META-ANALYSIS OF THE ANTIDEPRESSANT RESPONSE TO SLEEP DEPRIVATION AND ITS CORRELATES: TOWARDS A BETTER ANTIDEPRESSANT THERAPY

by

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ABSTRACT

Unlike antidepressant drugs, which typically require several weeks to produce an antidepressant response, sleep deprivation produces a response literally overnight. Quantification (meta-analysis) of 166 articles, including data from a total of 3951 depressed patients, reveals that consistently half of all depressed patients are responders to a night of sleep deprivation, with the degree of response shown by these responders being on average a 55% decrease in depression levels. While the level of this response depends upon both when the sleep deprivation occurs in the night and when response measurements are taken, no experimental treatment has yet been found to further enhance its response. The practicality of sleep deprivation as an antidepressant treatment has so far been limited by the fact that the majority of responders to sleep deprivation normally relapse by the day following a night of recovery sleep. However, there is some evidence that this relapse can be prevented or delayed, especially by depletion of the serotonergic system. The strength of reported correlates of response to sleep deprivation and of its relapse were examined and the nature of the most powerful correlates of response was found to depend upon their timing: correlates measured before sleep deprivation (thus related to the susceptibility to response) show between-subjects differences while correlates dependent upon measurements taken after a night of sleep deprivation (thus related to the response itself) show only within-subject changes

from before to after sleep deprivation. Since whether a patient is a responder to one night of sleep deprivation is unrelated to whether the same patient will be a responder to any other night of sleep deprivation, it is hypothesized that the activity levels of some of these predictor variables may also change across time in relation to the susceptibility to response. The discovery of such susceptibility-state markers and their temporal order could help shed light on the mechanism of susceptibility to response and thus offer new ways of improving current antidepressant treatments.

Keywords: SLEEP DEPRIVATION, DEPRESSION, META-ANALYSIS, CORRELATES OF ANTIDEPRESSANT RESPONSE, CORRELATES OF RELAPSE, ANTIDEPRESSANT TREATMENTS

DEDICATION

Emotions make the difference between life being a living heaven and hell. Happiness makes life worth living and depression can make us think it is not. An understanding of what determines our emotions is therefore essential to ensuring the good life.

This thesis is dedicated to the millions of individuals that suffer from depression in the hope that it may help contribute towards the eventual discovery of a cure for their condition.

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1. INTRODUCTION

1.1 Why study the effects of sleep deprivation upon depression?

At first thought, having depressed patients undergo sleep deprivation may seem an unusual or even cruel endeavour. In normal individuals sleep deprivation tends to slightly impair mood and produce a mild dysphoric effect (Gerner et al., 1979; Pilcher & Huffcutt, 1996). Furthermore, depressed patients commonly complain of having difficulty getting enough sleep and this insomnia has actually been argued to be a risk factor for the development of depression (Riemann & Voderholzer, 2003; Nutt et al., 2008). The fact that sleep deprivation, instead of worsening depression, actually produces an antidepressant response in depressed patients is thus a paradox needing to be solved.

One distinct advantage of the antidepressant response to sleep deprivation, compared to that of other antidepressant treatments, is its speed (see Post et al., 1987 for a direct comparison of the time course of antidepressant effects seen with sleep deprivation compared to common antidepressant treatments). While antidepressant medication on average requires several weeks to reach a level of response great enough to label patients as responders - a time course no different from that seen with placebo controls (Stassen et al. 1997) - the effects of sleep deprivation occur literally

overnight. Even with electroconvulsive therapy (ECT), the most common method of treatment in situations where it is desirable to relieve depressive symptoms as rapidly as possible (such as with suicidal patients), a similar level of response as seen with sleep deprivation is typically not reached until more than a week after the start of treatment (Post et al., 1987; Daly et al., 2001; Kho et al., 2003). Equally rapid, though, has been the reported rate of relapse seen following a night of recovery sleep from sleep deprivation. This makes sleep deprivation, by itself, not very clinically practical for the long-term treatment of depression. However, both aspects of its rapidity make sleep deprivation more appealing from a research perspective. First, understanding the mechanisms of these quick shifts in mood could help improve current antidepressant treatments by increasing the speed of onset of response and delaying/preventing relapse. Second, this speed suggests that the effects of sleep deprivation are closer to the underlying mechanism directly in control of depressed mood than are those of other antidepressant treatments. Third, sleep deprivation is a more practical method for studying influences upon antidepressant response and relapse, in terms of not having to wait weeks to see results.

1.2 Past & present reviews of the literature

For over 40 years, the scientific literature has reported that sleep deprivation produces an antidepressant effect in clinically depressed patients (Schulte, 1966; Vogel et al., 1968; Pflug & Tölle, 1971a,b). Although a number of

recent reviews have described and integrated findings on the antidepressant response to sleep deprivation (Wirz-Justice & Van den Hoofdakker, 1999; Holsboer-Trachsler & Seifritz, 2000; Ringel & Szuba, 2001; Giedke & Schwarzler, 2002; Riemann et al., 2002; Berger et al., 2003; Cano-Lozano et al., 2003; Giedke, 2004; Wirz-Justice et al., 2005; Svestka, 2008; Benedetti & Smeraldi, 2009; Ravindran et al., 2009; Hemmeter et al., 2010), the last comprehensive quantitative assessments of this literature were published over a decade ago (Gillin, 1983; Wehr, 1990; Wu & Bunney, 1990; Elsenga, 1992). In addition, there has been no meta-analysis published on the relative strengths of reported correlates of this antidepressant response to sleep deprivation. Therefore, I undertook a current quantitative evaluation of this literature guided by the following questions:

1) How effective is sleep deprivation at producing an antidepressant response?

2) How transient is the antidepressant response to sleep deprivation?

3) Which variables recorded either before, during, or after sleep deprivation correlate most strongly with the degree of antidepressant response to sleep deprivation?

4) Which variables recorded either before, during, or after recovery sleep correlate most strongly with the degree of relapse seen following recovery sleep?

5) How consistent is the antidepressant response to sleep deprivation within-subjects across multiple sleep deprivations? And what does this tell us about the

variables able to predict the antidepressant response to sleep deprivation between-subjects?

6) Can the antidepressant response to sleep deprivation be made more clinically practical, in terms of methods to either

a) Enhance or prolong the antidepressant response to sleep deprivation?

b) Use sleep deprivation to predict or enhance the response to antidepressant drugs?

Unfortunately, there is insufficient quantitative data reported in the literature on the adverse effects of sleep deprivation in depressed patients to include this topic in the current meta-analysis. However, for an excellent review of this topic the reader is encouraged to see the recent review by Hemmeter et al. (2010).

2. METHOD

2.1 Literature search

Studies included in the present meta-analysis were found through the Pubmed database and the reference sections of articles. The key words used in the Pubmed search were “depression sleep deprivation”. Based on this inclusive Pubmed search, 962 results were found. Articles were further screened and included in the present analyses only if they met the following three criteria: (a) they were written in English, (b) they studied patients with clinically diagnosed depression, and (c) they reported descriptive or inferential statistics either on the antidepressant effects of sleep deprivation or on variables related to the antidepressant response to sleep deprivation. Due to my lack of fluency in other languages, a total of 47 articles written in 8 other languages (Danish, Dutch, French, German, Japanese, Polish, Russian, and Spanish) were excluded from the present analyses. I apologize for this limitation and hope to include them in a future updated version of this meta-analysis.

In the case of separately published studies that used the same patient samples, the decision rule was adopted to treat these studies as a single study with potentially multiple independent variables (Hedges & Olkin, 1985). Conversely, multiple experiments using different groups of patients reported within the same published article were treated as separate studies.

2.2 Recorded variables

Averages on any variables relevant to the antidepressant response to sleep deprivation were then collected from these articles. If differences between responders and nonresponders to sleep deprivation were reported, the effect size was calculated using Cohen's *d* statistic, which describes the difference between group means in terms of their pooled standard deviations (Cohen, 1988). The formula for calculating this effect size is shown in Table 1. For each *d*, Cohen (1988) also provided a *U* statistic that represents the degree of nonoverlap in joint distributions of scores between groups. With a simple conversion (subtracting *U* from 100), this can also represent the degree of joint group overlap and can be approximated without the use of calculus by the formula shown in Table 1. Thus, for example, a *d* of 3.0 would correspond to a situation where there is a 7% overlap in the distributions of a variable between two groups, such as between responders and nonresponders.

In order to be included in the present analyses of differences between responders and nonresponders, two additional criteria were required of the data. First, patients had to have been classified as either responders or nonresponders based upon their immediate response to each individual sleep deprivation (i.e., on the day following the night of sleep deprivation) and not based upon the overall effect on depression of a series of sleep deprivations. This was chosen so as to avoid the assumption that the effects of sleep deprivation occur reliably

within-subject (see the 'Inconsistency of response to sleep deprivation within-subject' section below for testing of this assumption). Second, the reported differences between responders and nonresponders needed to include either measures of central tendency and dispersion (e.g., means and standard deviations) or inferential statistics capable of being converted to effect sizes (e.g., *F*, *t*; see Thalheimer & Cook, 2002).

The strength of reported correlations was also recorded between any variable and either the degree of antidepressant response seen following one night of sleep deprivation or the degree of relapse seen following recovery sleep. In order to make direct comparisons between the strength of correlations and Cohen's *d* effect sizes, the latter were also converted to Pearson product-moment correlation coefficients using the formula described by Cohen (1988) and shown in Table 1.

2.3 Statistical analyses

N in this paper refers to the number of studies used in each analysis and not the actual number of patients involved in the primary studies. Since the number of patients per study varied widely, weighted statistics were used where indicated in order to correct for the number of patients in each study (see Table 1 for how these weighted statistics were calculated). This procedure gives greater weight to studies that had larger sample sizes and hence to ones that have more

reliable findings (Bland & Altman, 1995; Bland & Kerry, 1998; Bills & Guohua, 2005; Kercheval et al., 2008).

For assessing the number of primary studies reporting significant versus nonsignificant results for a given relationship, whether the probability (*p*) of each study's reported effect was lesser or greater than .05, respectively, was tallied. For any statistical comparisons, two-tailed significance tests were used with alpha set at 0.05 and with family-wise error corrected for by the Bonferonni procedure. For comparisons of depression levels between responders and nonresponders and between two specific days, one-sample t-tests were used, with a null hypothesis value of Cohen's *d* being equal to zero. For comparisons between clinician- and self-rated measurements of depression, two-sample t-tests were used. For assessing the degree of consistency in antidepressant response seen within-subjects across different sleep deprivation trials, the intraclass correlation coefficient (ICC) was computed by statistical software (SPSS for Windows, version 17.02; SPSS, Chicago, USA) using the one-way random-effects model with single and average measures. The ICC is the most statistically valid method for estimating the degree to which subjects' responses remain constant across observation periods (Dunn, 1992; McGraw & Wong, 1996) and has been used previously to measure possible trait-like effects of sleep deprivation seen in healthy subjects (Van Dongen et al., 2004). Its value reflects the proportion of total variance in the data that is explained by systematic between-subjects differences (see Table 1 for formulas to derive the two versions of this statistic that were used in this paper). The remaining unexplained variance

(calculated as 1 minus the ICC value) reflects the total variance due to within-subject differences and could result from such possible sources as endogenous variability within subjects, situational variance, and random measurement error.

3. RESULTS AND DISCUSSION

3.1 Antidepressant effects of sleep deprivation

3.1.1 Number of studies

One hundred and forty-nine articles, published between 1974 and 2010 (see Figure 1), met criteria for inclusion in the present analyses on the antidepressant response to sleep deprivation shown in Table 2. Since seventeen of these articles reported multiple studies with different groups of patients, a total of one hundred and sixty-six studies were actually used in the present analyses. These studies represent a total of 3951 depressed patients. In contrast, previous meta-analyses of this literature contained less than half this number of studies and patients (Gillin, 1983; Wehr, 1990; Wu & Bunney, 1990; Elsenga, 1992).

Since in eleven studies patients were sleep deprived more than once, the present analyses included a total of 4575 sleep deprivations. Eliminating the studies that used multiple sleep deprivations per patient (but that reported the effects of each sleep deprivation) did not essentially change any of the results from the meta-analysis, and therefore these studies were left included in the present analyses.

3.1.2 Response to sleep deprivation

On average across these studies, on the day following a night of sleep deprivation approximately half (49%) of all patients attain an antidepressant response great enough for them to be labelled as responders (Table 2; see the 'Study methods' section below for a detailed description of the various criteria used by the studies to define responders). This percentage is lower than previous estimates, with averages provided by other meta-analyses of this literature ranging from 56-59% (Gillin, 1983; Wehr, 1990; Wu & Bunney, 1990; Elsenga, 1992). However, it is equivalent to the 50% estimate previously given by Elsenga (1992) when their analysis was restricted to the literature from the most recent decade (1981-1990) that was available to them.

The actual degree of this response can be described in either within-subject terms (% change from each patient's baseline) or between-groups terms (difference between responders and nonresponders), and based on either clinician-rated measurements (such as the Hamilton Depression Rating Scale) or self-rated measurements (such as a Visual Analogue Scale). Using within-subject terms based on clinician-rated measurements, depression significantly decreases from baseline in all patients by a third (33%; in comparison to a null hypothesis average effect size of zero, $t_w(53) = 11.45$, $p < .0001$), in responders by more than half (55%; in comparison to a null hypothesis average effect size of zero, $t_w(28) = 9.61$, $p < .0001$), and in nonresponders by only one-fourteenth

(7%; in comparison to a null hypothesis average effect size of zero, $t_w(29) = 3.37$, $p = .002$). The degree of decrease from baseline in all patients based on self-rated measurements of depression (30%, $n = 27$) is smaller but nonsignificantly different from that based on clinician-rated measurements ($t_w(113) = 1.23$, $p = .22$). The decrease in depression seen in responders using self-rated measurements (41%, $n = 3$) is smaller than that seen with clinician-rated measurements, while for nonresponders the decrease in depression using self-rated measurements (14%, $n = 2$) is larger than that seen with clinician-rated measurements. However, there were an insufficient number of studies that reported self-rated measurements of depression for responder and nonresponder groups to statistically test whether these values significantly differ from the clinician-rated measurements for those groups.

Not surprisingly, when using between-groups terms based on clinician-rated measurements, responders show significantly less depression than nonresponders on the day following a night of sleep deprivation (in comparison to a null hypothesis average effect size of zero, $t_w(28) = 9.34$, $p < .0001$), with a 20% overlap in depression levels between these groups. In contrast, on the day prior to sleep deprivation responders are slightly, but nonsignificantly (in comparison to a null hypothesis average effect size of zero, $t_w(35) = 0.50$, $p = .62$), more depressed than nonresponders, with a 96% overlap in depression levels between these groups.

3.1.3 Relapse following a night of recovery sleep

Nearly two-thirds (65%) of responders to sleep deprivation relapse by the day after the first night of recovery sleep. In almost all studies reporting this information (13 out of 14), the criteria used to define relapse in responders involved a minimum percentage increase (typically by at least 30%) in Hamilton Depression Rating Scale scores. Two previous meta-analyses (Wu & Bunney, 1990; Elsenga, 1992) have examined the rate of relapse of responders on the day following a night of recovery sleep, with estimates reported separately for studies with patients on antidepressant medication versus studies that did not provide such medication. When these two categories of drug condition are averaged across, the estimates of relapse rate given by the two previous meta-analyses (71% and 60% for Wu & Bunney, 1990 and Elsenga, 1992, respectively) are within the 95% confidence interval of the estimate reported here.

While the degree of response produced by sleep deprivation is significantly lessened in responders after a night of recovery sleep (in comparison to a null hypothesis average effect size of zero, $t_w(3) = 7.33$, $p = .005$), the majority of it still remains, with two-thirds (66%) of the response to sleep deprivation retained on average by responders. Unfortunately, there is insufficient data reported in the literature to determine the exact degree of change in depression levels for relapsing versus non-relapsing responders. In

contrast to the responder group, there are no reliable changes after a night of recovery sleep in all patients as a whole (in comparison to a null hypothesis average effect size of zero, $t_w(23) = 1.64$, $p = .11$), with 97% of the response to sleep deprivation remaining. In the nonresponder group, the relatively minor response to sleep deprivation nonsignificantly increases after a night of recovery sleep (in comparison to a null hypothesis average effect size of zero, $t_w(2) = 2.51$, $p = .13$) by 42%. This is consistent with some reports (Giedke et al., 1992, 2003) that 15-18% of patients only show a response to sleep deprivation after a night of recovery sleep. However, due to insufficient data reported in the literature, it cannot be determined what percentage of patients within the nonresponder group are responsible for this change in depression levels. Using between-groups terms based on clinician-rated measurements, on the day following a night of recovery sleep the responder group shows only a trend towards significantly less depression than the nonresponder group in the few studies reporting this information (in comparison to a null hypothesis average effect size of zero, $t_w(3) = 2.07$, $p = .07$), with a 69% overlap in depression levels between these two groups.

There is insufficient quantitative data reported in the literature on what the rate of relapse is for more than the first day after a night of recovery sleep in order to examine this in the present meta-analysis. Informally, some studies have said that by 4-7 days later all responders are back to original baseline levels of depression (reviewed in Giedke & Schwarzler, 2002). Also regrettably, no study has reported studying the effects of more than one consecutive night of total

sleep deprivation to see if it is the sleep that occurs during the recovery night that is producing the relapse observed on the following day. However, it has been shown that partial sleep deprivation (for either the first or the second half of the night) on the recovery night following a night of sleep deprivation is insufficient to sustain the antidepressant response to sleep deprivation (Elsenga et al., 1990) and that relapse can occur during the recovery night before any sleep has actually taken place (Southmayd et al., 1990).

3.2 Study methods

3.2.1 Responder criteria

Of the 166 studies whose antidepressant effects were examined in Table 2, 7% failed to report what type of depression scale was used for defining their responder criteria. The majority (70%) of studies that did report this information used versions of the Hamilton Depression Rating Scale. Items #4, 5, & 6 dealing with sleep, #16 dealing with weight loss, and #18 dealing with diurnal variation were typically omitted in abridged versions of the Hamilton Depression Rating Scale since changes in these items could not be meaningfully assessed due to the lack of sleep to report on and to the short time intervals between depression measurements used in these studies. Within the studies using versions of the Hamilton Depression Rating Scale, 24% of studies failed to report what specific criteria for discriminating between responders and nonresponders were used,

69% reported using a percentage decrease in scores from baseline as their criteria, and 7% reported using an absolute difference in scores from baseline as their criteria. Across these studies, the mode for this percentage decrease criteria was ≥ 30% and the range was from ≥ 25 to ≥ 50%. As could be expected, studies using more stringent percentage decrease criteria tended to report less patients labelled as responders ($r_w(68) = -.23$, $p = .06$) and reported significantly greater degrees of response seen in responders ($r_w(29) = .53$, $p = .002$).

3.2.2 Sleep deprivation method

Of the 166 studies whose antidepressant effects were examined in Table 2, 2% failed to report what type of sleep deprivation they used. The majority (73%) of studies that did report this information used the total sleep deprivation method, 23% kept patients awake during only the second half of the night, and 4% kept patients awake during only the first half of the night. In studies using the second half of the night sleep deprivation method, patients went to bed at their regular time but were awoken at a mode time of 0130 (with a range of 0000-0330 across studies), and were then kept awake throughout the entire following day. In studies using the first half of the night sleep deprivation method, patients stayed awake throughout the entire day prior to the night of sleep deprivation and into the night, had a mode time of going to sleep of 0200 (with a range of 0200-0300 across studies), and then were only allowed to sleep until a mode time of 0700

(with a range of 0500-0800 across studies) before being kept awake throughout the entire following day.

Surprisingly, there are no significant differences between studies using total versus second half of the night sleep deprivation methods in the antidepressant effects they report on the day following a night of sleep deprivation (see Table 3), with the range of *p* values being .42 to .83. This lack of difference is in contrast to the findings of the two primary studies (Giedke et al., 1990, 2003) which experimentally compared these two methods and which both found the total sleep deprivation method to be significantly superior to the second half of the night sleep deprivation method.

