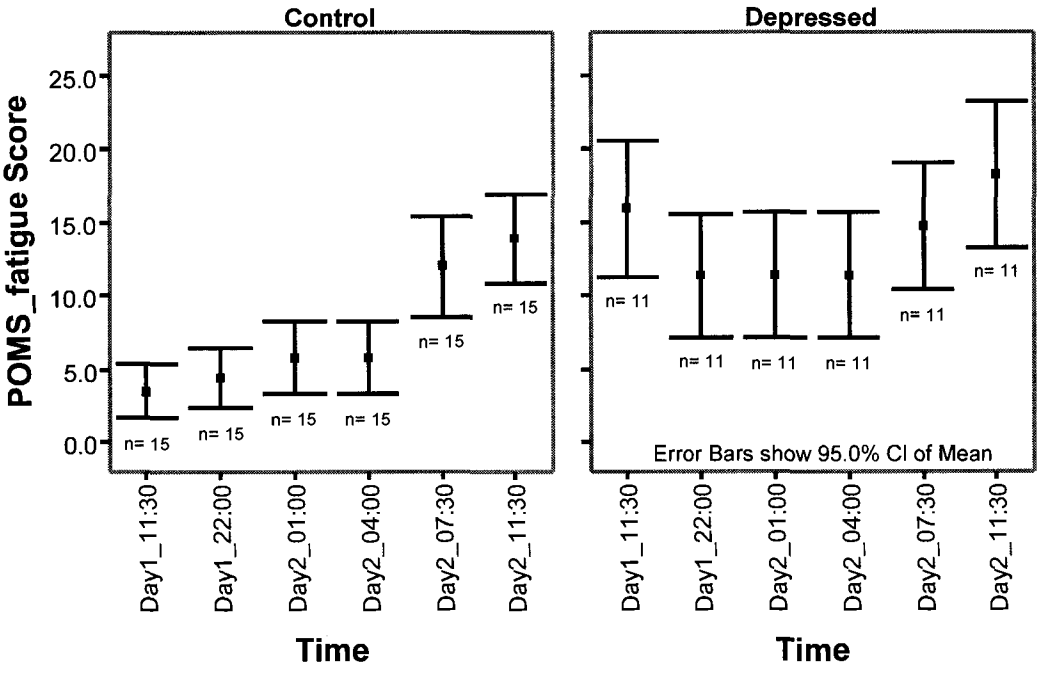


Figure 12 continued

POMS_fatigue Self-report Scores Over Time

Significant Follow-up Paired Comparisons for POMS_fatigue Raw Scores

Control group	Depressed group
Day1_11:30 < Day2_07:30**	
Day1_11:30 < Day2_11:30**	
Day1_22:00 < Day2_01:00**	
Day1_22:00 < Day2_04:00**	
Day1_22:00 < Day2_07:30**	
Day1_22:00 < Day2_11:30**	
Day2_01:00 < Day2_11:30*	
Day2_04:00 < Day2_07:30*	
Day2_04:00 < Day2_11:30**	

* $p < .05$; ** $p < .01$.

Figure 13

POMS_confusion Self-report Scores Over Time

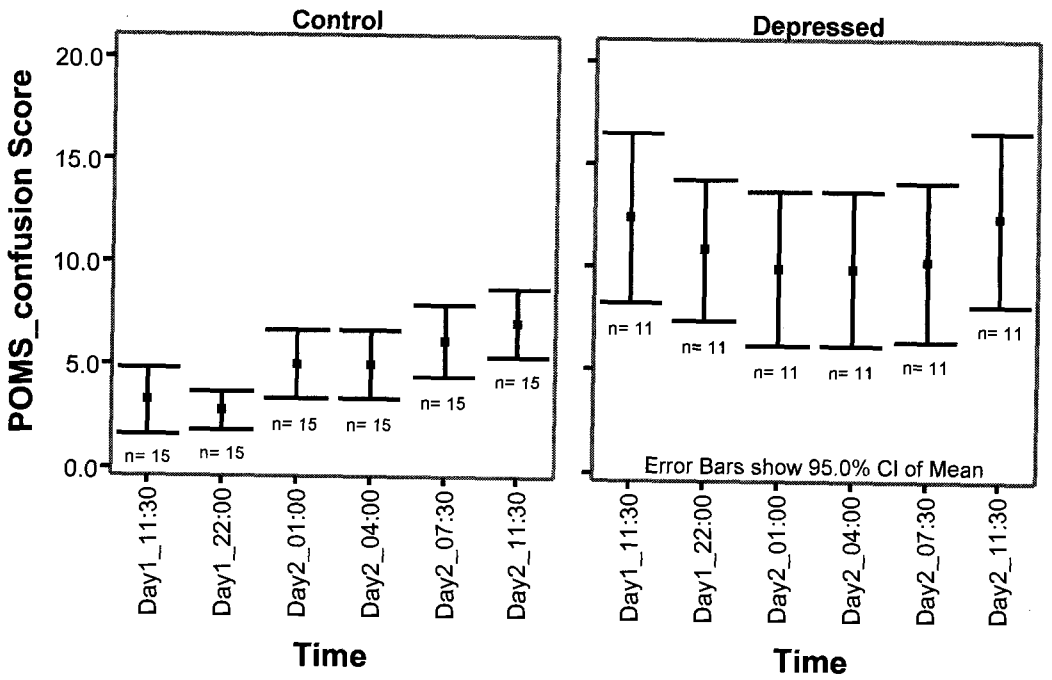


Figure 13 continued

POMS_confusion Self-report Scores Over Time

Significant Follow-up Paired Comparisons for POMS_confusion Raw Scores

Control group	Depressed group
Day1_11:30 < Day2_07:30**	Day1_11:30 > Day2_01:00*
Day1_11:30 < Day2_11:30**	Day2_04:00 < Day2_11:30**
Day1_22:00 < Day2_01:00**	Day2_07:30 < Day2_11:30*
Day1_22:00 < Day2_04:00**	
Day1_22:00 < Day2_07:30**	
Day1_22:00 < Day2_11:30**	
Day2_01:00 < Day2_11:30*	
Day2_04:00 < Day2_11:30*	

* $p < .05$; ** $p < .01$.

Figure 14

POMS_tension Self-report Scores Over Time

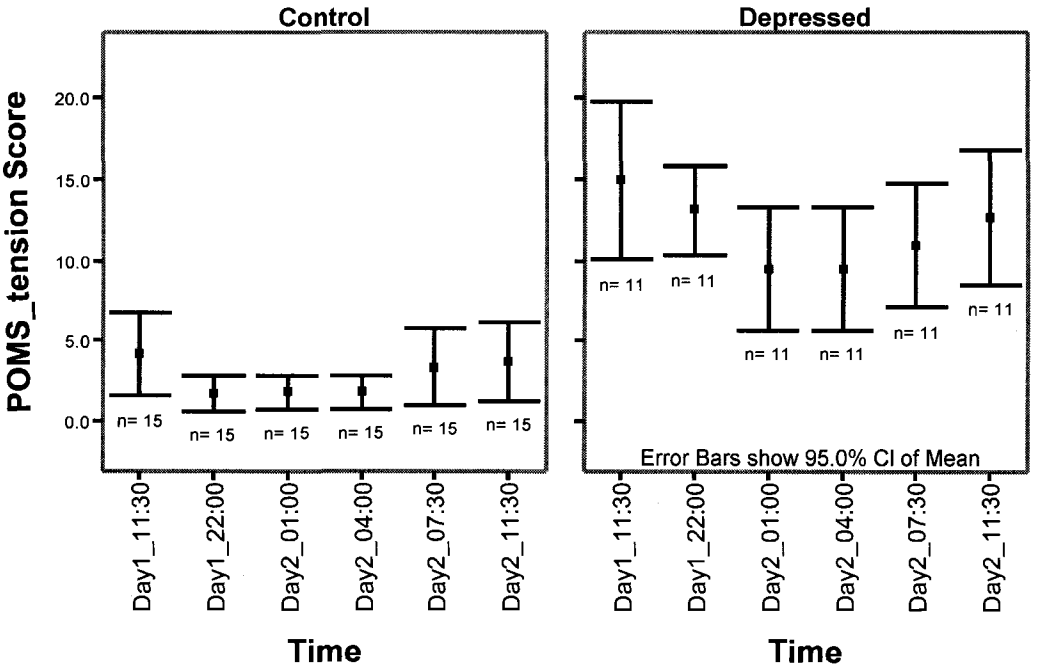


Figure 14 continued

POMS_tension Self-report Scores Over Time

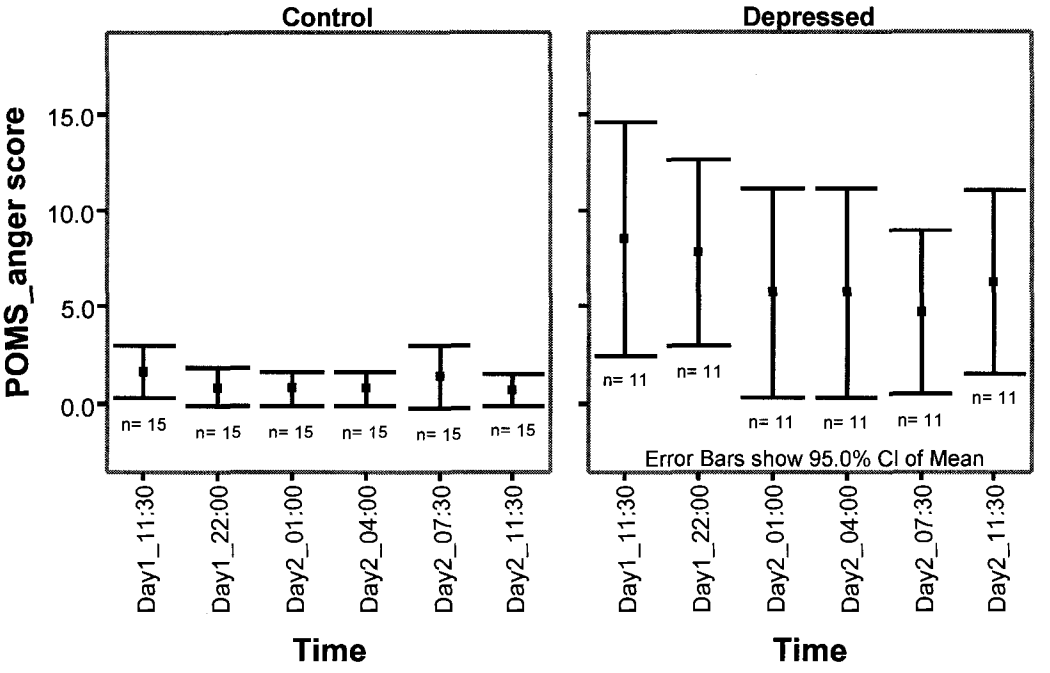
Significant Follow-up Paired Comparisons for POMS_tension Raw Scores

Control group	Depressed group
Day1_11:30 > Day1_22:00*	Day1_11:30 > Day2_01:00*
Day1_11:30 > Day2_01:00*	Day1_11:30 > Day2_04:00*
Day1_11:30 > Day2_04:00*	Day1_11:30 > Day2_07:30*
Day1_22:00 < Day2_07:30*	Day1_22:00 > Day2_01:00*
Day1_22:00 < Day2_11:30**	Day1_22:00 > Day2_04:00*
Day1_01:00 < Day2_07:30*	Day2_01:00 < Day2_11:30*
Day2_01:00 < Day2_11:30**	Day2_04:00 < Day2_11:30*
Day1_04:00 < Day2_07:30*	
Day1_04:00 < Day2_11:30**	

* $p < .05$; ** $p < .01$.

Figure 15

POMS_anger Self-report Scores Over Time



Significant Follow-up Paired Comparisons for POMS_anger Raw Scores

Control group	Depressed group
	Day1_11:30 > Day2_07:30*
	Day1_22:00 > Day2_07:30*
	Day2_07:30 < Day2_11:30*

* $p < .05$.

Figure 16

Group Differences in HDI_7-item Difference Scores

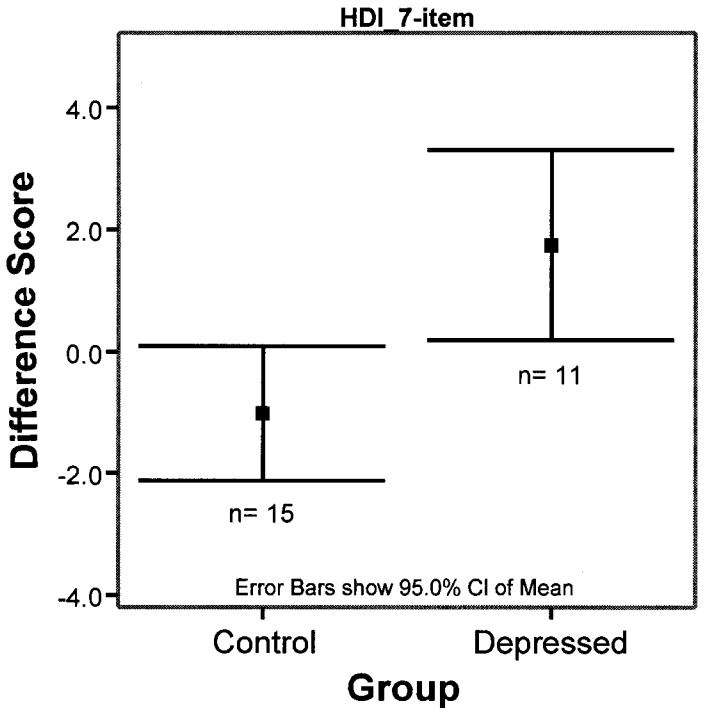


Figure 17

Group Differences in HDI_sad-mood Difference Scores

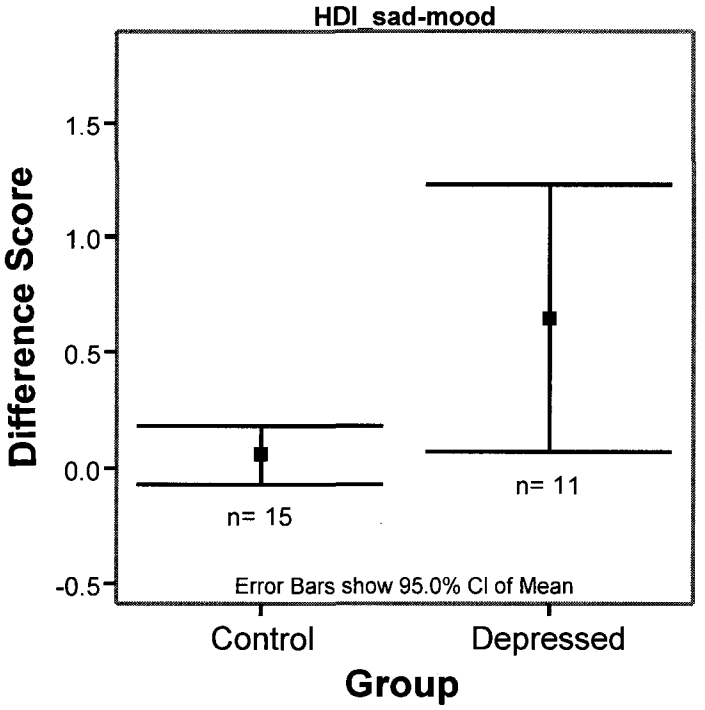


Figure 18

Group Differences in HDI_anhedonia Difference Scores

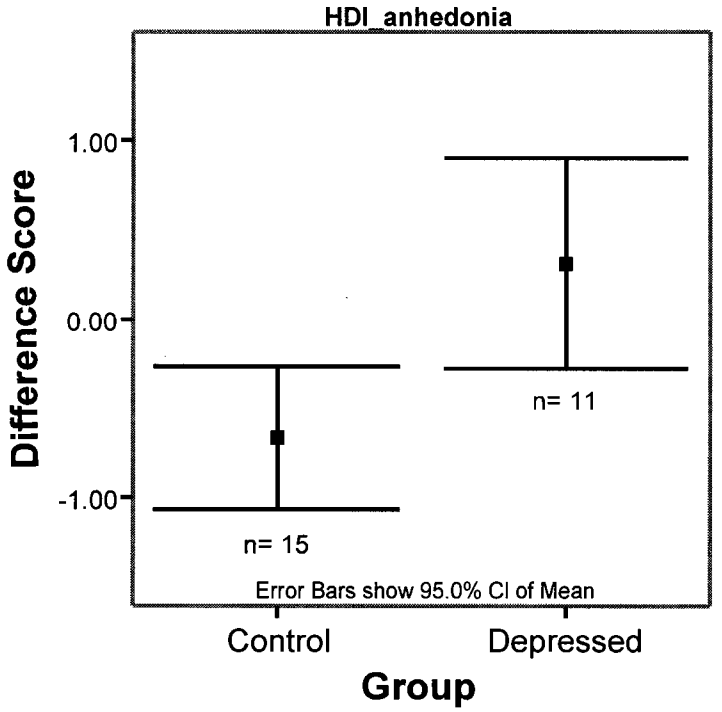


Figure 19

Group Differences in HDI_energy-loss Difference Scores

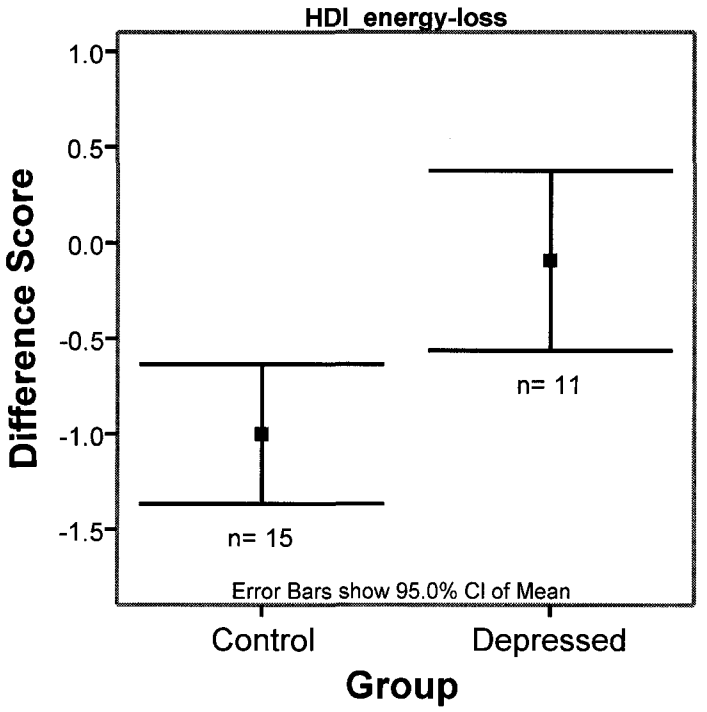


Figure 20

Group Differences in POMS_total Difference Scores

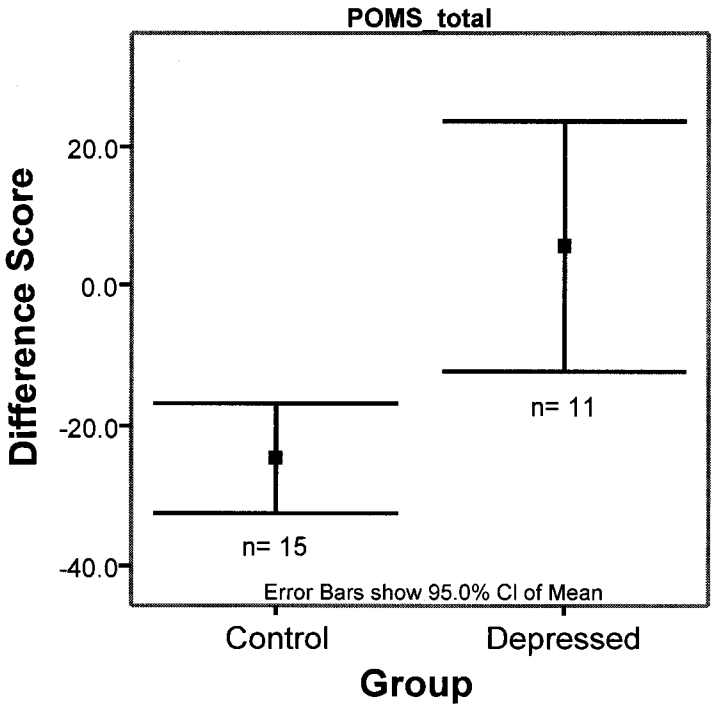


Figure 21

Group Differences in POMS_depression Difference Scores

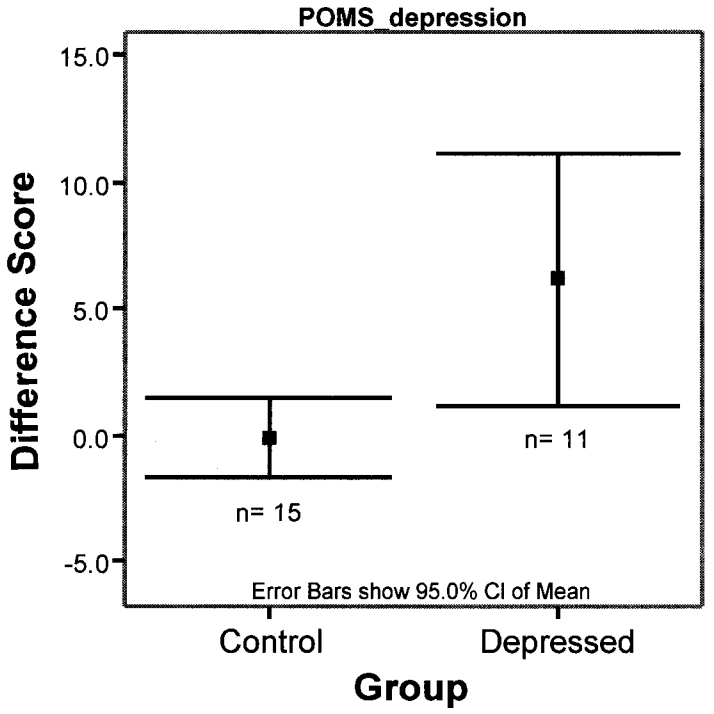


Figure 22

Group Differences in POMS_vigour Difference Scores

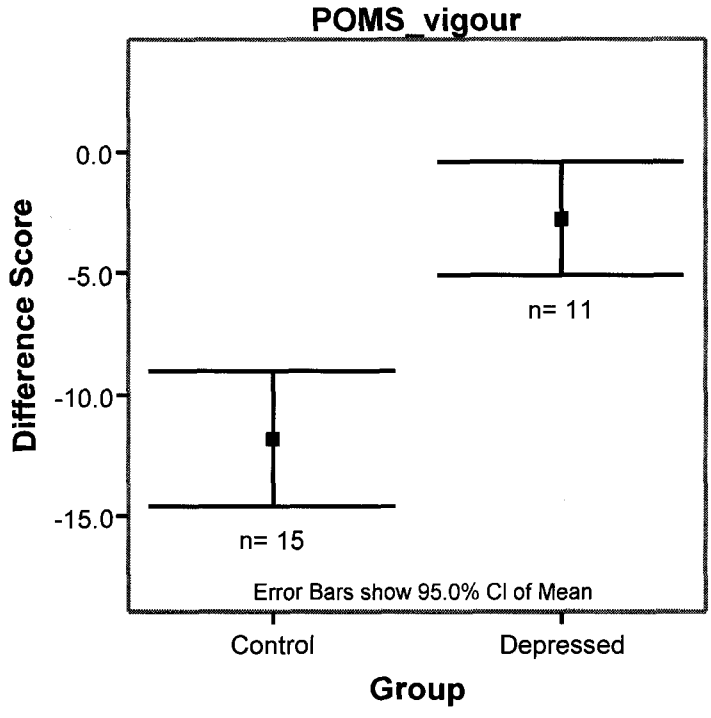


Figure 23

Group Differences in POMS_fatigue Difference Scores

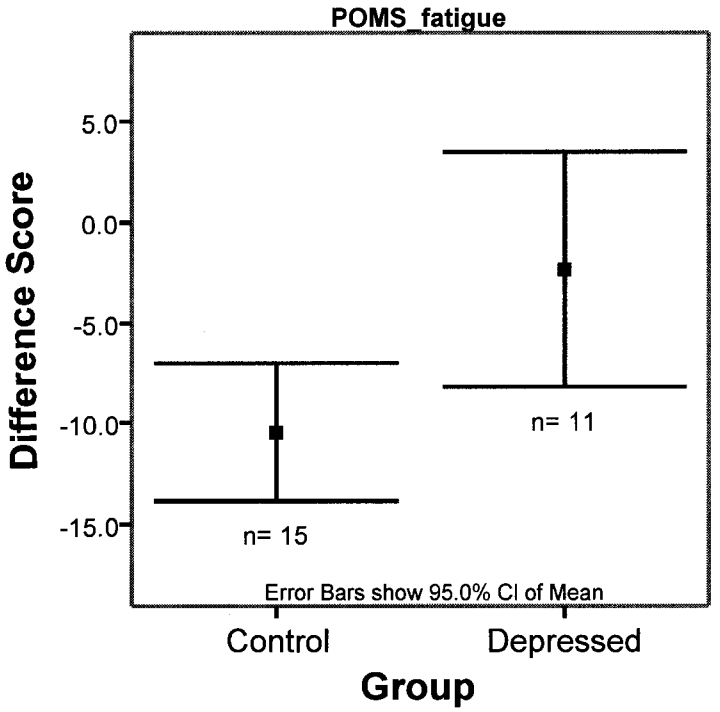


Figure 24

Group Differences in POMS_confusion Difference Scores

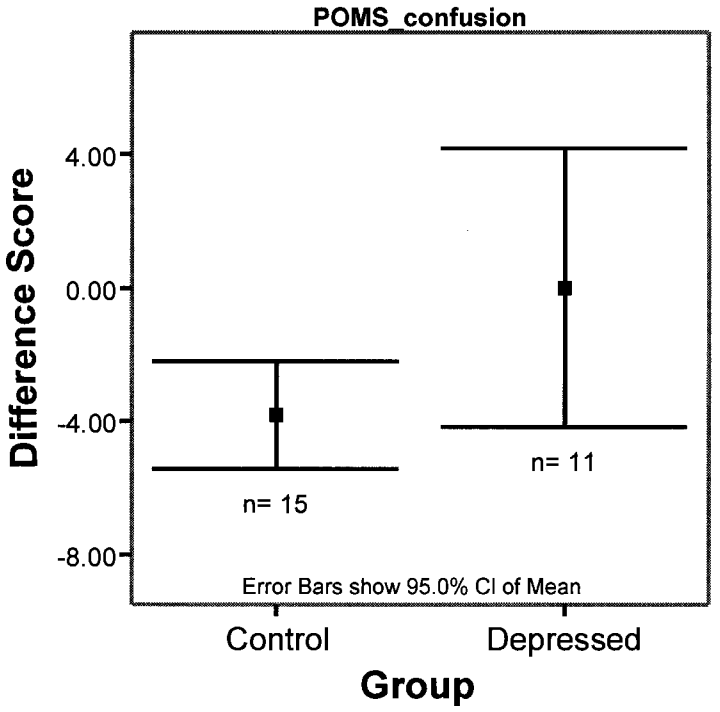


Figure 25

Correlation Between HDI_sad-mood Scores and NAA Concentrations Acquired at Scan Time A in the Left Dorsal Prefrontal Region for the Depressed Group

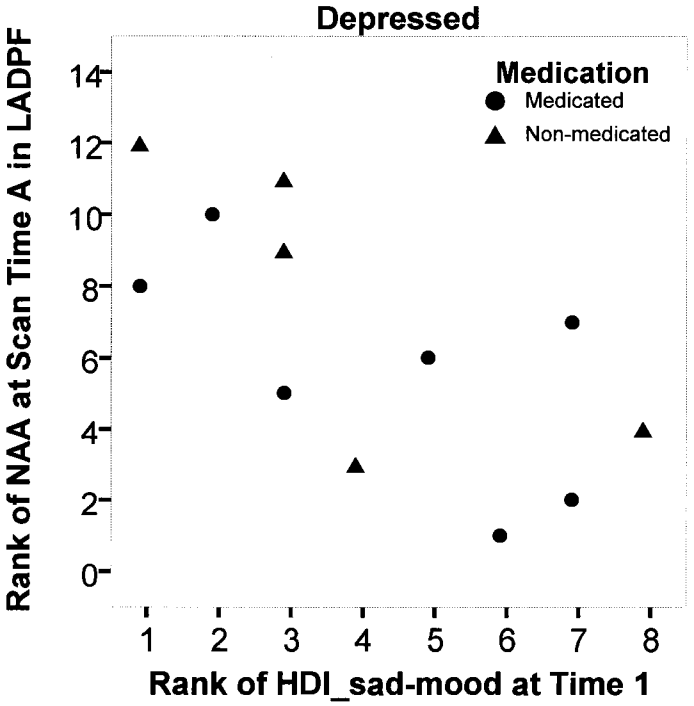


Figure 26

Correlation Between HDI_7-item Difference Scores and NAA Difference Scores Acquired in the Pons for the Control Group

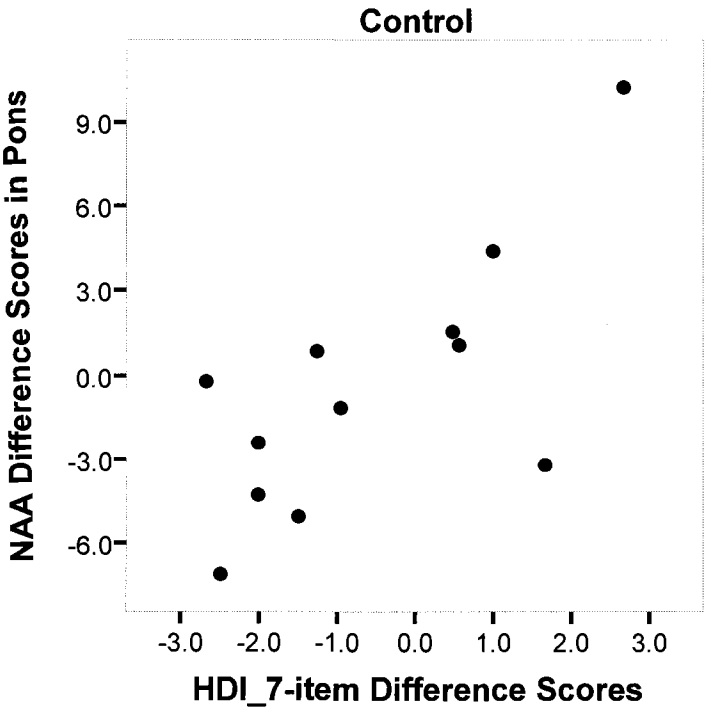


Figure 27

Correlation Between POMS_fatigue Difference Scores and Choline Compounds Difference Scores Acquired in the Pons for the Depressed Group