Although few studies have examined the antidepressant effects of the first half of the night sleep deprivation method, it can be seen that these studies do report significantly lower percentages of responders (58% lower than with the total sleep deprivation method, $t_w(91) = 7.59$, $p < .0001$; 60% lower than with the second half of the night sleep deprivation method, $t_w(32) = 6.92$, $p < .0001$) and smaller responses in all patients on the day following a night of sleep deprivation (49% lower than with the total sleep deprivation method, $t_w(64) = 4.04$, $p = .0001$; 48% lower than with the second half of the night sleep deprivation method, $t_w(22) = 3.69$, $p = .001$). These results are in agreement with the majority (67%) of primary studies (Sack et al., 1988; Giedke et al., 1992; Leibenluft et al., 1993; Szuba et al., 1994; Parry et al., 1995, 2000) which experimentally compared the antidepressant effects of second half versus first half of the night sleep

deprivation methods and found the latter method to be less effective. The relatively inferior antidepressant effects of the first half of the night sleep deprivation method may be due to the recovery sleep it allows immediately following sleep deprivation since a nap following sleep deprivation has been shown to increase the probability of relapse (see the 'Correlates of relapse following response to sleep deprivation' section below).

Although there was a trend for studies that report later times in the night for the start of the second half of the night sleep deprivation method to show lower levels of response in responders ($r_w(10) = -.70$, $p = .01$; see Table 4) and higher levels of response in nonresponders ($r_w(8) = .76$, $p = .01$; see Table 4), after correcting for the family-wise error rate that results from the multiple measures of antidepressant effect shown in Table 4 these correlations are no longer statistically significant.

3.2.3 Time of response measurement

Of the 166 studies whose antidepressant effects were examined in Table 2, 21% failed to report what time of day response measurements were taken. In the remaining studies that did report this information, the time of day when response measurements were taken can be divided into 3 categories: morning (5:00-12:00), afternoon (12:00-16:59), and evening (17:00-24:00). The percentage of these studies that recorded response measurement at these

different times are as follows in order of their frequency: 45% in the morning only, 24% in both the morning and the evening, 17% throughout the day at times that included all three time of day categories, 11% in the afternoon only, 3% in both the morning and the afternoon, and 2% in the evening only. Studies using a single time of response measurement do not significantly different from studies using multiple times of response measurement in the percentages of responders ($t_w(317) = 0.62$, $p = .54$) or the degree of response in all patients on the day following a night of sleep deprivation ($t_w(69) = 0.96$, $p = .34$) that they report.

There are several reports (van den Burg & van den Hoofdakker, 1975; Post et al., 1976; Rudolf & Tölle, 1978; Haug & Fähndrich, 1988; Szuba et al., 1991; Hemmeter et al., 1998) that responders do not begin to diverge from nonresponders in depression levels on the night of sleep deprivation until after 6:00-8:00 in the morning. Since this was reported across studies independent of whether a total or second half of the night sleep deprivation method was used, this suggests that a circadian factor influences the timing of expression of the antidepressant response to sleep deprivation. Improvements in responders occur either abruptly or gradually (Post et al., 1976), with response level of the responder group as a whole continuing to improve throughout the rest of the day and beginning to reach asymptotic levels of response by early afternoon (van den Burg & van den Hoofdakker, 1975; Gerner et al., 1979; Rudolf & Tölle, 1978; Szuba et al., 1991; Hemmeter et al., 1998; see Figure 2). In agreement with these findings, across studies that recorded response measurement at only a single time of day, the level of response of responders improves in a decelerating

nonlinear fashion with increasingly later times of day of response measurement (see Figure 3; after log transformation using the equation shown in Figure 3, $r_w(16) = .32$, $p = .20$, and with the three outliers removed $r_w(13) = .74$, $p = .002$).

The time of day pattern of these changes appears similar to what has been reported for spontaneous diurnal variations of mood of specifically positive affect (which is characterized by feelings such as enthusiasm, interest, and satisfaction) in both normal subjects (Clark et al., 1989; Wood & Magnello, 1992; Watson et al., 1999; Peeters et al., 2006; Murray, 2007) and depressed patients (Peeters et al., 2006). Positive affect tends to rise throughout the morning and then remains elevated throughout the rest of the day before showing a substantial decline very late in the evening (around 22:00 onwards). In contrast, negative affect (which is characterized by feelings of anxiety, nervousness, tension, and guilt) shows no systematic rhythm across the day in normal subjects (Clark et al., 1989; Wood & Magnello, 1992; Watson et al., 1999; Peeters et al., 2006; Murray, 2007) and a rise in the morning followed by a linear decline throughout the rest of the day in depressed patients (Peeters et al., 2006).

3.3 Correlates of response to sleep deprivation

3.3.1 Demographic & clinical variables

Table 5 shows the sample characteristics of the studies used in the analysis on the antidepressant effects of sleep deprivation that were described in Table 2. Demographic and clinical characteristics were typical of those seen in depressed patients in general (Goodwin et al., 1996; Lam & Mok, 2008). Patients in these sleep deprivation studies typically were in their mid-forties, had experienced their first bout of depression in their mid-thirties, had four previous bouts of depression, had their current depressive episode last for 20 weeks, and suffered from moderately severe levels of clinical depression. The majority of patients were female (64%), experienced unipolar depression (66%), were without psychotic symptoms (94%), and were not on antidepressant medication (67%) or mood stabilizers (96%) at the time of sleep deprivation.

Based on percentages of primary studies that reported a significant effect and on average effect sizes, it can be seen that there is very little evidence that demographic and clinical variables influence the antidepressant effects seen on the day after a night of sleep deprivation (see Table 6). Except for psychotic symptoms, for all of the other variables the majority of studies failed to find significant results. The primarily significant finding with psychotic symptoms is based on only one study (Elsenga & Van den Hoofdakker, 1987) which statistically examined this variable and found that psychotic depressed patients show a greater response to sleep deprivation than nonpsychotic depressed

patients. However, even in this case the effect size (r = .27) is relatively small, with presence of psychotic symptoms accounting for only 7% of the variability in response to sleep deprivation across patients. Two additional studies, although lacking statistical analysis, also addressed this question and found results contradictory to each other: one study (Benedetti et al., 1999c) found that all five of their psychotic depressed patients became worse after a night of sleep deprivation while the other study (Post et al., 1976) found that all four of their psychotic depressed patients responded to sleep deprivation.

Two statistically significant findings can be seen based on correlations across studies between their sample characteristics and the antidepressant effects of sleep deprivation that they reported (see Table 7). First, studies with larger percentages of males report larger differences in depression levels between responder and nonresponder groups on the day following a night of sleep deprivation ($r_w(27) = .58$, $p = .001$). Second, studies with larger percentages of bipolar patients report better levels of response in all patients on the day following a night of recovery sleep ($r_w(21) = .62$, $p = .002$). However, as can be seen in Figures 4a&b, the latter two correlations are not based upon a full range of the possible intermediate values. In particular, there are few studies where male or bipolar patients represent greater than half but less than the entire patient sample. Since the strengths of these two correlations depend almost entirely upon findings from studies which have used 100% male or bipolar patient samples, and given the fact that sex and bipolarity have not been found to be significantly related to response in the majority of primary studies (see Table 6),

this suggests that these two correlations may be due to some third factor (such as sample selection bias) rather than to direct effects of sex or bipolarity on response.

3.3.2 Environmental variables

Light and motor activity do not appear to mediate the antidepressant effect of sleep deprivation (see Table 8). No significant differences in response are observed between patients given low versus bright levels of light intensity (<1 vs. >3000 lux in Wehr et al., 1985a; <60 vs. >2000 lux in van den Burg et al., 1990) during sleep deprivation. Similarly, no significant differences in response are seen between patients restricted to bed during sleep deprivation vs. conventional sleep deprivation in which patients are allowed to move about freely (Baumgartner & Sucher, 1990). Indeed, even in a strict constant routine protocol in which patients are kept in a slightly inclined position and locomotor activity is completely restricted for 40hours, an expected percentage of patients (45%) still become responders to sleep deprivation (Graw et al., 1998).

3.3.3 Spontaneous behavior variables

While amounts of motor activity may not causally determine the antidepressant response shown to sleep deprivation, their spontaneous levels do predict the degree of response (see Table 9), with responders showing more

fidgeting-type behavior on the day before sleep deprivation. Studies (Matussek et al., 1974; Elsenga & Van den Hoofdakker, 1988; Szuba et al., 1991; Ebert et al., 1994b; Brückner & Wiegand, 2010) examining motor activity, as measured by actometers worn on their wrists or ankles, do not consistently report significant differences between responders and nonresponders before, during, or after sleep deprivation. However, based on one study's (Bouhuys et al., 1989) analysis of video-taped 20-minute interviews on the day before sleep deprivation, the level of antidepressant response seems particularly related to the frequency to which patients touch their bodies or objects, with 24% of the variability in antidepressant response accounted for by this behavior.

In addition, although on the day before and after a night of sleep deprivation responder and nonresponder groups show little difference in their absolute levels of eye-blink rate as assessed by analysis of video-taped 3-minute periods, the relative degree of increase in eye-blink rate following sleep deprivation accounts for 56% of the variability in antidepressant response (Ebert et al., 1996). This difference between the groups is due to the fact that following sleep deprivation eye-blink rates increase in responders while not significantly changing in nonresponders and normal subjects. Based on the fact that spontaneous eye-blink rates correlate positively with central dopamine activity, the authors of the above finding (Ebert et al., 1996) suggested that an increase in dopamine release could be responsible for the antidepressant response to sleep deprivation (see the ‘Summary of the most powerful correlates’ section below for a further discussion of this theory’).

3.3.4 Psychological variables

On the day before sleep deprivation, responder and nonresponder groups do not appear to differ widely between each other in any psychological variable (see Table 10) in addition to their having similar depression levels (Table 2). Prior to sleep deprivation, similar levels of activation/energy/vigor (Bouhuys et al., 1990a), anxiety/strain/stress/tension (Bouhuys et al., 1990a; Volk et al., 1997; Clark & Golshan, 2007a), pain threshold (Kundermann et al., 2008), and expectation about therapeutic effects of sleep deprivation (Buddeberg & Dittrich 1978; Leibenluft et al., 1993; Reynolds et al., 2005) are seen between these two groups, and only slightly less fatigue/tiredness (Van Den Burg et al., 1992; Bouhuys et al., 1995) and more vigilance (Wu et al., 1992, 1999) in responders. Following sleep deprivation, there are no significant relationships between antidepressant response and the levels of any of these psychological variables (activation/energy/vigor - Szuba et al., 1991; anxiety/strain/stress/tension - Szuba et al., 1991; Volk et al., 1997; Clark & Golshan, 2007a; fatigue/tiredness - Szuba et al., 1991; Van Den Burg et al., 1992; Bouhuys et al., 1995; Hemmeter et al., 1998; pain threshold - Wu et al., 1992, 1999).

However, similar to the pattern seen with eye-blink rate described above, the relative degree of increase in activation/energy/vigor following sleep deprivation is higher in responders, accounting for 58% of the variability in antidepressant response (Van den Hoofdakker et al., 1989). Also, within-subjects

across the day following a night of sleep deprivation, the specific timing of the increases in response (specifically of decreases in depressive mood) is significantly correlated with the timing of increases in activation/energy/vigor (average *r* across studies = .69; Bouhuys et al., 1990a; Van Den Burg et al., 1992) and of decreases in anxiety/strain/stress/tension (average *r* across studies = -.77; Bouhuys et al., 1990a; Van Den Burg et al., 1992) but not with the timing of increases in tiredness (*r* = -.23; Van Den Burg et al., 1992). This correlation between when response and increases in activation/energy/vigor occur is consistent with the similar time of day pattern for when response and spontaneous diurnal variations of positive affect occur (see the 'Time of response measurement' section above).

3.3.5 Evoked potential variables

Evoked potentials are electrical potentials recorded from the nervous system following the presentation of a stimulus and averaged across repeated trials to eliminate background noise from spontaneous potentials. Evoked potentials recorded from the cerebral cortex of the brain are known as event-related potentials (ERPs) and the timing of each of their waveform components following stimulus presentation can be related to the level of information processing occurring in the brain. In the typical nomenclature, these waveform components are referred to by a preceding letter indicating the polarity and by a following number indicating the typical latency in deciseconds/milliseconds. For

example, the earliest of these detected ERP components is known as the P1 because it shows a positive potential and occurs around 100 milliseconds following stimulus presentation, thus reflecting the time it takes for the information to reach the cortex. In contrast, the P300 occurs around 300 milliseconds following stimulus presentation and is thought to reflect a higher level of cognitive processing.

On the day before sleep deprivation, lower amplitudes in the earliest of these ERPs, the P1 and N1, predict a better antidepressant response to sleep deprivation (see Table 11), with 53% and 34% of the variability in response accounted for by the P1 and N1, respectively (Buchsbaum et al., 1981; Danos et al., 1994). In addition, responders show a lower rate of increase in P1 amplitudes with increasing intensities of stimulus (Buchsbaum et al., 1981). Thus, on the day prior to sleep deprivation, responders can be characterized as showing less brain excitability to external stimuli. Following sleep deprivation, P1 and N1 amplitudes increase in responders but decrease in nonresponders. This dissociation reduces differences in absolute levels of event-related potential amplitudes between responders and nonresponders following sleep deprivation but enlarges differences between the two groups in the relative degree of change in these levels from before to after a night of sleep deprivation, with 45% of the variability in response accounted for by the increase in N1 amplitude from before to after a night of sleep deprivation (Danos et al., 1994). While prior to sleep deprivation there is no evidence of differences between responders and nonresponders in amplitudes of later ERPs or in the latencies of any ERPs, responders do show

less of a decrease in P300 amplitudes and N1 latencies from before to after a night of sleep deprivation relative to nonresponders, with 32% of the variability in response accounted for separately by these two ERP characteristics (Danos et al., 1994). All of the above ERP results were seen equally across the different EEG electrode derivatives measured across the scalp.

Although the intensity of environmental light levels during sleep deprivation does not determine the antidepressant response to sleep deprivation (see the 'Environmental variables' section above), a relative increase from before to after a night of sleep deprivation in the amplitude peak of corneo-fundal potentials in reaction to light adaptation is predictive of a greater antidepressant response to sleep deprivation, with 36% of the variability in response accounted for by this variable (Sokolski et al., 1995). This difference between the groups is due to the fact that following sleep deprivation light-adapted corneo-fundal potentials increase in responders while decreasing in nonresponders and normal subjects. Interestingly, changes from before to after a night of sleep deprivation in corneo-fundal potentials in reaction to darkness adaptation do not significantly relate to the degree of antidepressant response. The fundamental difference in mechanisms of light versus dark adaptation in the eye is that dark adaptation is dependent upon regeneration of photopigments, whereas light adaptation is due to a switch in mode from rod-dominated to cone-dominated signaling (Krizaj, 2000; Sherwood, 2005). Since dopamine has long been known to play a key role in mediating this switch for light adaptation (for recent reviews see Krizaj, 2000; Witkovsky, 2004), the authors of the above mentioned finding (Sokolski et al.,

1995) suggested that an increase in either dopamine release or dopamine receptor sensitivity could be responsible for the antidepressant and light adaptation effects of sleep deprivation seen in responders (see the 'Summary of the most powerful correlates' section below for a further discussion of this theory).

3.3.6 Sleep variables

Prior to sleep deprivation, the only sleep characteristic that the majority of studies to statistically examine it have found can significantly predict the antidepressant response to sleep deprivation is a lower amount of microsleeps occurring during the daytime (see Table 12), with 40% of the variability in response accounted for by this sleep variable (Hemmeter et al., 1998). A microsleep was defined as any polysomnographically-detected sleep period lasting 15 or more seconds, and patients were continuously electrographically recorded starting on the night before the night of sleep deprivation and ending after the night of recovery sleep. The pattern of lower amounts of microsleeps seen in responders prior to sleep deprivation remains during and following sleep deprivation, with this difference from nonresponders being on average across studies only slightly diminished following sleep deprivation (Hemmeter et al., 1998, 2007).

Following sleep deprivation, responders display several other differences in sleep characteristics from nonresponders that, in general, are known to be indicative of a greater homeostatic sleep drive (Dijk & Czeisler, 1995; Khalsa et al., 2002). First, in the majority of studies responders show significantly decreased REM sleep amounts and rapid eye movement densities within REM sleep during a nap in the daytime following sleep deprivation, with 16% and 7% of the variability in response accounted for by these two REM sleep characteristics, respectively (Wiegand et al., 1993; Reist et al., 1994). Second, responders show during the recovery night significantly increased delta power and slow wave sleep amounts in the first Non-REM sleep period compared to nonresponders, with 22% and 25% of the variability in response accounted for by these two sleep variables, respectively (Gillin et al., 1989). Third, responders show an increase from before to after sleep deprivation in waking EEG power density in the theta range that is significantly greater than what is seen in nonresponders, with 48% of the variability in response accounted for by this variable (Danilenko & Putilov, 2005). This theta power increases in an exponentially accelerating fashion throughout the day following a night of sleep deprivation in responders as in normal subjects but not in nonresponders.

3.3.7 Functional brain imaging variables

Within at least the first two days (36 hours) prior to the night of sleep deprivation, responders show lower levels of activity bilaterally in the

anterolateral prefrontal cortex (Ebert et al., 1991), especially within its upper portions, and higher levels of activity in the limbic system (Wu et al., 1992), especially within the right amygdala (Clark et al., 2006a), and in paralimbic regions, especially within the right orbitofrontal cortex (Ebert et al., 1991; Ebert et al., 1994a; Volk et al., 1997; see Table 13). The activity of these brain regions highly discriminates between responders and nonresponders, with 56-64% of the variability in response accounted for across them. This pattern of regional brain activity appears similar to the inverse relationship between the activity of the dorsolateral prefrontal cortex and that of limbic-paralimbic regions previously reported to occur in both depressed patients in general and in normal subjects experiencing sadness (Mayberg et al., 1999). The lower levels of prefrontal activity that predict responders may also be related to findings of lower prefrontal activity being predictive of vulnerability to the cognitive impairments caused by sleep deprivation in healthy nonclinical subjects and that have been related to a "cognitive reserve hypothesis" of such vulnerability (Goel et al., 2009).

Despite these large differences in regional brain activity levels between responders and nonresponders prior to sleep deprivation, following sleep deprivation there are no consistent reports of significant differences in regional brain activity levels between the two groups. This is due to decreases after a night of sleep deprivation in the activity of brain regions, such as the right amygdala (Clark et al., 2006a) and the left ventral anterior cingulate (Smith et al., 1999; Clark et al., 2001, 2006b), which were previously hyperactive in responders prior to sleep deprivation. In contrast, in nonresponders and normal

subjects increases in the activity of these same brain regions are seen following sleep deprivation. One brain region which may be a possible exception to this is the upper portions of the anterolateral prefrontal cortex which has been reported to continue showing decreased levels of activity in responders following sleep deprivation (Ebert et al., 1991). Even though this finding did not attain statistical significance, 42% and 33% of the variability in response can be accounted for by the activity of this brain structure's left and right sides, respectively, following sleep deprivation. However, a more recent study (Wu et al., 2008), which unfortunately did not report statistical results on these details, casts doubt on even this difference from nonresponders being maintained, with instead the activity of the dorsolateral prefrontal cortex described as increasing in responders following sleep deprivation. This would support the idea that the reciprocal relationship between changes in activity levels of the dorsolateral prefrontal cortex and those of limbic-paralimbic regions is maintained following sleep deprivation.

3.3.8 Neurochemical variables

For measurements taken prior to or during the night of sleep deprivation, there are three neurochemical variables that the majority of reports show can significantly predict the antidepressant response to sleep deprivation (see Table 14). First, although the dopamine metabolite homovanillic acid (HVA; measured from either urinary or cerebral fluid samples), that is used as a marker of

dopaminergic activity, does not consistently show significant differences between responders and nonresponders (Post et al., 1976; Gerner et al., 1979; Müller et al., 1993), using single photon emission computed tomography (SPECT) responders have been found to have greater occupancy for dopamine D2 receptor radioligands in the right basal ganglia before sleep deprivation, with 26% of the variability in response accounted for (Ebert 1994b). Only the basal ganglia region was chosen to be evaluated in that study because the resolution of SPECT cameras at the time it was conducted did not allow quantification of D2 receptor radioligand occupancy in extrastriatal brain regions. This greater D2 receptor radioligand occupancy in responders prior to sleep deprivation presumably reflects greater D2 receptor vacancies and three possible causes for this were suggested: decreased amounts of dopamine release in responders, increased affinity of D2 receptors in responders, and/or increased numbers of D2 receptors in responders. Given the lack of consistently significant differences between responders and nonresponders in HVA levels, it would appear that either of the latter two interpretations is correct and/or, as suggested by the fact that significant effects were not seen for D2 receptor radioligand occupancy in the left basal ganglia, this difference is due to only very localized changes in dopamine release in the brain. Second, although markers of serotonergic activity, including levels of the metabolite 5-Hydroxyindole-3-acetic acid (5HIAA; measured from cerebral fluid samples; Post et al., 1976; Gerner et al., 1979) and of imipramine binding to blood platelets (Haug et al., 1988), do not consistently show significant differences between responders and nonresponders,

responders do show before sleep deprivation a significantly smaller inhibition of prolactin release in response to administration of the serotonin agonist dl-fenfluramine, with 17% of the variability in response accounted for by this insensitivity to serotonin changes (Kasper et al., 1988c). Third, responders show before sleep deprivation greater levels of choline compounds in the pons (measured by magnetic resonance spectroscopy) than nonresponders, with this difference in pons choline levels accounting for 72% of the variability in response (Bernier et al., 2009).The difference reflects a decrease in nonresponders pons choline levels relative to healthy control individuals whereas responder levels do not differ from controls. The authors of this finding suggested that these choline levels may reflect phospholipid metabolic activity in the pons.

After a night of sleep deprivation, the only neurochemical variable above for which the majority of studies still report significant differences between responders and nonresponders is dopamine D2 receptor vacancies in the right basal ganglia. However, instead of being higher than nonresponders, as was the situation prior to sleep deprivation, after a night of sleep deprivation responders show lower D2 receptor vacancies, with 30% of the variability in response accounted for (Ebert 1994b). Due to this reversal, the relative degree of decrease from before to after a night of sleep deprivation in D2 receptor vacancies of the right basal ganglia highly differentiates between responders and nonresponders, with 70% of the variability in response accounted for by this change. This suggests that it is the relative degree of increase in D2 receptors, rather than its absolute levels, which primarily relates to the antidepressant response to sleep

deprivation. Similarly, the relative degree of increase from before to after a night of sleep deprivation, but not absolute difference between-subjects, in the disinhibition of prolactin release in response to administration of the D2 receptor antagonist sulpiride is significantly related to the antidepressant response, with 57% of the variability in antidepressant response accounted for by this sensitivity to dopamine changes (Ebert et al., 1993). Presumably, this relatively greater disinhibition of prolactin release following sleep deprivation that can be produced in responders is due to a greater tonic inhibition of prolactin by dopaminergic activity during sleep deprivation, and thus suggests that relatively increased dopaminergic activity or sensitivity to its effects is related to the antidepressant response to sleep deprivation (see the 'Summary of the most powerful correlates' section below for a further discussion of this theory).

Although the norepinephrine/epinephrine metabolite vanillylmandelic acid (VMA; measured from urinary samples) measured before or during the night of sleep deprivation has not consistently been reported to predict the antidepressant response to sleep deprivation (Matussek et al., 1974; Müller et al., 1993), the sole study to examine relative changes from before to after a night of sleep deprivation in VMA reported that its increase significantly predicted the antidepressant response to sleep deprivation, with 52% of the variability in antidepressant response accounted for (Müller et al., 1993). The explanation given in that study for why VMA shows this significant effect but the other norepinephrine/epinephrine metabolite 3-Methoxy-4-hydroxyphenylglycol (MHPG; measured from either urinary or cerebral fluid samples) does not was

that, while MHPG can be used as a marker of norepinephrine/epinephrine activity in the central nervous system, the primary source of urinary VMA is from adrenergic neurons in the peripheral nervous system. Accordingly, responders would be expected to show greater relative increases in sympathetic nervous system activity from before to after a night of sleep deprivation than nonresponders. Following sleep deprivation responders also show a greater increase in BDNF (measured from blood samples; Gorgulu & Caliyurt, 2009) and glutamine (measured in the left prefrontal cortex by magnetic resonance spectroscopy; Murck et al., 2009), which account for 21% and 35% of the variability in response, respectively.

3.3.9 Genetic variables

Genetic variables are not highly predictive of the antidepressant response to sleep deprivation (see Table 15). The only gene for which primarily significant results have been reported between its variants and the antidepressant response to sleep deprivation is the glycogen synthase kinase 3-β gene (Benedetti et al., 2004). However, even in this case, only a relatively small effect size was shown, with 10% of the variability in antidepressant response accounted for.

3.3.10 Hormonal variables

Prior to sleep deprivation, across studies responders show primarily significant differences from nonresponders in a number of hormonal variables, especially interleukin-6 and reverse T3 activity (see Table 16). First, responders have lower levels of the cytokine interleukin-6 (IL-6), with 44% of the variability in response accounted for by this variable before sleep deprivation (Benedetti et al., 2002). IL-6 is involved in the acute-phase response to infection (Janeway et al., 2005) and has been speculated to play a causal role in depression (Maes, 2008). Second, while primarily showing only nonsignificant differences from nonresponders in most thyroid-related hormones (thyrotropin, triiodothyronine, & thyroxine), responders have significantly higher levels of reverse triiodothyronine (rT3), with 46% of the variability in response accounted for (Baumgartner et al., 1990a). rT3 is created when thyroxine (T4) that would otherwise have been converted into triiodothyronine (T3) is instead converted into rT3. Although large increases in the conversion of T4 into rT3 are normally only seen during times of catabolic conditions, such as starvation or severe illness (Hennemann et al., 1988; De Groot, 2006), levels of rT3 are also positively correlated with the state-dependent severity of depression (Kjellman et al., 1983). Since rT3 acts as a competitive antagonist to T3 by binding to its receptors but not stimulating them, the elevation of rT3 seen in responders prior to sleep deprivation is probably responsible for the decreased triiodothyronine uptake (T3U) also observed in responders before sleep deprivation (David et al., 2000).

In addition to the above differences, across studies responders also show primarily significant, although relatively minor, differences from nonresponders before sleep deprivation in androgen-related hormones and metabolites of progesterone. First, responders show increased androgen activity before sleep deprivation, with 18% and 29% of the variability in response accounted for by levels of dehydroepiandrosterone (DHEA; Schule et al., 2004) and testosterone (Baumgartner et al., 1990a), respectively. Secondly, responders show increased levels of the progesterone metabolites allopregnanolone (3α,5α-THP) and pregnanolone (3α,5β-THP), with 29% of the variability in response accounted for by 3α,5α-THP before sleep deprivation (Schule et al., 2004).

Of all the hormonal variables described above, the only ones in which the majority of studies still report significant differences between responders and nonresponders following sleep deprivation are DHEA (Schule et al., 2004) and 3α,5β-THP (Schule et al., 2004). In addition, the sensitivity of thyrotropin response to thyrotropin-releasing hormone has been reported to be higher in responders following sleep deprivation, with 10% of the variability in response accounted for by this variable (Orth et al., 2001).The only hormonal variable in which the majority of studies reported a significant difference between responders and nonresponders in its rate of increase from before to after sleep deprivation was beta-endorphin, with 25% of the variability in response accounted for by this variable (Ebert et al., 1994c).

3.3.11 Circadian rhythm variables

Prior to sleep deprivation, responders can be characterized as showing a longer duration of melatonin phase, a greater propensity towards diurnal variations of mood, and differences from nonresponders in the amplitude of their circadian rhythms (see Table 17). The greater duration of melatonin phase found in responders several months prior to sleep deprivation (Parry et al., 2008) might suggest a difference in chronotype between responders and nonresponders. Chronotype has been shown to play a role in mood changes after sleep deprivation in healthy subjects (Selvi et al., 2007), with early chronotypes showing an increase and late chronotypes showing a decrease in their depression levels. However, to my knowledge a role of chronotype has not yet been examined in the antidepressant effects of sleep deprivation in depressed patients. Similarly, I am not aware of any studies examining the possible effects of the season of testing on the antidepressant response to sleep deprivation. The antidepressant effect of sleep deprivation reported in patients with seasonal affective disorder (Graw et al., 1998), on the other hand, is equivalent to what is typically seen on average across all depressed patients.

Although the occurrence of a diurnal variation in mood (defined as a difference from morning to evening in mood scores) on either of the two days prior to the night of sleep deprivation has only weakly and not consistently been found to predict the occurrence of a response to sleep deprivation (Elsenga & Van den Hoofdakker, 1987; Reinink et al., 1990; Schilgen & Tölle, 1980;

Bouhuys, 1991; Riemann et al., 1991; Szuba et al., 1991; Haug, 1992; Leibenluft et al., 1993; Naylor et al., 1993; Bouhuys et al., 1995), an increased amplitude and frequency of diurnal variations seen on average across several days prior to sleep deprivation is strongly related, with 32% and 41% of the variance in response accounted for, respectively (Bouhuys et al., 1990b; Reinink et al., 1993; Gordijn et al., 1994).). In agreement with the interpretation that it is the propensity towards having diurnal variations and not their actual occurrence immediately before sleep deprivation which is most predictive of response, experimental attempts to enhance the response to sleep deprivation by timing it to occur on a night immediately following a day with versus without diurnal variation of mood have failed to produce any significant effect (Reinink et al., 1993). Whether the diurnal variations in mood consist primarily of increases (termed 'positive DVs') or decreases (termed 'negative DVs') in mood from morning to evening does not appear to be related to response, but instead it is the degree and likelihood of having either type of diurnal variation of mood that is most related to response to sleep deprivation (Reinink et al., 1993; Gordijn et al., 1994). As a side note, it is important that diurnal variations in mood be assessed longitudinally to predict the response to sleep deprivation since retrospective assessment by patients of the frequency of their diurnal variations in mood has been found to not reliably match their actual longitudinal assessment (Reinink et al., 1993; Gordijn et al., 1994).

While there are no reports of significant differences between responders and nonresponders prior to sleep deprivation in the average cortisol or body

temperature levels seen across the day, the amplitude of their circadian changes has been reported to be significantly different from nonresponders, albeit not in the same direction for these two variables. The daily peak in cortisol that is seen during the morning has been reported to be significantly lower in responders on the day before, but not after, a night of sleep deprivation (Yamaguchi et al., 1978a). In contrast, the circadian rhythm of rectal temperature before sleep deprivation has been reported to be blunted in nonresponders while responders appear similar to normal subjects in this respect (Lee & Taylor, 1983). This amplitude difference in rectal temperature then reverses itself during sleep deprivation with responders showing an attenuation from before to during sleep deprivation of the body temperature nadir (i.e., responders have relatively greater body temperature during the night of sleep deprivation) but not of the body temperature peak seen during the daytime, with 16% of the variability in response accounted for by the change in minimum body temperature (Elsenga & Van den Hoofdakker, 1988).

Significant relationships between response and shifts in circadian rhythms during sleep deprivation have been reported for certain variables, however not always in the same direction and only for the second half of the night sleep deprivation method. While response is not significantly related to phase shifts in the peak time of cortisol (Bouhuys et al., 1990a) or thyrotropin (Parry et al., 1996) rhythms, the degree of phase advance in the prolactin rhythm that follows from the second half of the night sleep deprivation method accounts for 40% of the variability in response (Parry et al., 1996). However, in the same article, a

separate study that instead used the first half of the night sleep deprivation method found that the prolactin rhythm showed a phase delay and that this was not significantly related to response. Similarly, response has been found to be significantly related to changes in the duration and offset times of melatonin that occur only with the second but not the first half of the night sleep deprivation method (Parry et al., 2008). These results have led the authors (Parry et al., 1996, 2008) to conclude that the response to sleep deprivation is not mediated by shifts in these circadian rhythms.

3.3.12 Summary of the most powerful correlates

Table 18 shows the variables that, across the diverse categories examined above, are most highly correlated with the antidepressant response to sleep deprivation. As cut-off criteria for inclusion in this table, each variable needed to not only have been reported to be significantly related to the antidepressant response to sleep deprivation in the majority of studies that examined this relationship but also to account for at least a third of the variance in response ($r^2 \geq 33\%$; which is also equivalent to saying the overlap in distributions of the variable between responders and nonresponders is less than a third). What can be seen is that the most powerful variables pertain to specific differences in neurochemicals, brain activity, hormones, waking arousal, and psychological functions rather than in demographics, pre-existing clinical symptoms, environmental factors, sleep characteristics, or genetics. In addition,

other than actual differences in depression levels themselves, in no variable were between-subject differences either during or following a night of sleep deprivation powerful enough to be included in this table. Instead, only findings pertaining to either between-subject differences seen before sleep deprivation or the relative degree of change seen from before to after sleep deprivation were found to be highly sensitive to the antidepressant response to sleep deprivation.

Figure 5 summarizes within thirteen factors the twenty-four variables listed in Table 18, based on their similar appearances or possible underlying mechanisms as described above for each variable. It is important to note that the levels of correlates reported here (i.e., whether an increase or decrease in that correlate is associated with an increased probability of response) are relative differences between responders and nonresponders, and that in many cases it is unknown which of the two groups (if any) has normal levels relative to healthy control subjects. Between-subject differences that can predict ahead of time the antidepressant response to sleep deprivation are labelled factors related to the susceptibility to response. These include increases in pons phospholipid metabolic activity, the limbic:DLPFC brain activity ratio, duration of melatonin phase, reverse T3 levels, the propensity towards spontaneous shifts in mood, and waking arousal, as well as decreases in both brain excitability in response to external stimuli and pro-inflammatory cytokines. In contrast, any differences that depend upon measurements taken after sleep deprivation and that are highly related to the antidepressant response to sleep deprivation are labelled as factors related to the response itself. As described above, the only differences

that were found to be highly sensitive to the antidepressant response were relative within-subject changes from before to after sleep deprivation and include increases in dopaminergic-related activity, psychophysiological arousal, homeostatic sleep drive, brain excitability in response to external stimuli, and prefrontal glutamine levels.

Increases in dopaminergic activity have previously been suggested to be not only correlated with, but causally responsible for the antidepressant response to sleep deprivation based on the fact that psychostimulant drugs which enhance dopamine release also lead to elevations of mood (Ebert & Berger, 1998). The results of the present meta-analysis would appear to lend support for this dopaminergic theory if it were not for the following three facts. First, only relative changes in dopaminergic-related activity have been found, as opposed to absolute differences seen between patients. Second, more direct measurements of dopaminergic activity themselves, such as levels of dopamine metabolites, do not support the conclusion that dopamine levels are increased in responders. Third, drug treatments that enhance dopaminergic activity do not significantly affect the antidepressant response to sleep deprivation (Benedetti et al., 1996; Benedetti et al., 2001b).

3.4 Correlates of relapse following response to sleep deprivation

Prior to sleep deprivation, there are only two characteristics which the majority of studies to examine them have found can significantly, albeit only slightly, predict the degree of relapse seen following response to sleep deprivation (see Table 19). These predictors of increased relapse include variants of the angiotensin-converting enzyme gene (Baghai et al., 2003b) and of the serotonin 5-HT2A receptor gene (Benedetti et al., 2008), with 17% and 9% of the variance in relapse accounted for by these genetic variables, respectively.

Following sleep deprivation but still prior to relapse, a greater degree of relapse can be predicted by increased antidepressant response to sleep deprivation (Elsenga et al., 1990) and amount of Non-REM sleep (in particular Stage 2 sleep) during a post-sleep deprivation nap (Reist et al., 1994), and by decreases in the latency to fall asleep and the amount of Stage 1 sleep that occurs during the recovery night (Elsenga et al., 1990). Relative changes from during sleep deprivation to after a night of recovery sleep that predict a greater degree of relapse include decreases in minimum body temperature (Elsenga & Van den Hoofdakker, 1988; Elsenga et al., 1990) and psychological activation (Van den Hoofdakker et al., 1989), and an increase in psychological stress (Van den Hoofdakker et al., 1989).

Using the same methods as done above with correlates of response, the most powerful correlates of relapse can be identified (see Table 20) by using as cut-off criteria that at least a third of the variance in relapse ($r^2 \geq 33\%$) be accounted for by variables that have been found to be significantly related to the

relapse in the majority of studies that examined this relationship. Variables which meet this criteria and were measured prior to the relapse, thus indicating a greater susceptibility for relapse, include having a larger antidepressant response to sleep deprivation and showing increased Non-REM sleep, in particular Stage 2 sleep, during a nap following sleep deprivation. In terms of whether Non-REM sleep is playing a causal role in this relapse, it can be seen in Table 19 that only half of the studies to examine whether the occurrence of a nap following sleep deprivation impairs mood reported significant results. However, upon closer inspection, the two studies (Dressing et al., 1992; Riemann et al., 1993) that reported significant effects of having a nap upon depression levels (with r^2 = 13% across all patients and 51% across just responders) examined naps that were at least an hour in length whereas the two studies (Kraft et al., 1984; Gillin et al., 1989) that found nonsignificant results examined only brief 10-minute naps. This suggests that that there is a threshold of Non-REM sleep duration which must be passed in order for a nap to increase the probability of relapse. This may be similar to the effect observed in normal subjects who have been partially sleep deprived the night before, where a brief 10-minute nap has been found to produce immediate improvements in mood and cognition whereas a nap that is 30 minutes or longer in duration produces immediate impairments (Brooks & Lack, 2006).

3.5 Inconsistency of response to sleep deprivation within-subject

The fact that certain variables can predict with a high degree of accuracy which depressed patients will be responders to sleep deprivation has generally been interpreted to mean that responders and nonresponders reflect different types of patients. However, the majority of studies (4 out of 6) to examine the effects of giving repeated sleep deprivations to the same patients over multiple separate occasions show that how a patient responds to sleep deprivation on one occasion is not significantly related to how they respond to sleep deprivation on any other occasion (Kasper et al., 1990; Leibenluft et al., 1993; Kuhs et al., 1996a; Kuhs et al., 1998; Wiegand et al., 2001). In fact, the probability of a patient being a responder to sleep deprivation at any given time appears to be random, with on average across the studies to examine this probability (Telger et al., 1990; Kuhs et al., 1996a; Wiegand et al., 2001) there being an approximately 50% chance (48%, with a 12% standard deviation for the variation in means across these studies) that the same patient will be a responder to sleep deprivation at any time in a series of repeated sleep deprivations.

These results raise the following question: How can it be predicted ahead of time who will respond to sleep deprivation when the response to sleep deprivation is thus inconsistent within-subject? This contradiction can be reconciled in two ways:

1) The activity of some predictor variables may also fluctuate over time within-subject - with such variables hereafter referred to as *susceptibility-state markers* since they reflect the changing susceptibility to response. These

susceptibility-state markers would owe the strength of their associations to response by how closely related they are to the mechanism directly in control of the timing for when sleep deprivation will be effective at producing a response - hereafter referred to as the *susceptibility mechanism*. To help put this in perspective, a susceptibility-state marker can be thought of as analogous to measuring changes in a barometer to predict the weather.

2) Some predictor variables could instead remain stable and yet be related to the conditions that either increase or decrease the probability of response seen between-subjects - with such variables hereafter referred to as *susceptibility-trait markers* since they remain relatively constant within a patient. These susceptibility-trait markers would owe the strength of their associations to response by the degree to which they increase or decrease the frequency, amplitude, or output of the susceptibility mechanism, or by being related to other susceptibility-trait markers which do this. To help conceptualize this, the susceptibility-trait markers can be thought of as analogous to how differences in topography between regions result in their different climates: on average, changes in weather within a region are still random (you cannot accurately predict what today's whether will be based upon yesterday's) but some regions may have a greater tendency towards rain than others (e.g., the coastal & mountainous region of Vancouver versus the flat & dry prairies around Saskatoon).