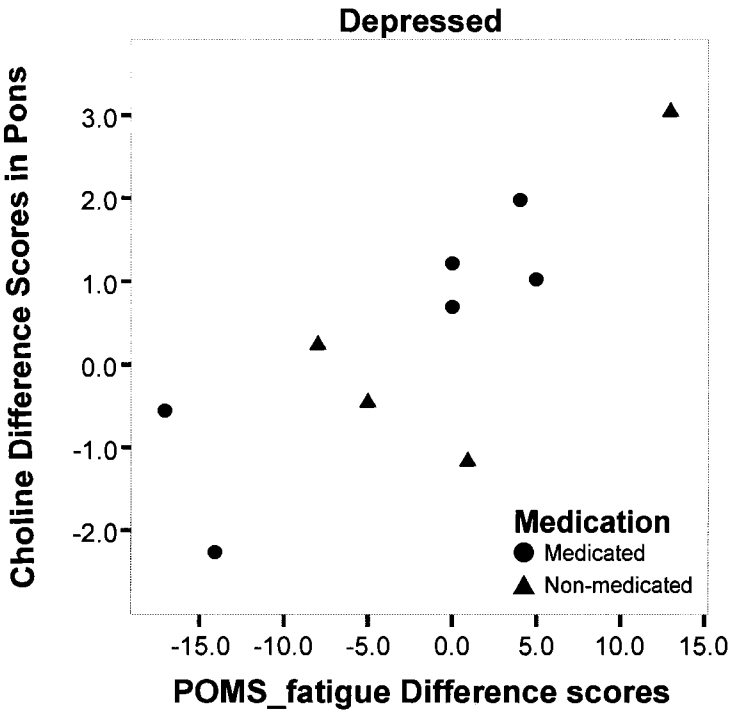
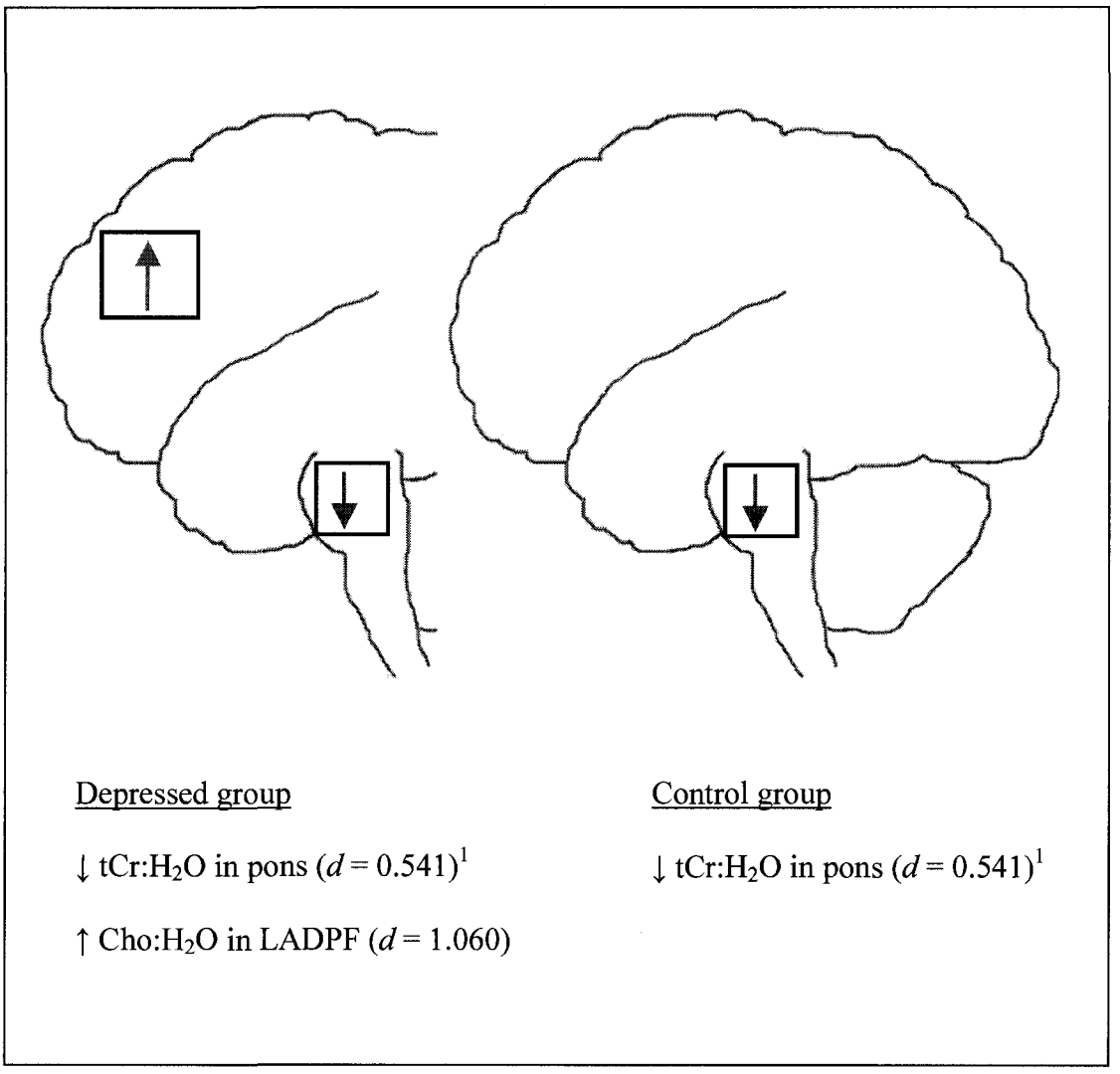


Figure 28

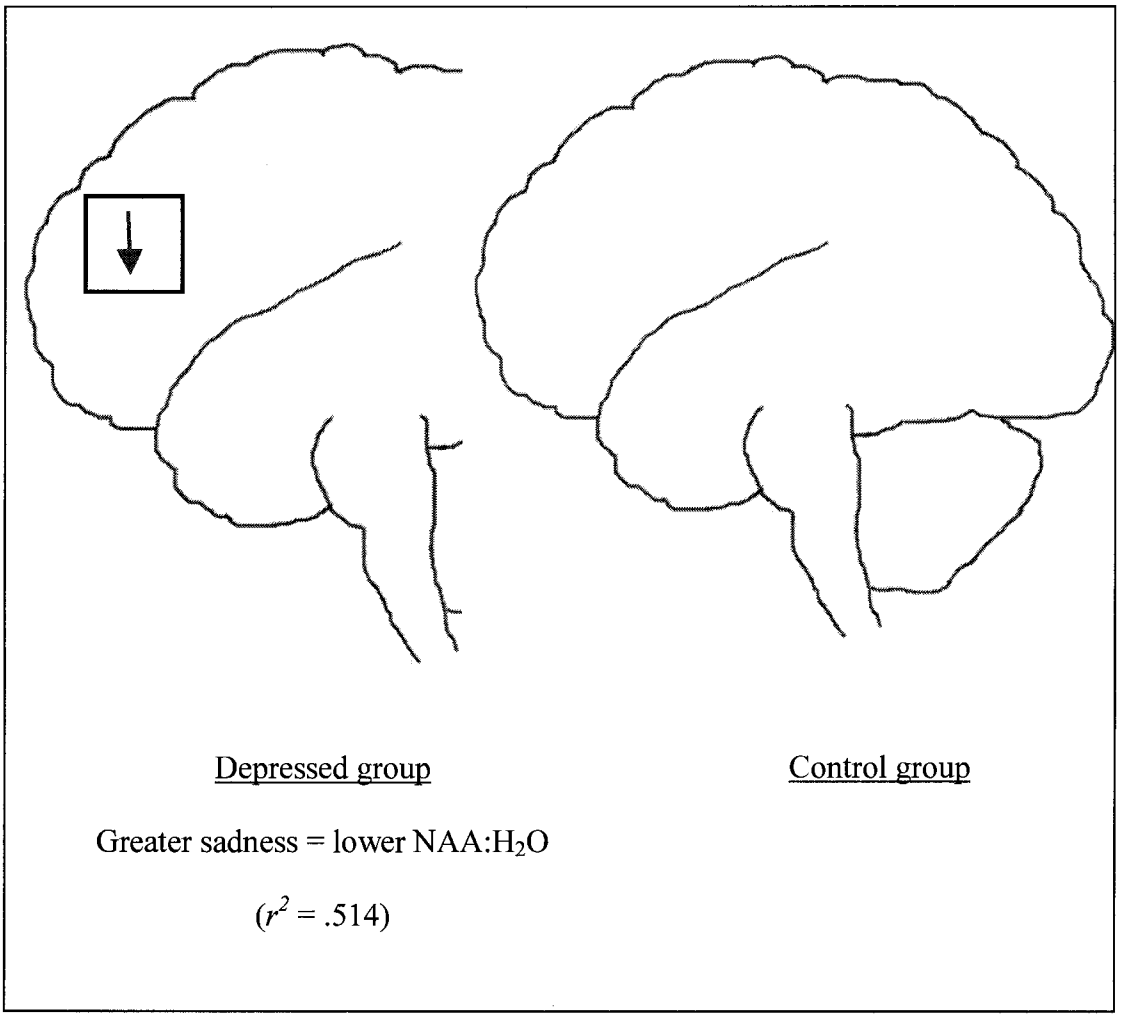
Summary of Significant Post-treatment Changes in Neurochemical Concentrations Relative to Pre-treatment Values for Each Group



Note. [1]Effect size for both groups pooled. See also Figures 1, 2, 3 and 4.

Figure 29

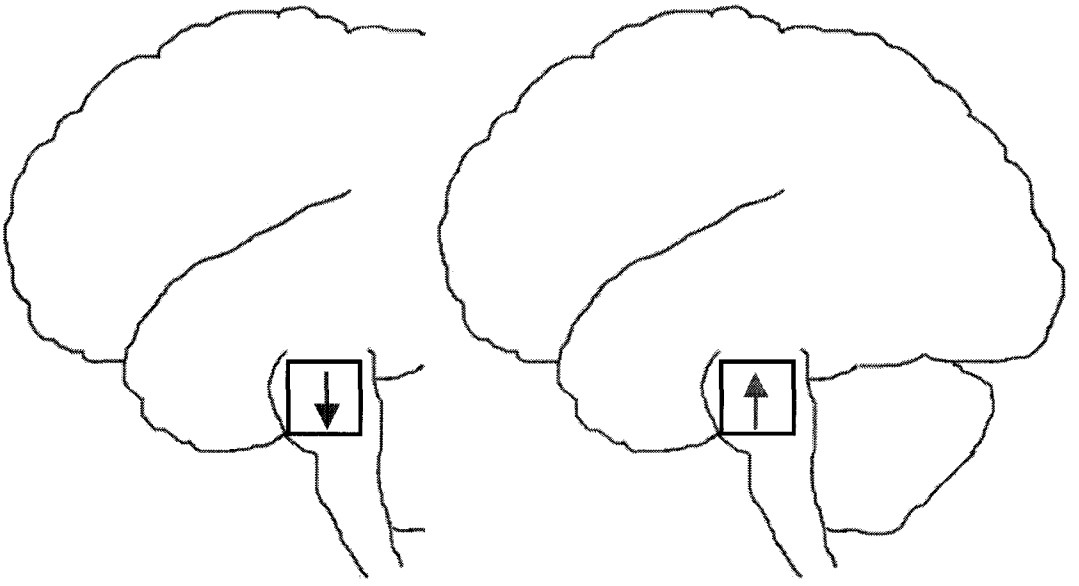
Summary of Significant Association Between Neurochemical Concentrations and Depression Scores at Baseline



Note. See also Figure 25.

Figure 30

Summary of Significant Associations Between Neurochemical and Depression Difference Scores for Each Group



Depressed group	Control group
Alleviation in POMS_fatigue	Increase in HDI_total
= ↓ Cho:H_2O	= ↑ NAA:H_2O
(r^2 = .629)	(r^2 = .508)

Note. See also Figures 26 and 27.

Appendix 1

Functional Roles of Some Neurochemicals Detectable With Two Different Methods of *In Vivo* Magnetic Resonance Spectroscopy

Spectroscopy method	Neurochemical peak	Postulated functional roles in the brain[1]
Proton magnetic resonance spectroscopy (^{1}H-MRS)	Creatine plus phosphocreatine (tCr)	Involved in the brain energy metabolism.
	Choline peak (Cho): -phosphorylcholine (PC) -glycerophosphorylcholine (GPC)	PC is an anabolic constituent of the phospholipid metabolic cycle, and a crucial second messenger for the proliferating activity of several growth factors. GPC is a breakdown product of the phospholipid metabolic cycle in the brain.
	N-acetylaspartate (NAA)	1) Involved in the myelination process in the brain. 2) Precursor in the formation of *N*-acetylaspartylglutamate (NAAG), which is involved in excitatory neurotransmission 3) Osmoregulation (modulating water balance in neurons) 4) A central role in the metabolism of glutamate (an amino acid involved in brain metabolic activity and in neurotransmission). 5) Concentration levels were associated in time to changes in levels of adenosine triphosphate (thus, related to brain energy metabolism).

Appendix 1 (continued)

Functional Roles of Some Neurochemicals Detectable With Two Different Methods of *In Vivo* Magnetic Resonance Spectroscopy

Spectroscopy method	Neurochemical peak	Postulated functional roles in the brain[1]
Phosphorus magnetic resonance spectroscopy (^{31}P-MRS)	Creatine (Cr) Phosphocreatine (Pcr)	Both involved in the brain energy metabolism.
	Nucleoside triphosphate (NTP) and Adenosine triphosphate (ATP)	Involved in the brain energy metabolism.
	Phosphomonoester peak (PME): -PC -phosphoethanolamine	Both precursors to membrane synthesis phospholipid metabolism.
	Phosphodiester peak (PDE): -GPC -glycerophosphodiesters	Breakdown products of the phospholipid metabolism in the brain.

Note. [1]For more detailed descriptions and for appropriate references, see section 1.6 in text.

Appendix 2

Expressions Used to Probe for Feelings

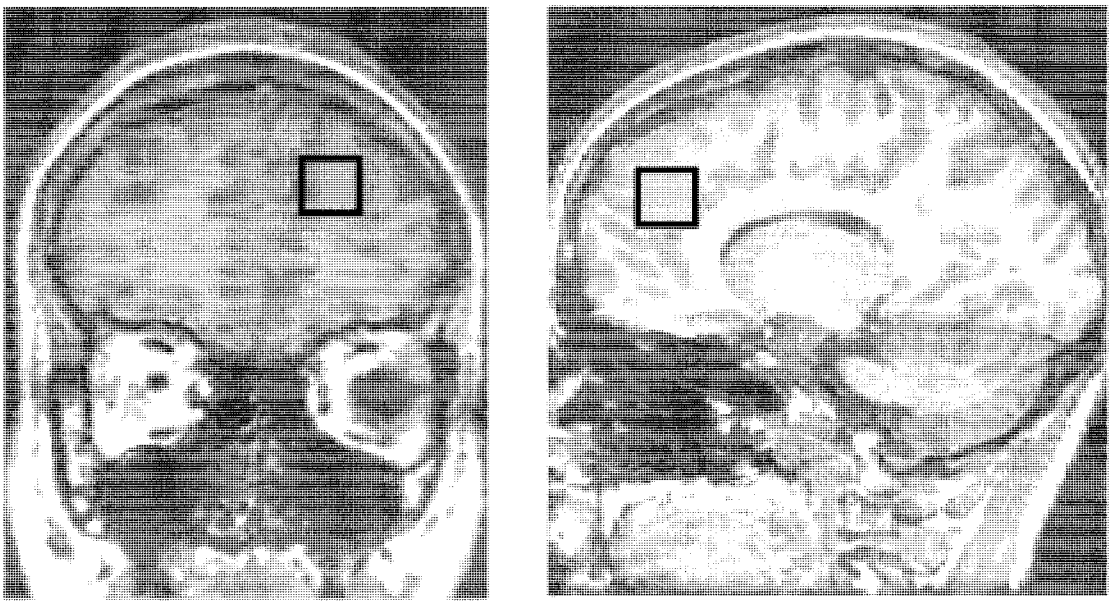
Scale / Item	Expressions used to probe for feelings
HDI	
Sad-mood	Feeling depressed, sad, blue, "down in the dumps"
Guilt	Blaming yourself or feeling like you should be punished
Anhedonia	Interest and ability to enjoy usual activities
Subjective-tension	Feeling anxious; feeling nervous
Physical-anxiety	Heart pounding; sweating; indigestion; heartburn; stomach aches
Energy-loss	As much (or less) physical energy than usual; feeling tired
Suicidal ideations	Feel like life is not worth living; thinking about (planning) suicide
POMS	
Tension	Tensed, shaky, on edge, panicky, uneasy, restless, nervous, anxious
Depression	Unhappy, sad, blue, hopeless, unworthy, discouraged, helpless
Anger	Grouchy, annoyed, peeved, furious, bitter, resentful, bad-tempered
Vigour	Active, alert, vigourous, lively, energetic, full of pep, cheerful
Fatigue	Worn-out, fatigued, exhausted, sluggish, weary, bushed
Confusion	Unable to concentrate, forgetful, confused, uncertain about things

Note. [1]HDI: Hamilton Depression Inventory; POMS: Profile of Mood States.

Appendix 3

Spectroscopic Volumes of Interest

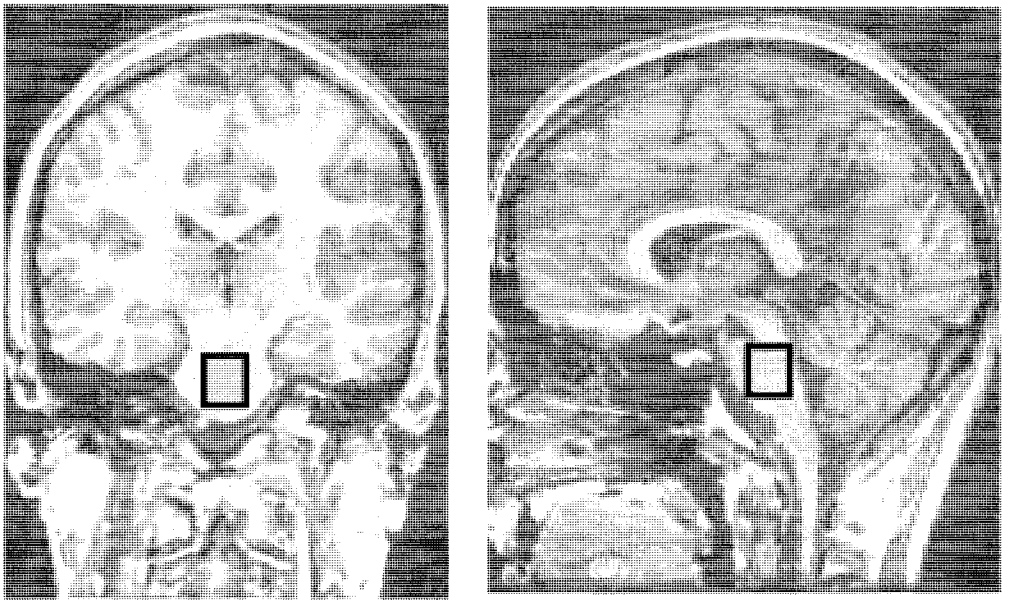
Left Dorsal Prefrontal Region



Appendix 3 (continued)

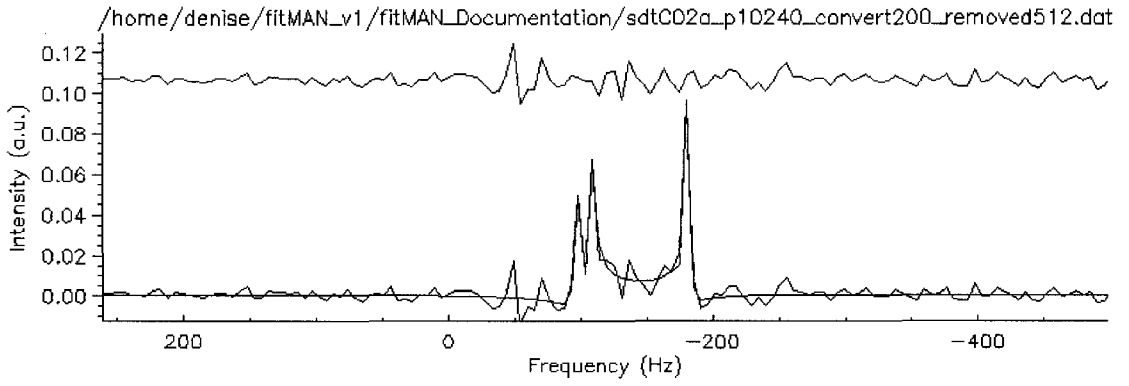
Spectroscopic Volumes of Interest

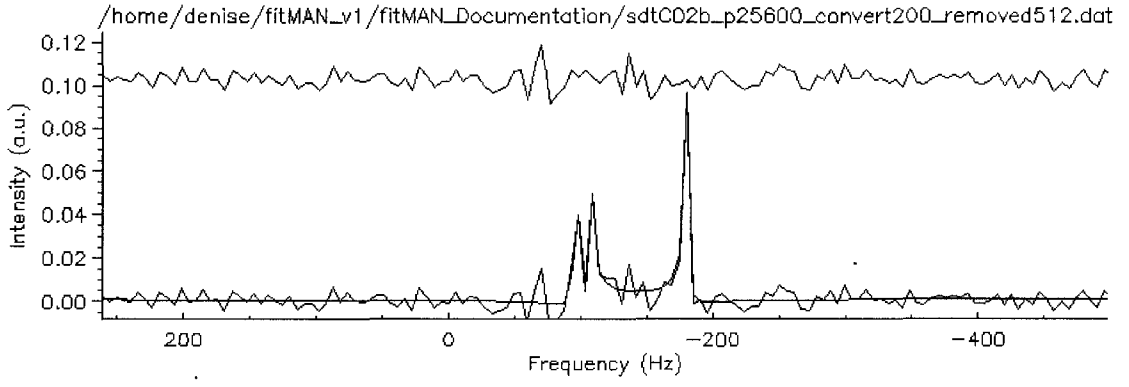
Pontine Region

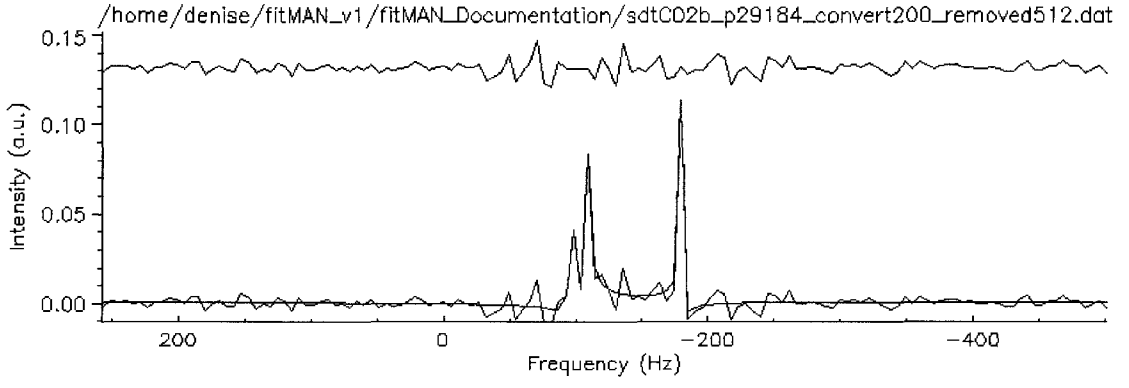


Appendix 4

Examples of 3-Peak Manual Fits for the Spectral Profiles

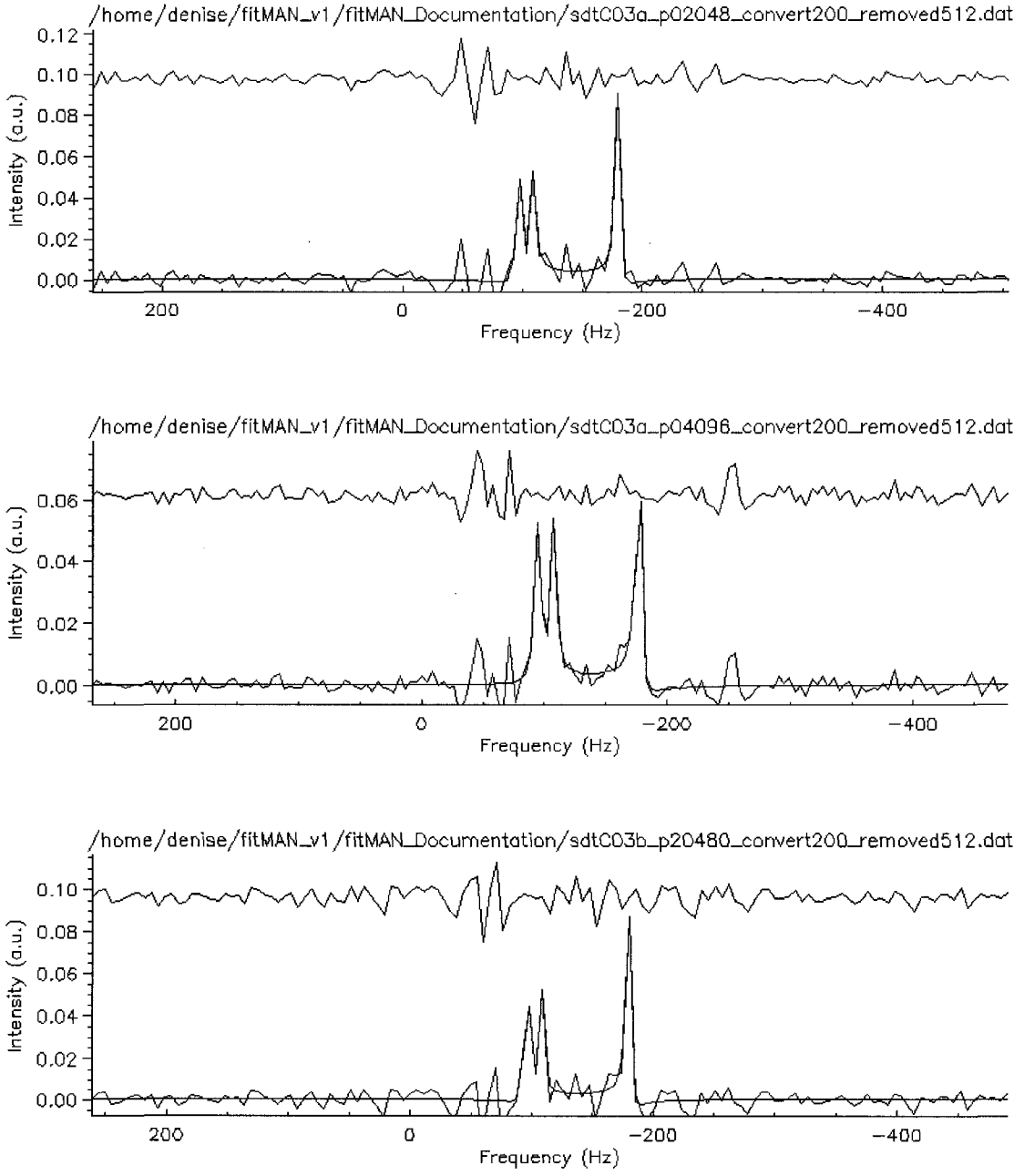






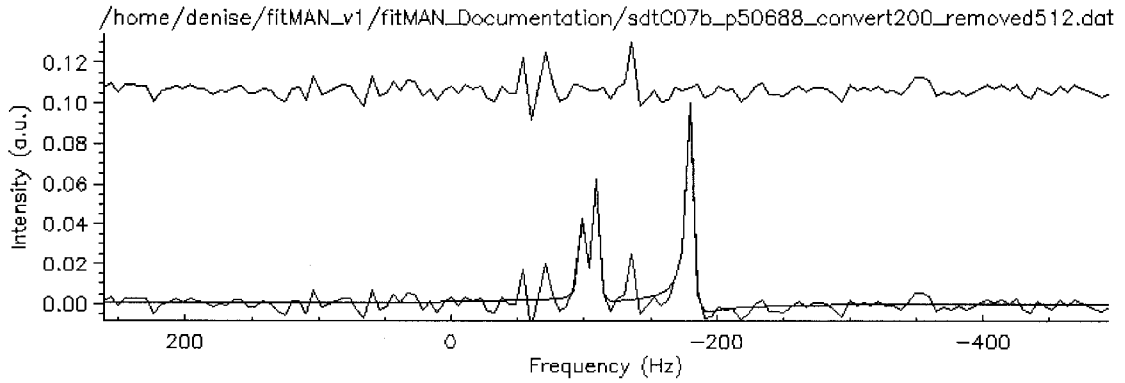
Appendix 4 continued

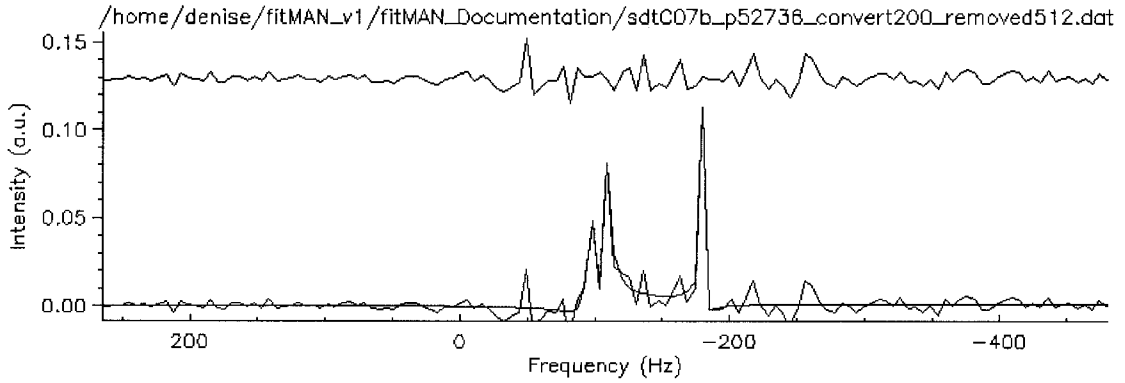
Examples of 3-Peak Manual Fits for the Spectral Profiles

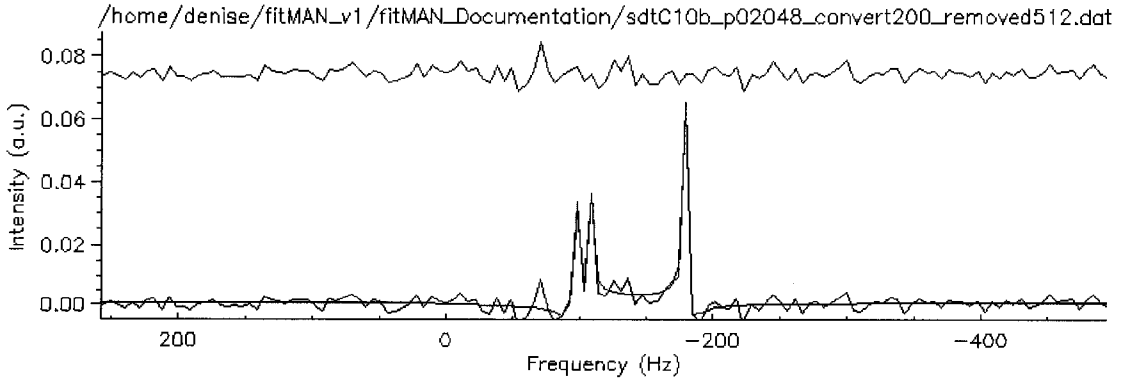


Appendix 4 continued

Examples of 3-Peak Manual Fits for the Spectral Profiles







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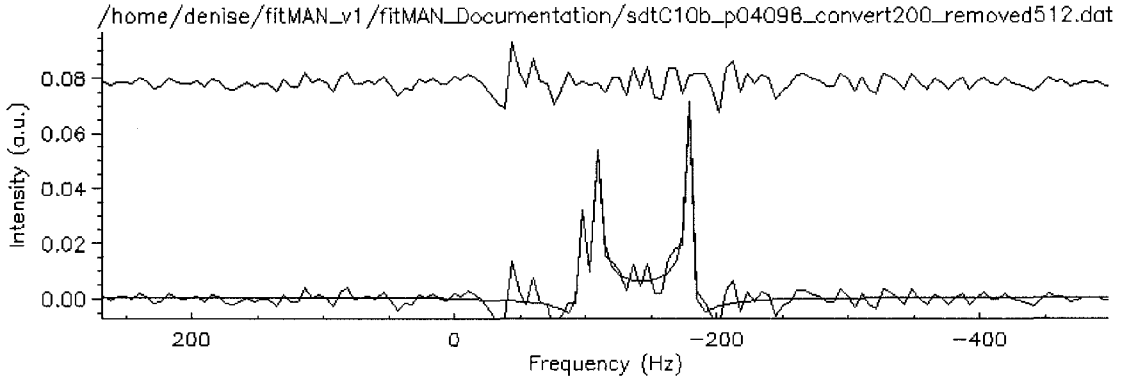
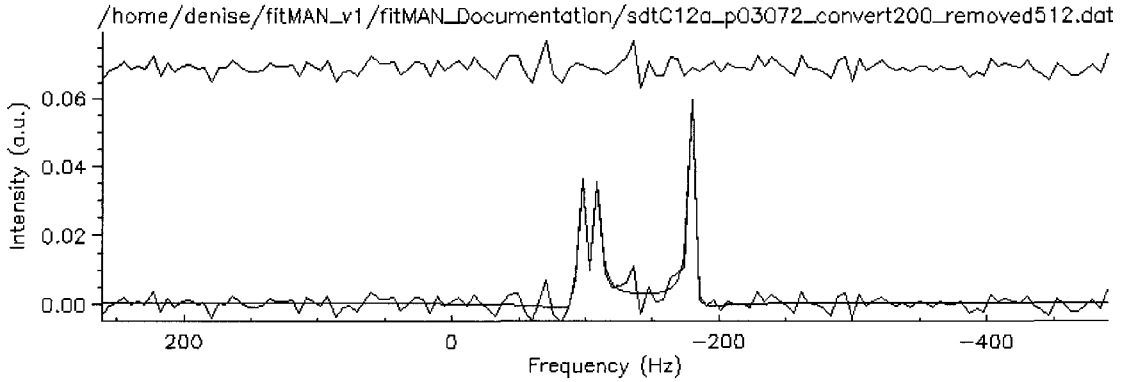
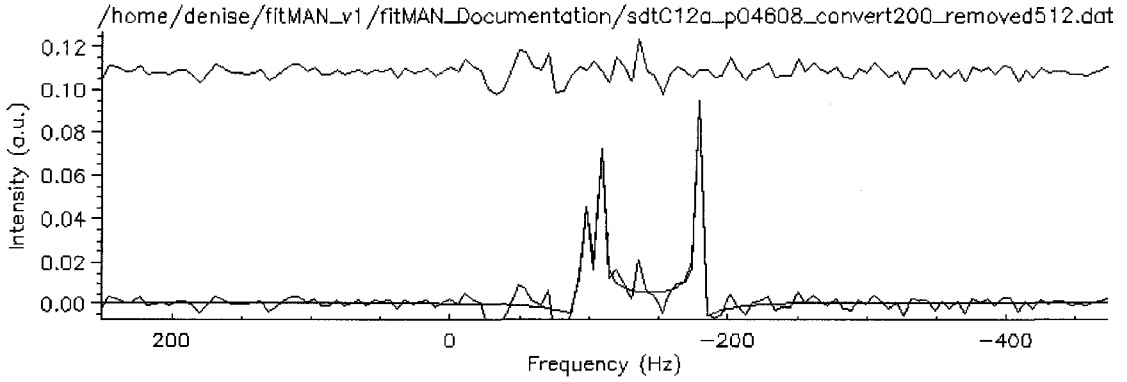
Examples of 3-Peak Manual Fits for the Spectral Profiles







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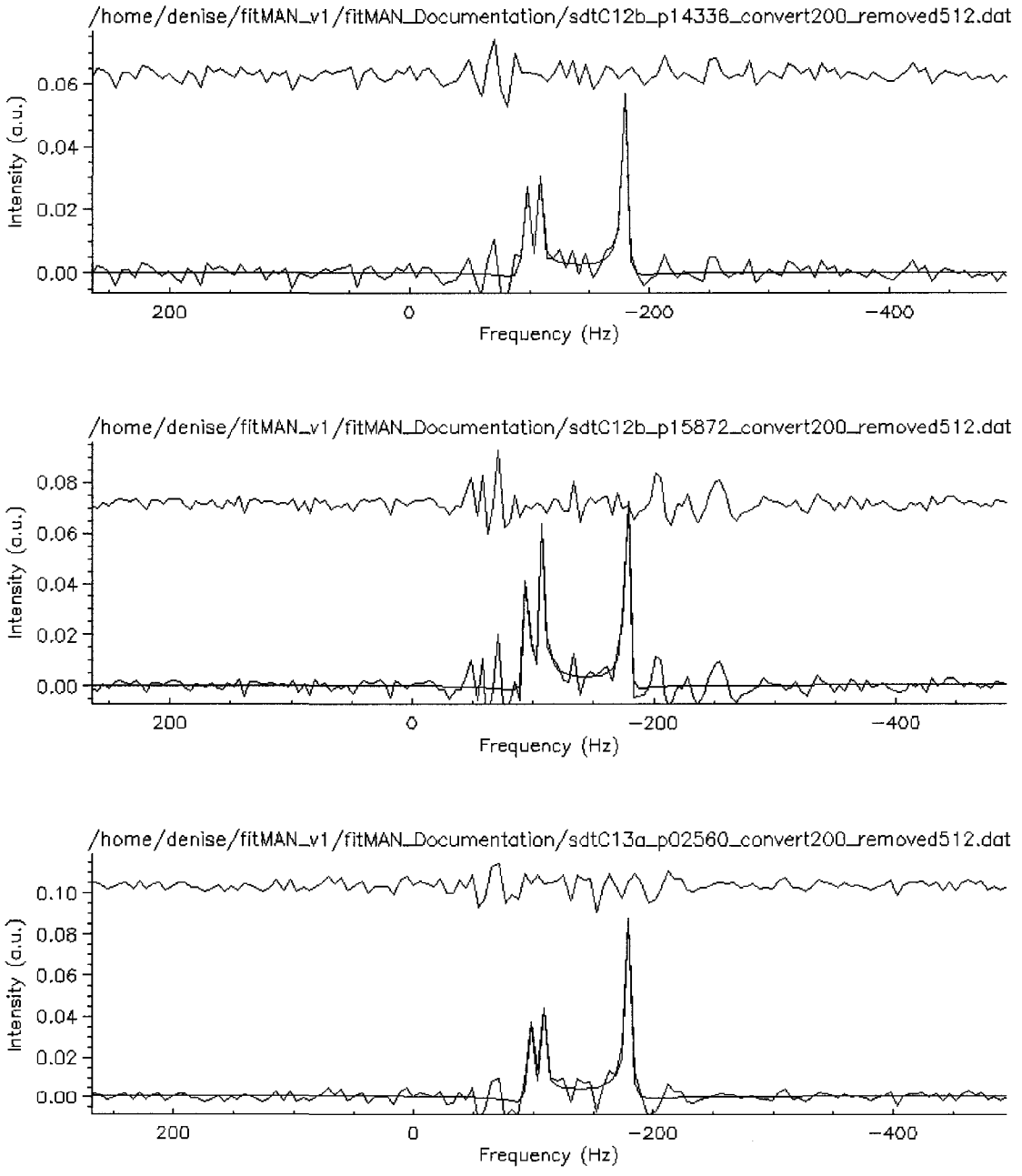
Examples of 3-Peak Manual Fits for the Spectral Profiles



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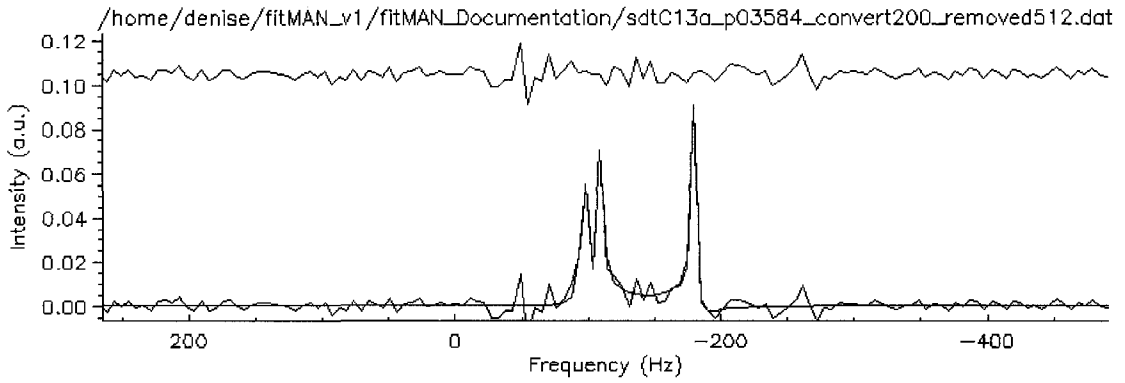

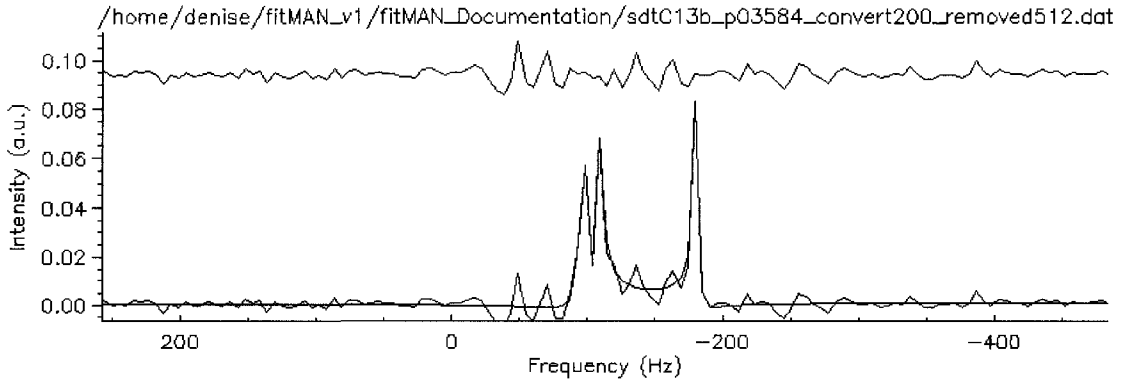

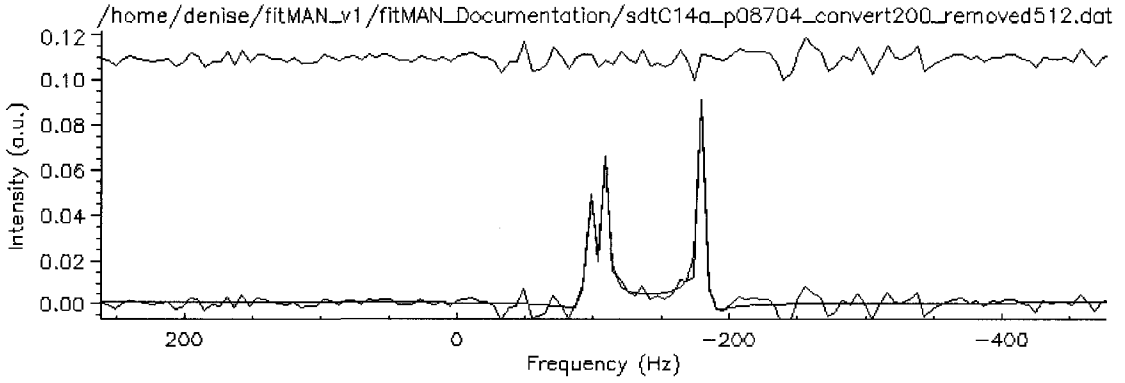

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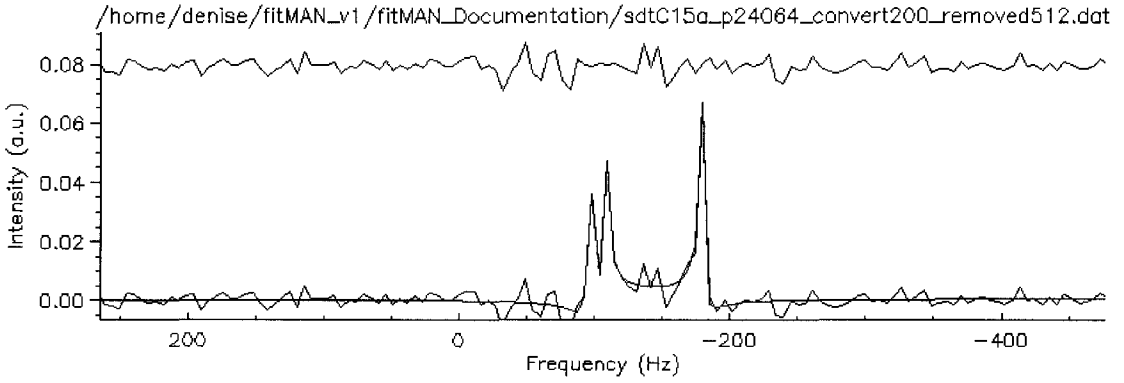

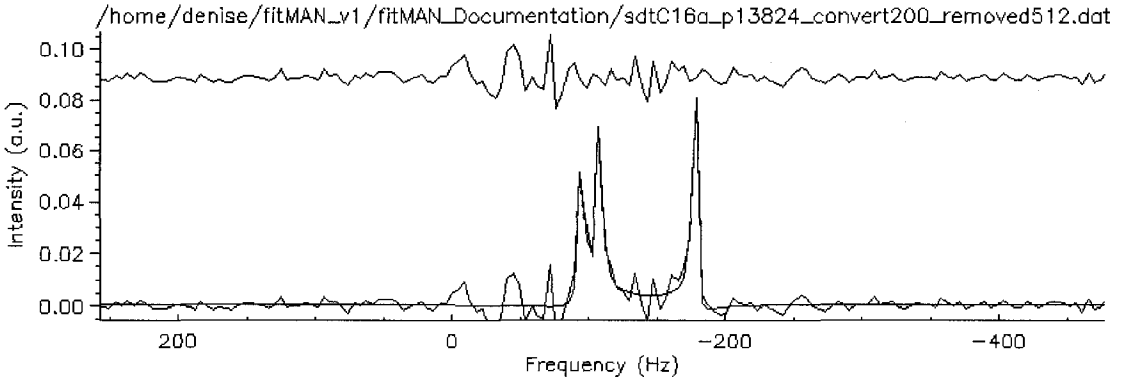

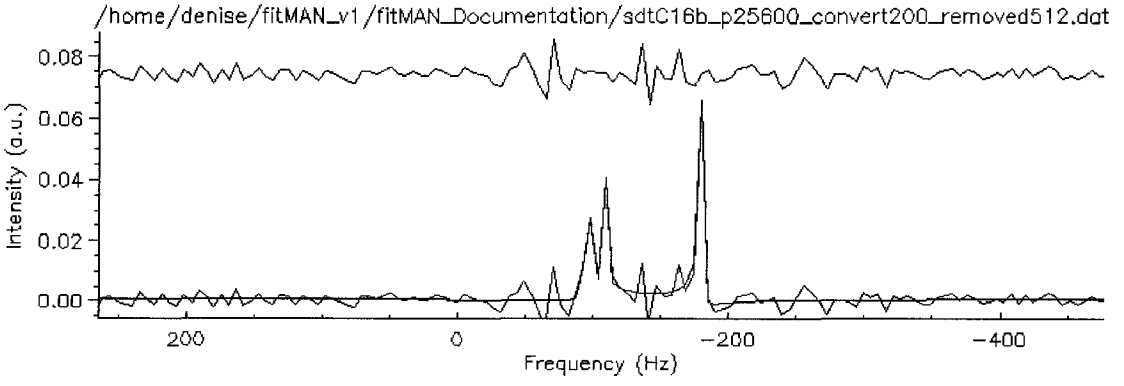

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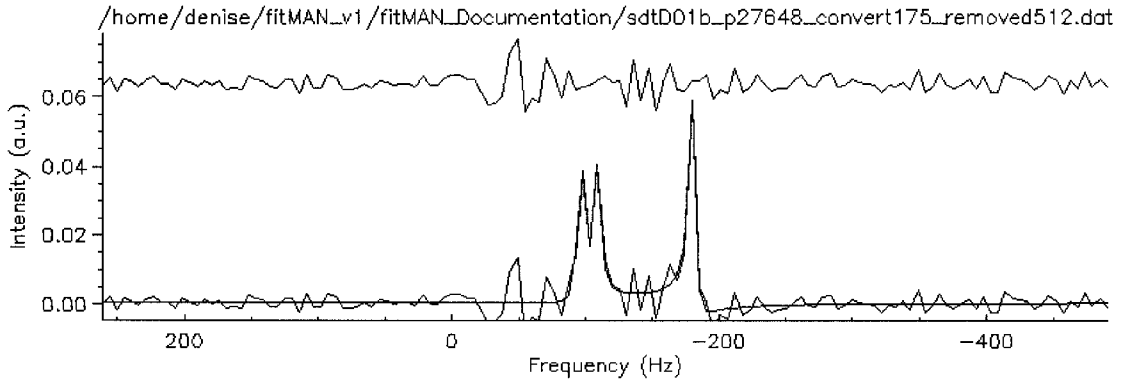

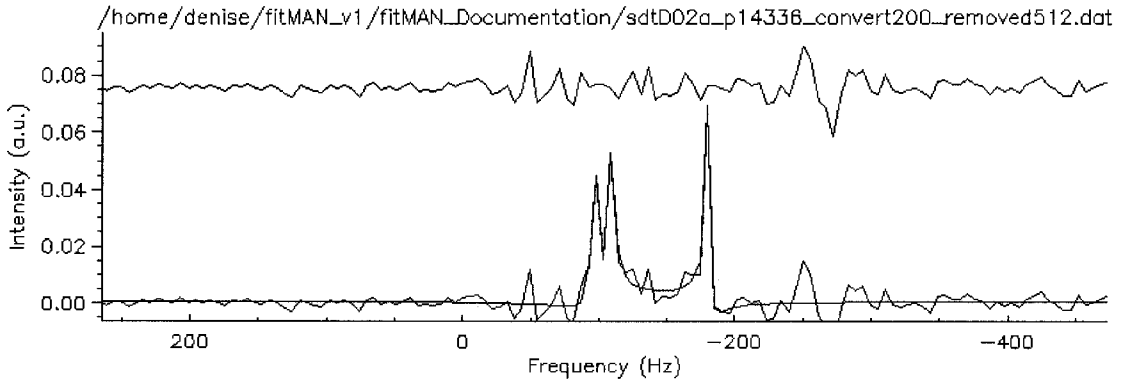

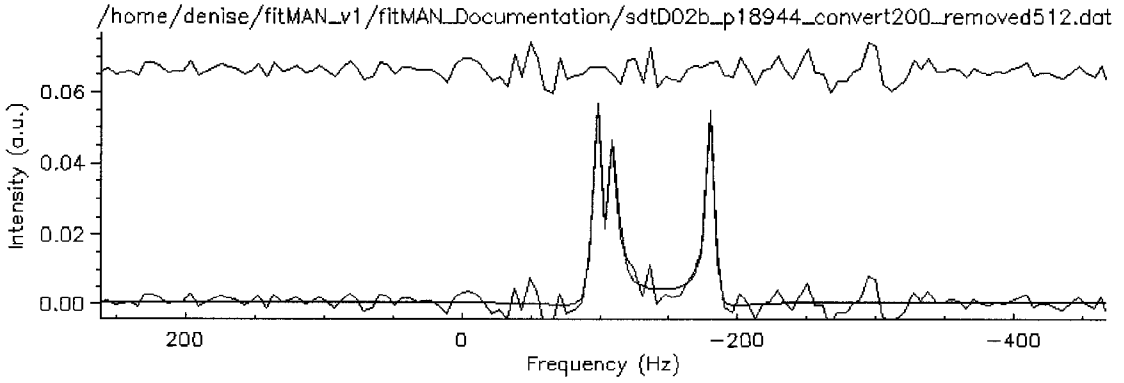

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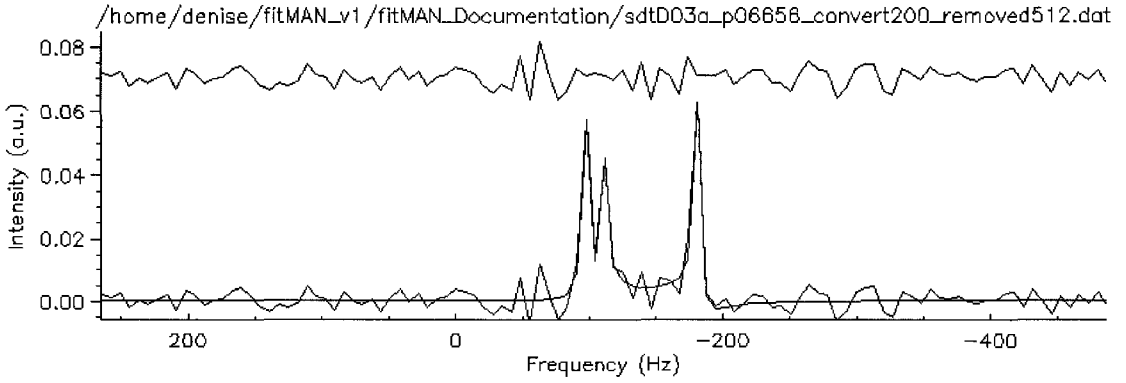
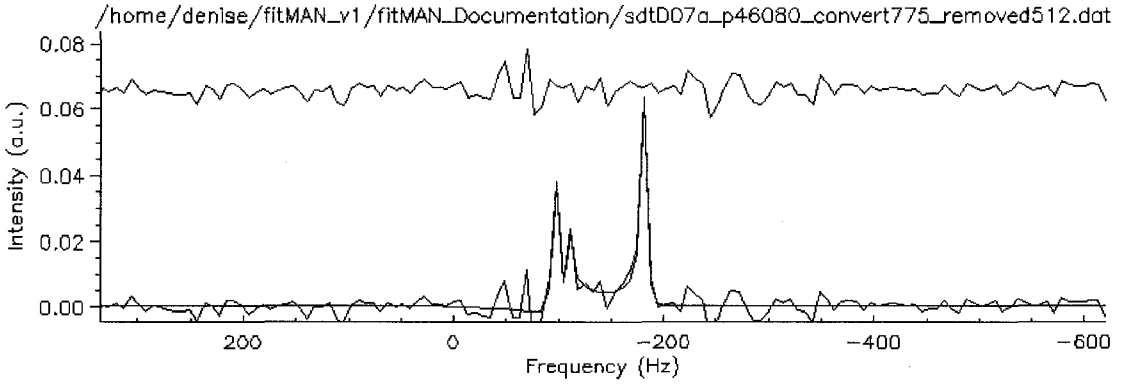
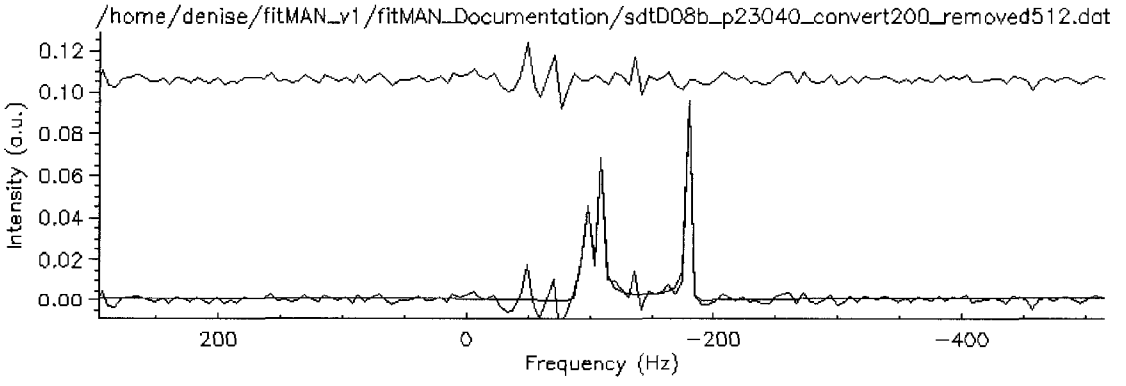
Examples of 3-Peak Manual Fits for the Spectral Profiles