The possible existence of susceptibility-trait markers as described in the second scenario above is dependent upon the assumption that some patients

have a consistent tendency towards greater or lesser responses to sleep deprivation than average. To test this assumption, a pooled analysis of within-subject responses to sleep deprivation was performed based on data from three studies (Telger et al., 1990; Kuhs et al., 1996a; Wiegand et al., 2001) that list the number of sleep deprivations each patient was a responder to across a series of sleep deprivations. This data includes a total of 76 patients and 342 sleep deprivations, with 3-6 sleep deprivations per patient and a time interval of 4-7 days between each night of sleep deprivation. The average response seen across patients did not significantly differ between trials of sleep deprivation ($F_{5,336}$ =1.41, p = .22). The single measure intraclass correlation coefficient (ICC) revealed that the response to any given trial of sleep deprivation accounted for 10% (with a 95% CI of 0.3% to 25%, p=.02) of the variance in response seen on any other trial of sleep deprivation. This indicates only a “slight” stability of interindividual differences in response, according to commonly used benchmarks for evaluating ICC values (Landis & Koch, 1977). The vast majority of variance (90%), on the other hand, can be accounted for by seemingly random within-subjects fluctuations from trial to trial. However, in addition to this single measure of reliability, an average measure ICC can also be calculated which, in this case, would reflect the reliability of interindividual differences in the response seen on average across sleep deprivation trials. Using the average measure ICC, 40% (with a 95% CI of 20% to 66%, p=.02) of the variance in response across trials can be accounted for by between-subjects differences in the average trend shown by a patient's responses to sleep deprivations, indicating a “fair” to

“moderate” degree of stability in response on average across trials. Thus, although the response to a single night of sleep deprivation is not highly predictive of the type of response seen on any other night of sleep deprivation, subjects do show trait-like trends for the way in which they typically respond and this is compatible with the possible existence of susceptibility-trait markers. The existence of such susceptibility-trait markers in depressed patients may be similar, albeit weaker and with an opposite effect upon mood, to the stable trait-like between-subjects differences in vulnerability to mood-disruptive effects of sleep deprivation that have been found in healthy nonclinical subjects (Van Dongen et al., 2004).

Of the variables listed on the left-hand side of Table 18 as being capable of predicting the response to sleep deprivation before it occurs, the only one to have been measured at a time interval greater than 36 hours before sleep deprivation and whose within-subject changes have been studied longitudinally in depressed patients is diurnal rhythms of mood. The occurrence of diurnal variations of mood has been found to be completely random within-subject, even on a day-to-day basis (Stallone et al., 1973). On average across studies that examined diurnal variations of mood in depressed patients longitudinally (Stallone et al., 1973; Tolle & Goetze, 1987; Reinink et al., 1993; Gordijn et al., 1994), there is a one-third chance (33%, with a 6% standard deviation for the variation in means across these studies) that a patient will experience a diurnal variation of mood on any given day. Although diurnal variations of mood may thus at first appear to be a susceptibility-state marker due to the variability of its

activity over time, it must be remembered that since it is not the occurrence of any one diurnal variation of mood before sleep deprivation but rather the average frequency and amplitude of their occurrence across long periods of time which are the characteristics of diurnal rhythms of mood most strongly predictive of the response to sleep deprivation (see the 'Circadian rhythm variables' section above) this makes diurnal variations of mood a susceptibility-trait marker. Amazingly, the 40% of variability in response that was described above to be accounted for by trait-like trends in the way patients respond to sleep deprivation across trials is almost exactly the same amount as what would predicted based on the amount of variance in response accounted for by the average tendency of a patient to show diurnal rhythms of mood. This latter variable accounted for 40% and 42% of the variability in response to sleep deprivation in the two studies (Reinink et al., 1993 and Gordijn et al., 1994, respectively) to examine it. Presumably whatever is causing some patients to typically have greater or lesser diurnal variations of mood than average is also responsible for these same individuals having greater or lesser responses to sleep deprivation than average. Since, in addition to their correlation, the response to sleep deprivation and diurnal variations of mood share similar time of day patterns (see the 'Time of response measurement" section above), it may also be the case that the same susceptibility mechanism controls the timing of both and that the response to sleep deprivation is simply a result of a positive enhancement of already spontaneously occurring diurnal variations of mood.

3.6 Attempts to make sleep deprivation more clinically practical

3.6.1 Treatments to enhance or prolong the response to sleep deprivation

To date, no treatment has yet been found to significantly affect the response to sleep deprivation. Extending the duration of sleep deprivation in the night does not appear to enhance the response on the following day since there are no significant differences between the level of response reported by studies using total versus the second half of the night sleep deprivation method (see the 'Sleep deprivation method' section above), with half of patients still responding to even the latest time in the night (0300) at which sleep deprivation has been reported to be started (Clark et al., 2000, 2001; Clark & Golshan, 2007b). Neither do increased levels of light intensity nor locomotor activity during sleep deprivation enhance the response (see the 'Environmental variables" section above). Furthermore, neurochemical treatments, such as the application of stimulants, antidepressants, or other drugs, do not enhance the response to sleep deprivation (see Table 21). In the case of antidepressant medications, the timing of when these drugs were first given does not appear to make a difference, with start times varying across studies from several months prior (Baumgartner et al., 1990a; Baumgartner & Sucher, 1990) to only on the night of the sleep deprivation (Bouhuys, 1991).

However, a number of treatments have been reported to help maintain the antidepressant effects of sleep deprivation beyond a single night of recovery sleep (see Table 22). Of particular note, there are two treatments, both involving

manipulations of the serotonergic system, whose effect sizes are far above those of the other treatments listed in Table 22. The first of these two treatments is a delayed effect of acute tryptophan depletion (Neumeister et al., 1998) where drug-free depressed patients, after being placed under a 24-hour low-tryptophan diet begun on the day prior to the night of sleep deprivation, received a tryptophan-free amino acid beverage on the day following a night of sleep deprivation. Although the acute tryptophan depletion that this beverage induced, and the serotonin reduction assumed to result from it, did not have any effect upon the antidepressant response seen on the day following a night of sleep deprivation, after patients were returned to a normal diet in the evening and allowed a night of recovery sleep those responders that had received this beverage were less likely to relapse (only 1 out of 11 of these responders relapsed) on the day following the night of recovery sleep than those that had instead received a sham drink supplemented with tryptophan (9 out of 11 of these control responders relapsed), with 43% of the variability in depression levels at this time point accounted for by whether patients had received the experimental or control condition. The response-prolonging effects of this acute tryptophan depletion were found to last a maximum of 4 days, by which point all patients became fully symptomatic again. This effect appears similar to the transient and 24-hour delayed antidepressant response seen without sleep deprivation in depressed patients given either acute tryptophan depletion (Delgado et al., 1994; Booij et al., 2005) or injection of the serotonin depleting drug reserpine (Poldinger, 1959, 1963; Haskovec & Rysanek, 1967; Carney et

al., 1969; Hopkinson & Kenny, 1975; Forsman et al., 1983; Ayd, 1985). Since less than half of the patients given tryptophan depletion without sleep deprivation showed the delayed response (16 out of 43 patients in Delgado et al., 1994; 6 out of 14 in Booij et al., 2005), this raises the possibility that sleep deprivation has a potentiating effect upon this delayed response. However, since Neumeister et al. (1998) administered the tryptophan-depletion challenge to only responders to sleep deprivation, it is not known whether sleep deprivation has such a potentiating effect or whether responders to sleep deprivation (as opposed to nonresponders) are just selectively more likely to produce this delayed response.

The second of the two most powerful treatments listed in Table 21 is the administration of the serotonergic 5-HT1A autoreceptor antagonist pindolol (Smeraldi et al., 1999) where patients received the drug for 9 days in combination with a series of 3 sleep deprivations during this period. Patients receiving pindolol did not show any deviance from the typical response-relapse pattern seen with sleep deprivation and recovery sleep until after the night of recovery sleep from the third sleep deprivation, at which time levels of depression were significantly lower than that of placebo controls with 41% of the variability in depression levels accounted for by whether patients received the experimental or control condition. The response to this final sleep deprivation was sustained in the previously pindolol-treated patients for at least an additional 3 days and depression levels continued to remain reduced compared to previously placebo-treated controls in a 6 months follow-up treatment with lithium.

3.6.2 Use of sleep deprivation to predict or enhance the response to antidepressant drugs

The level of response that a patient has to sleep deprivation does not reliably predict the level of response seen to subsequent treatment by antidepressant drugs. On average across the studies that statistically examined this relationship, only 42% (10 out of 24 studies) reported significant results (Amin, 1978; Wirz-Justice et al., 1979; Elsenga & Van den Hoofdakker, 1982; Fähndrich, 1983; Roy-Byrne et al., 1984; Dessauer et al., 1985; Höchli et al., 1986; Reynolds et al., 1987b; Kasper et al., 1990; Riemann &, Berger, 1990; Kasper et al., 1991; Holsboer-Trachsler et al., 1994; Szuba et al., 1994; Hemmeter et al., 1995; Kuhs et al., 1996a; Kuhs et al., 1998; Hernandez et al., 2000; Güdücü et al., 2005; Reynolds et al., 2005). The average reported correlation between the response to these two types of treatments is r = -.02, with a 95% confidence interval of -.29 to .25 across studies (Höchli et al., 1986; Reynolds et al., 1987b; Kasper et al., 1990; Riemann &, Berger, 1990; Kasper et al., 1991; Hernandez et al., 2000).

There is greater evidence in support of the claim that it is the degree of response to sleep deprivation maintained after a night of recovery sleep, as opposed to the degree of response seen on the day immediately following a night of sleep deprivation, which is most related to the degree of response to subsequent treatment with antidepressant medication. While only 50% (10 out of

20) of the studies to statistically examine the former relationship reported significant results (Wirz-Justice et al., 1979; Höchli et al., 1986; Kasper et al., 1990; Kasper et al., 1991; Bump et al., 1997; Hernandez et al., 2000), the average reported correlation between the level of response seen at these two times is r = .44, with a 95% confidence interval of .17 to .70 across studies (Kasper et al., 1990; Kasper et al., 1991; Bump et al., 1997; Hernandez et al., 2000). However, no simple interpretation of the results appears to be possible in terms of a dependence of effects upon whether predominantly serotonergic or noradrenergic transmission was enhanced by the medication used, in contrast to what has previously been proposed (Kasper et al., 1991).

There have been several reports that sleep deprivation can actually enhance the subsequent response to antidepressant medication, in terms of both decreasing the latency of response to antidepressant medication and augmenting the degree of this response. With regards to the former claim, half of studies (5 out of 10) to statistically examine this relationship reported a decrease in the time to onset of response to antidepressant drugs when sleep deprivation was applied in comparison to when drug alone was given (Elsenga & Van den Hoofdakker, 1982; Holsboer-Trachsler et al., 1994; Hemmeter et al., 1995; Kuhs et al., 1996a; Benedetti et al., 1997; Green et al., 1999; Güdücü et al., 2005; Reynolds et al., 2005; Gorgulu & Caliyurt, 2009; Smith et al., 2009). However, it should be noted that in four of the studies that found nonsignificant results (Holsboer-Trachsler et al., 1994; Hemmeter et al., 1995; Reynolds et al., 2005; Smith et al., 2009), patients with combined sleep deprivation and antidepressant

drug treatment actually had a smaller antidepressant effect than those patients given antidepressant drugs alone. The majority of experimental studies (5 out of 6) that recorded mood multiple times over several weeks found diminishing returns over time from the combined treatment of sleep deprivation and antidepressant medication, with the best or least worst effect typically seen in the first week (Holsboer-Trachsler et al., 1994; Kuhs et al., 1996a; Benedetti et al., 1997; Güdücü et al., 2005; Reynolds et al., 2005; Gorgulu & Caliyurt, 2009). With regards to the claim of sleep deprivation augmenting the degree of response to antidepressant drugs, less than half of the studies (2 out of 5) found that sleep deprivation improved the final outcome of treatment, as measured after at least 4 weeks of treatment with antidepressant drugs, in comparison to control patients that received antidepressant drugs alone (Holsboer-Trachsler et al., 1994; Kuhs et al., 1996a; Benedetti et al., 1997; Güdücü et al., 2005; Gorgulu & Caliyurt, 2009). However the average effect size across these studies is quite small, with only 4% of the variance in depression levels accounted for by which experimental condition patients were assigned to, and no significant difference in depression levels are evident between these two conditions by this time point (in comparison to a null hypothesis average effect size of zero, $t_w(4) = 1.26$, $p = .28$).

3.7 Limitations

The quality of any meta-analysis is dependent upon the quality of the studies it analyzes (Lam & Kennedy, 2005) and the results of a meta-analysis do

not carry any more weight than those of the well-designed primary studies it utilizes. Therefore, in an attempt to avoid biasing of the information, the results from both primary studies and across-study meta-analysis have been provided in the present article. However, it is also acknowledged that any threats to the internal validity of the studies included in a meta-analysis can undermine the conclusions of that meta-analysis. In the case of studies reporting an antidepressant effect of sleep deprivation there exist four major methodological limitations which have the potential to alter the conclusions of the present meta-analysis.

First, an adequate control condition has not yet been developed to counter any possible placebo effects of sleep deprivation. Researchers attempted to use partial sleep deprivation of the first half of the night as one such control but discovered that even this condition produces a significant, albeit lesser, antidepressant response (see the 'Sleep deprivation method' section above). However, it is unlikely that the reported antidepressant effects of sleep deprivation are due to a placebo effect since (1) patient expectations about the therapeutic effects of sleep deprivation have been shown to not predict the response to sleep deprivation (Buddeberg & Dittrich 1978; Leibenluft et al., 1993; Reynolds et al., 2005) and (2) the timecourse of antidepressant placebo effects have been shown to require on average several weeks to attain the same level of response (50% decrease in depression scores in responders; Stassen et al. 1997) which the present meta-analysis shows that patients can attain overnight with sleep deprivation.

Other factors specific to the designs of sleep deprivation studies, such as the short duration of treatment, the transient nature of the evaluation of mood change, the increased attention given to patients within the protocol, and the frequent assessment of mood are unlikely to promote a placebo response. The short duration of treatment and of evaluation periods for sleep deprivation studies are unlikely to since longer treatment exposure has been predicted to enhance the placebo response to antidepressant treatments (Brunoni et al., 2009). An effect of the level of attention given to patients in order to maintain sleep deprivation is not supported by the lack of statistical difference in antidepressant effects seen between studies using total vs. partial (2nd half of the night) sleep deprivation methods (see the 'Sleep deprivation method' section above). Similarly, the frequency of mood assessments does not significantly predict the degree of antidepressant effect to sleep deprivation (see the 'Time of response measurement' section above). Finally, if the antidepressant effect of sleep deprivation is due to how much an individual believes a certain treatment will work, then it is unclear why this response should fluctuate so much and so randomly within-subjects across trials (see the 'Inconsistency of response to sleep deprivation within-subject' section above).

The problem of finding an adequate control condition is also shared with light therapy, where it is obvious to patients whether the have received light or not. Therefore in meta-analyses of antidepressant light therapy (e.g., Golden et al., 2005) the use of a below minimum treatment dose (lux by time) is accepted as a credible placebo control condition. Currently it is not known what the

minimum dose of sleep deprivation required to produce an antidepressant response is, as even the latest time in the night (0330) at which partial sleep deprivation is begun still produces a response in half the patients (Clark et al., 2000, 2001; Clark & Golshan, 2007b). Thus, one attempt to create an adequate control condition would be to discover what this minimum amount of sleep deprivation is. Alternatively, it would be interesting to see if experimental sleep fragmentation would also produce an antidepressant effect, with a lowered frequency of arousals used as a placebo control condition. The rationale for this comes from studies with healthy subjects (Bonnet, 1986) where brief arousals produced at intervals of 2.5 hours have little effect on subsequent sleepiness and performance but arousals at 1 minute intervals produce the same effects as total sleep deprivation, even though total sleep amounts are only reduced by a third. Partial effects are seen with 10 minute intervals.

Second, without a control condition there can be no true random assignment of patients to the sleep deprivation condition to counter any possible sampling bias. However, since sleep deprivation studies make use of a within-subjects design where each subject's own baseline data is used as a comparison, this eliminates the problem as patients in the comparison condition are now the same people. So, for example, patients who tend to frequently show spontaneous shifts in mood (such as diurnal variations) would be just as likely to do so on baseline days as on the day following a night of sleep deprivation if there was no added effect of the sleep deprivation. As described above (see the 'Response to sleep deprivation' section above) this is not the case, with the

reported levels of patients' depression significantly decreasing from baseline following a night of sleep deprivation.

Third, ratings of depression levels in sleep deprivation studies are typically unblinded as to whether they have been sleep deprived yet or not due to the difficulty in concealing signs of tiredness following sleep deprivation. These unblinded ratings expose sleep deprivation studies to the threat of experimenter expectancy effects.

Fourth, although a large number of studies have demonstrated the antidepressant properties of sleep deprivation (see the 'Number of studies' section above), for each of the most powerful correlates of response there have been only a few studies to describe them (see Table 18). Therefore, there is a need for future studies to replicate the results of these correlate studies.

In addition to limitations due to methodological issues with the studies utilized in the present meta-analysis, there is also the concern that the results gathered from these studies could be biased due to a selective reporting in the literature of only studies with significant results. The tendency for studies with non-significant results to remain unpublished and buried away in file drawers has been called the "file-drawer problem" (Rosenthal, 1979). To help give an indication of the degree of such nonsignificant results, the percentage of studies with significant results was reported for each of the correlates examined in the present article. The file drawer problem would predict that this percentage reflects only the tip of the iceberg and that any correlate for which a large percentage of nonsignificant results have been reported should be taken highly

cautiously. It was thus decided that only those correlates for which the majority of studies (> 50%) had found significant results would be highlighted for further discussion in the text in order to have greater confidence in the conclusions drawn therein. Furthermore, in order to deal with the file drawer problem with regards to the efficacy of sleep deprivation, Orwin's (1983) fail-safe *N* procedure for effect size in meta-analysis was calculated (see Table 1 for its formula). Based on the fail-safe *N*, it is estimated that 297 unpublished studies with small effect sizes ($d_{Critical} \leq 0.2$) would be required in to order to reduce to null conditions ($d = 0$) the effect size ($d = 1.30$, N = 54 studies) reported in Table 2 for the difference in depression levels between the day before a night of sleep deprivation vs. the day after a night of sleep deprivation in all patients. Similarly, 354 studies are estimated to be required in order to reduce to null conditions the effect size ($d = 2.64$, N = 29 studies) for the same difference in depressions levels but for responders only. Although the existence of these unpublished studies cannot be ruled out, it seems unlikely that such large numbers of studies with small effect sizes remain buried in file drawers.

4. CONCLUSION

A quantified review of the literature shows that there is an approximate 50% probability, both between-subjects and within-subject, of a depressed patient having an antidepressant response to a night of sleep deprivation that is significant enough to label the patient a responder. The timing of both sleep deprivation and response measurements influence the degree of this response, with better results seen when recovery sleep is not allowed until the following night and response measurements are taken at times later in the daytime. No additional experimental treatment has yet been found to significantly enhance the response to sleep deprivation.

By the day after a night of recovery sleep, the majority of responders relapse into depression, although on average two-thirds of their response is still maintained by this point. However, unlike attempts to enhance the response to sleep deprivation, there is some exciting evidence to suggest that this relapse can be delayed, especially by depletion of the serotonergic system. There is also greater evidence in support of the claim that it is the degree of response to sleep deprivation maintained after a night of recovery sleep, as opposed to the degree of response seen on the day immediately following a night of sleep deprivation, which is most related to the degree of response to subsequent treatment with antidepressant medication. There is only inconsistent evidence that sleep

deprivation leads to a shortened latency to response from antidepressant medication and the consensus is that any possible additive effects of combining these two treatments are limited to the first few weeks of treatment.

Several strong correlates of response to sleep deprivation exist and show a general pattern where those which occur before the night of sleep deprivation are absolute differences between-subjects and those which occur afterwards are relative within-subject changes from before to after sleep deprivation. With regards to the latter type of correlate, a large amount of indirect evidence points towards a dopamine-related mechanism for the response to sleep deprivation. However, a definitive answer to this puzzle still remains elusive since all possible direct evidence in favor of the dopaminergic theory has so far turned up nonsignificant.

The seeming contradiction between the existence of strong predictors of the response to sleep deprivation and the inconsistency of this response within-subject lead to the prediction of variations in the activity of susceptibility factors across time within depressed patients. It is hoped that this review and formulation will help to stimulate a search for such susceptibility-state markers in the attempt to pin down the mechanism that provides the necessary preconditions for sleep deprivation to be effective. This can be done by not only replicating the findings of these strong predictors of the level of response seen across patients but, in addition, to examine within the same patients how consistent they are across different nights of sleep deprivation (e.g., separated by a week). Future studies should also examine the temporal order of changes in such susceptibility-state

markers in the hopes of unraveling their causal relationships, since changes in variables that follow later cannot be responsible for changes in variables that occur earlier in time.

Perhaps our current level of understanding of the changing susceptibility for response may be similar to the situation with weather forecasting in the mid 19th century. At that time, Ralph Waldo Emerson (1860) first drew this parallel when he wrote, “We cannot write the order of the variable winds. How can we penetrate the law of our shifting moods and susceptibility?” While the accuracy of our meteorological predictions has since advanced, our understanding of what determines the susceptibility to mood shifts, such as by sleep deprivation, still baffles us. But perhaps, just as the strength and direction of the wind were later able to be successfully predicted by examining which of the variables further upwind was the best predictor (namely, differences in atmospheric pressure), so too by discovering the susceptibility mechanism - which is further upstream in the brain from the mechanisms in control of overt changes in response but on which these depend - may we come to predict and ultimately control our shifts in mood.

REFERENCES

[For articles whose studies were included in the present meta-analysis, a list of the tables that their data were used in is given in brackets at the end of the reference for that article.]

Albert R, Merz A, Schubert J, Ebert D. (1998). Sleep deprivation and subsequent sleep phase advance stabilizes the positive effect of sleep deprivation in depressive episodes. Nervenarzt. 69(1):66-9. [Included in Tables #2, 3, 5, 6, 7, 22]

Amin M. (1978). Response to sleep deprivation and therapeutic results with antidepressants. Lancet. 2(8081):165. [Included in Tables #2, 3, 5, 6, 7]

Amin MM, Khalid R, Khan P. (1980). Relationship between sleep deprivation and urinary MHPG levels. Int Pharmacopsychiatry. 15(2):81-5. [Included in Tables #2, 3, 5, 6, 7, 14]

Asakura W, Matsumoto K, Ohta H, Watanabe H. (1993a). Effect of alpha 2-adrenergic drugs on REM sleep deprivation-induced increase in swimming activity. Pharmacol Biochem Behav. 46(1):111-5.

Asakura W, Matsumoto K, Ohta H, Watanabe H. (1993b). REM sleep deprivation potentiates the effects of imipramine and desipramine but not that of clomipramine in the forced swimming test. Jpn J Pharmacol. 63(4):455-60.

Asakura W, Matsumoto K, Ohta H, Watanabe H. (1994a). Involvement of dopamine D2 receptor mechanism in the REM sleep deprivation-induced increase in swimming activity in the forced swimming test. Pharmacol Biochem Behav. 48(1):43-6.

Asakura W, Matsumoto K, Ohta H, Watanabe H. (1994b). Monoamine depletion attenuates the REM sleep deprivation-induced increase in clonidine response in the forced swimming test. Pharmacol Biochem Behav. 49(1):79-84.

Asakura W, Matsumoto K, Watanabe H. (1995). REM sleep deprivation treatment enhances the effect of clozapine in the forced swimming test. Gen Pharmacol. 26(6):1225-8.

Ayd FJ, Jr (1985). Reserpine therapy for tricyclic-resistant depressions. Int Drug Ther Newslett. 20:17-18

Baghai TC, Schule C, Zwanzger P, Zill P, Ella R, Eser D, Deiml T, Minov C, Rupprecht R, Bondy B. (2003a). No Influence of a functional polymorphism within the serotonin transporter gene on partial sleep deprivation in major depression. World J Biol Psychiatry. 4(3):111-4. [Included in Tables #2, 3, 4, 5, 6, 7, 15, 19]

Baghai TC, Schule C, Zwanzger P, Zill P, Ella R, Eser D, Deiml T, Minov C, Rupprecht R, Bondy B. (2003b). Influence of a functional polymorphism within

the angiotensin I-converting enzyme gene on partial sleep deprivation in patients with major depression. Neurosci Lett. 339(3):223-6. [Included in Tables #2, 3, 4, 5, 6, 7, 15, 19]

Barbini B, Colombo C, Benedetti F, Campori E, Bellodi L, Smeraldi E. (1998). The unipolar-bipolar dichotomy and the response to sleep deprivation. Psychiatry Res. 79(1):43-50. [Included in Tables #2, 3, 5, 6, 7]

Baumgartner A, Gräf KJ, Kürten I, Meinhold H. (1990c). Thyrotropin (TSH) and thyroid hormone concentrations during partial sleep deprivation in patients with major depressive disorder. J Psychiatr Res. 24(4):281-92. [Included in Tables #2, 3, 4, 5, 6, 7, 16]

Baumgartner A, Graf KJ, Kurten I, Meinhold H, Scholz P. (1990a). Neuroendocrinological investigations during sleep deprivation in depression. I. Early morning levels of thyrotropin, TH, cortisol, prolactin, LH, FSH, estradiol, and testosterone. Biol Psychiatry. 28(7):556-68. [Included in Tables #2, 3, 5, 6, 7, 16, 18, 21]

Baumgartner A, Meinhold H. (1986). Sleep deprivation and thyroid hormone concentrations. Psychiatry Res. 19(3):241-2. [Included in Tables #16]

Baumgartner A, Riemann D, Berger M. (1990b). Neuroendocrinological investigations during sleep deprivation in depression. II. Longitudinal measurement of thyrotropin, TH, cortisol, prolactin, GH, and LH during sleep and sleep deprivation. Biol Psychiatry. 28(7):569-87. [Included in Tables #2, 3, 5, 6, 7, 16]

Baumgartner A, Sucher N. (1990). The influence of physical activity and posture on the antidepressant effect of sleep deprivation in depressed patients. J Affect Disord. 20(2):93-9. [Included in Tables #2, 3, 5, 6, 7, 8, 21]

Baxter LR Jr. (1985). Can lithium carbonate prolong the antidepressant effect of sleep deprivation? Arch Gen Psychiatry. 42(6):635. [Included in Tables #2, 3, 4, 5, 6, 7, 22]

Baxter LR Jr, Liston EH, Schwartz JM, Altshuler LL, Wilkins JN, Richeimer S, Guze BH. (1986). Prolongation of the antidepressant response to partial sleep deprivation by lithium. Psychiatry Res. 19(1):17-23. [Included in Tables #2, 3, 4, 5, 6, 7, 22]

Beck J, Hemmeter U, Brand S, Muheim F, Hatzinger M, Holsboer-Trachsler E. (2010). Modafinil reduces microsleep during partial sleep deprivation in depressed patients. J Psychiatr Res. [Epub ahead of print]. [Included in Tables #2, 3, 4, 5, 6, 7, 21]

Benedetti F, Bernasconi A, Blasi V, Cadioli M, Colombo C, Falini A, Lorenzi C, Radaelli D, Scotti G, Smeraldi E. (2007b). Neural and genetic correlates of antidepressant response to sleep deprivation: a functional magnetic resonance imaging study of moral valence decision in bipolar depression. Arch Gen Psychiatry. 64(2):179-87. [Included in Tables #2, 3, 5, 6, 7]

Benedetti F, Barbini B, Bernasconi A, Fulgosi MC, Colombo C, Dallaspezia S, Gavinelli C, Marino E, Pirovano A, Radaelli D, Smeraldi E. (2008). Serotonin 5-HT(2A) receptor gene variants influence antidepressant response to

repeated total sleep deprivation in bipolar depression. Prog Neuropsychopharmacol Biol Psychiatry. [Epub ahead of print] [Included in Tables #2, 3, 5, 6, 7, 15, 19]

Benedetti F, Barbini B, Campori E, Colombo C, Smeraldi E. (1996). Dopamine agonist amineptine prevents the antidepressant effect of sleep deprivation. Psychiatry Res. 65(3):179-84. [Included in Tables #2, 3, 5, 6, 7, 21]

Benedetti F, Barbini B, Campori E, Fulgosi MC, Pontiggia A, Colombo C. (2001a). Sleep phase advance and lithium to sustain the antidepressant effect of total sleep deprivation in bipolar depression: new findings supporting the internal coincidence model? J Psychiatr Res. 35(6):323-9. [Included in Tables #2, 3, 5, 6, 7, 21, 22]

Benedetti F, Barbini B, Fulgosi MC, Colombo C, Dallaspezia S, Pontiggia A, Smeraldi E. (2005). Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. J Clin Psychiatry. 66(12):1535-40. [Included in Tables #22]

Benedetti F, Barbini B, Lucca A, Campori E, Colombo C, Smeraldi E. (1997). Sleep deprivation hastens the antidepressant action of fluoxetine. Eur Arch Psychiatry Clin Neurosci. 247(2):100-3.

Benedetti F, Campori E, Barbini B, Fulgosi MC, Colombo C. (2001b). Dopaminergic augmentation of sleep deprivation effects in bipolar depression. Psychiatry Res. 104(3):239-46. [Included in Tables #2, 3, 5, 6, 7, 21]

Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. (1999a). Ongoing lithium treatment prevents relapse after total sleep deprivation. J Clin Psychopharmacol. 19(3):240-5. [Included in Tables #22]

Benedetti F, Lucca A, Brambilla F, Colombo C, Smeraldi E. (2002). Interleukine-6 serum levels correlate with response to antidepressant sleep deprivation and sleep phase advance. Prog Neuropsychopharmacol Biol Psychiatry. 26(6):1167-70. [Included in Tables #2, 3, 5, 6, 7, 16, 18, 22]

Benedetti F, Serretti A, Colombo C, Lilli R, Lorenzi C, Smeraldi E. (2003). Dopamine receptor D2 and D3 gene variants are not associated with the antidepressant effect of total sleep deprivation in bipolar depression. Psychiatry Res. 118(3):241-7. [Included in Tables #2, 3, 5, 6, 7, 15, 19]

Benedetti F, Serretti A, Colombo C, Campori E, Barbini B, di Bella D, Smeraldi E. (1999b). Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. Am J Psychiatry. 156(9):1450-2. [Included in Tables #2, 3, 5, 6, 7, 15, 19]

Benedetti F, Serretti A, Colombo C, Lorenzi C, Tubazio V, Smeraldi E. (2004). A glycogen synthase kinase 3-beta promoter gene single nucleotide polymorphism is associated with age at onset and response to total sleep deprivation in bipolar depression. Neurosci Lett. 368(2):123-6. [Included in Tables #2, 3, 5, 6, 7, 15, 19]

Benedetti F, Smeraldi E. (2007). Comment on the potential role of ghrelin in the mechanism of sleep deprivation therapy for depression. Sleep Med Rev. 11(6):524-5. [Included in Tables #16]

Benedetti F, Smeraldi E. (2009). Neuroimaging and genetics of antidepressant response to sleep deprivation: implications for drug development. Curr Pharm Des. 15(22):2637-49.

Benedetti F, Zanardi R, Colombo C, Smeraldi E. (1999c). Worsening of delusional depression after sleep deprivation: case reports. J Psychiatr Res. 33(1):69-72. [Included in Tables #2, 3, 5, 6, 7]

Benjamin J, Zohar J. (1992). Sleep deprivation in rapid-cycling bipolar affective disorder: case report. Eur Neuropsychopharmacol. 2(4):463-5. [Included in Tables #2, 3, 5, 6, 7]

Berger M, van Calker D, Riemann D. (2003). Sleep and manipulations of the sleep-wake rhythm in depression. Acta Psychiatr Scand Suppl. (418):83-91.

Berger M, Vollmann J, Hohagen F, König A, Lohner H, Voderholzer U, Riemann D. (1997). Sleep deprivation combined with consecutive sleep phase advance as a fast-acting therapy in depression: an open pilot trial in medicated and unmedicated patients. Am J Psychiatry. 154(6):870-2. [Included in Tables #22]

Bernier D, Bartha R, Devarajan S, Macmaster FP, Schmidt MH, Rusak B. (2009). Effects of overnight sleep restriction on brain chemistry and mood in women with unipolar depression and healthy controls. J Psychiatry Neurosci. 34(5):352-60. [Included in Table #2, 3, 4, 5, 6, 7, 14]

Bhanji S, Roy GA, Baulieu C. (1978). Analysis of mood change during and following sleep deprivation therapy. Acta Psychiatr Scand. 58(5):379-83. [Included in Tables #2, 3, 5, 6, 7, 21]

Bills CB, Guohua L. (2005). Correlating homicide and suicide. Int J Epidem. 34:837-45.

Bland JM, Altman DG. (1995). Calculating correlation coefficients with repeated observations: Part 2-correlation between subjects. BMJ. 310(6980):633.

Bland JM, Kerry SM. (1998). Statistics notes. Weighted comparison of means. BMJ. 316(7125):129.

Bonnet MH. (1986). Performance and sleepiness as a function of frequency and placement of sleep disruption. Psychophysiology. 23(3):263-71.

Booij L, Van der Does AJ, Haffmans PM, Riedel WJ. (2005). Acute tryptophan depletion in depressed patients treated with a selective serotonin-noradrenalin reuptake inhibitor: augmentation of antidepressant response? J Affect Disord. 86(2-3):305-11.

Bouhuys AL. (1991). Towards a model of mood responses to sleep deprivation in depressed patients. Biol Psychiatry. 29(6):600-12. [Included in Tables #17, 21]

Bouhuys AL, Beersma DG, van den Hoofdakker RH. (1989). Observed behavior as a predictor of the response to sleep deprivation in depressed patients. Psychiatry Res. 28(1):47-61. [Included in Tables #9]

Bouhuys AL, Flentge F, Van den Hoofdakker RH. (1990a). Effects of total sleep deprivation on urinary cortisol, self-rated arousal, and mood in depressed patients. Psychiatry Res. 34(2):149-62. [Included in Tables #2, 3, 5, 6, 7, 10, 16, 17]

Bouhuys AL, Schutte HK, Beersma DG, Nieboer GL. (1990b). Relations between depressed mood and vocal parameters before, during and after sleep deprivation: a circadian rhythm study. J Affect Disord. 19(4):249-58. [Included in Tables #17]

Bouhuys AL, van den Burg W, van den Hoofdakker RH. (1995). The relationship between tiredness prior to sleep deprivation and the antidepressant response to sleep deprivation in depression. Biol Psychiatry. 37(7):457-61. [Included in Tables #2, 3, 5, 6, 7, 10, 17]

Brock JW, Farooqui SM, Ross KD, Payne S, Prasad C. (1994). Stress-related behavior and central norepinephrine concentrations in the REM sleep-deprived rat. Physiol Behav. 55(6):997-1003.

Brooks A, Lack L. (2006). A brief afternoon nap following nocturnal sleep restriction: which nap duration is most recuperative? Sleep. 29(6):831-40.

Brückner TU, Wiegand MH. (2010). Motor activity in depressed patients during therapeutic sleep deprivation. Eur Psychiatry. [Epub ahead of print] [Included in Tables #2, 3, 5, 6, 7, 9]

Brunoni AR, Lopes M, Kaptchuk TJ, Fregni F. (2009). Placebo response of non-pharmacological and pharmacological trials in major depression: a systematic review and meta-analysis. PLoS One. 2009;4(3):e4824.

Buchsbaum MS, Gerner R, Post RM. (1981). he effects of sleep deprivation on average evoked responses in depressed patients and in normals. Psychiatry Res. 16(4):351-63. [Included in Tables #11, 18]

Buddeberg C, Dittrich A. (1978). Psychological aspects of sleep deprivation. A controlled study on depressives and normals (author's transl). Arch Psychiatr Nervenkr. 225(3):249-61. [Included in Table #10]

Bump GM, Reynolds CF 3rd, Smith G, Pollock BG, Dew MA, Mazumdar S, Geary M, Houck PR, Kupfer DJ. (1997). Accelerating response in geriatric depression: a pilot study combining sleep deprivation and paroxetine. Depress Anxiety. 6(3):113-8.

Caliyurt O, Guducu F. (2005). Partial sleep deprivation therapy combined with sertraline induces more rapid improvements in quality of life items in major depressive disorder. J Affect Disord. 88(1):75-8.

Cano-Lozano MC, Miro E, Fernandez-Espinosa L, Buela-Casal G. (2003). Therapeutic effect of sleep deprivation in depression. In J Clin Health Psychol.3(3):541-563.

Carney MW, Thakurdas H, Sebastian J. (1969). Effects of imipramine and reserpine in depression. Psychopharmacologia. 14(4):349-50.

Churchill CM, Dilsaver SC. (1990). Partial sleep deprivation to prevent 48-hour mood cycles. Acta Psychiatr Scand. 81(4):398-9. [Included in Tables #2, 3, 4, 5, 6, 7]

Clark CP, Brown GG, Archibald SL, Fennema-Notestine C, Braun DR, Thomas LS, Sutherland AN, Gillin JC. (2006a). Does amygdalar perfusion correlate with antidepressant response to partial sleep deprivation in major depression? Psychiatry Res. 146(1):43-51. [Included in Tables #2, 3, 4, 5, 6, 7, 13, 18]

Clark CP, Brown GG, Frank L, Thomas L, Sutherland AN, Gillin JC. (2006b). Improved anatomic delineation of the antidepressant response to partial sleep deprivation in medial frontal cortex using perfusion-weighted functional MRI. Psychiatry Res. 146(3):213-22. [Included in Tables #13]

Clark CP, Dupont R, Golshan S, Gillin JC, Rapaport MH, Kelsoe JR. (2000). Preliminary evidence of an association between increased REM density and poor antidepressant response to partial sleep deprivation. J Affect Disord. 59(1):77-83. [Included in Tables #2, 3, 4, 5, 6, 7, 12]

Clark CP, Frank LR, Brown GG. (2001). Sleep deprivation, EEG, and functional MRI in depression: preliminary results. Neuropsychopharmacology. 25(5 Suppl):S79-84. [Included in Tables #2, 3, 4, 5, 6, 7, 13]

Clark CP, Golshan S. (2007a). Antidepressant response to partial sleep deprivation in unipolar depression is not related to state anxiety. Depress Anxiety. Epub ahead of print. [Included in Tables #10]

Clark CP, Golshan S. (2007b). Polysomnography and criteria for the antidepressant response to sleep deprivation. J Affect Disord. 101(1-3):195-200. [Included in Tables #2, 3, 4, 5, 6, 7]

Clark LA, Watson D, Leeka J. (1989). Diurnal variation in the positive affect. Motiv Emot. 13(3):205-34.

Cohen J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). New York: Academic Press.

Cole MG, Muller HF. (1976). Sleep deprivation in the treatment of elderly depressed patients. J Am Geriatr Soc. 24(7):308-13. [Included in Tables #2, 3, 5, 6, 7, 21]

Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E. (2000). Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. Psychiatry Res. 95(1):43-53. [Included in Tables #22]

Cryan JF, Valentino RJ, Lucki I. (2005). Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. Neurosci Biobehav Rev. 29(4-5):547-69.

Daly JJ, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Roose SP, Sackeim HA. (2001). ECT in bipolar and unipolar depression: differences in speed of response. Bipolar Disord. 3(2):95-104.

Danilenko KV, Putilov AA. (2005). Melatonin treatment of winter depression following total sleep deprivation: waking EEG and mood correlates.