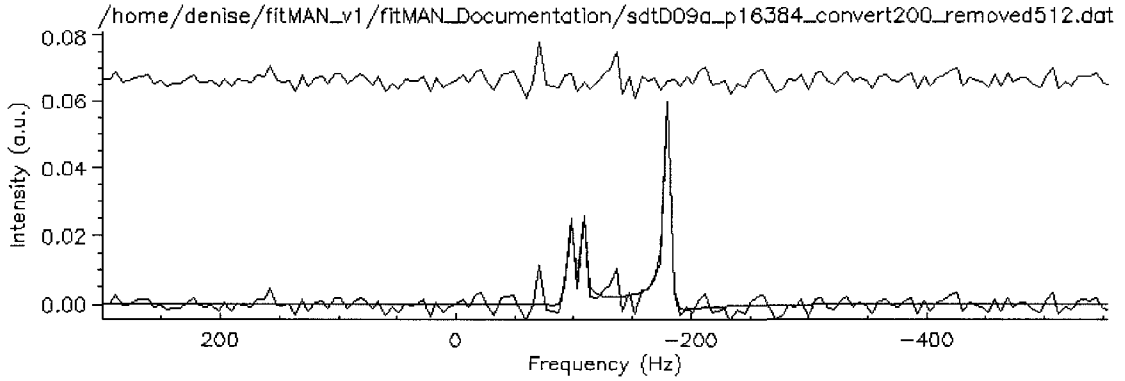


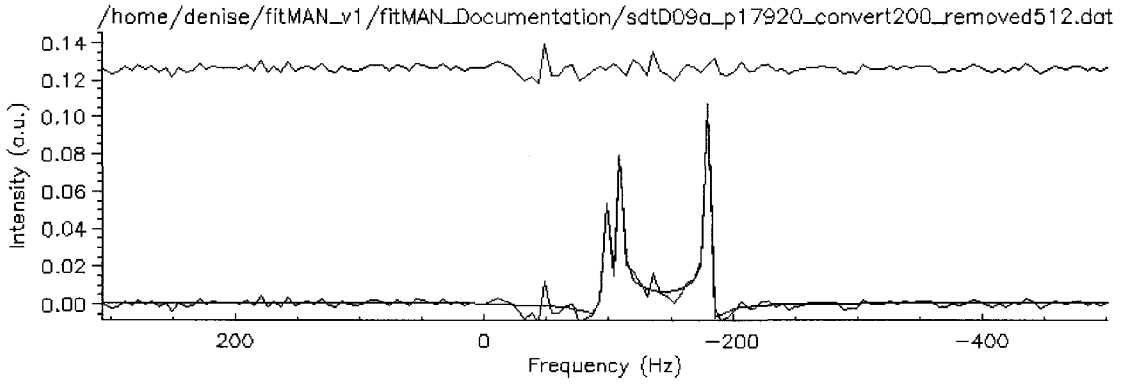


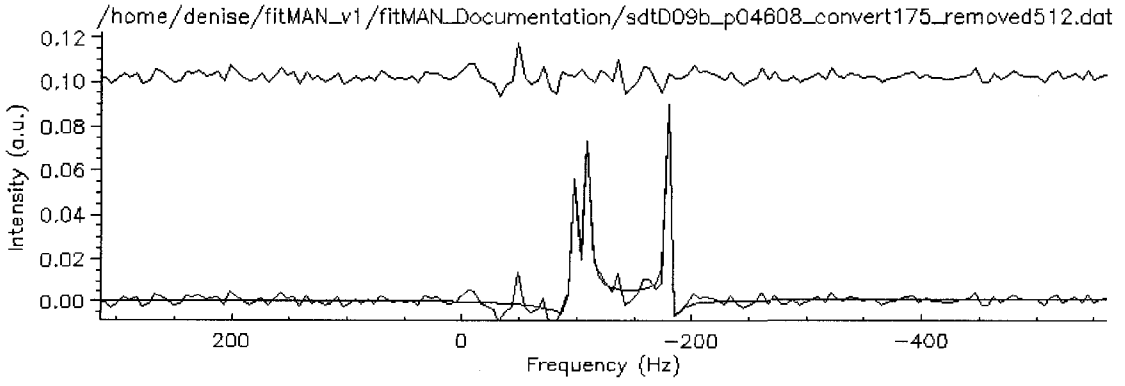


Appendix 4 continued

Examples of 3-Peak Manual Fits for the Spectral Profiles

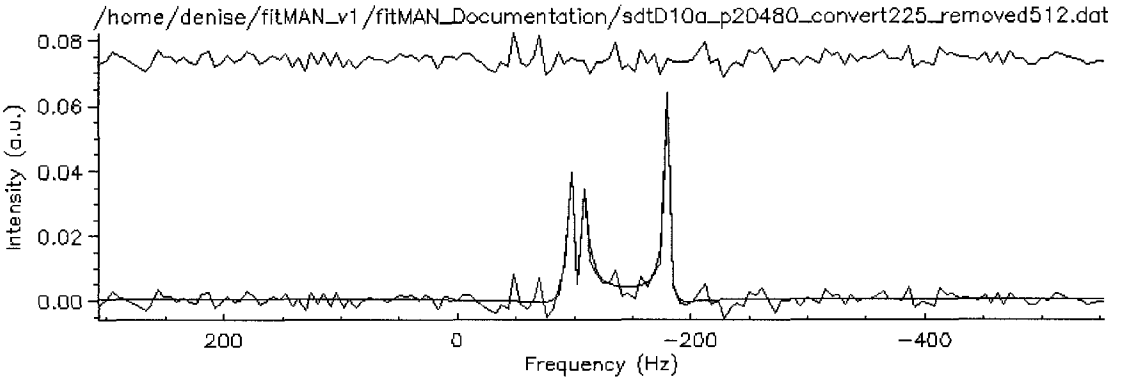


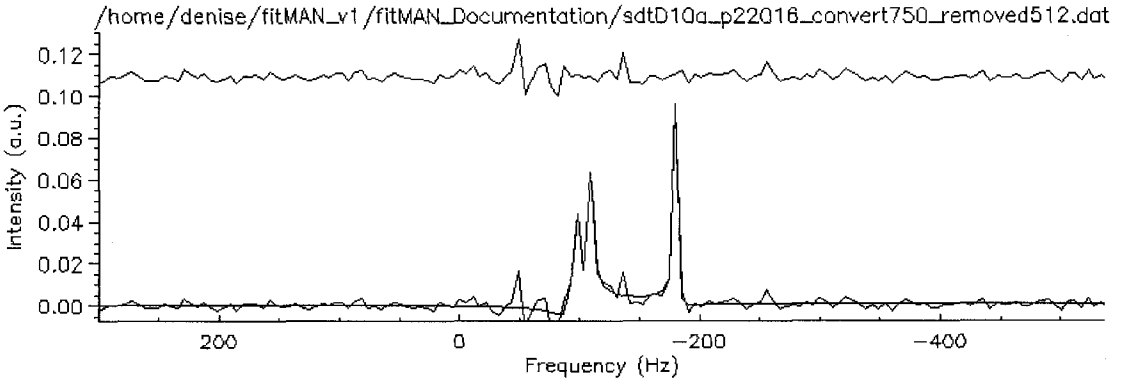


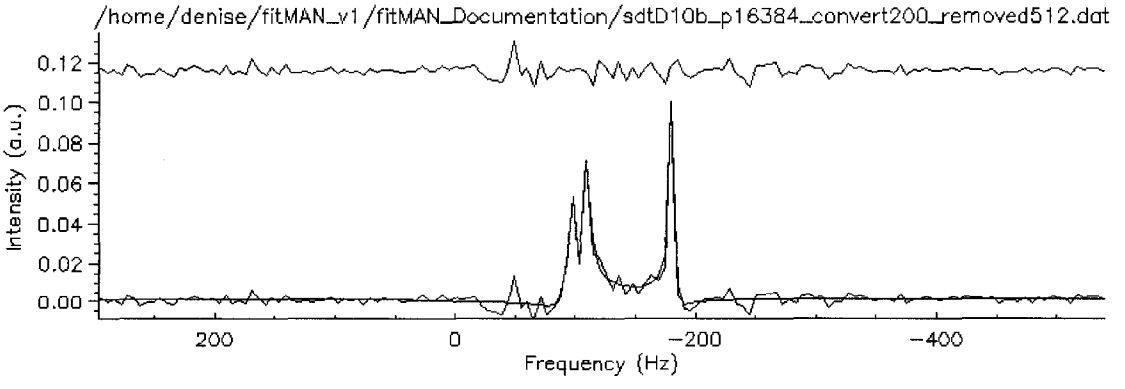


Appendix 4 continued

Examples of 3-Peak Manual Fits for the Spectral Profiles

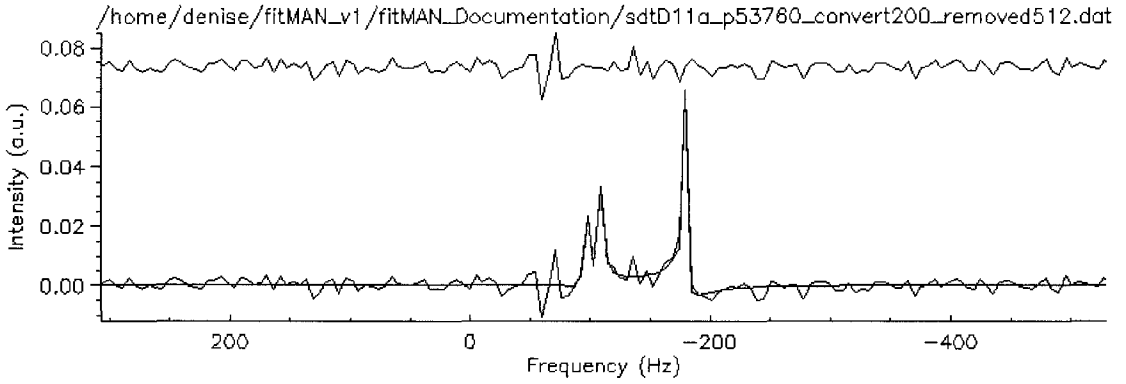


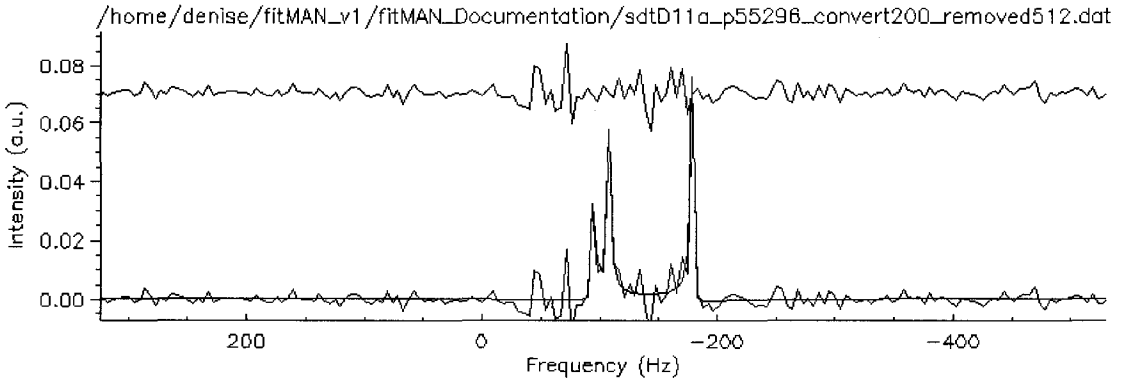


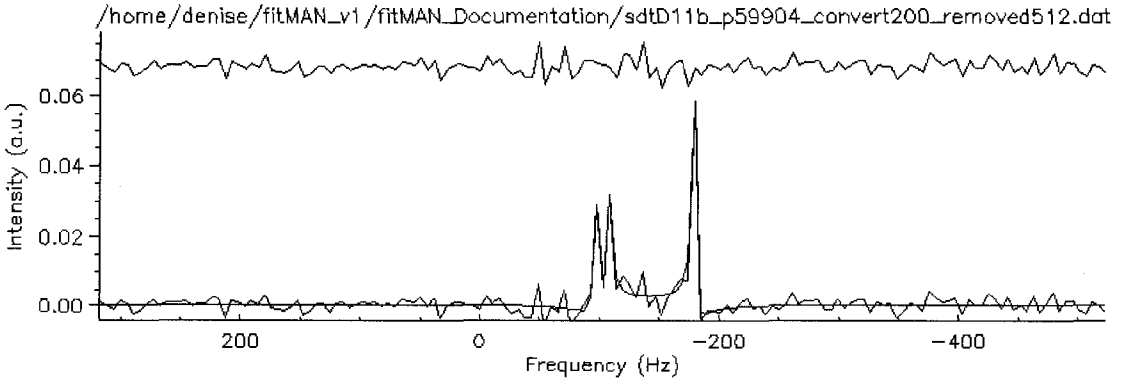


Appendix 4 continued

Examples of 3-Peak Manual Fits for the Spectral Profiles

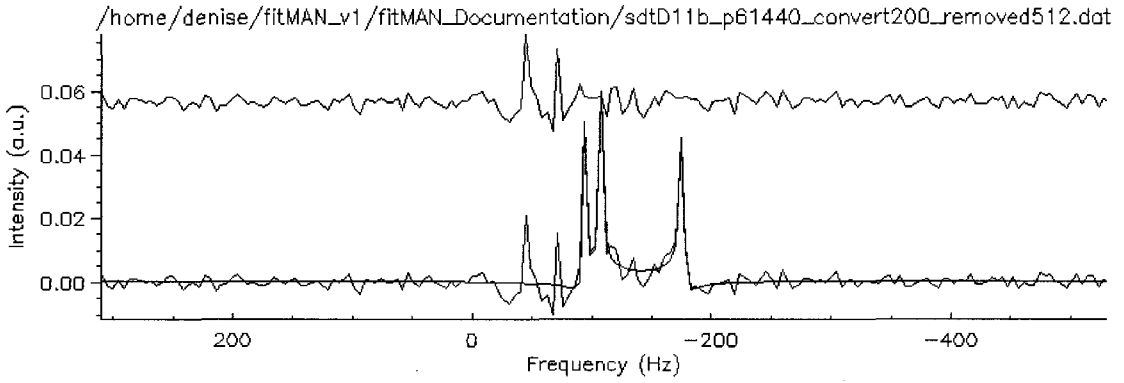


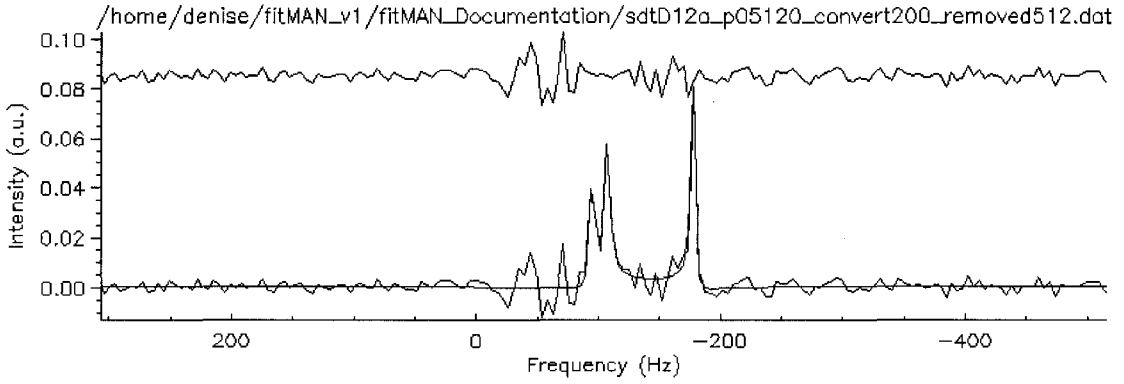


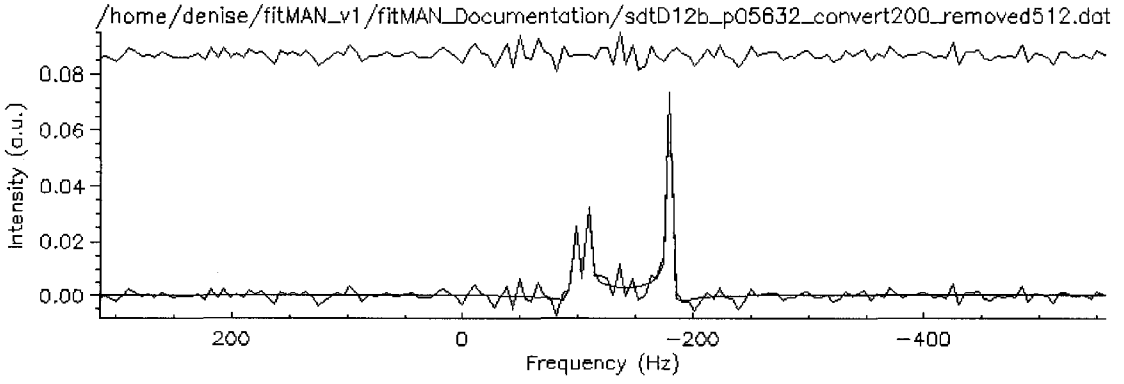


Appendix 4 continued

Examples of 3-Peak Manual Fits for the Spectral Profiles

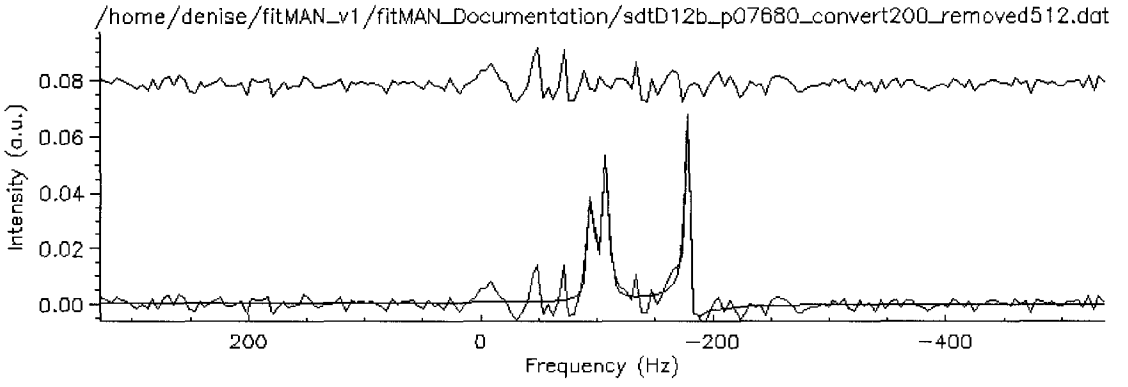


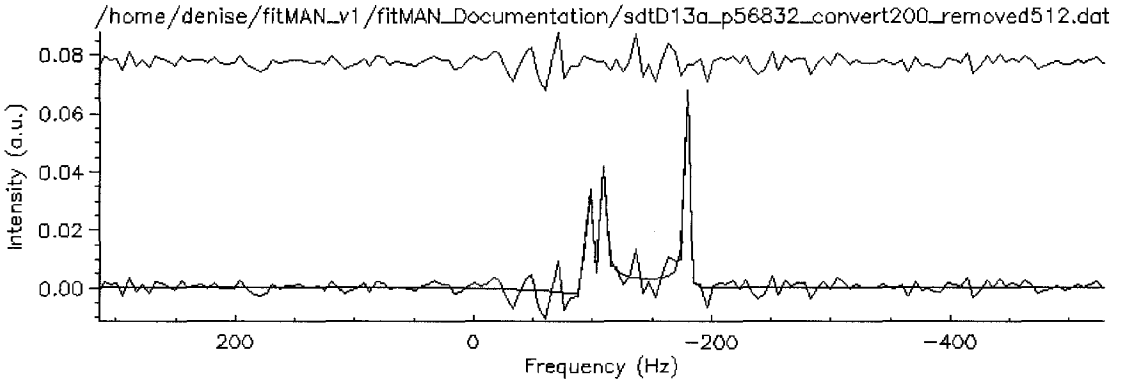


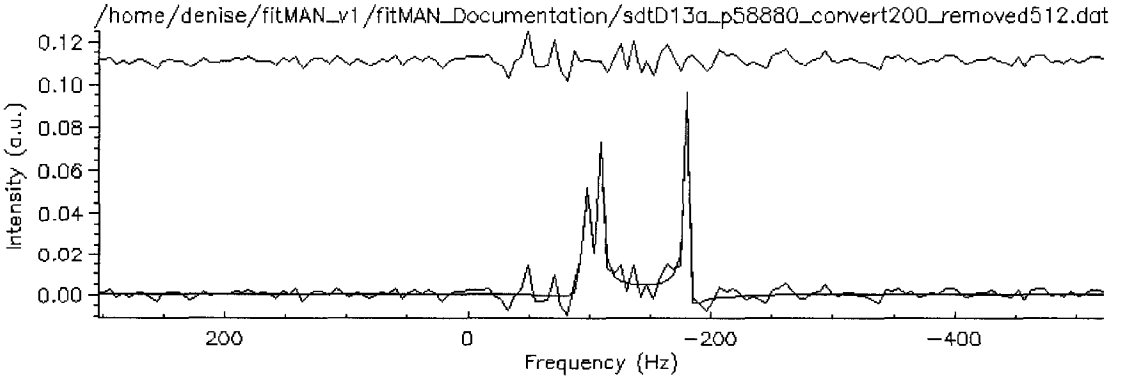


Appendix 4 continued

Examples of 3-Peak Manual Fits for the Spectral Profiles







Appendix 5

Frequency[1] of Good Quality Neurochemical Peaks

Group/ID	Scan time[2] A			Scan time B			Difference scores		
	Cho	tCr	NAA	Cho	tCr	NAA	Cho	tCr	NAA
	Left anterior dorsal prefrontal region								
Control									
c01	x	x	x						
c02	x	x	x	x	x	x	x	x	x
c03	x	x	x	x	x	x	x	x	x
c04	x	x	x	x	x	x	x	x	x
c06	x	x	x	x	x	x	x	x	x
c07	x	x	x	x	x	x	x	x	x
c08	x	x	x	x	x	x	x	x	x
c09	x	x	x	x	x	x	x	x	x
c10				x	x	x			
c11	x	x	x	x	x	x	x	x	x
c12	x	x	x	x	x	x	x	x	x
c13	x	x	x	x	x	x	x	x	x
c14	x	x	x	x	x	x	x	x	x
c15	x	x	x	x	x	x	x	x	x
c16	x	x	x	x	x	x	x	x	x
Total	14	14	14	14	14	14	13	13	13

Appendix 5 continued

Frequency[1] of Good Quality Neurochemical Peaks

Group/ID	Scan time[2] A			Scan time B			Difference scores		
	Cho	tCr	NAA	Cho	tCr	NAA	Cho	tCr	NAA
Depressed									
d01	x	x	x	x	x	x	x	x	x
d02	x	x	x	x	x	x	x	x	x
d03	x	x	x	x	x	x	x	x	x
d05	x	x	x	x	x	x	x	x	x
d06	x	x	x						
d07	x	x	x	x	x	x	x	x	x
d08	x	x	x	x	x	x	x	x	x
d09	x	x	x	x	x	x	x	x	x
d10	x	x	x	x	x	x	x	x	x
d11	x	x	x	x	x	x	x	x	x
d12	x	x	x	x	x	x	x	x	x
d13	x	x	x						
Total	12	12	12	10	10	10	10	10	10
				Pons					
Control									
c01									
c02	x	x	x	x	x	x	x	x	x

Appendix 5 continued

Frequency[1] of Good Quality Neurochemical Peaks

Group/ID	Scan time[2] A			Scan time B			Difference scores		
	Cho	tCr	NAA	Cho	tCr	NAA	Cho	tCr	NAA
c03	x	x	x	x	x	x	x	x	x
c04				x	x	x			
c06	x	x	x	x	x	x	x	x	x
c07	x	x	x	x	x	x	x	x	x
c08	x	x	x						
c09	x	x	x			x			x
c10			x	x	x	x			x
c11	x	x	x			x			x
c12	x	x	x	x	x	x	x	x	x
c13	x	x	x			x			x
c14	x	x	x	x	x	x	x	x	x
c15	x	x	x	x	x	x	x	x	x
c16	x	x	x	x	x	x	x	x	x
Total	12	12	13	10	10	13	8	8	12
Depressed									
d01									
d02	x	x	x	x	x	x	x	x	x
d03	x	x	x	x	x	x	x	x	x

Appendix 5 continued

Frequency[1] of Good Quality Neurochemical Peaks

Group/ID	Scan time[2] A			Scan time B			Difference scores		
	Cho	tCr	NAA	Cho	tCr	NAA	Cho	tCr	NAA
d05	x	x	x	x	x	x	x	x	x
d06	x	x	x	x	x	x	x	x	x
d07	x	x	x	x	x	x	x	x	x
d08	x	x	x	x	x	x	x	x	x
d09	x	x	x	x	x	x	x	x	x
d10	x	x	x	x	x	x	x	x	x
d11	x	x	x	x	x	x	x	x	x
d12	x	x	x	x	x	x	x	x	x
d13	x	x	x						
Total	11	11	11	10	10	10	10	10	10

Note. [1] Frequency: x represents data of good quality retained for statistical analyses, and empty spaces represent data that was not retained. [2] Scan time A was Day 1 at 12:00; Scan time B was Day 2 at 12:00; Difference scores refer to the difference in concentration levels between Scan time A and Scan time B.

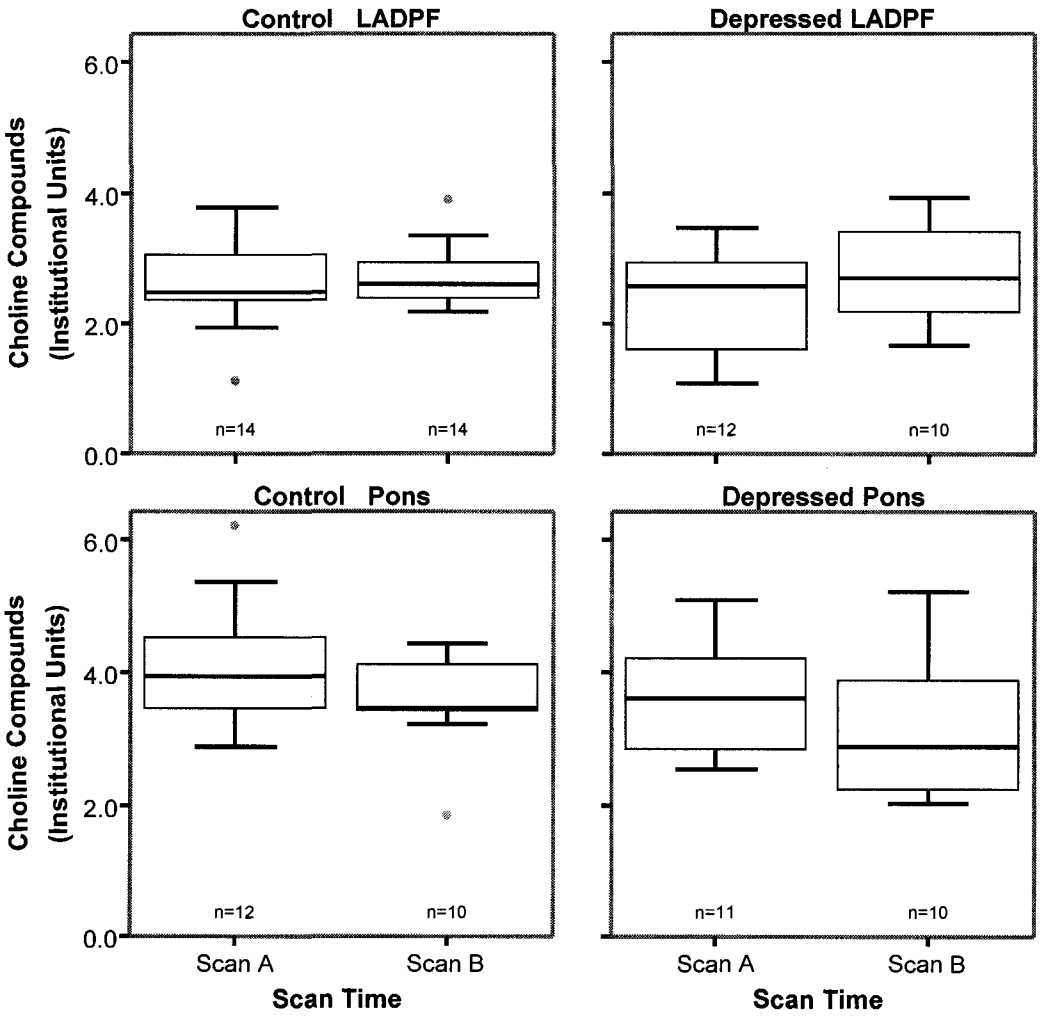
Appendix 6

Descriptive Statistics and Preliminary Analyses for Age (Month) at Time of Brain Scan

	Descriptive statistics		
	M (month)	*SD*	*n*
Control	292.92	44.23	15
Depressed	300.15	41.24	12
	Shapiro-Wilk test for normality of distribution		
	Statistic	*p*	*n*
Control	.911	.142	15
Depressed	.892	.124	12
	Levene test for equality of error variance		
	Statistic	*p*	*df*
Control vs. Depressed	.042	.839	25

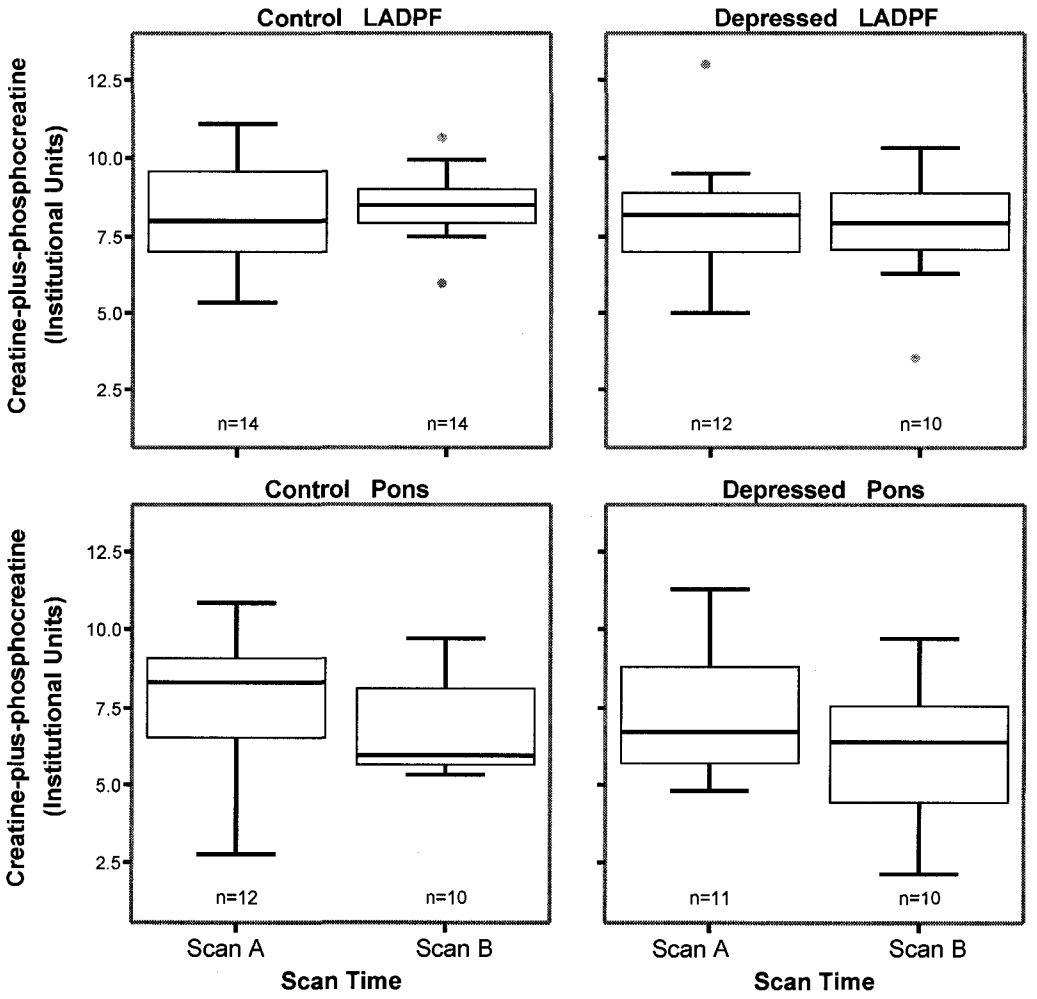
Appendix 7

Box-plots for Choline Compounds As a Function of Scan Time, Group and Volume of Interest



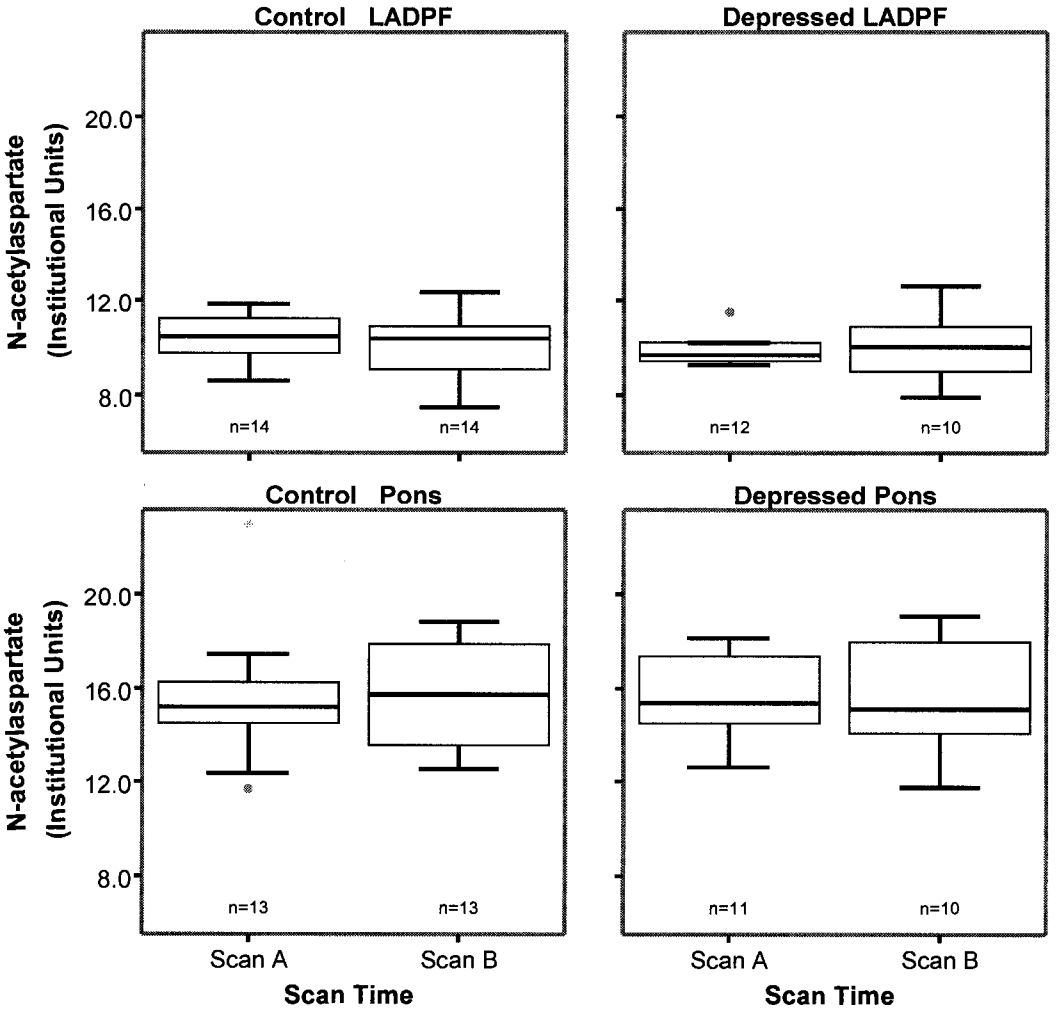
Appendix 8

Box-plots for Total Creatine-plus-phosphocreatine As a Function of Scan Time, Group and Volume of Interest



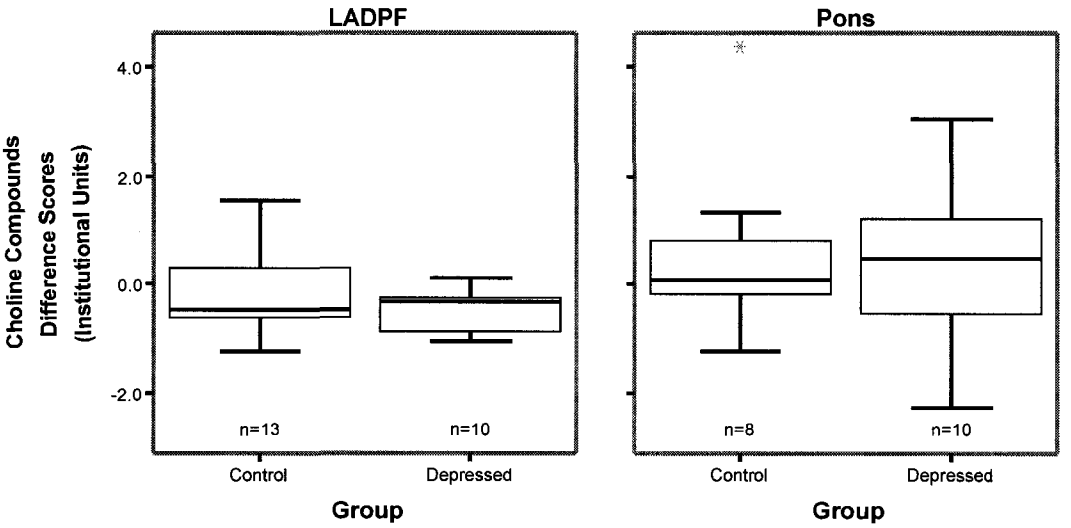
Appendix 9

Box-plots for *N*-acetylaspartate As a Function of Scan Time, Group and Volume of Interest



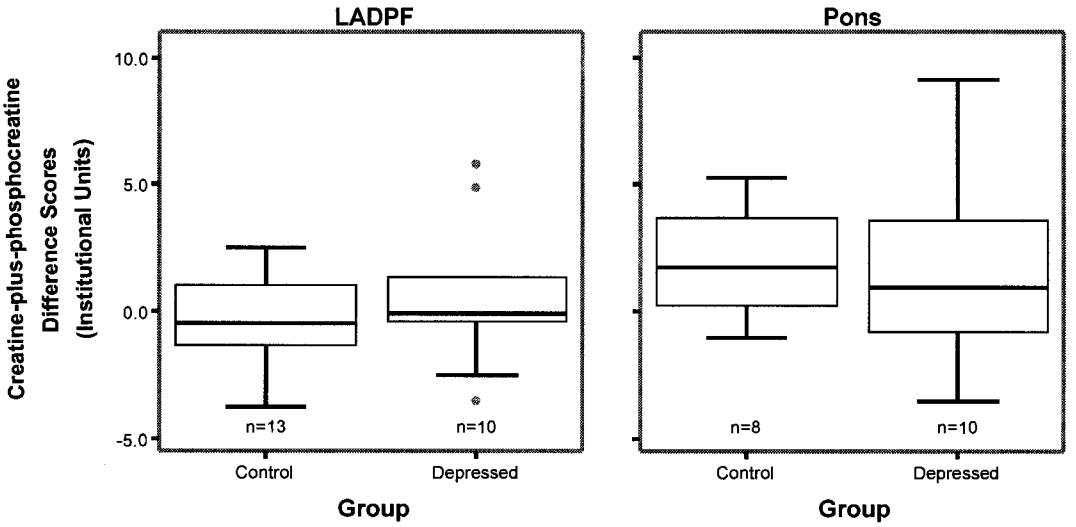
Appendix 10

Box-plots for Choline Compounds Difference Scores As a Function of Group and Volume of Interest



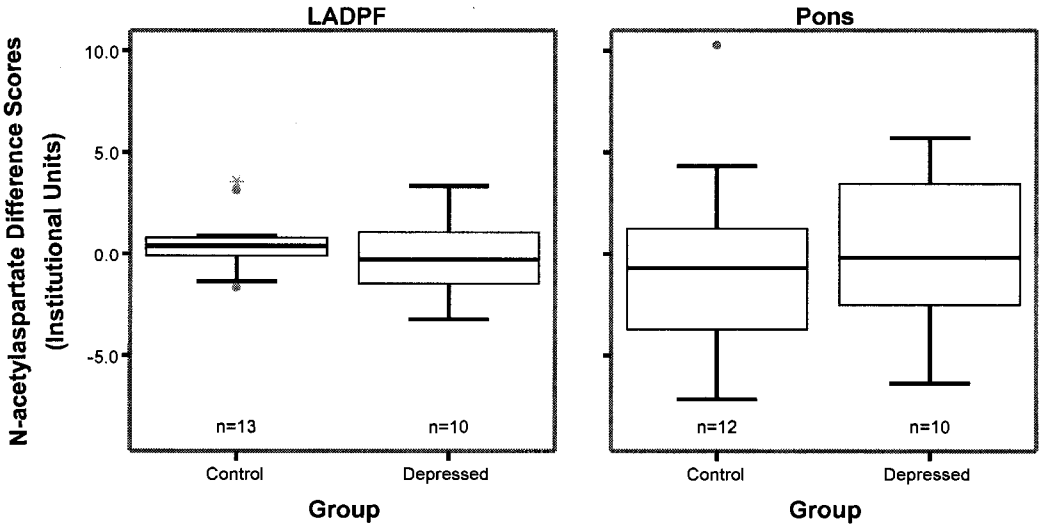
Appendix 11

Box-plots for Creatine-plus-phosphocreatine Difference Scores As a Function of Group and Volume of Interest



Appendix 12

Box-plots for *N*-acetylaspartate Difference Scores As a Function of Group and Volume of Interest



Appendix 13

Means, Standard Deviations (SD) and Sample Sizes for Neurochemical Raw and Difference Concentrations (Institutional Units) Analyzed with ANOVAs and *t* Tests As a Function of Brain Volume of Interest (VOI), Scan Time and Group

VOI	Scan time[1]	Neurochemical	Control group			Depressed group		
			M	*SD*	*n*	*M*	*SD*	*n*
Pons	A	Cho:H_2O_A	4.12	1.02	8	3.53	0.98	10
		tCr:H_2O_A	8.86	1.02	8	7.56	2.46	10
		NAA:H_2O_A	15.32	2.91	12	15.80	1.93	10
	B	Cho:H_2O_B	3.55	0.80	8	3.14	1.04	10
		tCr:H_2O_B	6.97	1.57	8	6.12	2.15	10
		NAA:H_2O_B	15.78	2.25	12	15.65	2.43	10
	D	Cho:H_2O_D	0.57	1.69	8	0.39	1.56	10
		tCr:H_2O_D	1.89	2.17	8	1.44	3.69	10
		NAA:H_2O_D	-0.46	4.67	12	0.15	3.87	10
LADPF[2]	A	Cho:H_2O_A	2.58	0.68	13	2.38	0.75	10
		tCr:H_2O_A	8.22	1.77	13	8.20	2.08	10
		NAA:H_2O_A	10.26	0.97	13	9.83	0.68	10
	B	Cho:H_2O_B	2.76	0.49	13	2.80	0.76	10
		tCr:H_2O_B	8.53	1.14	13	7.63	1.83	10
		NAA:H_2O_B	9.79	1.28	13	9.99	1.42	10
	D	Cho:H_2O_D	-0.17	0.74	13	-0.42	0.40	10

Appendix 13 continued

Means, Standard Deviations (SD) and Sample Sizes for Neurochemical Raw and Difference Concentrations (Institutional Units) Analyzed with ANOVAs and *t* Tests As a Function of Brain Volume of Interest (VOI), Scan Time and Group

VOI	Scan time[1]	Neurochemical	Control group			Depressed group		
			M	*SD*	*n*	*M*	*SD*	*n*
		tCr:H_2O_D	-0.31	2.06	13	0.57	2.88	10
		NAA:H_2O_D	0.47	1.49	13	-0.16	1.91	10

Note. [1] Scan time A was Day 1 at 12:00; Scan time B was Day 2 at 12:00; D refers to the difference scores between Scan time A and Scan time B. [2] Left anterior dorsal prefrontal.

Appendix 14

Shapiro-Wilk Test for Normality of Distribution for Neurochemical Concentration Raw and Difference Scores Analyzed with ANOVAs and *t* Tests As a Function of Brain Volume of Interest (VOI) and Scan Time

Group	VOI	Scan time[1]	Neurochemical	Shapiro-Wilk test		
				Statistic	*p*	*n*
Control	Pons	A	Cho:H_2O_A	.913	.234	12
			tCr:H_2O_A	.933	.416	12
			NAA:H_2O_A	.875	.061	13
		B	Cho:H_2O_B	.852	.061	10
			tCr:H_2O_B	.826 *	.030	10
			NAA:H_2O_B	.897	.122	13
		D	Cho:H_2O_D	.784 *	.019	8
			tCr:H_2O_D	.969	.891	8
			NAA:H_2O_D	.947	.594	12
	LADPF[2]	A	Cho:H_2O_A	.964	.781	14
			tCr:H_2O_A	.963	.767	14
			NAA:H_2O_A	.941	.430	14
		B	Cho:H_2O_B	.907	.141	14
			tCr:H_2O_B	.966	.813	14
			NAA:H_2O_B	.945	.489	14
		D	Cho:H_2O_D	.925	.289	13
			tCr:H_2O_D	.946	.535	13
			NAA:H_2O_D	.894	.111	13

Appendix 14 continued

Shapiro-Wilk Test for Normality of Distribution for Neurochemical Concentration Raw and Difference Scores Analyzed with ANOVAs and *t* Tests As a Function of Brain Volume of Interest (VOI) and Scan Time

Group	VOI	Scan time[1]	Neurochemical	Shapiro-Wilk test		
				Statistic	*p*	*n*
Depressed	Pons	A	Cho:H_2O_A	.893	.152	11
			tCr:H_2O_A	.893	.150	11
			NAA:H_2O_A	.929	.405	11
		B	Cho:H_2O_B	.917	.334	10
			tCr:H_2O_B	.982	.975	10
			NAA:H_2O_B	.936	.511	10
		D	Cho:H_2O_D	.994	.999	10
			tCr:H_2O_D	.954	.710	10
			NAA:H_2O_D	.974	.926	10
	LADPF	A	Cho:H_2O_A	.919	.279	12
			tCr:H_2O_A	.924	.320	12
			NAA:H_2O_A	.832 *	.022	12
		B	Cho:H_2O_B	.965	.840	10
			tCr:H_2O_B	.928	.433	10
			NAA:H_2O_B	.973	.915	10
		D	Cho:H_2O_D	.927	.416	10
			tCr:H_2O_D	.917	.336	10
			NAA:H_2O_D	.980	.965	10

Appendix 14 continued

Shapiro-Wilk Test for Normality of Distribution for Neurochemical Concentration Raw and Difference Scores Analyzed with ANOVAs and *t* Tests As a Function of Brain Volume of Interest (VOI) and Scan Time

Group	VOI	Scan time[1]	Neurochemical	Shapiro-Wilk test		
				Statistic	*p*	*n*
Both	Pons	A	Cho:H_2O_A	.950	.297	23
			tCr:H_2O_A	.980	.914	23
			NAA:H_2O_A	.920	.059	24
		B	Cho:H_2O_B	.967	.695	20
			tCr:H_2O_B	.980	.914	20
			NAA:H_2O_B	.931	.117	23
		D	Cho:H_2O_D	.950	.425	18
			tCr:H_2O_D	.969	.776	18
			NAA:H_2O_D	.985	.986	22
	LADPF	A	Cho:H_2O_A	.951	.241	26
			tCr:H_2O_A	.969	.590	26
			NAA:H_2O_A	.955	.311	26
		B	Cho:H_2O_B	.955	.352	24
			tCr:H_2O_B	.923	.067	24
			NAA:H_2O_B	.966	.580	24
		D	Cho:H_2O_D	.930	.108	23
			tCr:H_2O_D	.958	.422	23
			NAA:H_2O_D	.953	.340	23

Appendix 14 continued

Shapiro-Wilk Test for Normality of Distribution for Neurochemical Concentration Raw and Difference Scores Analyzed with ANOVAs and *t* Tests As a Function of Brain Volume of Interest (VOI) and Scan Time

Group	VOI	Scan time[1]	Neurochemical	Shapiro-Wilk test		
				Statistic	*p*	*n*

Note. [1] Scan time A was Day 1 at 12:00; Scan time B was Day 2 at 12:00; D refers to the difference scores between Scan time A and Scan time B. [2] Left anterior dorsal prefrontal.

* $p < .05$.

Appendix 15

Levene Test of Equality of Error Variances for Neurochemical Concentrations Raw and Difference Scores Analyzed with ANOVAs and *t* Tests As a Function of Brain Volume of Interest (VOI) and Scan Time

Group	VOI	Scan time[1]	Neurochemical	Levene test			
				Statistic	*p*	*df1*	*df2*
Control	Pons	A	Cho:H_2O_A	0.082	.778	1	16
versus			tCr:H_2O_A	6.223 *	.024	1	16
Depressed			NAA:H_2O_A	0.084	.775	1	16
		B	Cho:H_2O_B	1.476	.242	1	16
			tCr:H_2O_B	0.459	.508	1	16
			NAA:H_2O_B	0.005	.942	1	16
		D	Cho:H_2O_D	0.018	.895	1	16
			tCr:H_2O_D	1.577	.227	1	16
			NAA:H_2O_D	0.069	.796	1	20
	LADPF[2]	A	Cho:H_2O_A	0.318	.579	1	21
			tCr:H_2O_A	0.063	.804	1	21
			NAA:H_2O_A	2.733	.113	1	21
		B	Cho:H_2O_B	3.070	.094	1	21
			tCr:H_2O_B	1.228	.280	1	21
			NAA:H_2O_B	0.001	.971	1	21
		D	Cho:H_2O_D	3.084	.094	1	21

Appendix 15 continued

Levene Test of Equality of Error Variances for Neurochemical Concentrations Raw and Difference Scores Analyzed with ANOVAs and *t* Tests As a Function of Brain Volume of Interest (VOI) and Scan Time

Group	VOI	Scan time[1]	Neurochemical	Levene test			
				Statistic	*p*	*df1*	*df2*
			tCr:H_2O_D	0.558	.464	1	21
			NAA:H_2O_D	1.411	.248	1	21

Note. [1] Scan time A was Day 1 at 12:00; Scan time B was Day 2 at 12:00; D refers to the difference scores between Scan time A and Scan time B. [2] Left anterior dorsal prefrontal.

* $p < .05$.

Appendix 16

Shapiro-Wilk Test for Normality of Distribution for Creatine-plus-phosphocreatine Raw and Difference Values Used for Follow-up Tests

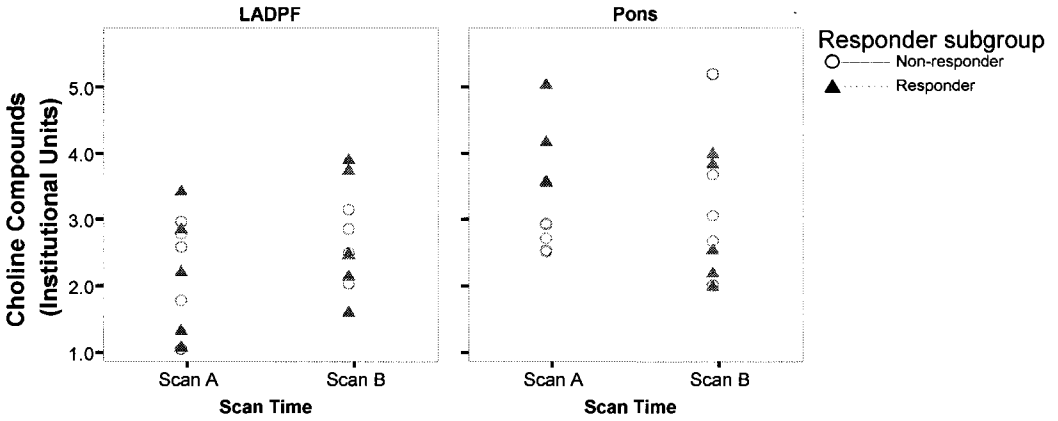
Group	Brain region	Scan time[1]	Neurochemical	Shapiro-Wilk test		
				Statistic	*p*	*n*
Both	Pons	A	tCr:H_2O A	.956	.519	18
		B	tCr:H_2O_B	.976	.903	18
		D	tCr:H_2O_D	.969	.776	18

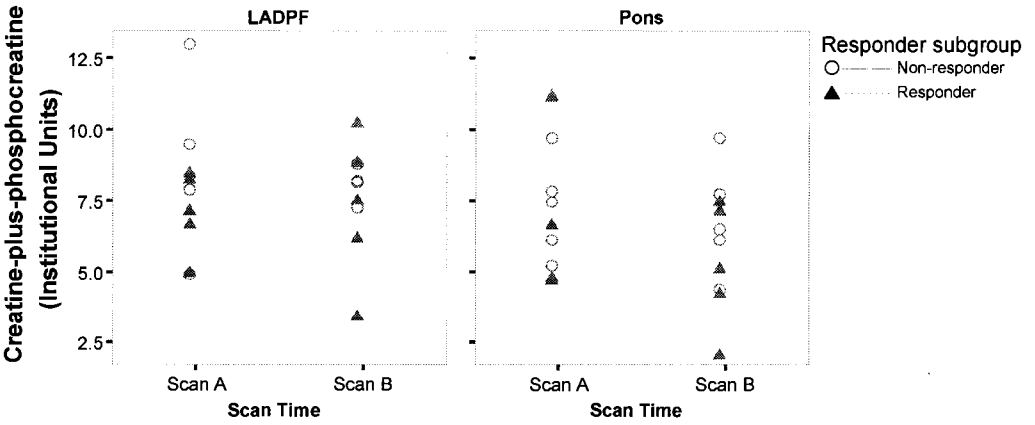
Note. [1] Scan time A was Day 1 at 12:00; Scan time B was Day 2 at 12:00; D refers to the difference scores between Scan time A and Scan time B.

* $p < .05$.

Appendix 17

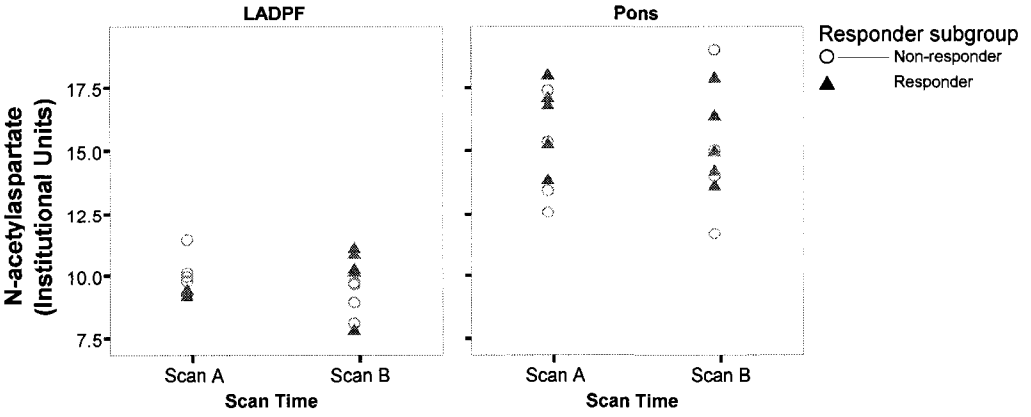
Neurochemical Data for the Responder and Non-responder Subgroups





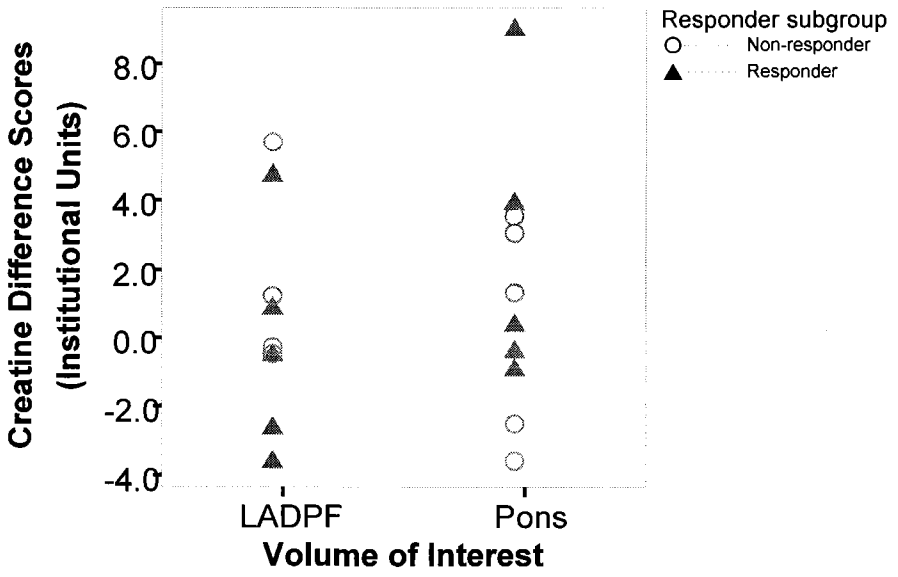
Appendix 17 continued

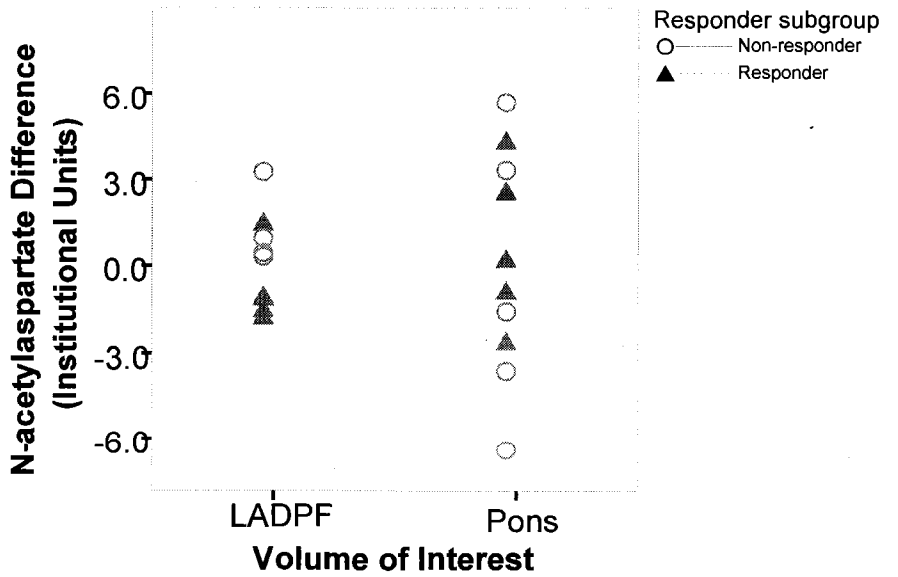
Neurochemical Data for the Responder and Non-responder Subgroups



Appendix 17 continued

Neurochemical Data for the Responder and Non-responder Subgroups





Appendix 18

Means, Standard Deviations (SD) and Sample Sizes for Choline Compounds Acquired in the Pons As a Function of Scan Time and Group (Subgroup)

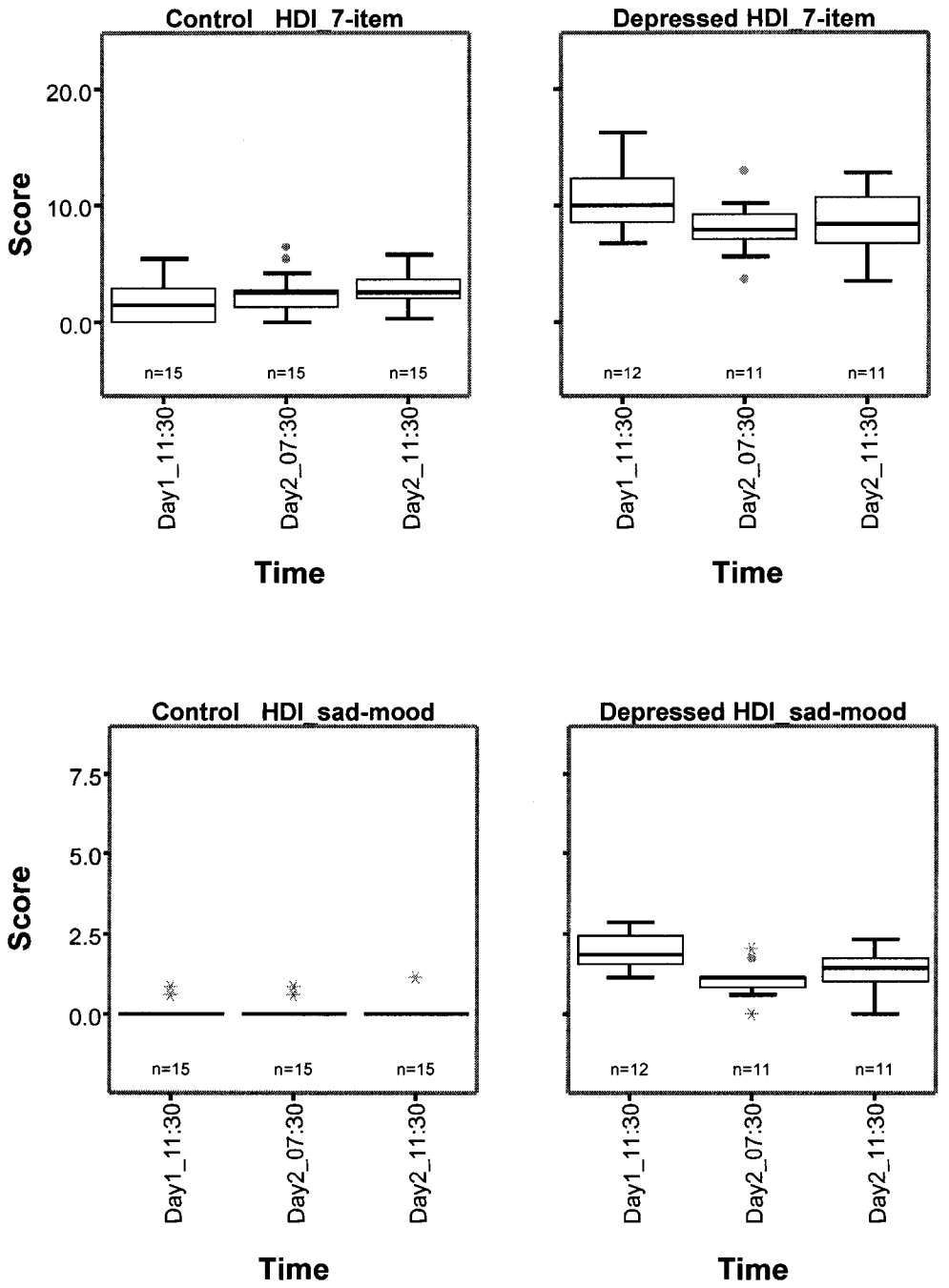
	Scan time A			Scan time B			Difference scores[1]		
Group (subgroup)	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
Control	4.09	0.95	12	3.51	0.72	10	0.57	1.69	8
Depressed									
(Responders)	4.31	0.74	5	2.94	0.94	5	1.37	1.28	5
(Non-responders)	2.74**	0.21	5	3.34	1.21	5	-0.60*	1.18	5

Note. [1] Difference scores refer to concentration values at Scan time A minus values at Scan time B.

* $p < .05$; ** $p < .01$.