Neuropsychopharmacology. 30(7):1345-52. [Included in Tables #2, 3, 5, 6, 7, 12, 18]

Danos P, Kasper S, Scholl HP, Kaiser J, Ruhrmann S, Höflich G, Möller HJ. (1994). Clinical response to sleep deprivation and auditory-evoked potentials--preliminary results. Pharmacopsychiatry. 27(2):70-1. [Included in Tables #2, 3, 5, 6, 7, 11, 18]

David MM, Owen JA, Abraham G, Delva NJ, Southmayd SE, Wooltorton E, Lawson JS. (2000). Thyroid function and response to 48-hour sleep deprivation in treatment-resistant depressed patients. Biol Psychiatry. 48(4):323-6. [Included in Tables #2, 3, 5, 6, 7, 16, 18]

De Groot LJ. (2006). Non-thyroidal illness syndrome is a manifestation of hypothalamic-pituitary dysfunction, and in view of current evidence, should be treated with appropriate replacement therapies. Crit Care Clin. 22(1):57-86, vi.

Delgado PL, Price LH, Miller HL, Salomon RM, Aghajanian GK, Heninger GR, Charney DS. (1994). Serotonin and the neurobiology of depression. Effects of tryptophan depletion in drug-free depressed patients. Arch Gen Psychiatry. 51(11):865-74.

de Oliveira RA, Cunha GM, Borges KD, de Bruin GS, dos Santos-Filho EA, Viana GS, de Bruin VM. (2004). The effect of venlafaxine on behaviour, body weight and striatal monoamine levels on sleep-deprived female rats. Pharmacol Biochem Behav. 79(3):499-506.

Dessauer M, Goetze U, Tölle R. (1985). Periodic sleep deprivation in drug-refractory depression. Neuropsychobiology. 13(3):111-6.

Dijk DJ, Czeisler CA. (1995). Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci. 15(5 Pt 1):3526-38.

Dressing H, Riemann D, Gann H, Berger M. (1992). The effects of biperiden on nap sleep after sleep deprivation in depressed patients. Neuropsychopharmacology. 7(1):1-5. [Included in Tables #2, 3, 5, 6, 7, 12, 19, 21]

Duncan WC Jr, Gillin JC, Post RM, Gerner RH, Wehr TA. (1980). Relationship between EEG sleep patterns and clinical improvement in depressed patients treated with sleep deprivation. Biol Psychiatry. 15(6):879-89. [Included in Tables #2, 3, 5, 6, 7, 12]

Dunn G. (1992). Design and analysis of reliability studies. Stat Methods Med Res. 1(2):123–157.

Ebert D, Albert R, Hammon G, Strasser B, May A, Merz A. (1996). Eye-blink rates and depression. Is the antidepressant effect of sleep deprivation mediated by the dopamine system? Neuropsychopharmacology. 15(4):332-9. [Included in Tables #2, 3, 5, 6, 7, 9, 18]

Ebert D, Berger M. (1998). Neurobiological similarities in antidepressant sleep deprivation and psychostimulant use: a psychostimulant theory of antidepressant sleep deprivation. Psychopharmacology (Berl). 140(1):1-10.

Ebert D, Feistel H, Barocka A. (1991). Effects of sleep deprivation on the limbic system and the frontal lobes in affective disorders: a study with Tc-99m-HMPAO SPECT. Psychiatry Res. 40(4):247-51. [Included in Tables #2, 3, 5, 6, 7, 13, 18]

Ebert D, Feistel H, Barocka A, Kaschka W. (1994a). Increased limbic blood flow and total sleep deprivation in major depression with melancholia. Psychiatry Res. 55(2):101-9. [Included in Tables #2, 3, 5, 6, 7, 13, 18, 21]

Ebert D, Feistel H, Kaschka W, Barocka A, Pirner A. (1994b). Single photon emission computerized tomography assessment of cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation--preliminary results. Biol Psychiatry. 35(11):880-5. [Included in Tables #2, 3, 5, 6, 7, 9, 14, 18]

Ebert D, Kaschka WP, Loew T, Beck G. (1994c). Cortisol and beta-endorphin responses to sleep deprivation in major depression--the hyperarousal theories of sleep deprivation. Neuropsychobiology. 29(2):64-8. [Included in Tables #2, 3, 5, 6, 7, 16]

Ebert D, Kaschka W, Stegbauer P, Schrell U. (1993). Prolactin response to sulpiride before and after sleep deprivation in depression. Biol Psychiatry. 33(8-9):666-9. [Included in Tables #2, 3, 5, 6, 7, 14, 16, 18]

Eichhammer P, Kharraz A, Wiegand R, Langguth B, Frick U, Aigner JM, Hajak G. (2002). Sleep deprivation in depression stabilizing antidepressant effects by repetitive transcranial magnetic stimulation. Life Sci. 70(15):1741-9. [Included in Tables #2, 3, 4, 5, 6, 7, 22]

Elsenga S. (1992). Sleep deprivation and depression. Thesis, Rijksuniversiteit Groningen, Netherlands. Franeker: Drukkerij Telenga.

Elsenga S, Beersma D, Van den Hoofdakker RH. (1990). Total and partial sleep deprivation in clomipramine-treated endogenous depressives. J Psychiatr Res. 24(2):111-9. [Included in Tables #2, 3, 5, 6, 7, 12, 19, 20]

Elsenga S, Van den Hoofdakker RH. (1982). Clinical effects of sleep deprivation and clomipramine in endogenous depression. J Psychiatr Res. 17(4):361-74. [Included in Tables #2, 3, 5, 6, 7, 21]

Elsenga S, Van den Hoofdakker RH. (1987). Response to total sleep deprivation and clomipramine in endogenous depression. J Psychiatr Res. 21(2):151-61. [Included in Tables #2, 3, 5, 6, 7, 17]

Elsenga S, Van den Hoofdakker RH. (1988). Body core temperature and depression during total sleep deprivation in depressives. Biol Psychiatry. 24(5):531-40. [Included in Tables #2, 3, 5, 6, 7, 9, 17, 19]

Emerson RW. (1860). Illusions. In: The Conduct of Life. Boston, Ticknor and Fields.

Fähndrich E. (1981). Effects of sleep deprivation on depressed patients of different nosological groups. Psychiatry Res. 5(3):277-85. [Included in Tables #2, 3, 5, 6, 7]

Fähndrich E. (1983). Effect of sleep deprivation as a predictor of treatment response to antidepressant medication. Acta Psychiatr Scand. 68(5):341-4. [Included in Tables #2, 3, 5, 6, 7]

Feldman-Naim S, Turner EH, Leibenluft E. (1997). Diurnal variation in the direction of mood switches in patients with rapid-cycling bipolar disorder. J Clin Psychiatry. 58(2):79-84.

Forsman A, Dahlstrom A, Wahlstrom J, Wendestam C, Akesson HO (1983). Reserpine treatment of certain depressive conditions: Case report, treatment, and possible mechanisms of action. Curr Ther Res. 34:991-998

Fritzsche M, Heller R, Hill H, Kick H. (2001). Sleep deprivation as a predictor of response to light therapy in major depression. J Affect Disord. 62(3):207-15. [Included in Tables #2, 3, 5, 6, 7]

Gann H, Riemann D, Hohagen F, Strauss LG, Dressing H, Müller WE, Berger M. (1993). 48-hour rapid cycling: results of psychopathometric, polysomnographic, PET imaging and neuro-endocrine longitudinal investigations in a single case. J Affect Disord. 28(2):133-40. [Included in Tables #2, 3, 5, 6, 7]

Gelenberg AJ, Chesen CL. (2000). How fast are antidepressants? J Clin Psychiatry. 61(10):712-21.

Gerner RH, Post RM, Gillin JC, Bunney WE Jr. (1979). Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. J Psychiatr Res. 15(1):21-40. [Included in Tables #2, 3, 5, 6, 7, 12, 14]

Geyer MA, Markou A. (1995) Animal models of psychiatric disorders. In: Bloom FE, Kupfer, DJ (eds). Psychopharmacology: The Fourth Generation of Progress. Raven Press. pp. 787–798.

Giedke H. (2004). The usefulness of therapeutic sleep deprivation in depression. J Affect Disord. 78(1):85-6

Giedke H, Geilenkirchen R, Hauser M. (1992). The timing of partial sleep deprivation in depression. J Affect Disord. 25(2):117-28. [Included in Tables #2, 3, 4, 5, 6, 7, 12]

Giedke H, Klingberg S, Schwarzler F, Schweinsberg M. (2003). Direct comparison of total sleep deprivation and late partial sleep deprivation in the treatment of major depression. J Affect Disord. 76(1-3):85-93. [Included in Tables #2, 3, 4, 5, 6, 7]

Giedke H, Schwarzler F. (2002). Therapeutic use of sleep deprivation in depression. Sleep Med Rev. 6(5):361-77.

Gillin JC. (1983). The sleep therapies of depression. Prog Neuropsychopharmacol Biol Psychiatry. 7(2-3):351-64.

Gillin JC, Kripke DF, Janowsky DS, Risch SC. (1989). Effects of brief naps on mood and sleep in sleep-deprived depressed patients. Psychiatry Res. 27(3):253-65. [Included in Tables #2, 3, 5, 6, 7, 12, 19]

Goel N, Rao H, Durmer JS, Dinges DF. (2009). Neurocognitive consequences of sleep deprivation. Semin Neurol. 29(4):320-39.

Golden RN, Gaynes BN, Ekstrom RD, Hamer RM, Jacobsen FM, Suppes T, Wisner KL, Nemeroff CB. (2005). The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry. 162(4):656-62.

Goodwin RD, Jacobi F, Bittner A, Wittchen H. (2006). Epidemiology of mood disorders. In: Stein DJ, Kupfer DJ, Schatzberg AF (eds). The American Psychiatric Publishing textbook of mood disorders. Washington, DC: American Psychiatric Publishing. 33-54.

Gordijn MC, Beersma DG, Bouhuys AL, Reinink E, Van den Hoofdakker RH. (1994). A longitudinal study of diurnal mood variation in depression; characteristics and significance. J Affect Disord. 31(4):261-73. [Included in Tables #17, 18]

Gorgulu Y, Caliyurt O. (2009). Rapid antidepressant effects of sleep deprivation therapy correlates with serum BDNF changes in major depression. Brain Res Bull. 80(3):158-62. [Included in Table #2, 3, 5, 6, 7, 14]

Graw P, Haug HJ, Leonhardt G, Wirz-Justice A. (1998). Sleep deprivation response in seasonal affective disorder during a 40-h constant routine. J Affect Disord. 48(1):69-74. [Included in Tables #2, 3, 5, 6, 7]

Green TD, Reynolds CF 3rd, Mulsant BH, Pollock BG, Miller MD, Houck PR, Mazumdar S, Dew MA, Kupfer DJ. (1999). Accelerating antidepressant response in geriatric depression: a post hoc comparison of combined sleep deprivation and paroxetine versus monotherapy with paroxetine, nortriptyline, or placebo. J Geriatr Psychiatry Neurol. 12(2):67-71.

Grube M, Hartwich P. (1990). Maintenance of antidepressant effect of sleep deprivation with the help of lithium. Eur Arch Psychiatry Clin Neurosci. 240(1):60-1. [Included in Tables #2, 3, 5, 6, 7, 22]

Güdücü F, Caliyurt O, Vardar E, Tuglu C, Abay E. (2005). Combination therapy using sertraline with sleep deprivation and light therapy compared to sertraline monotherapy for major depressive disorder. Turk Psikiyatri Derg. 16(4):245-51.

Haskovec L, Rysánek K. (1967). The action of reserpine in imipramine-resistant depressive patients. Clinical and biochemical study. Psychopharmacologia. 11(1):18-30.

Haug HJ. (1992). Prediction of sleep deprivation outcome by diurnal variation. Biol Psychiatry. 31(3):271-8. [Included in Tables #2, 3, 5, 6, 7, 17]

Haug HJ, Fahndrich E, Strauss S, Rommelspacher H. (1988). Sleep deprivation and imipramine binding sites in depressed patients and healthy subjects. Psychiatry Res. 25(2):135-44. [Included in Tables #14]

Hawkins J, Phillips N, Moore JD, Gilliland MA, Dunbar S, Hicks RA. (1980). Emotionality and REMD: a rat swimming model. Physiol Behav. 25(2):167-71.

Hedges LV, Olkin I. (1985). Statistical methods for meta-analysis. New York: Academic Press.

Hemmeter U, Bischof R, Hatzinger M, Seifritz E, Holsboer-Trachsler E. (1998). Microsleep during partial sleep deprivation in depression. Biol Psychiatry. 43(11):829-39. [Included in Tables #2, 3, 4, 5, 6, 7, 10, 18]

Hemmeter U, Hatzinger M, Brand S, Holsboer-Trachsler E. (2007). Effect of flumazenil-augmentation on microsleep and mood in depressed patients during partial sleep deprivation. J Psychiatr Res. 41(10):876-84. [Included in Tables #2, 3, 4, 5, 6, 7, 21, 22]

Hemmeter UM, Hemmeter-Spernal J, Krieg JC. (2010). Sleep deprivation in depression. Expert Rev Neurother. 10(7):1101-15.

Hemmeter U, Seifritz E, Hatzinger M, Müller MJ, Holsboer-Trachsler E. (1995). Serial partial sleep deprivation as adjuvant treatment of depressive insomnia. Prog Neuropsychopharmacol Biol Psychiatry. 19(4):593-602.

Hennemann G, Docter R, Krenning EP. (1988). Causes and effects of the low T3 syndrome during caloric deprivation and non-thyroidal illness: an overview. Acta Med Austriaca. 15 Suppl 1:42-5.

Hernandez CR, Smith GS, Houck PR, Pollock BG, Mulsant B, Dew MA, Reynolds CF 3rd. (2000). The clinical response to total sleep deprivation and recovery sleep in geriatric depression: potential indicators of antidepressant treatment outcome. Psychiatry Res. 97(1):41-9. [Included in Tables #2, 3, 5, 6, 7]

Höchli D, Riemann D, Zulley J, Berger M. (1986). Is there a relationship between response to total sleep deprivation and efficacy of clomipramine treatment in depressed patients? Acta Psychiatr Scand. 74(2):190-2. [Included in Tables #2, 3, 5, 6, 7]

Hodgson JA. (1984). Swimming immobility of REM sleep deprived rats reared in different environments. Physiol Behav. 32(1):17-23.

Holsboer-Trachsler E, Ernst K. (1986). Sustained antidepressive effect of repeated partial sleep deprivation. Psychopathology. 19 Suppl 2:172-6. [Included in Tables #2, 3, 4, 5, 6, 7]

Holsboer-Trachsler E, Hemmeter U, Hatzinger M, Seifritz E, Gerhard U, Hobi V. (1994). Sleep deprivation and bright light as potential augmenters of antidepressant drug treatment--neurobiological and psychometric assessment of course. J Psychiatr Res. 28(4):381-99.

Holsboer-Trachsler E, Seifritz E. (2000). Sleep in depression and sleep deprivation: a brief conceptual review. World J Biol Psychiatry. 1(4):180-6.

Holsboer-Trachsler E, Wiedemann K, Holsboer F. (1988). Serial partial sleep deprivation in depression--clinical effects and dexamethasone suppression test results. Neuropsychobiology. 19(2):73-8. [Included in Tables #2, 3, 4, 5, 6, 7]

Hopkinson G, Kenny F. (1975). Treatment with reserpine of patients resistant to tricyclic antidepressants. A double-blind trial. Psychiatr Clin (Basel). 8(3):109-14.

Janeway CA, Travers P, Walport M, Shlomchik MJ (eds). (2005). Immunobiology. The immune system in Health and Disease (6th ed.). New York: Taylor & Francis Group; Garland Science.

Jimerson DC, Lynch HJ, Post RM, Wurtman RJ, Bunney WE Jr. (1977). Urinary melatonin rhythms during sleep deprivation in depressed patients and normals. Life Sci. 20(9):1501-8. [Included in Tables #2, 3, 5, 6, 7, 14]

Joffe R, Brown P, Bienenstock A, Mitton J. (1984). Neuroendocrine predictors of the antidepressant effect of partial sleep deprivation. Biol Psychiatry. 19(3):347-52. [Included in Tables #2, 3, 4, 5, 6, 7]

Jones G. (1979). Self-report of sleep deprivation therapy. Br J Psychiatry.134:317. [Included in Tables #2, 5, 6, 7]

Kaschka WP, Flügel O, Negele-Anetsberger J, Schlecht A, Marienhagen J, Bratenstein P. (1989). Total sleep deprivation and thyroid function in depression. Psychiatry Res. 29(2):231-4. [Included in Tables #2, 5, 6, 7, 16]

Kasper S, Katzinski L, Lenarz T, Richter P. (1988a). Auditory evoked potentials and total sleep deprivation in depressed patients. Psychiatry Res. 25(1):91-100. [Included in Tables #2, 3, 5, 6, 7, 11]

Kasper S, Kick H, Voll G, Vieira A. (1991). Therapeutic sleep deprivation and antidepressant medication in patients with major depression. Eur Neuropsychopharmacol. 1(2):107-11.

Kasper S, Sack DA, Wehr TA, Kick H, Voll G, Vieira A. (1988b). Nocturnal TSH and prolactin secretion during sleep deprivation and prediction of

antidepressant response in patients with major depression. Biol Psychiatry. 24(6):631-41. [Included in Tables #2, 3, 5, 6, 7, 16]

Kasper S, Vieira A, Wehr TA, Schmidt R, Kick H, Voll G, Murphy DL. (1988c). Serotonergically induced hormonal responses and the antidepressant effect of total sleep deprivation in patients with major depression. Psychopharmacol Bull. 24(3):450-3. [Included in Tables #2, 3, 5, 6, 7, 14]

Kasper S, Voll G, Vieira A, Kick H. (1990). Response to total sleep deprivation before and during treatment with fluvoxamine or maprotiline in patients with major depression--results of a double-blind study. Pharmacopsychiatry. 23(3):135-42. [Included in Tables #2, 3, 5, 6, 7]

Kercheval AN, Goldberg LR, Lee K. (2008). t-Statistics for Weighted Means in Credit Risk Modelling. Journal of Risk Finance, Forthcoming. Available at SSRN: http://ssrn.com/abstract=722503.

Khalsa SB, Conroy DA, Duffy JF, Czeisler CA, Dijk DJ. (2002). Sleep- and circadian-dependent modulation of REM density. J Sleep Res. 11(1):53-9.

Kho KH, van Vreeswijk MF, Simpson S, Zwinderman AH. (2003). A meta-analysis of electroconvulsive therapy efficacy in depression. J ECT. 19(3):139-47.

King D, Russell M, Smith D. (1983). Response to dexamethasone suppression and total night sleep deprivation in an affectively disordered Klinefelter patient. J Nerv Ment Dis. 171(1):59-61. [Included in Tables #2, 3, 5, 6, 7, 16]

Kjellman BF, Ljunggren JG, Beck-Friis J, Wetterberg L. (1983). Reverse T3 levels in affective disorders. Psychiatry Res. 10(1):1-9.

Knowles JB, Southmayd SE, Delva N, Prowse A, MacLean AW, Cairns J, Letemendia FJ, Waldron J. (1981). Sleep deprivation: outcome of controlled single case studies of depressed patients. Can J Psychiatry. 26(5):330-3. [Included in Tables #2, 3, 5, 6, 7, 12]

Kraft AM, Willner P, Gillin CG, Janowsky D, Neborsky R. (1984). Changes in thought content following sleep deprivation in depression. Compr Psychiatry. 25(3):283-9. [Included in Tables #2, 3, 5, 6, 7, 19]

Krizaj D. (2000). Mesopic state: cellular mechanisms involved in pre- and post-synaptic mixing of rod and cone signals. Microsc Res Tech. 50(5):347-59.

Kuhs H. (1985). Dexamethasone suppression test and sleep deprivation in endogenous depression. J Affect Disord. 9(2):121-6. [Included in Tables #2, 3, 5, 6, 7]

Kuhs H, Färber D, Borgstädt S, Mrosek S, Tölle R. (1996a). Amitriptyline in combination with repeated late sleep deprivation versus amitriptyline alone in major depression. A randomised study. J Affect Disord. 37(1):31-41. [Included in Tables #2, 3, 4, 5, 6, 7]

Kuhs H, Farber D, Tolle R. (1996b). Serum prolactin, growth hormone, total corticoids, thyroid hormones and thyrotropine during serial therapeutic sleep deprivation. Biol Psychiatry. 39(10):857-64. [Included in Tables #2, 3, 4, 5, 6, 7, 16]

Kuhs H, Kemper B, Lippe-Neubauer U, Meyer-Dunker J, Tölle R. (1998). Repeated sleep deprivation once versus twice a week in combination with amitriptyline. J Affect Disord. 47(1-3):97-103. [Included in Tables #2, 3, 4, 5, 6, 7]

Kundermann B, Hemmeter-Spernal J, Huber MT, Krieg JC, Lautenbacher S. (2008). Effects of total sleep deprivation in major depression: overnight improvement of mood is accompanied by increased pain sensitivity and augmented pain complaints. Psychosom Med. 70(1):92-101. [Included in Tables #10]

Lam RW, Kennedy SH. (2005). Using metaanalysis to evaluate evidence: practical tips and traps. Can J Psychiatry. 50(3):167-74.

Lam RW, Mok H. (2008). Depression. New York : Oxford University Press.

Landis JR, Koch GG. (1977). The measurement of observer agreement for categorical data. Biometrics. 33:159-74.

Larsen JK, Lindberg ML, Skovgaard B. (1976). Sleep deprivation as treatment for endogenous depression. Acta Psychiatr Scand. 54(3):167-73. [Included in Tables #2, 3, 5, 6, 7]

Lee MA, Taylor MA. (1983). Cortisol suppression and circadian rhythm in endogenous depression: a preliminary report. Biol Psychiatry. 18(10):1127-32. [Included in Tables #2, 3, 5, 6, 7, 17]

Leibenluft E, Moul DE, Schwartz PJ, Madden PA, Wehr TA. (1993). A clinical trial of sleep deprivation in combination with antidepressant medication. Psychiatry Res. 46(3):213-27. [Included in Tables #10, 16, 17]

Loosen PT, Merkel U, Amelung U. (1976a). Letter: Combined sleep deprivation and clomipramine in primary depression. Lancet. 2(7977):156-7.

Lucki I. (1997). The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. Behav Pharmacol. 8(6-7):523-32.

Machado RB, Hipólide DC, Benedito-Silva AA, Tufik S. (2004). Sleep deprivation induced by the modified multiple platform technique: quantification of sleep loss and recovery. Brain Res. 1004(1-2):45-51.

Maes M. (2008). The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. Neuro Endocrinol Lett. 29(3):287-91.

Matussek N, Ackenheil M, Athen D, Beckmann H, Benkert O, Dittmer T, Hippius H, Loosen P, Rüther E, Scheller M. (1974). Catecholamine metabolism under sleep deprivation therapy of improved and not improved depressed patients. Contributions to biochemistry. Pharmakopsychiatr Neuropsychopharmakol. 7(2):108-14. [Included in Tables #2, 3, 5, 6, 7, 9, 14]

Matussek N, Römisch P, Ackenheil M. (1977). MHPG excretion during sleep deprivation in endogenous depression. Neuropsychobiology. 3(1):23-9. [Included in Tables #14]

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT. (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry. 156(5):675-82.

McGraw KO, Wong SP. (1996). Forming inferences about some intraclass correlation coefficients. Psychol Methods. 1(1):30-46.

Meerlo P, Overkamp GJ, Benning MA, Koolhaas JM, Van den Hoofdakker RH. (1996). Long-term changes in open field behaviour following a single social defeat in rats can be reversed by sleep deprivation. Physiol Behav. 60(1):115-9.

Mistlberger RE, Bergmann BM, Rechtschaffen A. (1987). Relationships among wake episode lengths, contiguous sleep episode lengths, and electroencephalographic delta waves in rats with suprachiasmatic nuclei lesions. Sleep. 10:12–24.

Mistlberger RE, Bergmann BM, Waldenar W, Rechtschaffen A. (1983). Recovery sleep following sleep deprivation in intact and suprachiasmatic nuclei-lesioned rats. Sleep. 6:217–233.

Müller HU, Riemann D, Berger M, Müller WE. (1993). The influence of total sleep deprivation on urinary excretion of catecholamine metabolites in major depression. Acta Psychiatr Scand. 88(1):16-20. [Included in Tables #2, 3, 5, 6, 7, 14, 18]

Murck H, Schubert MI, Schmid D, Schüssler P, Steiger A, Auer DP. (2009). The glutamatergic system and its relation to the clinical effect of therapeutic-sleep deprivation in depression - an MR spectroscopy study. J Psychiatr Res. 43(3):175-80. [Included in Table #2, 3, 5, 6, 7, 14]

Murray G. (2007). Diurnal mood variation in depression: a signal of disturbed circadian function? J Affect Disord. 102(1-3):47-53.

Nasrallah HA, Coryell WH. (1982). Dexamethasone nonsuppression predicts the antidepressant effects of sleep deprivation. Psychiatry Res. 6(1):61-64. [Included in Tables #2, 3, 5, 6, 7]

Naylor MW, King CA, Lindsay KA, Evans T, Armelagos J, Shain BN, Greden JF. (1993). Sleep deprivation in depressed adolescents and psychiatric controls. J Am Acad Child Adolesc Psychiatry. 32(4):753-9. [Included in Tables #2, 3, 5, 6, 7, 17]

Neumeister A, Goessler R, Lucht M, Kapitany T, Bamas C, Kasper S. (1996). Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. Biol Psychiatry. 39(1):16-21. [Included in Tables #2, 3, 4, 5, 6, 7, 22]

Neumeister A, Praschak-Rieder N, Hesselmann B, Vitouch O, Rauh M, Barocka A, Tauscher J, Kasper S. (1998). Effects of tryptophan depletion in drug-free depressed patients who responded to total sleep deprivation. Arch Gen Psychiatry. 55(2):167-72. [Included in Tables #2, 3, 5, 6, 7, 21, 22]

Neumeister A, Praschak-Rieder N, Willeit M, Stastny J, Kasper S. (1999). Monoamine depletion in non-pharmacological treatments for depression. Adv Exp Med Biol. 467:29-33.

Nissen C, Feige B, Konig A, Voderholzer U, Berger M, Riemann D. (2001). Delta sleep ratio as a predictor of sleep deprivation response in major depression. J Psychiatr Res. 35(3):155-63. [Included in Tables #2, 3, 5, 6, 7, 12]

Nutt D, Wilson S, Paterson L. (2008). Sleep disorders as core symptoms of depression. Dialogues Clin Neurosci. 10(3):329-36.

Orth DN, Shelton RC, Nicholson WE, Beck-Peccoz P, Tomarken AJ, Persani L, Loosen PT. (2001). Serum thyrotropin concentrations and bioactivity during sleep deprivation in depression. Arch Gen Psychiatry. 58(1):77-83. [Included in Tables #2, 3, 5, 6, 7, 14, 16]

Orwin RG. (1983). A fail-safe N for effect size. Journal of Educational Statistics. 8:157-9.

Padberg F, Schüle C, Zwanzger P, Baghai T, Ella R, Mikhaiel P, Hampel H, Möller HJ, Rupprecht R. (2002). Relation between responses to repetitive transcranial magnetic stimulation and partial sleep deprivation in major depression. J Psychiatr Res. 36(3):131-5. [Included in Tables #2, 3, 4, 5, 6, 7]

Parekh PI, Ketter TA, Altshuler L, Frye MA, Callahan A, Marangell L, Post RM. (1998). Relationships between thyroid hormone and antidepressant responses to total sleep deprivation in mood disorder patients. Biol Psychiatry. 43(5):392-4. [Included in Tables #2, 3, 5, 6, 7, 16]

Parry BL, Cover H, Mostofi N, LeVeau B, Sependa PA, Resnick A, Gillin JC. (1995). Early versus late partial sleep deprivation in patients with premenstrual dysphoric disorder and normal comparison subjects. Am J Psychiatry. 152(3):404-12. [Included in Tables #2, 3, 4, 5, 6, 7]

Parry BL, Hauger R, LeVeau B, Mostofi N, Cover H, Clopton P, Gillin JC. (1996). Circadian rhythms of prolactin and thyroid-stimulating hormone during the menstrual cycle and early versus late sleep deprivation in premenstrual dysphoric disorder. Psychiatry Res. 62(2):147-60. [Included in Tables #17]

Parry BL, Curran ML, Stuenkel CA, Yokimozo M, Tam L, Powell KA, Gillin JC. (2000). Can critically timed sleep deprivation be useful in pregnancy and postpartum depressions? J Affect Disord. 60(3):201-12. [Included in Tables #2, 3, 4, 5, 6, 7]

Parry BL, Meliska CJ, Martínez LF, López AM, Sorenson DL, Hauger RL, Elliott JA. (2008). Late, but not early, wake therapy reduces morning plasma melatonin: relationship to mood in Premenstrual Dysphoric Disorder. Psychiatry Res. 161(1):76-86. [Included in Table #17]

Parry BL, Wehr TA. (1987). Therapeutic effect of sleep deprivation in patients with premenstrual syndrome. Am J Psychiatry. 144(6):808-10. [Included in Tables #2, 3, 4, 5, 6, 7]

Pflug B. (1978). The influence of sleep deprivation on the duration of endogenous depressive episodes. Arch Psychiatr Nervenkr. 225(2):173-7.

Pflug B, Tölle R. (1971a). Therapy of endogenous depressions using sleep deprivation. Practical and theoretical consequences. Nervenarzt. 42(3):117-24.

Pflug B, Tölle R. (1971b). Disturbance of the 24-hour rhythm in endogenous depression and the treatment of endogenous depression by sleep deprivation. Int Pharmacopsychiatry. 6(3):187-96.

Philipp M, Werner C. (1979). Prediction of lofepramine-response in depression based on response to partial sleep deprivation. Pharmakopsychiatr Neuropsychopharmakol. 12(4):346-8.

Pilcher JJ, Huffcutt AI. (1996). Effects of sleep deprivation on performance: a meta-analysis. Sleep. 19(4):318-26.

Poldinger W (1959). Diskussionsbemerkung an der 129. Versammlung der Schweiz. Ges. ffir Psychiatric. Schweiz Arch Neurol Psychiatr. 84:327.

Poldinger W (1963). Combined administration of desipramine and reserpine of tetrabenazine in depressive patients. Psychopharmacologia. 4:308-10.

Pollock MS, Mistlberger RE. (2003). Rapid eye movement sleep induction by microinjection of the GABA-A antagonist bicuculline into the dorsal subcoeruleus area of the rat. Brain Res. 962(1-2):68-77.

Porsolt RD, Anton G, Blavet N, Jalfre M. (1978). Behavioural despair in rats: a new model sensitive to antidepressant treatments. Eur J Pharmacol. 47(4):379-91.

Porsolt RD, Brossard G, Hautbois C, Roux S. (2001). Rodent models of depression: forced swimming and tail suspension behavioral despair tests in rats and mice. Curr Protoc Neurosci. Chapter 8:Unit 8.10A.

Post RM, Kotin J, Goodwin FK. (1976). Effects of sleep deprivation on mood and central amine metabolism in depressed patients. Arch Gen Psychiatry. 33(5):627-32. [Included in Tables #2, 3, 5, 6, 7, 12, 14]

Post RM, Uhde TW, Rubinow DR, Huggins T. (1987). Differential time course of antidepressant effects after sleep deprivation, ECT, and carbamazepine: clinical and theoretical implications. Psychiatry Res. 22(1):11-9. [Included in Tables #2, 3, 5, 6, 7]

Priebe S, Haug HJ. (1992). Interactional pattern in sleep deprivation therapy: an empirical study. J Nerv Ment Dis. 180(1):59-60. [Included in Tables #2, 3, 5, 6, 7]

Putilov AA, Danilenko KV. (2005). Antidepressant effects of combination of sleep deprivation and early evening treatment with melatonin or placebo for winter depression. Biol. Rhythm Res. 36(5):389–403. [Included in Table #2, 3, 5, 6, 7, 22]

Putilov AA, Pinchasov BB, Poljakova EY. (2005). Antidepressant effects of mono- and combined non-drug treatments for seasonal and nonseasonal depression. Biol Rhythm Res. 36(5):405–421. [Included in Tables #2, 3, 5, 6, 7, 22]

Ravindran AV, Lam RW, Filteau MJ, Lespérance F, Kennedy SH, Parikh SV, Patten SB; Canadian Network for Mood and Anxiety Treatments (CANMAT). (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. V. Complementary and alternative medicine treatments. J Affect Disord. 117 Suppl 1:S54-64.

Reinink E, Bouhuys AL, Gordijn MC, Van Den Hoofdakker RH. (1993). Prediction of the antidepressant response to total sleep deprivation of depressed patients: longitudinal versus single day assessment of diurnal mood variation. Biol Psychiatry. 34(7):471-81. [Included in Tables #17, 18]

Reinink E, Bouhuys N, Wirz-Justice A, van den Hoofdakker R. (1990). Prediction of the antidepressant response to total sleep deprivation by DIURNAL VARIATION. Psychiatry Res. 32(2):113-24. [Included in Tables #17]

Reist C, Chen CC, Chhoeu A, Berry RB, Bunney WE Jr. (1994). Effects of sleep on the antidepressant response to sleep deprivation. Biol Psychiatry. 35(10):794-7. [Included in Tables #2, 3, 5, 6, 7, 12, 19, 20]

Reynolds CF 3rd, Kupfer DJ, Hoch CC, Houck PR, Stack JA, Berman SR, Campbell PI, Zimmer B. (1987a). Sleep deprivation as a probe in the elderly. Arch Gen Psychiatry. 44(11):982-90. [Included in Tables #2, 3, 5, 6, 7]

Reynolds CF 3rd, Kupfer DJ, Hoch CC, Stack JA, Houck PA, Berman SR. (1987b). Sleep deprivation effects in older endogenous depressed patients. Psychiatry Res. 21(2):95-109. [Included in Tables #2, 3, 5, 6, 7, 12]

Reynolds CF 3rd, Smith GS, Dew MA, Mulsant BH, Miller MD, Schlernitzauer M, Stack JA, Houck PR, Pollock BG. (2005). Accelerating symptom-reduction in late-life depression: a double-blind, randomized, placebo-controlled trial of sleep deprivation. Am J Geriatr Psychiatry. 13(5):353-8. [Included in Table #10]

Riemann D, Berger M. (1990). The effects of total sleep deprivation and subsequent treatment with clomipramine on depressive symptoms and sleep electroencephalography in patients with a major depressive disorder. Acta Psychiatr Scand. 81(1):24-31. [Included in Tables #2, 3, 5, 6, 7, 12]

Riemann D, Hohagen F, Konig A, Schwarz B, Gomille J, Voderholzer U, Berger M. (1996). Advanced vs. normal sleep timing: effects on depressed mood after response to sleep deprivation in patients with a major depressive disorder. J Affect Disord. 37(2-3):121-8. [Included in Tables #22]

Riemann D, Konig A, Hohagen F, Kiemen A, Voderholzer U, Backhaus J, Bunz J, Wesiack B, Hermle L, Berger M. (1999). How to preserve the antidepressive effect of sleep deprivation: A comparison of sleep phase advance and sleep phase delay. Eur Arch Psychiatry Clin Neurosci.249(5):231-7. [Included in Tables #2, 3, 5, 6, 7, 22]

Riemann D, Voderholzer U. (2003). Primary insomnia: a risk factor to develop depression? J Affect Disord. 76(1-3):255-9.

Riemann D, Voderholzer U, Berger M. (2002). Sleep and sleep-wake manipulations in bipolar depression. Neuropsychobiology. 45 Suppl 1:7-12.

Riemann D, Wiegand M, Berger M. (1991). Are there predictors for sleep deprivation response in depressed patients? Biol Psychiatry. 29(7):707-10. [Included in Tables #2, 3, 5, 6, 7, 12, 17]

Riemann D, Wiegand M, Lauer CJ, Berger M. (1993). Naps after total sleep deprivation in depressed patients: are they depressiogenic? Psychiatry Res. 49(2):109-20. [Included in Tables #2, 3, 5, 6, 7, 12, 19]

Ringel BL, Szuba MP. (2001). Potential mechanisms of the sleep therapies for depression. Depress Anxiety. 14(1):29-36.

Rosenthal R. (1979). The file drawer problem and tolerance for null results. Psychological Bulletin. 86:638-41.

Roy-Byrne PP, Uhde TW, Post RM. (1986). Effects of one night's sleep deprivation on mood and behavior in panic disorder. Patients with panic disorder compared with depressed patients and normal controls. Arch Gen Psychiatry. 43(9):895-9. [Included in Tables #2, 3, 5, 6, 7]

Roy-Byrne P, Uhde TW, Post RM, Joffe RT. (1984). Relationship of response to sleep deprivation and carbamazepine in depressed patients. Acta Psychiatr Scand. 69(5):379-82.

Rudolf GA, Tölle R. (1978). Sleep deprivation and circadian rhythm in depression. Psychiatr Clin (Basel). 11(4):198-212. [Included in Tables #2, 3, 5, 6, 7]

Sack DA, Duncan W, Rosenthal NE, Mendelson WE, Wehr TA. (1988). The timing and duration of sleep in partial sleep deprivation therapy of depression. Acta Psychiatr Scand. 77(2):219-24. [Included in Tables #2, 3, 4, 5, 6, 7, 12]

Salomon RM, Delgado PL, Licinio J, Krystal JH, Heninger GR, Charney DS. (1994). Effects of sleep deprivation on serotonin function in depression. Biol Psychiatry. 36(12):840-6. [Included in Tables #2, 3, 5, 6, 7, 14]

Schilgen B, Tölle R. (1980). Partial sleep deprivation as therapy for depression. Arch Gen Psychiatry. 37(3):267-71. [Included in Tables #2, 3, 4, 5, 6, 7, 17]

Schüle C, Baghai T, Zwanzger P, Minov C, Padberg F, Rupprecht R. (2001). Sleep deprivation and hypothalamic-pituitary-adrenal (HPA) axis activity in depressed patients. J Psychiatr Res. 35(4):239-47. [Included in Tables #2, 3, 4, 5, 6, 7, 16, 19]

Schule C, di Michele F, Baghai T, Romeo E, Bernardi G, Zwanzger P, Padberg F, Pasini A, Rupprecht R. (2003). Influence of sleep deprivation on neuroactive steroids in major depression. Neuropsychopharmacology. 28(3):577-81. [Included in Tables #16]

Schule C, Di Michele F, Baghai T, Romeo E, Bernardi G, Zwanzger P, Padberg F, Pasini A, Rupprecht R. (2004). Neuroactive steroids in responders and nonresponders to sleep deprivation. Ann N Y Acad Sci. 1032:216-23. [Included in Tables #2, 3, 4, 5, 6, 7, 16]

Schulte W. (1966). Kombinierte Psycho- und Phm-makotherapie bei Melancholikem. In: Kranz HN, Petrilowitsch N (eds). Probleme der

pharmakopsychiatrischen Kombinations- und Langzeitbehandlung. Basel: Karger. 150-169.

Schumann G, Benedetti F, Voderholzer U, Kammerer N, Hemmeter U, Travers HW, Fiebich B, Holsboer-Trachsler E, Berger M, Seifritz E, Ebert D. (2001). Antidepressive response to sleep deprivation in unipolar depression is not associated with dopamine D3 receptor genotype. Neuropsychobiology. 43(3):127-30. [Included in Tables #2, 3, 5, 6, 7, 15, 19]

Schwartzhaupt AW, Lara DR, Hirakata VN, Schuch A, Almeida E, Silveira L, Caldieraro MA, Fleck MP. (2008). Does caffeine change the effect of sleep deprivation on moderate to severe depressed patients? J Affect Disord. 2008. [Epub ahead of print] [Included in Tables #2, 3, 5, 6, 7, 21]

Selvi Y, Gulec M, Agargun MY, Besiroglu L. (2007). Mood changes after sleep deprivation in morningness-eveningness chronotypes in healthy individuals. J Sleep Res. 16:241-4.

Serretti A, Benedetti F, Colombo C, Lilli R, Lorenzi C, Smeraldi E. (1999). Dopamine receptor D4 is not associated with antidepressant activity of sleep deprivation. Psychiatry Res. 89(2):107-14. [Included in Tables #2, 3, 5, 6, 7, 15, 19]

Shelton RC, Loosen PT. (1993). Sleep deprivation accelerates the response to nortriptyline. Prog Neuropsychopharmacol Biol Psychiatry. 17(1):113-23. [Included in Tables #2, 3, 5, 6, 7]

Sherwood L. (2005). Fundamentals of physiology: a human perspective. 3rd ed. Belmont, Calif: Brooks/Cole. 161.