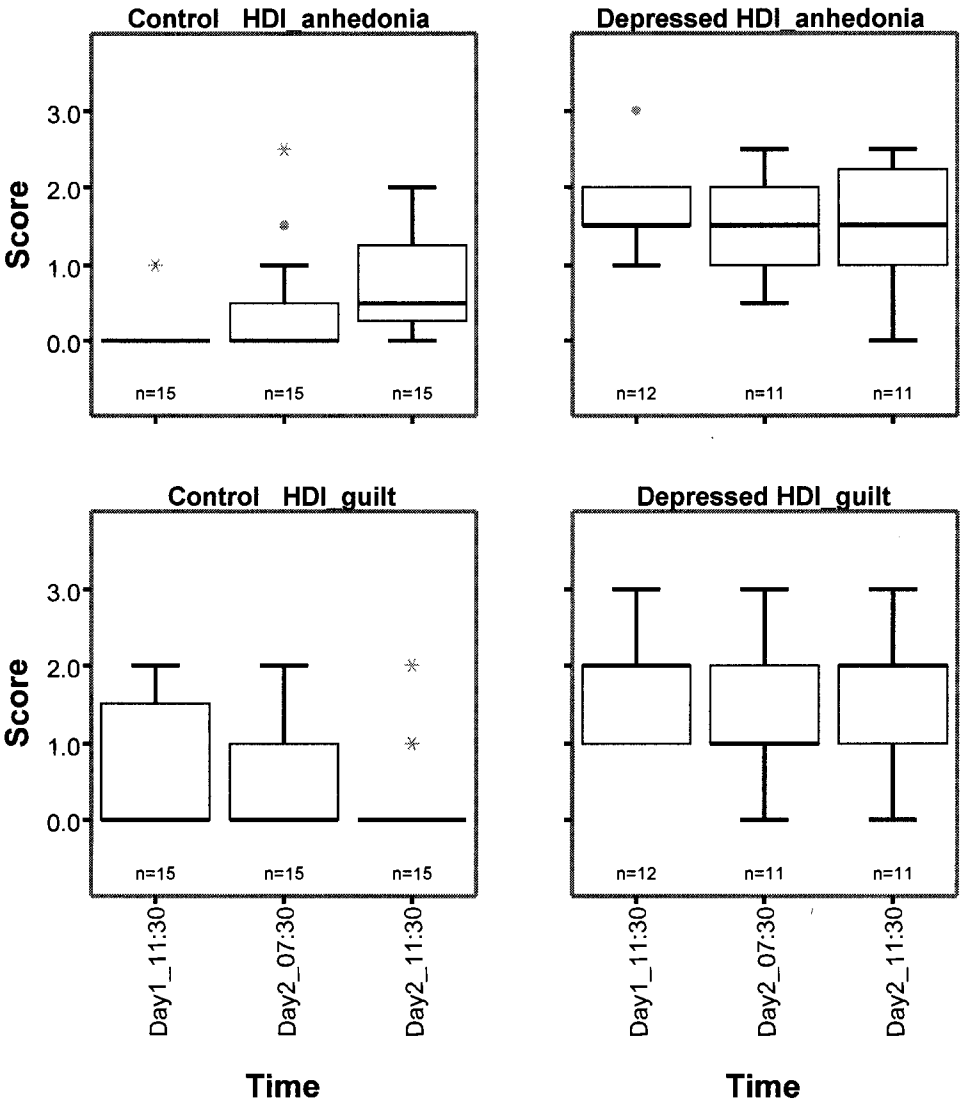
Appendix 19

Box-plots for Depression Raw Scores As a Function of Time and Group



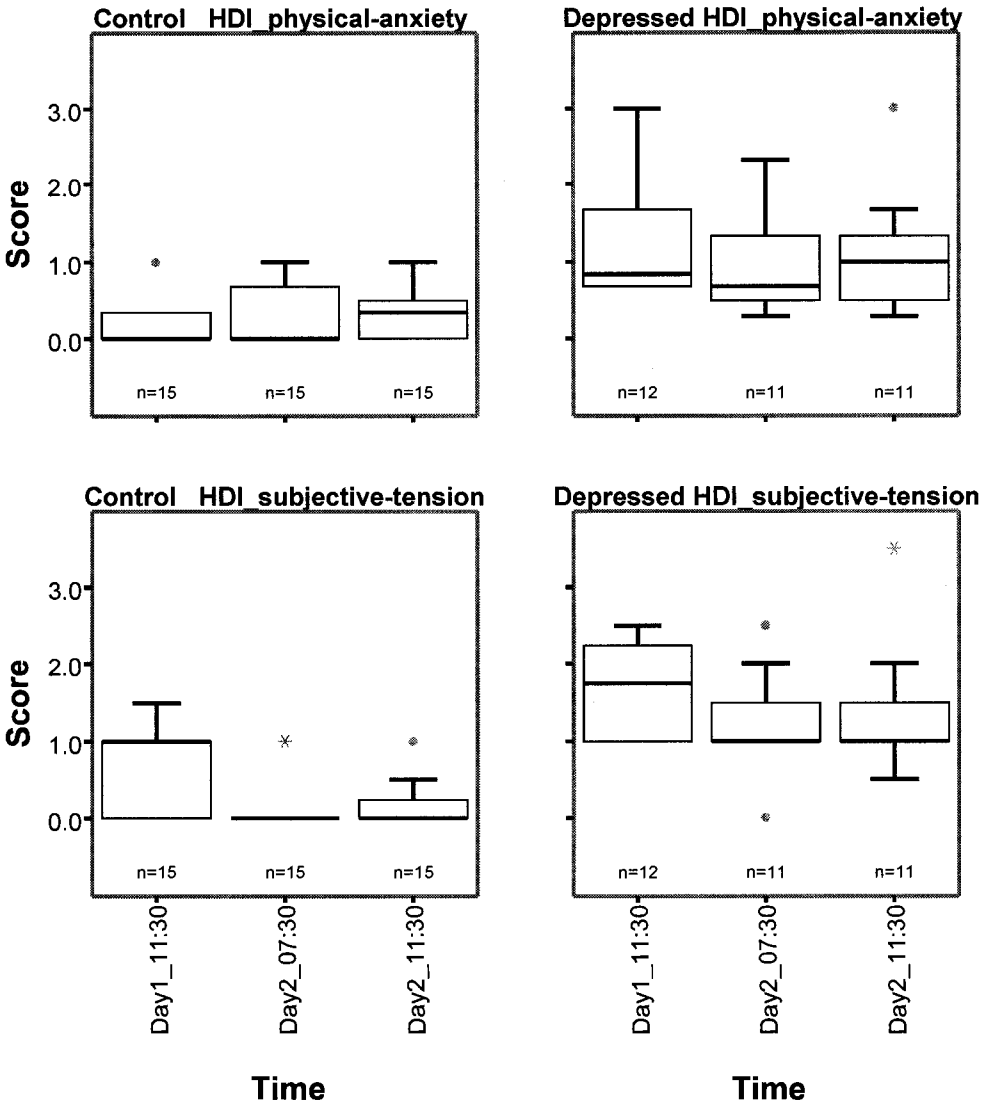
Appendix 19 continued

Box-plots for Depression Raw Scores As a Function of Time and Group



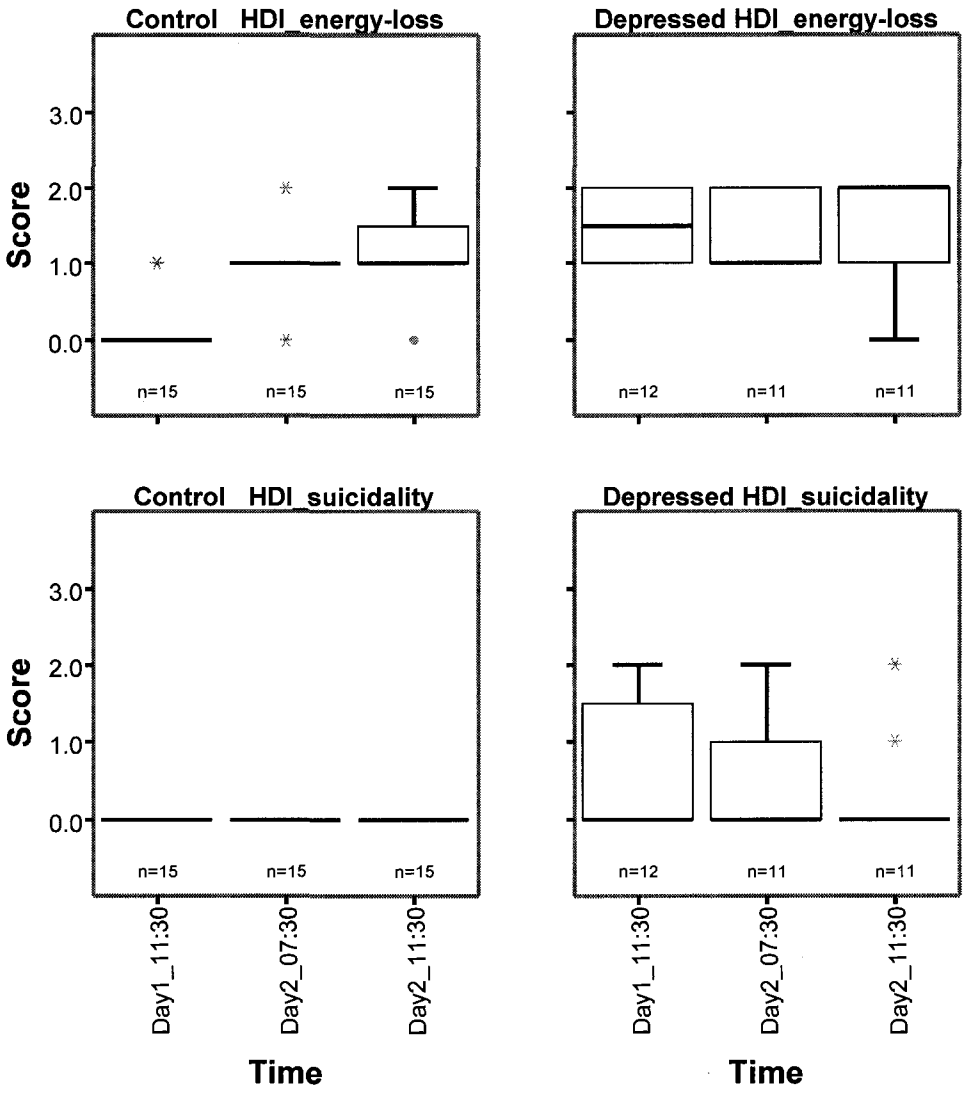
Appendix 19 continued

Box-plots for Depression Raw Scores As a Function of Time and Group



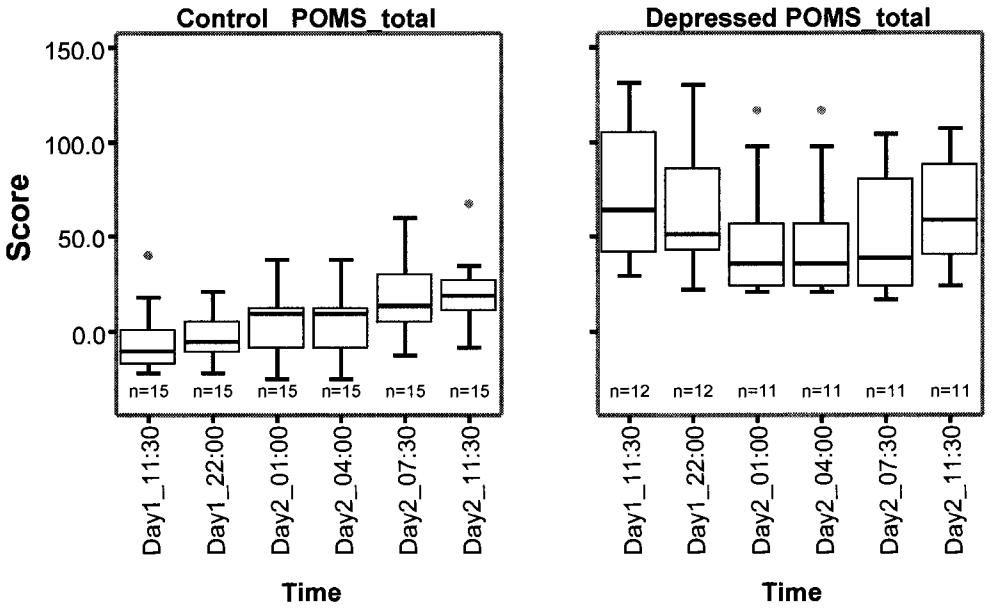
Appendix 19 continued

Box-plots for Depression Raw Scores As a Function of Time and Group



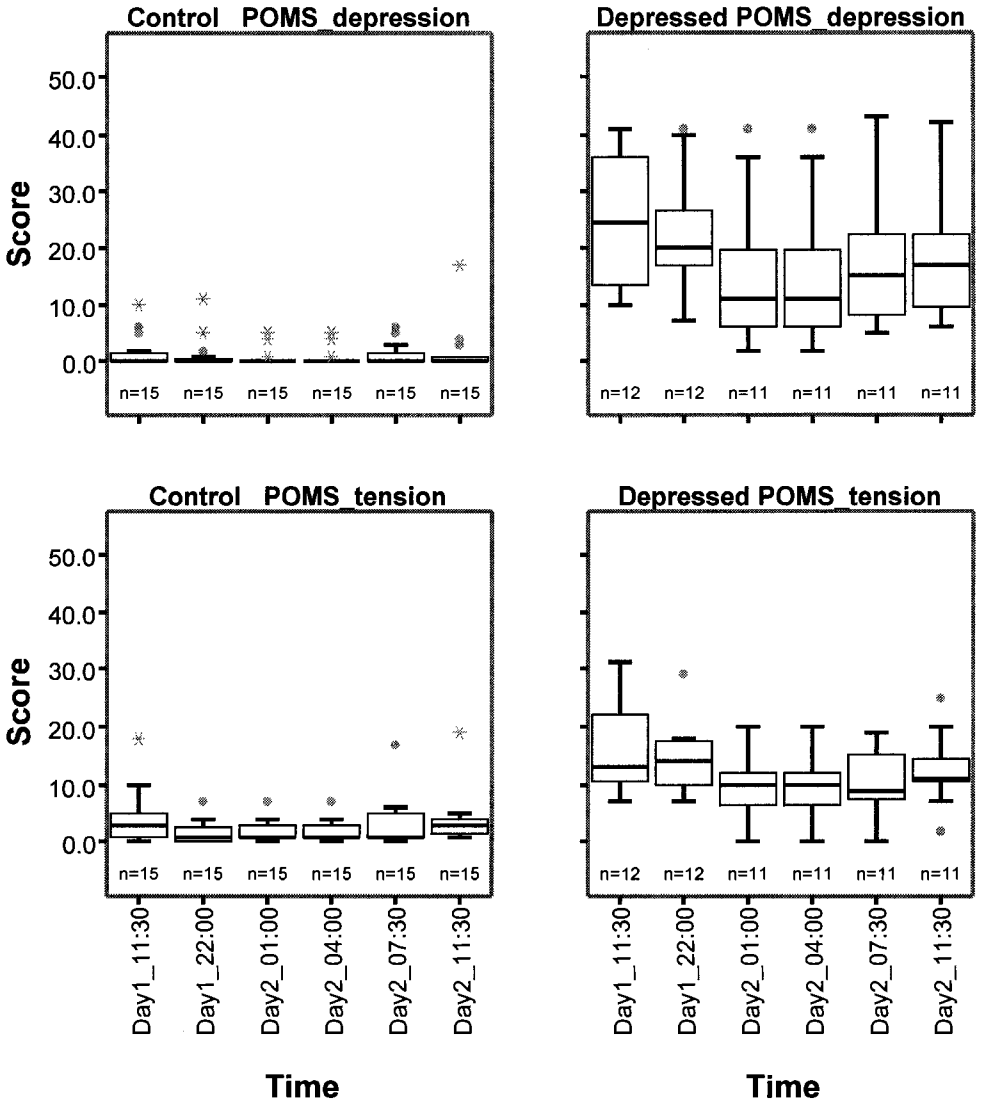
Appendix 19 continued

Box-plots for Depression Raw Scores As a Function of Time and Group



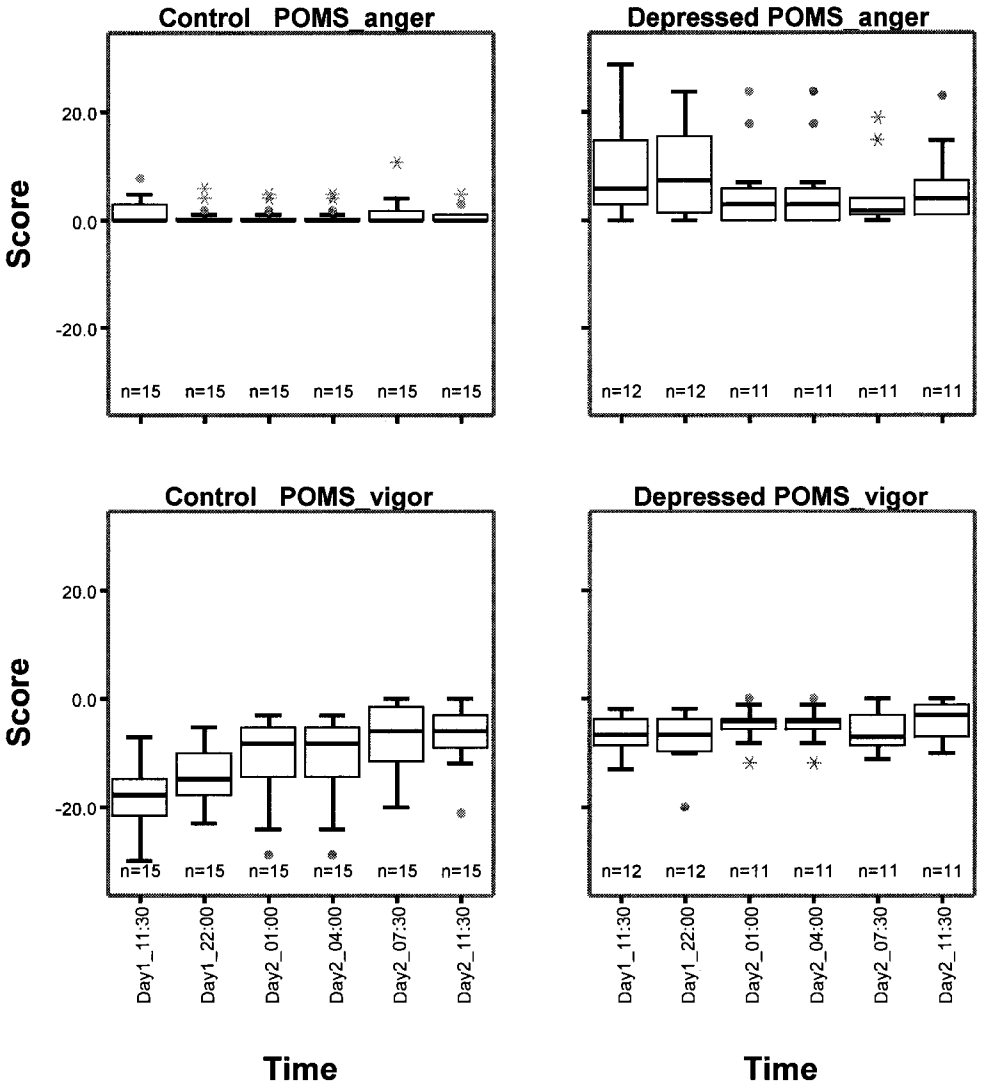
Appendix 19 continued

Box-plots for Depression Raw Scores As a Function of Time and Group



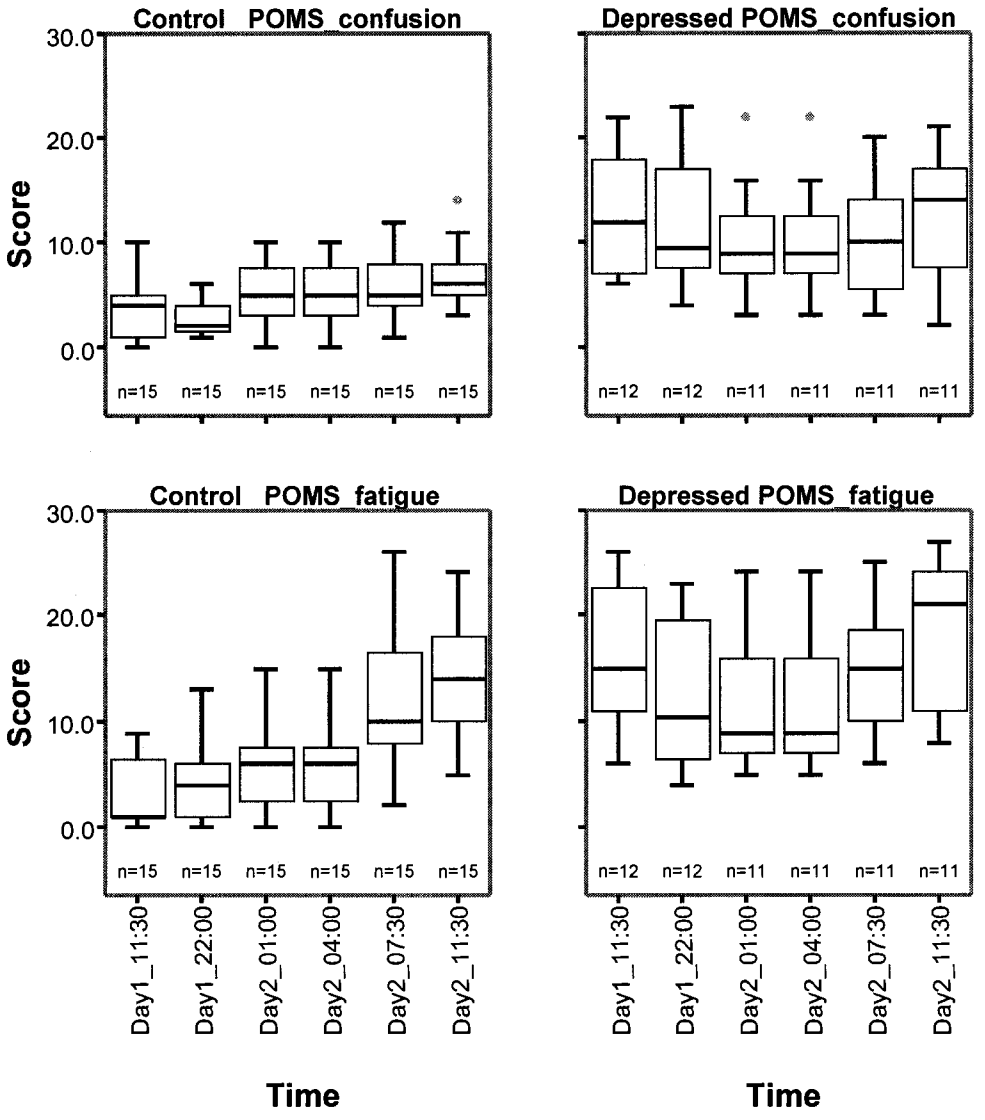
Appendix 19 continued

Box-plots for Depression Raw Scores As a Function of Time and Group



Appendix 19 continued

Box-plots for Depression Raw Scores As a Function of Time and Group



Appendix 20

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores As a Function of Time and Group

Scale[1] / variable	Time of self-report[2]						
	1	2	3	4	5	6	1 - 6
				Control group (n = 15)			
HDI							
7-item	1.73(1.79)				2.51(1.82)	2.75(1.54)	-1.02(2.00)
Sad-mood	0.13(0.28)				0.13(0.28)	0.08(0.29)	0.06(0.22)
Guilt	0.67(0.90)				0.60(0.74)	0.33(0.72)	0.33(1.05)
Anhedonia	0.07(0.26)				0.40(0.74)	0.73(0.65)	-0.67(0.72)
Subjective-tension	0.60(0.54)				0.07(0.26)	0.23(0.42)	0.37(0.64)
Physical-anxiety	0.20(0.35)				0.31(0.37)	0.31(0.32)	-0.11(0.39)
Energy-loss	0.07(0.26)				1.00(0.65)	1.07(0.70)	-1.00(0.65)
Suicidality	0.00(0.00)				0.00(0.00)	0.00(0.00)	0.00(0.00)

Appendix 20 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores As a Function of Time and Group

Scale[1] / variable	Time of self-report[2]						
	1	2	3	4	5	6	1 - 6
POMS							
Total	-4.53(17.42)	-3.27(12.72)	3.13(16.48)	1.60(11.54)	17.40(19.34)	20.20(17.30)	-24.73(13.99)
Tension	4.20(4.63)	1.8(2.01)	1.87(1.88)	1.93(1.91)	3.40(4.24)	3.73(4.42)	0.47(2.70)
Depression	1.60(3.02)	1.27(3.01)	0.67(1.59)	0.33(0.72)	1.20(1.97)	1.73(4.40)	-0.13(2.85)
Anger	1.60(2.41)	0.87(1.81)	0.80(1.61)	0.33(0.82)	1.40(2.92)	0.73(1.44)	0.87(2.50)
Vigour	-18.40(5.96)	-14.13(5.73)	-10.87(7.86)	-10.93(6.77)	-6.80(5.87)	-6.6(5.34)	-11.80(5.06)
Fatigue	3.47(3.31)	4.40(3.78)	5.73(4.42)	5.80(2.98)	12.00(6.26)	13.87(5.48)	-10.40(6.17)
Confusion	3.27(2.87)	2.80(1.66)	5.00(2.98)	4.40(2.44)	6.20(3.21)	7.07(2.91)	-3.80(2.91)
	Depressed group (n = 11)						
HDI							
7-item	10.34(2.67)				8.11(2.45)	8.59(2.79)	1.75(2.33)

Appendix 20 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores As a Function of Time and Group

Scale[1] / variable	Time of self-report[2]						
	1	2	3	4	5	6	1 - 6
Sad-mood	1.97(0.59)				1.04(0.53)	1.33(0.63)	0.65(0.86)
Guilt	1.73(0.65)				1.45(0.82)	1.55(0.82)	0.18(0.60)
Anhedonia	1.77(0.68)				1.45(0.72)	1.45(0.85)	0.32(0.87)
Subjective-tension	1.64(0.60)				1.23(0.65)	1.36(0.81)	0.27(0.61)
Physical-anxiety	1.18(0.75)				0.94(0.65)	1.09(0.79)	0.10(0.58)
Energy-loss	1.45(0.52)				1.45(0.52)	1.55(0.69)	-0.09(0.70)
Suicidality	0.64(0.92)				0.55(0.82)	0.27(0.65)	0.36(0.92)
POMS							
Total	69.27(36.97)	56.73(23.34)	47.36(32.72)	45.00(29.41)	52.00(32.21)	63.64(29.50)	5.64(26.85)
Tension	14.91(7.23)	13.09(4.13)	9.45(5.59)	9.27(4.05)	10.91(5.66)	12.64(6.15)	2.27(3.95)
Depression	24.27(11.74)	20.55(9.06)	15.55(12.72)	10.09(12.10)	17.27(11.95)	18.09(10.93)	6.18(7.45)

Appendix 20 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores As a Function of Time and Group

Scale[1] / variable	Time of self-report[2]						
	1	2	3	4	5	6	1 - 6
Anger	8.55(9.00)	7.82(7.26)	5.73(8.01)	4.18(5.98)	4.73(6.29)	6.27(6.99)	2.27(6.00)
Vigour	-6.73(3.52)	-6.91(5.13)	-4.64(3.26)	-6.27(5.22)	-5.91(3.83)	-4.00(3.69)	-2.73(3.47)
Fatigue	15.91(6.98)	11.36(6.30)	11.36(6.41)	12.45(7.29)	14.73(6.48)	18.27(7.47)	-2.36(8.65)
Confusion	12.36(6.14)	10.82(5.15)	9.91(5.58)	9.27(5.46)	10.27(5.71)	12.36(6.23)	0.00(6.23)
			Both groups (n = 26)				
HDI							
7-item	5.37(4.84)				4.88(3.50)	5.22(3.62)	0.15(2.52)
Sad-mood	0.91(1.02)				0.52(0.60)	0.60(0.78)	0.31(0.64)
Guilt	1.12(0.95)				0.96(0.87)	0.85(0.97)	0.27(0.87)
Anhedonia	0.79(0.98)				0.85(0.89)	1.04(0.81)	-0.25(0.92)
Subjective-tension	1.04(0.76)				0.56(0.74)	0.71(0.83)	0.33(0.62)

Appendix 20 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores As a Function of Time and Group

Scale[1] / variable	Time of self-report[2]						
	1	2	3	4	5	6	1 - 6
Physical-anxiety	0.62(0.74)				0.58(0.59)	0.64(0.68)	-0.02(0.48)
Energy-loss	0.65(0.80)				1.19(0.63)	1.27(0.72)	-0.62(0.80)
Suicidality	0.27(0.67)				0.23(0.59)	0.12(0.43)	0.15(0.61)
POMS							
Total	26.69(45.82)	22.12(34.96)	21.85(32.82)	19.96(29.98)	32.04(30.47)	38.58(31.54)	-11.88(25.14)
Tension	8.73(7.88)	6.58(6.44)	5.08(5.40)	5.04(4.72)	6.58(6.10)	7.50(6.80)	1.23(3.34)
Depression	11.19(13.81	9.42(11.50)	6.96(11.06)	7.00(11.04)	8.00(11.17)	8.65(11.25)	2.54(6.07)
Anger	4.54(6.92)	3.81(5.93)	2.88(5.77)	1.96(4.29)	2.81(4.84)	3.08(5.34)	1.46(4.29)
Vigour	-13.46(7.71)	-11.08(6.49)	-8.23(6.98)	-8.96(6.48)	-6.42(5.04)	-5.50(4.81)	-7.96(6.33)
Fatigue	8.73(8.06)	7.35(6.01)	8.12(5.95)	8.62(6.12)	13.15(6.37)	15.73(6.64)	-7.00(8.23)
Confusion	7.12(6.38)	6.19(5.34)	7.08(4.85)	6.46(4.62)	7.92(4.80)	9.31(5.24)	-2.19(4.89)

Appendix 20 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores As a Function of Time and Group

Scale[1] / variable	Time of self-report[2]						
	1	2	3	4	5	6	1 - 6

Note. [1] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [2] 1, 2, 3, 4, 5, and 6 refer to Time 1 (Day 1 at 11:30), Time 2 (Day 1 at 22:00), Time 3 (Day 2 at 01:00), Time 4 (Day 2 at 04:00), Time 5 (Day 2 at 07:30), and Time 6 (Day 2 at 11:30), respectively; 1 - 6 refers to the difference scores between Time 1 and Time 6.

Appendix 21

Shapiro-Wilk Tests for Normality of Distribution for Depression Raw and Difference Scores As a Function of Time and Group

Scale[1]_variable_Time[2]	Control group			Depressed group		
	Statistic	*p*	*n*	Statistic	*p*	*n*
HDI_7-item_1	.870*	.034	15	.908	.228	11
HDI_sad-mood_1	.533**	.000	15	.939	.505	11
HDI_guilt_1	.686**	.000	15	.793**	.008	11
HDI_anhedonia_1	.284**	.000	15	.827*	.021	11
HDI_subjective-tension_1	.778**	.002	15	.855	.050	11
HDI_physical-anxiety_1	.619**	.000	15	.732**	.001	11
HDI_energy-loss_1	.284**	.000	15	.649**	.000	11
HDI_suicidality_1[0]			15	.662**	.000	11
POMS_total_1	.873*	.037	15	.881	.106	11
POMS_tension_1	.758**	.001	15	.864	.064	11
POMS_depression_1	.620**	.000	15	.896	.166	11
POMS_anger_1	.721**	.000	15	.850*	.043	11
POMS_vigour_1	.988	.998	15	.936	.479	11
POMS_fatigue_1	.826**	.008	15	.919	.311	11
POMS_confusion_1	.882	.051	15	.865	.066	11
HDI_7-item_6	.960	.684	15	.982	.975	11
HDI_sad-mood_6	.284**	.000	15	.965	.831	11

Appendix 21 continued

Shapiro-Wilk Tests for Normality of Distribution for Depression Raw and Difference Scores As a Function of Time and Group

Scale[1]_variable_Time[2]	Control group			Depressed group		
	Statistic	*p*	*n*	Statistic	*p*	*n*
HDI_guilt_6	.514**	.000	15	.893	.150	11
HDI_anhedonia_6	.886	.059	15	.921	.329	11
HDI_subjective-tension_6	.581**	.000	15	.737**	.001	11
HDI_physical-anxiety_6	.843*	.014	15	.866	.070	11
HDI_energy-loss_6	.815**	.006	15	.701**	.000	11
HDI_suicidality_6[0]			15	.504**	.000	11
POMS_total_6	.918	.181	15	.923	.347	11
POMS_tension_6	.551**	.000	15	.951	.655	11
POMS_depression_6	.459**	.000	15	.910	.245	11
POMS_anger_6	.592**	.000	15	.782**	.006	11
POMS_vigour_6	.733**	.001	15	.893	.153	11
POMS_fatigue_6	.952	.561	15	.858	.054	11
POMS_confusion_6	.875*	.040	15	.934	.456	11
HDI_7-item_D	.973	.898	15	.968	.867	11
HDI_sad-mood_D	.578**	.000	15	.947	.602	11
HDI_guilt_D	.757**	.001	15	.774**	.004	11
HDI_anhedonia_D	.935	.324	15	.937	.491	11
HDI_subjective-tension_D	.888	.063	15	.882	.110	11

Appendix 21 continued

Shapiro-Wilk Tests for Normality of Distribution for Depression Raw and Difference Scores As a Function of Time and Group

Scale[1]_variable_Time[2]	Control group			Depressed group		
	Statistic	*p*	*n*	Statistic	*p*	*n*
HDI_physical-anxiety_D	.887	.060	15	.964	.817	11
HDI_energy-loss_D	.799**	.004	15	.822*	.018	11
HDI_suicidality_D[0]			15	.772**	.004	11
POMS_total_D	.964	.764	15	.954	.700	11
POMS_tension_D	.972	.890	15	.853*	.047	11
POMS_depression_D	.795**	.003	15	.945	.581	11
POMS_anger_D	.697**	.000	15	.990	.997	11
POMS_vigour_D	.710**	.000	15	.954	.692	11
POMS_fatigue_D	.952	.561	15	.978	.952	11
POMS_confusion_D	.977	.947	15	.959	.756	11

Note. [1] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [2] 1 and 6 refer to Time 1 (Day 1 at 11:30) and Time 6 (Day 2 at 11:30), respectively; D refers to the difference scores between Time 1 and Time 6. [0] Variable not assessed when all scores were 0.

* $p < .05$; $p < .01$.

Appendix 22

Shapiro-Wilk Tests for Normality of Distribution for Depression Raw Scores As a Function of Group and Scan Time (Supplementary Tests for Follow-up)

Scale[1]_variable_Time[2]	Control group			Depressed group		
	statistic	*p*	n	statistic	*p*	n
HDI_7-item_5				.971	.897	11
HDI_sad-mood_5				.935	.463	11
POMS_total_2	.970	.861	15	.929	.396	11
POMS_total_3	.912	.144	15	.786**	.006	11
POMS_total_4	.912	.144	15	.786**	.006	11
POMS_total_5	.949	.511	15	.875	.091	11
POMS_tension_2	.842*	.013	15	.910	.244	11
POMS_tension_3	.826**	.008	15	.984	.985	11
POMS_tension_4	.826**	.008	15	.984	.985	11
POMS_tension_5	.668**	.000	15	.950	.643	11
POMS_depression_2				.944	.571	11
POMS_depression_3				.862	.061	11
POMS_depression_4				.862	.061	11
POMS_depression_5				.904	.208	11
POMS_anger_2				.903	.203	11
POMS_anger_3				.743**	.002	11
POMS_anger_4				.743**	.002	11

Appendix 22 continued

Shapiro-Wilk Tests for Normality of Distribution for Depression Raw Scores As a Function of Group and Scan Time (Supplementary Tests for Follow-up)

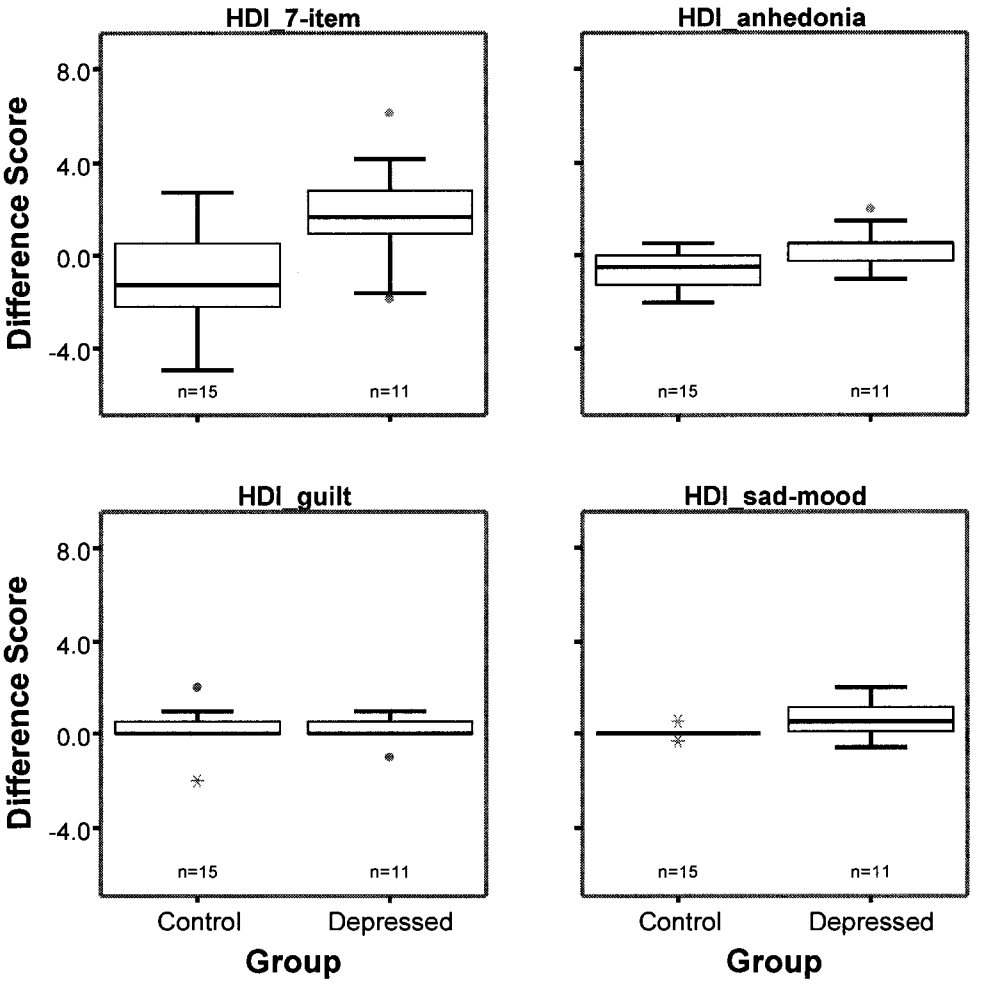
Scale[1]_variable_Time[2]	Control group			Depressed group		
	statistic	*p*	n	statistic	*p*	n
POMS_anger_5				.695**	.000	11
POMS_vigour_2	.958	.654	15	.833*	.026	11
POMS_vigour_3	.869*	.032	15	.913	.264	11
POMS_vigour_4	.869*	.032	15	.913	.264	11
POMS_vigour_5	.910	.136	15	.908	.229	11
POMS_fatigue_2	.898	.088	15	.886	.122	11
POMS_fatigue_3	.947	.474	15	.865	.066	11
POMS_fatigue_4	.947	.474	15	.865	.066	11
POMS_fatigue_5	.934	.312	15	.948	.618	11
POMS_confusion_2	.894	.078	15	.906	.221	11
POMS_confusion_3	.974	.917	15	.920	.319	11
POMS_confusion_4	.974	.917	15	.920	.319	11
POMS_confusion_5	.921	.199	15	.953	.686	11

Note. [1] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [2] 2, 3, 4, and 5 refer to Time 2 (Day 1 at 22:00), Time 3 (Day 2 at 01:00), Time 4 (Day 2 at 04:00), and Time 5 (Day 2 at 07:30), respectively.

* $p < .05$; ** $p < .01$.

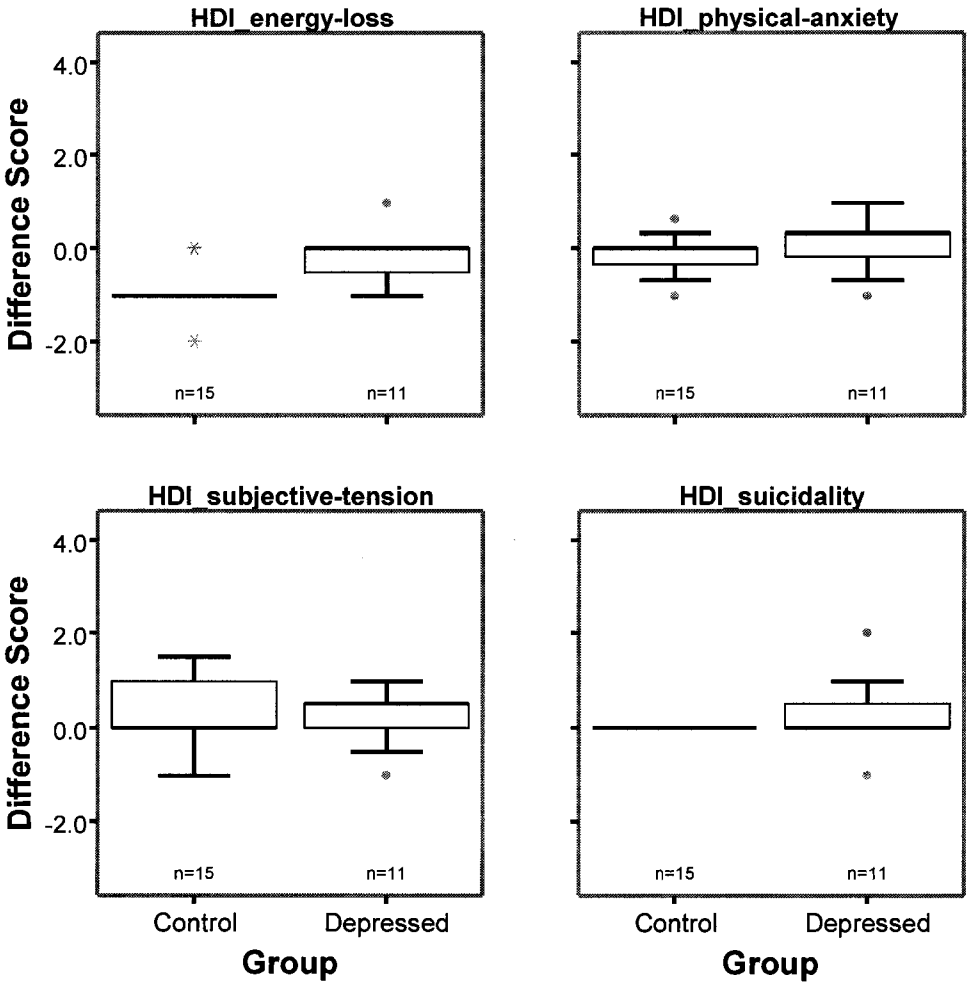
Appendix 23

Box-plots for Depression Difference Scores



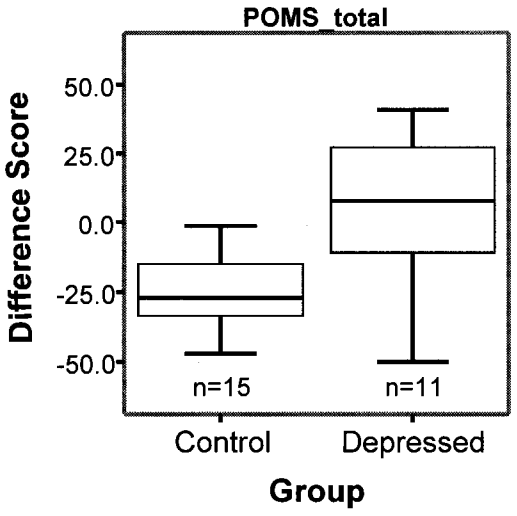
Appendix 23 continued

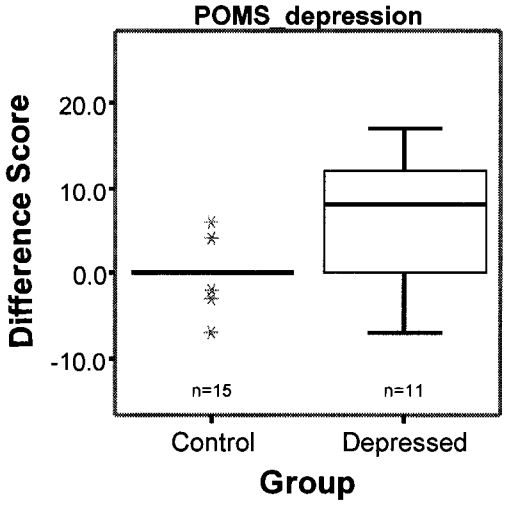
Box-plots for Depression Difference Scores

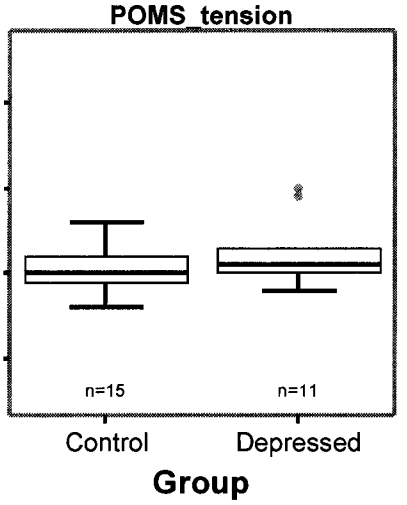


Appendix 23 continued

Box-plots for Depression Difference Scores

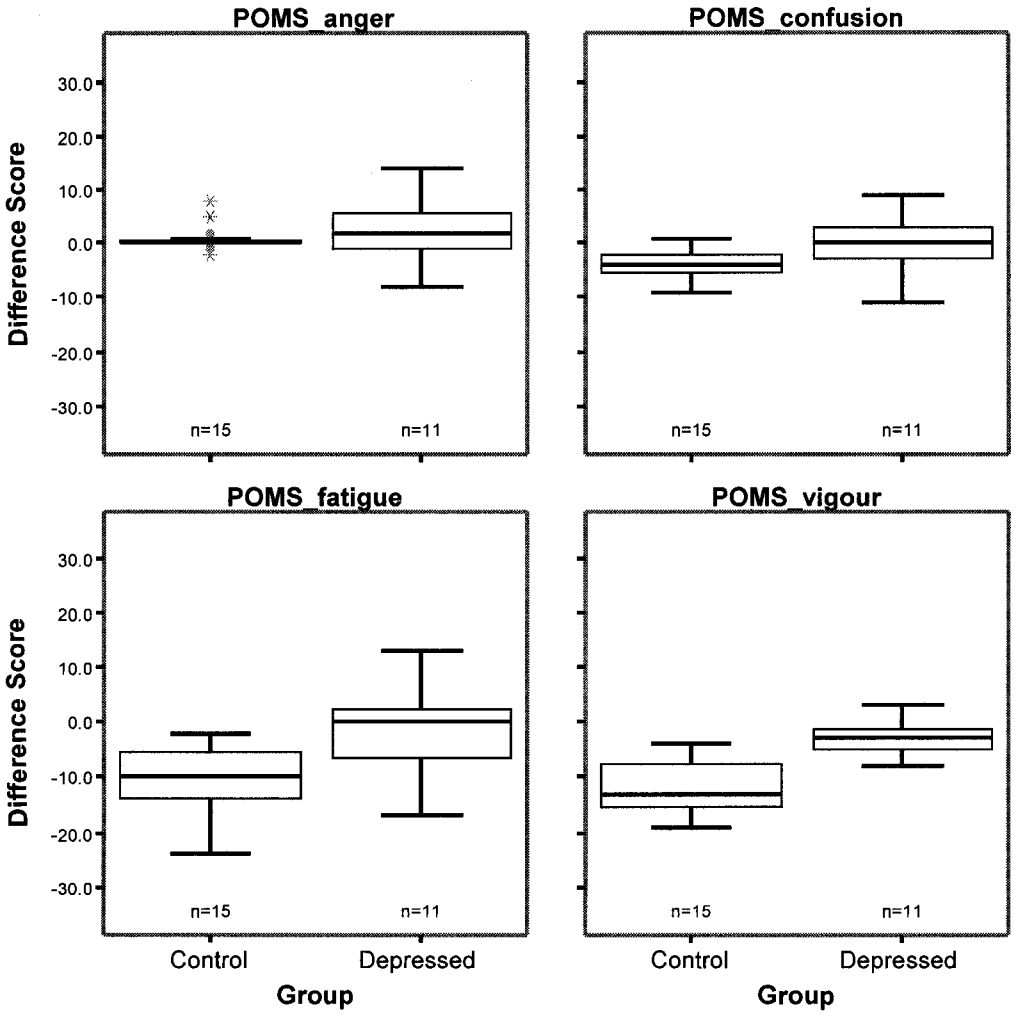






Appendix 23 continued

Box-plots for Depression Difference Scores



Appendix 24

Levene Test of Equality of Error Variances Between the Two Groups for Depression Difference Scores

Scale[1]_variable_Time[2]	Levene test			
	F	*p*	*df* 1	*df* 2
HDI_7-item_D	0.038	.847	1	24
HDI_sad-mood_D	22.283*	.000	1	24
HDI_guilt_D	1.773	.195	1	24
HDI_anhedonia_D	0.087	.770	1	24
HDI_subjective-tension_D	0.152	.700	1	24
HDI_physical-anxiety_D	2.052	.165	1	24
HDI_energy-loss_D	0.241	.628	1	24
HDI_suicidality_D	25.743*	.000	1	24
POMS_total_D	4.386*	.047	1	24
POMS_tension_D	0.852	.365	1	24
POMS_depression_D	14.568*	.001	1	24
POMS_anger_D	6.481*	.018	1	24
POMS_vigour_D	3.689	.067	1	24
POMS_fatigue_D	1.203	.284	1	24
POMS_confusion_D	3.747	.065	1	24

Note. [1] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [2] D refers to the difference scores between Day 1 at 11:30 and Day 2 at 11:30.

Appendix 24 continued

Levene Test of Equality of Error Variances Between the Two Groups for Depression Difference Scores

Scale[1]_variable_Time[2]	Levene test			
	F	*p*	*df*1	*df*2

* $p < .05$.

Appendix 25

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
Pons (Cho & tCr)	HDI_7-item_1	1.93	1.93	12	10.38	2.60	11	5.97	4.85	23
	HDI_sad-mood_1	0.17	0.31	12	1.92	0.59	11	1.01	1.00	23
	HDI_guilt_1	0.75	0.97	12	1.73	0.65	11	1.22	0.95	23
	HDI_anhedonia_1	0.08	0.29	12	1.64	0.55	11	0.83	0.90	23
	HDI_subjective-tension_1	0.63	0.57	12	1.73	0.65	11	1.15	0.82	23
	HDI_physical-anxiety_1	0.22	0.38	12	1.37	0.85	11	0.77	0.86	23
	HDI_energy-loss_1	0.08	0.28	12	1.55	0.52	11	0.78	0.85	23
	HDI_suicidality_1	0.00	0.00	12	0.45	0.82	11	0.22	0.60	23
	POMS_total_1	-3.50	19.08	12	70.73	38.45	11	32.00	47.87	23
	POMS_tension_1	5.00	4.88	12	16.27	8.72	11	10.39	8.92	23

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
	POMS_depression_1	2.00	3.28	12	23.73	11.06	11	12.39	13.57	23
	POMS_anger_1	2.00	2.56	12	8.18	8.61	11	4.96	6.85	23
	POMS_vigour_1	-19.08	6.39	12	-5.00	4.63	11	-12.35	9.05	23
	POMS_fatigue_1	3.33	3.17	12	16.45	7.22	11	9.61	8.58	23
	POMS_confusion_1	3.58	3.06	12	12.18	5.95	11	7.70	6.33	23
Pons (NAA)	HDI_7-item_1	1.88	1.86	13	10.38	2.60	11	5.78	4.84	24
	HDI_sad-mood_1	0.15	0.30	13	1.92	0.59	11	0.96	1.00	24
	HDI_guilt_1	0.69	0.95	13	1.73	0.65	11	1.17	0.96	24
	HDI_anhedonia_1	0.08	0.28	13	1.64	0.55	11	0.79	0.90	24
	HDI_subjective-tension_1	0.65	0.55	13	1.73	0.65	11	1.15	0.80	24

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
	HDI_physical-anxiety_1	0.23	0.37	13	1.37	0.85	11	0.75	0.85	24
	HDI_energy-loss_1	0.08	0.28	13	1.55	0.52	11	0.75	0.85	24
	HDI_suicidality_1	0.00	0.00	13	0.45	0.82	11	0.21	0.59	24
	POMS_total_1	-4.15	18.42	13	70.73	38.45	11	30.17	47.67	24
	POMS_tension_1	4.69	4.80	13	23.73	11.06	11	10.00	8.93	24
	POMS_depression_1	1.85	3.18	13	23.73	11.06	11	11.88	13.51	24
	POMS_anger_1	1.85	2.51	13	8.18	8.61	11	4.75	6.78	24
	POMS_vigour_1	-18.92	6.14	13	-5.00	4.63	11	-12.54	8.90	24
	POMS_fatigue_1	3.31	3.04	13	16.45	7.22	11	9.33	8.50	24
	POMS_confusion_1	3.38	3.01	13	12.18	5.95	11	7.42	6.34	24

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
LADPF (3 peaks)	HDI_7-item_1	1.76	1.85	14	10.55	2.55	12	5.82	4.96	26
	HDI_sad-mood_1	0.14	0.29	14	1.95	0.57	12	0.98	1.02	26
	HDI_guilt_1	0.71	0.91	14	1.75	0.62	12	1.19	0.94	26
	HDI_anhedonia_1	0.07	0.27	14	1.75	0.66	12	0.85	0.98	26
	HDI_subjective-tension_1	0.57	0.55	14	1.71	0.62	12	1.10	0.81	26
	HDI_physical-anxiety_1	0.19	0.36	14	1.31	0.83	12	0.71	0.83	26
	HDI_energy-loss_1	0.07	0.27	14	1.50	0.52	12	0.73	0.83	26
	HDI_suicidality_1	0.00	0.00	14	0.58	0.90	12	0.27	0.67	26
	POMS_total_1	-4.00	17.95	14	72.92	37.44	12	31.50	48.10	26
	POMS_tension_1	4.43	4.72	14	16.25	8.31	12	9.88	8.84	26

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
	POMS_depression_1	1.71	3.10	14	25.08	11.54	12	12.50	14.31	26
	POMS_anger_1	1.71	2.46	14	9.08	8.78	12	5.12	7.15	26
	POMS_vigour_1	-18.50	6.17	14	-5.67	4.98	12	-12.58	8.56	26
	POMS_fatigue_1	3.50	3.44	14	16.42	6.88	12	9.46	8.37	26
	POMS_confusion_1	3.43	2.90	14	12.75	6.00	12	7.73	6.53	26
Pons (Cho & tCr)	HDI_7-item_6	2.91	1.54	10	8.34	2.81	10	5.63	3.55	20
	HDI_sad-mood_6	0.11	0.36	10	1.23	0.57	10	0.67	0.74	20
	HDI_guilt_6	0.40	0.84	10	1.50	0.85	10	0.95	1.00	20
	HDI_anhedonia_6	0.90	0.70	10	1.45	0.90	10	1.18	0.83	20
	HDI_subjective-tension_6	0.20	0.42	10	1.40	0.84	10	0.80	0.89	20

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
	HDI_physical-anxiety_6	0.30	0.29	10	1.18	0.79	10	0.74	0.74	20
	HDI_energy-loss_6	1.00	0.67	10	1.50	0.71	10	1.25	0.72	20
	HDI_suicidality_6	0.00	0.00	10	0.10	0.32	10	0.05	0.22	20
	POMS_total_6	24.20	18.15	10	59.30	27.15	10	41.75	28.80	20
	POMS_tension_6	4.40	5.25	10	12.60	6.48	10	8.50	7.12	20
	POMS_depression_6	2.60	5.25	10	15.70	7.93	10	9.15	9.38	20
	POMS_anger_6	0.70	1.57	10	4.60	4.48	10	2.65	3.83	20
	POMS_vigour_6	-5.00	3.56	10	-3.50	3.47	10	-4.25	3.51	20
	POMS_fatigue_6	14.00	4.69	10	18.00	7.82	10	16.00	6.60	20
	POMS_confusion_6	8.00	3.06	10	11.90	6.37	10	9.95	5.26	20

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
Pons (NAA)	HDI_7-item_6	2.60	1.52	13	8.34	2.81	10	5.10	3.60	23
	HDI_sad-mood_6	0.09	0.32	13	1.23	0.57	10	0.58	0.72	23
	HDI_guilt_6	0.31	0.75	13	1.50	0.85	10	0.83	0.98	23
	HDI_anhedonia_6	0.73	0.70	13	1.45	0.90	10	1.04	0.85	23
	HDI_subjective-tension_6	0.19	0.38	13	1.40	0.84	10	0.72	0.86	23
	HDI_physical-anxiety_6	0.28	0.27	13	1.18	0.79	1010	0.67	0.71	23
	HDI_energy-loss_6	1.00	0.71	13	1.50	0.71	10	1.22	0.74	23
	HDI_suicidality_6	0.00	0.00	13	0.10	0.32	10	0.04	0.21	23
	POMS_total_6	21.00	18.48	13	59.30	27.15	10	37.65	29.41	23
	POMS_tension_6	3.69	4.75	13	12.60	6.48	10	7.57	7.06	23

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
	POMS_depression_6	2.00	4.69	13	15.70	7.93	10	7.96	9.27	23
	POMS_anger_6	0.85	1.52	13	4.60	4.48	10	2.48	3.62	23
	POMS_vigour_6	-2.85	7.85	13	-3.50	3.47	10	-3.13	6.22	23
	POMS_fatigue_6	13.77	5.73	13	11.90	6.37	10	15.61	6.89	23
	POMS_confusion_6	7.15	3.13	13	11.90	6.37	10	9.22	5.27	23
LADPF (3 peaks)	HDI_7-item_6	2.77	1.60	14	8.27	2.71	10	5.06	3.46	24
	HDI_sad-mood_6	0.08	0.30	14	1.26	0.62	10	0.57	0.74	24
	HDI_guilt_6	0.29	0.73	14	1.40	0.70	10	0.75	0.90	24
	HDI_anhedonia_6	0.75	0.67	14	1.35	0.82	10	1.00	0.78	24
	HDI_subjective-tension_6	0.25	0.43	14	1.30	0.82	10	0.69	0.81	24

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
	HDI_physical-anxiety_6	0.33	0.32	14	1.17	0.80	10	0.68	0.70	24
	HDI_energy-loss_6	1.07	0.73	14	1.50	0.71	10	1.25	0.74	24
	HDI_suicidality_6	0.00	0.00	14	0.30	0.67	10	0.13	0.45	24
	POMS_total_6	20.29	17.95	14	60.30	28.83	10	36.96	30.22	24
	POMS_tension_6	3.79	4.58	14	11.90	5.95	10	7.17	6.51	24
	POMS_depression_6	1.86	4.54	14	17.50	11.34	10	8.38	11.13	24
	POMS_anger_6	0.79	1.48	14	6.20	7.36	10	3.04	5.47	24
	POMS_vigour_6	-3.50	7.93	14	-4.40	3.63	10	-3.88	6.40	24
	POMS_fatigue_6	13.57	5.56	14	17.60	7.52	10	15.25	6.61	24
	POMS_confusion_6	7.14	3.01	14	11.50	5.84	10	8.96	4.82	24

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
Pons (Cho & tCr)	HDI_7-item_D	-1.09	1.50	8	1.83	2.38	10	0.53	2.48	18
	HDI_sad-mood_D	0.04	0.24	8	0.71	0.87	10	0.41	0.74	18
	HDI_guilt_D	0.38	1.30	8	0.20	0.63	10	0.28	0.96	18
	HDI_anhedonia_D	-1.06	0.68	8	0.20	0.82	10	-0.36	0.98	18
	HDI_subjective-tension_D	0.44	0.62	8	0.25	0.63	10	0.33	0.62	18
	HDI_physical-anxiety_D	-0.00	0.40	8	0.06	0.60	10	0.03	0.51	18
	HDI_energy-loss_D	-0.88	0.35	8	0.00	0.67	10	-0.39	0.70	18
	HDI_suicidality_D	0.00	0.00	8	0.40	0.97	10	0.22	0.73	18
	POMS_total_D	-25.13	13.92	8	7.20	27.77	10	-7.17	27.59	18
	POMS_tension_D	0.88	2.90	8	2.20	4.16	10	1.61	3.62	18

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
	POMS_depression_D	-1.00	3.16	8	7.00	7.32	10	3.44	7.01	18
	POMS_anger_D	1.63	3.29	8	2.90	5.93	10	2.33	4.85	18
	POMS_vigour_D	-12.00	5.50	8	-1.40	4.60	10	-6.11	7.28	18
	POMS_fatigue_D	-10.88	5.36	8	-2.10	9.07	10	-6.00	8.69	18
	POMS_confusion_D	-3.88	3.48	8	-0.20	6.53	10	-1.83	5.58	18
Pons (NAA)	HDI_7-item_D	-0.54	1.76	12	1.83	2.38	10	0.54	2.35	22
	HDI_sad-mood_D	0.07	0.25	12	0.71	0.87	10	0.36	0.68	22
	HDI_guilt_D	0.42	1.16	12	0.20	0.63	10	0.32	0.95	22
	HDI_anhedonia_D	-0.67	0.81	12	0.20	0.82	10	-0.27	0.91	22
	HDI_subjective-tension_D	0.50	0.56	12	0.25	0.63	10	0.39	0.60	22

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
	HDI_physical-anxiety_D	-0.03	0.33	12	0.06	0.60	10	0.01	0.46	22
	HDI_energy-loss_D	-0.83	0.58	12	0.00	0.67	10	-0.45	0.74	22
	HDI_suicidality_D	0.00	0.00	12	0.40	0.97	10	0.18	0.66	22
	POMS_total_D	-24.50	15.39	12	7.20	27.77	10	-10.09	26.75	22
	POMS_tension_D	0.92	2.84	12	2.20	4.16	10	1.50	3.47	22
	POMS_depression_D	-0.17	3.21	12	7.00	7.32	10	3.09	6.46	22
	POMS_anger_D	1.17	2.72	12	2.90	5.93	10	1.95	4.45	22
	POMS_vigour_D	-16.00	12.10	12	-1.40	4.60	10	-9.36	11.88	22
	POMS_fatigue_D	-10.25	6.86	12	-2.10	9.07	10	-6.55	8.79	22
	POMS_confusion_D	-3.75	3.17	12	-0.20	6.53	10	-2.14	5.18	22

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
LADPF (3 peaks)	HDI_7-item_D	-1.18	2.07	13	1.90	2.35	10	0.16	2.65	23
	HDI_sad-mood_D	0.07	0.24	13	0.66	0.90	10	0.32	0.67	23
	HDI_guilt_D	0.38	1.12	13	0.20	0.63	10	0.30	0.93	23
	HDI_anhedonia_D	-0.73	0.75	13	0.45	0.80	10	-0.22	0.96	23
	HDI_subjective-tension_D	0.31	0.66	13	0.25	0.63	10	0.28	0.64	23
	HDI_physical-anxiety_D	-0.13	0.42	13	0.03	0.57	10	-0.06	0.49	23
	HDI_energy-loss_D	-1.08	0.64	13	-0.10	0.74	10	-0.65	0.83	23
	HDI_suicidality_D	0.00	0.00	13	0.40	0.97	10	0.17	0.65	23
	POMS_total_D	-24.77	14.80	13	2.80	26.51	10	-12.78	24.54	23
	POMS_tension_D	0.92	2.60	13	1.50	3.17	10	1.17	2.81	23

Appendix 25 continued

Means, Standard Deviations (SD) and Sample Sizes for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Time and Group

VOI[1] (peak[2])	Scale[3]_variable_Time[4]	Control group			Depressed group			Both groups		
		M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
	POMS_depression_D	-0.15	3.08	13	5.10	6.89	10	2.13	5.63	23
	POMS_anger_D	1.00	2.68	13	1.70	6.00	10	1.30	4.33	23
	POMS_vigour_D	-15.31	11.72	13	-1.60	4.67	10	-9.35	11.50	23
	POMS_fatigue_D	-10.85	6.52	13	-2.60	9.08	10	-7.26	8.62	23
	POMS_confusion_D	-3.69	2.95	13	-0.10	6.56	10	-2.13	5.07	23

Note. [1] Brain volume of interest. [2] Certain neurochemicals acquired in the same VOI could have different sample sizes, due to rejection of spectral data based on quality criteria described in the Methods section. [3] HDI: Hamilton Depression Inventory; POMS: Profile of Mood States. [4] 1, 6, and D refer to Time 1 (Day 1 at 11:30), Time 6 (Day 2 at 11:30), and the difference scores between Time 1 and Time 6, respectively.

Appendix 26

Means, Standard Deviations (SD) and Sample Sizes for Neurochemical Raw and Difference Concentrations Used for Correlations with Depression Scores As a Function of Brain Region, Scan Time and Group

Brain region	Scan Time[1]	Neurochemical	Control group			Depressed group			Both groups		
			M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
Pons	A	Cho:H_2O_A	4.09	0.95	12	3.59	0.95	11	3.85	0.96	23
		tCr:H_2O_A	7.69	2.14	12	7.48	2.36	11	7.59	2.19	23
		NAA:H_2O_A	15.32	2.91	12	15.73	1.84	11	15.59	2.39	24
	B	Cho:H_2O_B	3.51	0.72	10	3.14	1.04	10	3.32	0.89	20
		tCr:H_2O_B	6.73	1.48	10	6.12	2.15	10	6.43	1.82	20
		NAA:H_2O_B	15.78	2.25	12	15.65	2.43	10	15.58	2.33	23
	D	Cho:H_2O_D	0.57	1.69	8	0.39	1.56	10	0.47	1.57	18
		tCr:H_2O_D	1.89	2.17	8	1.44	3.69	10	1.64	3.03	18
		NAA:H_2O_D	-0.46	4.67	12	0.15	3.87	10	-0.18	4.23	22
LADPF[2]	A	Cho:H_2O_A	2.58	0.65	14	2.33	0.82	12	2.46	0.73	26

Appendix 26 continued

Means, Standard Deviations (SD) and Sample Sizes for Neurochemical Raw and Difference Concentrations Used for Correlations with Depression Scores As a Function of Brain Region, Scan Time and Group

Brain region	Scan Time[1]	Neurochemical	Control group			Depressed group			Both groups		
			M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
		tCr:H_2O_A	8.25	1.70	14	8.02	2.13	12	8.14	1.87	26
		NAA:H_2O_A	10.37	1.03	14	9.87	0.62	12	10.14	0.89	26
	B	Cho:H_2O_B	2.76	0.49	14	2.80	0.76	10	2.76	0.60	24
		tCr:H_2O_B	8.53	1.14	14	7.63	1.83	10	8.11	1.49	24
		NAA:H_2O_B	9.97	1.41	14	9.99	1.42	10	9.98	1.38	24
	D	Cho:H_2O_D	-0.17	0.74	13	-0.42	0.40	10	-0.28	0.62	23
		tCr:H_2O_D	-0.31	2.06	13	0.57	2.88	10	0.07	2.43	23
		NAA:H_2O_D	0.47	1.49	13	-0.16	1.91	10	0.20	1.67	23

Note. [1] A, B and D refer to Scan time A (Day 1 at 12:00), Scan time B (Day 2 at 12:00), and the difference scores between Scan time A and Scan time B. [2] Left anterior dorsal prefrontal.

Appendix 27

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		Control group			
Pons	A	HDI_7-item_1	.878	.081	12
(Cho & tCr)		HDI_sad-mood_1	.597*	.000	12
		HDI_guilt_1	.680*	.001	12
		HDI_anhedonia_1	.327*	.000	12
		HDI_subjective-tension_1	.755*	.003	12
		HDI_physical-anxiety_1	.626*	.000	12
		HDI_energy-loss_1	.327*	.000	12
		HDI_suicidality_1[0]			12
		POMS_total_1	.878	.084	12
		POMS_tension_1	.805*	.011	12
		POMS_depression_1	.694*	.001	12
		POMS_anger_1	.794*	.008	12
		POMS_vigour_1	.974	.951	12
		POMS_fatigue_1	.778*	.005	12
		POMS_confusion_A	.904	.181	12

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
Pons	A	HDI_7-item_1	.884	.082	13
(NAA)		HDI_sad-mood_1	.574*	.000	13
		HDI_guilt_1	.662*	.000	13
		HDI_anhedonia_1	.311*	.000	13
		HDI_subjective-tension_1	.745*	.002	13
		HDI_physical-anxiety_1	.661*	.000	13
		HDI_energy-loss_1	.311*	.000	13
		HDI_suicidality_1[0]			13
		POMS_total_1	.872	.056	13
		POMS_tension_1	.791*	.005	13
		POMS_depression_1	.667*	.000	13
		POMS_anger_1	.768*	.003	13
		POMS_vigour_1	.980	.981	13
		POMS_fatigue_1	.808*	.009	13
		POMS_confusion_1	.888	.093	13
Pons	B	HDI_7-item_6	.984	.983	10
(Cho & tCr)		HDI_sad-mood_6	.366*	.000	10

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		HDI_guilt_6	.509*	.000	10
		HDI_anhedonia_6	.907	.263	10
		HDI_subjective-tension_6	.509*	.000	10
		HDI_physical-anxiety_6	.805*	.017	10
		HDI_energy-loss_6	.815*	.022	10
		HDI_suicidality_6[0]			10
		POMS_total_6	.881	.136	10
		POMS_tension_6	.567*	.000	10
		POMS_depression_6	.568*	.000	10
		POMS_anger_6	.527*	.000	10
		POMS_vigour_6	.944	.600	10
		POMS_fatigue_6	.930	.444	10
		POMS_confusion_6	.867	.093	10
Pons	B	HDI_7-item_6	.958	.719	13
(NAA)		HDI_sad-mood_6	.311*	.000	13
		HDI_guilt_6	.446*	.000	13
		HDI_anhedonia_6	.866*	.047	13

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		HDI_subjective-tension_6	.553*	.000	13
		HDI_physical-anxiety_6	.812*	.009	13
		HDI_energy-loss_6	.820*	.012	13
		HDI_suicidality_6[0]			13
		POMS_total_6	.932	.364	13
		POMS_tension_6	.536*	.000	13
		POMS_depression_6	.496*	.000	13
		POMS_anger_6	.637*	.000	13
		POMS_vigour_6	.706*	.001	13
		POMS_fatigue_6	.950	.605	13
		POMS_confusion_6	.880	.072	13
Pons	D	HDI_7-item_D	.907	.336	8
(Cho & tCr)		HDI_sad-mood_D	.673*	.001	8
		HDI_guilt_D	.877	.178	8
		HDI_anhedonia_D	.930	.512	8
		HDI_subjective-tension_D	.720*	.004	8
		HDI_physical-anxiety_D	.932	.534	8

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		HDI_energy-loss_D	.418*	.000	8
		HDI_suicidality_D[0]			8
		POMS_total_D	.988	.991	8
		POMS_tension_D	.946	.670	8
		POMS_depression_D	.904	.314	8
		POMS_anger_D	.840	.075	8
		POMS_vigour_D	.863	.129	8
		POMS_fatigue_D	.921	.442	8
		POMS_confusion_D	.946	.669	8
Pons	D	HDI_7-item_D	.924	.322	12
(NAA)		HDI_sad-mood_D	.643*	.000	12
		HDI_guilt_D	.813*	.013	12
		HDI_anhedonia_D	.907	.197	12
		HDI_subjective-tension_D	.782*	.006	12
		HDI_physical-anxiety_D	.875	.075	12
		HDI_energy-loss_D	.753*	.003	12
		HDI_suicidality_D[0]			12

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		POMS_total_D	.954	.689	12
		POMS_tension_D	.974	.994	12
		POMS_depression_D	.865	.056	12
		POMS_anger_D	.738*	.002	12
		POMS_vigour_D	.713*	.001	12
		POMS_fatigue_D	.929	.374	12
		POMS_confusion_D	.967	.879	12
LADPF[4]	A	HDI_7-item_1	.865*	.036	14
(3 peaks)		HDI_sad-mood_1	.552*	.000	14
		HDI_guilt_1	.703*	.000	14
		HDI_anhedonia_1	.297*	.000	14
		HDI_subjective-tension_1	.784*	.003	14
		HDI_physical-anxiety_1	.581*	.000	14
		HDI_energy-loss_1	.297*	.000	14
		HDI_suicidality_1[0]			14
		POMS_total_1	.878	.054	14
		POMS_tension_1	.775*	.003	14

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		POMS_depression_1	.642*	.000	14
		POMS_anger_1	.743*	.001	14
		POMS_vigour_1	.985	.995	14
		POMS_fatigue_1	.802*	.005	14
		POMS_confusion_1	.897	.102	14
	B	HDI_7-item_6	.965	.807	14
		HDI_sad-mood_6	.297*	.000	14
		HDI_guilt_6	.428*	.000	14
		HDI_anhedonia_6	.889	.078	14
		HDI_subjective-tension_6	.599*	.000	14
		HDI_physical-anxiety_6	.860*	.031	14
		HDI_energy-loss_6	.821*	.009	14
		HDI_suicidality_6[0]			14
		POMS_total_6	.926	.265	14
		POMS_tension_6	.562*	.000	14
		POMS_depression_6	.476*	.000	14
		POMS_anger_6	.614*	.000	14

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		POMS_vigour_6	.737*	.001	14
		POMS_fatigue_6	.948	.532	14
		POMS_confusion_6	.889	.077	14
	D	HDI_7-item_D	.964	.817	13
		HDI_sad-mood_D	.620*	.000	13
		HDI_guilt_D	.795*	.006	13
		HDI_anhedonia_D	.946	.544	13
		HDI_subjective-tension_D	.868	.050	13
		HDI_physical-anxiety_D	.925	.291	13
		HDI_energy-loss_D	.795*	.006	13
		HDI_suicidality_D[0]			13
		POMS_total_D	.958	.725	13
		POMS_tension_D	.963	.792	13
		POMS_depression_D	.841*	.022	13
		POMS_anger_D	.745*	.002	13
		POMS_vigour_D	.697*	.001	13
		POMS_fatigue_D	.954	.654	13

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		POMS_confusion_D	.978	.966	13
		Depressed group			
Pons	A	HDI_7-item_1	.908	.230	11
(3 peaks)		HDI_sad-mood_1	.934	.456	11
		HDI_guilt_1	.793*	.008	11
		HDI_anhedonia_1	.804*	.011	11
		HDI_subjective-tension_1	.822*	.019	11
		HDI_physical-anxiety_1	.805*	.011	11
		HDI_energy-loss_1	.649*	.000	11
		HDI_suicidality_1	.600*	.000	11
		POMS_total_1	.869	.074	11
		POMS_tension_1	.837*	.029	11
		POMS_depression_1	.922	.340	11
		POMS_anger_1	.838*	.029	11
		POMS_vigour_1	.902	.198	11
		POMS_fatigue_1	.894	.155	11
		POMS_confusion_1	.875	.091	11

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
	B	HDI_7-item_6	.982	.976	10
		HDI_sad-mood_6	.934	.493	10
		HDI_guilt_6	.906	.258	10
		HDI_anhedonia_6	.905	.246	10
		HDI_subjective-tension_6	.769*	.006	10
		HDI_physical-anxiety_6	.880	.130	10
		HDI_energy-loss_6	.731*	.002	10
		HDI_suicidality_6	.366*	.000	10
		POMS_total_6	.942	.581	10
		POMS_tension_6	.954	.721	10
		POMS_depression_6	.937	.522	10
		POMS_anger_6	.819*	.024	10
		POMS_vigour_6	.894	.188	10
		POMS_fatigue_6	.855	.066	10
		POMS_confusion_6	.952	.695	10
	D	HDI_7-item_D	.977	.945	10
		HDI_sad-mood_D	.936	.506	10

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		HDI_guilt_D	.794*	.012	10
		HDI_anhedonia_D	.902	.231	10
		HDI_subjective-tension_D	.903	.238	10
		HDI_physical-anxiety_D	.977	.944	10
		HDI_energy-loss_D	.815*	.022	10
		HDI_suicidality_D	.801*	.015	10
		POMS_total_D	.942	.578	10
		POMS_tension_D	.834*	.037	10
		POMS_depression_D	.935	.502	10
		POMS_anger_D	.979	.960	10
		POMS_vigour_D	.961	.797	10
		POMS_fatigue_D	.967	.865	10
		POMS_confusion_D	.956	.739	10
LADPF	A	HDI_7-item_1	.926	.344	12
(3 peaks)		HDI_sad-mood_1	.943	.538	12
		HDI_guilt_1	.780*	.006	12
		HDI_anhedonia_1	.806*	.011	12

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		HDI_subjective-tension_1	.846*	.033	12
		HDI_physical-anxiety_1	.777*	.005	12
		HDI_energy-loss_1	.650*	.000	12
		HDI_suicidality_1	.640*	.000	12
		POMS_total_1	.898	.148	12
		POMS_tension_1	.856*	.044	12
		POMS_depression_1	.907	.198	12
		POMS_anger_1	.883	.096	12
		POMS_vigour_1	.938	.478	12
		POMS_fatigue_1	.920	.286	12
		POMS_confusion_1	.894	.133	12
	B	HDI_7-item_6	.991	.998	10
		HDI_sad-mood_6	.961	.793	10
		HDI_guilt_6	.781*	.008	10
		HDI_anhedonia_6	.946	.627	10
		HDI_subjective-tension_6	.651*	.000	10
		HDI_physical-anxiety_6	.885	.150	10

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		HDI_energy-loss_6	.731 *	.002	10
		HDI_suicidality_6	.532 *	.000	10
		POMS_total_6	.918	.340	10
		POMS_tension_6	.911	.288	10
		POMS_depression_6	.879	.129	10
		POMS_anger_6	.761 *	.005	10
		POMS_vigour_6	.914	.307	10
		POMS_fatigue_6	.872	.105	10
		POMS_confusion_6	.898	.209	10
	D	HDI_7-item_D	.965	.843	10
		HDI_sad-mood_D	.928	.432	10
		HDI_guilt_D	.794 *	.012	10
		HDI_anhedonia_D	.893	.182	10
		HDI_subjective-tension_D	.903	.238	10
		HDI_physical-anxiety_D	.955	.733	10
		HDI_energy-loss_D	.833 *	.036	10
		HDI_suicidality_D	.801 *	.015	10

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		POMS_total_D	.970	.890	10
		POMS_tension_D	.864	.086	10
		POMS_depression_D	.907	.259	10
		POMS_anger_D	.970	.889	10
		POMS_vigour_D	.954	.718	10
		POMS_fatigue_D	.981	.972	10
		POMS_confusion_D	.960	.786	10
		Both groups			
Pons	A	HDI_7-item_1	.927	.093	23
(Cho & tCr)		HDI_sad-mood_1	.859*	.004	23
		HDI_guilt_1	.825*	.001	23
		HDI_anhedonia_1	.813*	.001	23
		HDI_subjective-tension_1	.880*	.010	23
		HDI_physical-anxiety_1	.830*	.001	23
		HDI_energy-loss_1	.760*	.000	23
		HDI_suicidality_1	.406*	.000	23
		POMS_total_1	.901*	.026	23

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		POMS_tension_1	.874*	.008	23
		POMS_depression_1	.846*	.002	23
		POMS_anger_1	.720*	.000	23
		POMS_vigour_1	.967	.615	23
		POMS_fatigue_1	.870*	.006	23
		POMS_confusion_1	.897*	.022	23
Pons	A	HDI_7-item_1	.920	.057	24
(NAA)		HDI_sad-mood_1	.846*	.002	24
		HDI_guilt_1	.820*	.001	24
		HDI_anhedonia_1	.801*	.000	24
		HDI_subjective-tension_1	.875*	.007	24
		HDI_physical-anxiety_1	.826*	.001	24
		HDI_energy-loss_1	.751*	.000	24
		HDI_suicidality_1	.396*	.000	24
		POMS_total_1	.892*	.014	24
		POMS_tension_1	.868*	.005	24
		POMS_depression_1	.833*	.001	24

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		POMS_anger_1	.710*	.000	24
		POMS_vigour_1	.973	.729	24
		POMS_fatigue_1	.865*	.004	24
		POMS_confusion_1	.890*	.013	24
Pons	B	HDI_7-item_6	.950	.361	20
(Cho & tCr)		HDI_sad-mood_6	.799*	.001	20
		HDI_guilt_6	.808*	.001	20
		HDI_anhedonia_6	.924	.119	20
		HDI_subjective-tension_6	.802*	.001	20
		HDI_physical-anxiety_6	.837*	.003	20
		HDI_energy-loss_6	.795*	.001	20
		HDI_suicidality_6	.236*	.000	20
		POMS_total_6	.930	.153	20
		POMS_tension_6	.879*	.017	20
		POMS_depression_6	.878*	.016	20
		POMS_anger_6	.723*	.000	20
		POMS_vigour_6	.919	.094	20

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		POMS_fatigue_6	.906	.054	20
		POMS_confusion_6	.945	.300	20
Pons	B	HDI_7-item_6	.929	.104	23
(NAA)		HDI_sad-mood_6	.760*	.000	23
		HDI_guilt_6	.771*	.000	23
		HDI_anhedonia_6	.904*	.030	23
		HDI_subjective-tension_6	.784*	.000	23
		HDI_physical-anxiety_6	.811*	.001	23
		HDI_energy-loss_6	.798*	.000	23
		HDI_suicidality_6	.215*	.000	23
		POMS_total_6	.942	.203	23
		POMS_tension_6	.845*	.002	23
		POMS_depression_6	.832*	.001	23
		POMS_anger_6	.711*	.000	23
		POMS_vigour_6	.729*	.000	23
		POMS_fatigue_6	.920	.066	23
		POMS_confusion_B	.920	.067	23

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
Pons	D	HDI_7-item_D	.939	.279	18
(Cho & tCr)		HDI_sad-mood_D	.908	.080	18
		HDI_guilt_D	.862*	.013	18
		HDI_anhedonia_D	.949	.405	18
		HDI_subjective-tension_D	.932	.208	18
		HDI_physical-anxiety_D	.964	.682	18
		HDI_energy-loss_D	.764*	.000	18
		HDI_suicidality_D	.617*	.000	18
		POMS_total_D	.964	.672	18
		POMS_tension_D	.894*	.045	18
		POMS_depression_D	.931	.205	18
		POMS_anger_D	.948	.398	18
		POMS_vigour_D	.957	.544	18
		POMS_fatigue_D	.945	.358	18
		POMS_confusion_D	.954	.485	18
Pons	D	HDI_7-item_D	.947	.279	22
(NAA)		HDI_sad-mood_D	.881*	.012	22

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		HDI_guilt_D	.831*	.002	22
		HDI_anhedonia_D	.939	.191	22
		HDI_subjective-tension_D	.919	.074	22
		HDI_physical-anxiety_D	.949	.303	22
		HDI_energy-loss_D	.846*	.003	22
		HDI_suicidality_D	.556*	.000	22
		POMS_total_D	.960	.499	22
		POMS_tension_D	.923	.088	22
		POMS_depression_D	.915	.061	22
		POMS_anger_D	.903*	.035	22
		POMS_vigour_D	.824*	.001	22
		POMS_fatigue_D	.984	.965	22
		POMS_confusion_D	.953	.359	22
LADPF	A	HDI_7-item_1	.910*	.027	26
(3 peaks)		HDI_sad-mood_1	.839*	.001	26
		HDI_guilt_1	.824*	.000	26
		HDI_anhedonia_1	.798*	.000	26

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		HDI_subjective-tension_1	.894*	.011	26
		HDI_physical-anxiety_1	.808*	.000	26
		HDI_energy-loss_1	.754*	.000	26
		HDI_suicidality_1	.441*	.000	26
		POMS_total_1	.898*	.014	26
		POMS_tension_1	.877*	.005	26
		POMS_depression_1	.820*	.000	26
		POMS_anger_1	.736*	.000	26
		POMS_vigour_1	.981	.904	26
		POMS_fatigue_1	.886*	.008	26
		POMS_confusion_1	.891*	.010	26
	B	HDI_7-item_6	.940	.164	24
		HDI_sad-mood_6	.756*	.000	24
		HDI_guilt_6	.714*	.000	24
		HDI_anhedonia_6	.920	.059	24
		HDI_subjective-tension_6	.749*	.000	24
		HDI_physical-anxiety_6	.826*	.001	24

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		HDI_energy-loss_6	.792*	.000	24
		HDI_suicidality_6	.316*	.000	24
		POMS_total_6	.922	.065	24
		POMS_tension_6	.852*	.002	24
		POMS_depression_6	.781*	.000	24
		POMS_anger_6	.603*	.000	24
		POMS_vigour_6	.752*	.000	24
		POMS_fatigue_6	.925	.077	24
		POMS_confusion_6	.913*	.041	24
	D	HDI_7-item_D	.974	.775	23
		HDI_sad-mood_D	.839*	.002	23
		HDI_guilt_D	.818*	.001	23
		HDI_anhedonia_D	.958	.422	23
		HDI_subjective-tension_D	.919	.064	23
		HDI_physical-anxiety_D	.951	.314	23
		HDI_energy-loss_D	.870*	.007	23
		HDI_suicidality_D	.542*	.000	23

Appendix 27 continued

Shapiro-Wilk Test for Normality of Distribution for Depression Raw and Difference Scores Used for Correlations with Neurochemical Concentrations As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI (peak)	Scan time[1]	Scale[2]_variable_Time[3]	Shapiro Wilk test		
			Statistic	*p*	*n*
		POMS_total_D	.967	.621	23
		POMS_tension_D	.944	.215	23
		POMS_depression_D	.893*	.018	23
		POMS_anger_D	.901*	.026	23
		POMS_vigour_D	.817*	.001	23
		POMS_fatigue_D	.982	.936	23
		POMS_confusion_D	.955	.378	23

Note. [1] A, B and D refer to Scan time A (Day 1 at 12:00), Scan time B (Day 2 at 12:00) and the difference scores between Scan time A and Scan time B. [2] HDI: Hamilton Depression Inventory; POMS: Profile of Mood states. [3] Time 1 and 6 were Day 1 at 11:30 and Day 2 at 11:30, respectively; D refers to the difference scores between Time 1 and Time 6. [4] Left anterior dorsal prefrontal. [0] Variable not assessed when all scores were 0.

* $p < .05$.

Appendix 28

Shapiro-Wilk Test for Normality of Distribution for Neurochemical Raw and Difference Concentrations Used for Correlations with Depression Scores As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI	Scan time[1]	Neurochemical	Shapiro-Wilk test		
			Statistic	*p*	*n*
		Control group			
Pons	A	Cho:H_2O	.913	.234	12
		tCr:H_2O	.933	.416	12
		NAA:H_2O	.875	.061	13
	B	Cho:H_2O	.852	.061	10
		tCr:H_2O	.826*	.030	10
		NAA:H_2O	.897	.122	13
	D	Cho:H_2O	.784*	.019	8
		tCr:H_2O	.969	.891	8
		NAA:H_2O	.947	.594	12
LADPF[2]	A	Cho:H_2O	.964	.781	14
		tCr:H_2O	.963	.767	14
		NAA:H_2O	.941	.430	14
	B	Cho:H_2O	.907	.141	14
		tCr:H_2O	.966	.813	14
		NAA:H_2O	.945	.489	14

Appendix 28 continued

Shapiro-Wilk Test for Normality of Distribution for Neurochemical Raw and Difference Concentrations Used for Correlations with Depression Scores As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI	Scan time[1]	Neurochemical	Shapiro-Wilk test		
			Statistic	*p*	*n*
	D	Cho:H_2O	.925	.289	13
		tCr:H_2O	.946	.535	13
		NAA:H_2O	.894	.111	13
		Depressed group			
Pons	A	Cho:H_2O	.893	.152	11
		tCr:H_2O	.893	.150	11
		NAA:H_2O	.929	.405	11
	B	Cho:H_2O	.917	.334	10
		tCr:H_2O	.982	.975	10
		NAA:H_2O	.936	.511	10
	D	Cho:H_2O	.994	.999	10
		tCr:H_2O	.954	.710	10
		NAA:H_2O	.974	.926	10
LADPF	A	Cho:H_2O	.919	.279	12
		tCr:H_2O	.924	.320	12
		NAA:H_2O	.832*	.022	12
	B	Cho:H_2O	.965	.840	10

Appendix 28 continued

Shapiro-Wilk Test for Normality of Distribution for Neurochemical Raw and Difference Concentrations Used for Correlations with Depression Scores As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI	Scan time[1]	Neurochemical	Shapiro-Wilk test		
			Statistic	*p*	*n*
		tCr:H_2O	.928	.433	10
		NAA:H_2O	.973	.915	10
	D	Cho:H_2O	.927	.416	10
		tCr:H_2O	.917	.336	10
		NAA:H_2O	.980	.965	10
		Both groups			
Pons	A	Cho:H_2O	.950	.297	23
		tCr:H_2O	.980	.914	23
		NAA:H_2O	.920	.059	24
	B	Cho:H_2O	.967	.695	20
		tCr:H_2O	.980	.914	20
		NAA:H_2O	.931	.117	23
	D	Cho:H_2O	.950	.425	18
		tCr:H_2O	.969	.776	18
		NAA:H_2O	.985	.986	22
LADPF	A	Cho:H_2O	.951	.241	26
		tCr:H_2O	.969	.590	26

Appendix 28 continued

Shapiro-Wilk Test for Normality of Distribution for Neurochemical Raw and Difference Concentrations Used for Correlations with Depression Scores As a Function of Brain Volume of Interest (VOI) and Scan Time

VOI	Scan time[1]	Neurochemical	Shapiro-Wilk test		
			Statistic	*p*	*n*
		$NAA:H_2O$	.955	.311	26
	B	$Cho:H_2O$	.955	.352	24
		$tCr:H_2O$	.923	.067	24
		$NAA:H_2O$	.966	.580	24
	D	$Cho:H_2O$	.930	.108	23
		$tCr:H_2O$	.958	.422	23
		$NAA:H_2O$	.953	.340	23

Note. [1] A, B and D refer to Scan time A (Day 1 at 12:00), Scan time B (Day 2 at 12:00) and the difference scores between Scan time A and Scan time B. [2] Left anterior dorsal prefrontal.

* $p < .05$.