Smeraldi E, Benedetti F, Barbini B, Campori E, Colombo C. (1999). Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression. A placebo-controlled trial. Neuropsychopharmacology. 20(4):380-5. [Included in Tables #22]

Smith C, Gisquet-Verrier P. (1996). Paradoxical sleep deprivation and sleep recording following training in a brightness discrimination avoidance task in Sprague-Dawley rats: paradoxical effects. Neurobiol Learn Mem. 66(3):283-94.

Smith GS, Reynolds CF 3rd, Houck PR, Dew MA, Ginsberg J, Ma Y, Mulsant BH, Pollock BG. (2009). Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression: a randomized, placebo-controlled study. Psychiatry Res. 171(1):1-9. [Included in Tables #2, 3, 5, 6, 7]

Smith GS, Reynolds CF 3rd, Houck PR, Dew MA, Ma Y, Mulsant BH, Pollock BG. (2002). Glucose metabolic response to total sleep deprivation, recovery sleep, and acute antidepressant treatment as functional neuroanatomic correlates of treatment outcome in geriatric depression. Am J Geriatr Psychiatry. 10(5):561-7. [Included in Tables #2, 3, 5, 6, 7, 13]

Smith GS, Reynolds CF 3rd, Pollock B, Derbyshire S, Nofzinger E, Dew MA, Houck PR, Milko D, Meltzer CC, Kupfer DJ. (1999). Cerebral glucose

metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression. Am J Psychiatry. 156(5):683-9. [Included in Tables #2, 3, 5, 6, 7, 13]

Sokolski KN, Reist C, Chen CC, DeMet EM. (1995). Antidepressant responses and changes in visual adaptation after sleep deprivation. Psychiatry Res. 57(3):197-207. [Included in Tables #2, 3, 5, 6, 7, 11, 18]

Souêtre E, Salvati E, Pringuey D, Plasse Y, Savelli M, Darcourt G. (1987). Antidepressant effects of the sleep/wake cycle phase advance. Preliminary report. J Affect Disord. 12(1):41-6. [Included in Tables #2, 3, 4, 5, 6, 7, 22]

Southmayd SE, David MM, Cairns J, Delva NJ, Letemendia FJ, Waldron JJ. (1990). Sleep deprivation in depression: pattern of relapse and characteristics of preceding sleep. Biol Psychiatry. 28(11):979-88. [Included in Tables #12, 19]

Southmayd SE, Kasurak P, MacDonald B, Waldron J. (1992). Therapeutic sleep deprivation in a depressed patient: prolongation of response with concurrent thyroxine. Acta Psychiatr Scand. 86(1):84-5. [Included in Tables #22]

Stallone F, Huba GJ, Lawlor WG, Fieve RR. (1973). Longitudinal studies of diurnal variations in depression: a sample of 643 patient days. Br J Psychiatry. 123(574):311-8.

Stassen HH, Angst J, Delini-Stula A. (1997). Delayed onset of action of antidepressant drugs? Survey of recent results. Eur Psychiatry. 12(4):166-76.

Strouse TB, Szuba MP, Baxter LR Jr. (1992). Response to sleep deprivation in three women with postpartum psychosis. J Clin Psychiatry. 53(6):204-6. [Included in Tables #2, 3, 4, 5, 6, 7]

Suchecki D, Duarte Palma B, Tufik S. (2000). Sleep rebound in animals deprived of paradoxical sleep by the modified multiple platform method. Brain Res. 875(1-2):14-22.

Suchecki D, Tufik S. (2000). Social stability attenuates the stress in the modified multiple platform method for paradoxical sleep deprivation in the rat. Physiol Behav. 68(3):309-16.

Svestka J. (2008). Sleep deprivation therapy. Neuro Endocrinol Lett. 29(Suppl1). [Epub ahead of print]

Szuba MP, Altshuler LL, Baxter LR Jr. (1992). Thyroid function and partial sleep deprivation response. Arch Gen Psychiatry. 49(7):581-2. [Included in Tables #2, 3, 4, 5, 6, 7, 16]

Szuba MP, Baxter LR Jr, Altshuler LL, Allen EM, Guze BH, Schwartz JM, Liston EH. (1994). Lithium sustains the acute antidepressant effects of sleep deprivation: preliminary findings from a controlled study. Psychiatry Res. 51(3):283-95. [Included in Tables #2, 3, 4, 5, 6, 7, 22]

Szuba MP, Baxter LR Jr, Fairbanks LA, Guze BH, Schwartz JM. (1991). Effects of partial sleep deprivation on the diurnal variation and motor activity in major depression. Biol Psychiatry. 30(8):817-29. [Included in Tables #2, 3, 4, 5, 6, 7, 9, 10, 17, 18, 21]

Thalheimer W, Cook S. (2002). How to calculate effect sizes from published research: A simplified methodology. Accessed at www.work-learning.com/effect_sizes.htm on January 4, 2006.

Tölle R, Goetze U. (1987). On the daily rhythm of depression symptomatology. Psychopathology. 20(5-6):237-49.

Treit D, Fundytus M. (1988). Thigmotaxis as a test for anxiolytic activity in rats. Pharmacol Biochem Behav. 31(4):959-62.

van Bemmel AL, van den Hoofdakker RH. (1981). Maintenance of therapeutic effects of total sleep deprivation by limitation of subsequent sleep. A pilot study. Acta Psychiatr Scand. 63(5):453-62. [Included in Tables #12, 22]

Van Den Burg W, Beersma DG, Bouhuys AL, Van Den Hoofdakker RH. (1992). Self-rated arousal concurrent with the antidepressant response to total sleep deprivation of patients with a major depressive disorder: a disinhibition hypothesis. J Sleep Res. 1(4):211-222. [Included in Tables #10]

Van Den Burg W, Bouhuys AL, van den Hoofdakker RH, Beersma DG. (1990). Sleep deprivation in bright and dim light: antidepressant effects on major depressive disorder. J Affect Disord. 19(2):109-17. [Included in Tables #2, 3, 5, 6, 7, 8, 22]

Van Den Hoofdakker RH, Bouhuys AL, Beersma DG. (1989). The effects of sleep deprivation and sleep on depressive mood and subjective arousal. Biol Psychiatry. 26(7):733-6. [Included in Tables #2, 3, 5, 6, 7, 10, 18, 19, 20]

Van Dongen HP, Baynard MD, Maislin G, Dinges DF. (2004). Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. Sleep. 27(3):423-33.

Van Luijtelaar EL, Coenen AM. (1985). Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. Sleep. 8(1):49-55.

Van Luijtelaar EL, Coenen AM. (1986). Electrophysiological evaluation of three paradoxical sleep deprivation techniques in rats. Physiol Behav. 36(4):603-9.

Voderholzer U, Valerius G, Schaerer L, Riemann D, Giedke H, Schwarzler F, Berger M, Wiegand M. (2003). Is the antidepressive effect of sleep deprivation stabilized by a three day phase advance of the sleep period? A pilot study. Eur Arch Psychiatry Clin Neurosci.253(2):68-72. [Included in Tables #2, 3, 5, 6, 7, 22]

Voderholzer U, Hohagen F, Klein T, Jungnickel J, Kirschbaum C, Berger M, Riemann D. (2004). Impact of sleep deprivation and subsequent recovery sleep on cortisol in unmedicated depressed patients. Am J Psychiatry.161(8):1404-10. [Included in Tables #2, 3, 5, 6, 7, 16]

Vogel GW, Traub AC, Ben-Horin P, Meyers GM. (1968). REM deprivation. II. The effects on depressed patients. Arch Gen Psychiatry. 18(3):301-11.

Vogel GW, Vogel F, McAbee RS, Thurmond AJ. (1980). Improvement of depression by REM sleep deprivation. New findings and a theory. Arch Gen Psychiatry. 37(3):247-53. [Included in Tables #12]

Volk SA, Kaendler SH, Hertel A, Maul FD, Manoocheri R, Weber R, Georgi K, Pflug B, Hor G. (1997). Can response to partial sleep deprivation in depressed patients be predicted by regional changes of cerebral blood flow? Psychiatry Res. 75(2):67-74. [Included in Tables #2, 3, 4, 5, 6, 7, 10, 13, 18]

Volk S, Kaendler SH, Weber R, Georgi K, Maul F, Hertel A, Pflug B, Hor G. (1992). Evaluation of the effects of total sleep deprivation on cerebral blood flow using single photon emission computerized tomography. Acta Psychiatr Scand. 86(6):478-83. [Included in Tables #2, 3, 5, 6, 7, 13]

Vollmann J, Berger M. (1993). Sleep deprivation with consecutive sleep-phase advance therapy in patients with major depression: a pilot study. Biol Psychiatry. 33(1):54-7. [Included in Tables #2, 3, 5, 6, 7, 22]

Watson D, Wiese D, Vaidya J, Tellegen A. (1999). The two general activation systems of affect: Structural findings, evolutionary considerations, and psychobiological evidence. J Pers Soc Psychol. 76(5):820-38.

Wehr T. (1990). Effects of wakefulness and sleep on depression and mania. In: Mountplaisir J, Godbout R (eds). Sleep and Biological Rhythms: Basic Mechanisms and Applications to Psychiatry. Oxford: Oxford University Press. 42-86.

Wehr TA, Goodwin FK, Wirz-Justice A, Breitmaier J, Craig C. (1982). 48-hour sleep-wake cycles in manic-depressive illness: naturalistic observations and sleep deprivation experiments. Arch Gen Psychiatry. 39(5):559-65. [Included in Tables #2, 3, 5, 6, 7]

Wehr TA, Rosenthal NE, Sack DA, Gillin JC. (1985a). Antidepressant effects of sleep deprivation in bright and dim light. Acta Psychiatr Scand. 72(2):161-5. [Included in Tables #2, 3, 5, 6, 7, 8]

Wiegand M, Berger M, Zulley J, Lauer C, von Zerssen D. (1987). The influence of daytime naps on the therapeutic effect of sleep deprivation. Biol Psychiatry. 22(3):389-92. [Included in Tables #2, 3, 5, 6, 7, 12, 19]

Wiegand MH, Lauer CJ, Schreiber W. (2001). Patterns of response to repeated total sleep deprivations in depression. J Affect Disord. 64(2-3):257-60. [Included in Tables #2, 3, 5, 6, 7]

Wiegand M, Riemann D, Schreiber W, Lauer CJ, Berger M. (1993). Effect of morning and afternoon naps on mood after total sleep deprivation in patients with major depression. Biol Psychiatry. 33(6):467-76. [Included in Tables #2, 3, 5, 6, 7, 12, 19]

Wirz-Justice A, Benedetti F, Berger M, Lam RW, Martiny K, Terman M, Wu JC. (2005). Chronotherapeutics (light and wake therapy) in affective disorders. Psychol Med. 35(7):939-44.

Wirz-Justice A, Pühringer W, Hole G. (1979). Response to sleep deprivation as a predictor of therapeutic results with antidepressant drugs. Am J Psychiatry. 136(9):1222-3. [Included in Tables #2, 5, 6, 7]

Wirz-Justice A, Van den Hoofdakker RH. (1999). Sleep deprivation in depression: what do we know, where do we go? Biol Psychiatry. 46(4):445-53.

Witkovsky P. (2004). Dopamine and retinal function. Doc Ophthalmol. 108(1):17-40.

Wu J, Buchsbaum MS, Gillin JC, Tang C, Cadwell S, Wiegand M, Najafi A, Klein E, Hazen K, Bunney WE Jr, Fallon JH, Keator D. (1999). Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. Am J Psychiatry. 156(8):1149-58. Erratum in: Am J Psychiatry 1999 Oct [Included in Tables #2, 3, 5, 6, 7, 10, 13, 18]

Wu JC, Bunney WE. (1990). The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. Am J Psychiatry. 147(1):14-21.

Wu JC, Gillin JC, Buchsbaum MS, Hershey T, Johnson JC, Bunney WE Jr. (1992). Effect of sleep deprivation on brain metabolism of depressed patients. Am J Psychiatry. 149(4):538-43. [Included in Tables #2, 3, 5, 6, 7, 10, 13, 18]

Wu JC, Gillin JC, Buchsbaum MS, Schachat C, Darnall LA, Keator DB, Fallon JH, Bunney WE. (2008). Sleep deprivation PET correlations of Hamilton symptom improvement ratings with changes in relative glucose metabolism in patients with depression. J Affect Disord. 107(1-3):181-6. [Included in Tables #2, 3, 5, 6, 7, 13]

Yamaguchi N, Maeda K, Kuromaru S. (1978a). The effects of sleep deprivation on the circadian rhythm of plasma cortisol levels in depressive patients. Folia Psychiatr Neurol Jpn. 32(4):479-87. [Included in Tables #2, 3, 5, 6, 7, 17]

APPENDIX

A.1 Antidepressant effects of sleep deprivation in the forced swim test animal model of depression

A.1.1 Introduction

In addition to the antidepressant response seen in depressed human patients following sleep deprivation, sleep deprivation has also been reported to have an antidepressant effect in animal models of depression. The forced swim test (Porsolt et al., 2001) has been the model of depression used almost exclusively to study the antidepressant effects of sleep deprivation in animals, with only one exception. That exception is a study (Meerlo et al., 1996) in which sleep deprivation of rats by forced locomotion in a slowly rotating cylinder was found to reverse the long-term inhibiting effects of a single social defeat upon open field activity. In the forced swim test studies, sleep deprivation performed by either the platform-over-water (Porsolt et al., 1978; Hawkins et al., 1980; Hodgson, 1984; van Luijtelaar & Coenen, 1985; Asakura et al., 1993a, 1993b, 1994a, 1994b, 1995; Brock et al., 1994; de Oliveira et al., 2004) or disk-over-water (Lopez-Rodriguez et al., 2004) method, but not by the swinging pendulum method (van Luijtelaar & Coenen, 1985), was found to prevent the normal increase in time spent immobile that results when rodents (rats & mice) are repeatedly placed in an inescapable body of water.

The advantage of studying the antidepressant effect of sleep deprivation in such an animal model of depression is that it can allow more invasive procedures for testing the possible causal mechanisms of this antidepressant effect than would be ethical or practical to do with human subjects. However, the generalizability of any conclusions from such animal studies to depressed human patients about the causal mechanisms involved is dependent upon not the face validity of the animal model but its etiological/construct validity. The latter type of validity can be based upon the degree to which effects seen in the animal model match reliably identified effects in the human condition (Geyer & Markou, 1995). In the case of the antidepressant response to sleep deprivation seen in depressed human patients, three consistent effects can be identified (see the 'Antidepressant effects of sleep deprivation' section above): (1) only half of depressed patients are responders to any given trial of sleep deprivation, (2) this response can be seen by the following day, and (3) a rapid relapse occurs in the majority of responders after an extended (> 1 hour) period of recovery sleep, although on average a large portion of the response is still retained for several days. The degree to which the animal sleep deprivation literature matches these characteristics varies for each of the characteristics.

First, with regards to efficacy, it has not been described in the literature what percentages of animals show this effect. Based on the fact that the variances of antidepressant effect within the experimental sleep deprived groups are small enough to allow for significant differences from control groups, it can be deduced that a large percentage of the sleep deprived animals must show this

response. However, the exact percentage has not yet been reported. Second, with regards to the time course of response, the ability of animals to show an antidepressant response within 24 hours from the start of sleep deprivation shows inconsistent results across studies. Two-thirds of studies to examine this effect within the first 12-24 hours of sleep deprivation reported significant differences from home cage controls (Porsolt et al., 1978; Brock et al., 1994; Meerlo et al., 1996; Lopez-Rodriguez et al., 2004), whereas the other one-third of studies reported that this effect did not appear until after 48 hours of sleep deprivation (Hawkins et al., 1980; Asakura et al, 1993a). In comparison to apparatus controls, only half of studies to examine this reported significant differences within the first 24 hours (Porsolt et al., 1978; Brock et al., 1994), with the other half of studies not seeing a difference until 48-96 hours of sleep deprivation (Hawkins et al., 1980; Lopez-Rodriguez et al., 2004). Third, with regards to the degree of relapse seen following recovery sleep, it has been reported that the antidepressant effect of sleep deprivation in animals is still significant at 1 hour (Asakura et al., 1993a) but not at 3 (Asakura et al., 1993a) or 24 (Hawkins et al., 1980; Brock et al., 1994) hours after the end of sleep deprivation. However, the degree of this relapse also varies across studies, with one report of a return to only baseline levels of immobility (Brock et al., 1994) and a separate report of an immediate catching up to the levels of immobility normally only seen by home cage and apparatus controls after repeated swim test sessions (Hawkins et al., 1980). If the latter finding is correct then it would appear that sleep deprivation merely masks behavioral despair and does not produce a

true antidepressant response that inhibits the underlying development of depression.

The present study was designed to extend our understanding of the validity of the antidepressant effects of sleep deprivation in animal models of depression by addressing of these issues. Adult rats were subjected to 96 hours of sleep deprivation and tested daily in the forced swim test. For the method of sleep deprivation, the multiple platform method was chosen to be replicated (de Oliveira et al., 2004). This procedure uses stable social groups of rats living on multiple small platforms over water to achieve near total REMS deprivation and partial NREMS deprivation while minimizing stress and permitting freedom of locomotor activity (Suchecki & Tufik, 2000). I found that the construct validity of this animal model was supported by its similar onset and offset time course of antidepressant effect to what has been reported in depressed human patients and by a degree of relapse seen following recovery sleep that is indicative of a true antidepressant response as opposed to merely a masking effect on behavioral despair. In addition, through the use of the modified forced swim test behavioral scoring system (Lucki, 1997), this animal model was also found to have discriminant validity against possible explanations of its immobility-reducing effects as being due instead to anxiety or gross impairments in learning/memory. However, the occurrence of an antidepressant response in all sleep deprived rats indicates that the construct validity of this animal model is limited to the mechanism of response seen in responders only and not to the susceptibility

mechanism which determines whether a depressed patient will be a responder or nonresponder to sleep deprivation.

A.1.2 Methods

Subjects

Male Long-Evans hooded rats (N = 24; from Charles River, Quebec) weighing 300–400 g each at the start of the experiment were housed in plexiglass cages in groups of six social littermates and kept within these groups throughout the duration of the experiment except during individual EEG recording. A 12:12-h light/dark cycle and constant room temperature were maintained. Food and water were available ad libitum. All rats were handled each day for one week prior to the start of experiments. Groups of subjects were then randomly assigned to the experimental conditions and weighed daily.

The multiple platform method of sleep deprivation

A large pool (45 cm high, 150 cm in diameter) divided in equal halves by a stainless steel grid was filled to a depth of 30 cm with 23° C water (see Figure 6a). One half of the pool served as the sleep deprivation (SD) condition for six rats. It contained 20 inverted flowerpot platforms, separated from each other by at least 8 cm, and collectively spread out over a total area of 3.56 m^2. The top of each platform was 1 cm above the water. The 6.5 cm diameter platforms were

large enough to permit NREMS but not REMS, because loss of muscle tone during REMS resulted in contact with the water and awakening. The multiple platforms also permitted locomotion and social interaction. Four to seven days prior to the start of the experiment, all rats were given a 1-h habituation session on the platforms.

The other half of the pool served as an apparatus control (AC) condition for an additional six rats. A wire mesh floor was placed 1 cm over the water, exposing the rats to similar environmental conditions but permitting both NREM and REM sleep. Metal grids placed on top of the pool prevented animals from escaping (see Figure 6b). Passive infrared motion detectors placed on top of each pool half detected locomotor activity separately for the sleep deprivation and apparatus control groups (see Figure 6c). Food and water were provided by overhead food dispensers and water bottles (see Figure 6d). During daily weighings, the water in the pool was drained and replaced. Sleep deprivation was carried out for 96 consecutive hours beginning 2-h after lights-on.

Finally, six additional rats were housed in their normal home cages throughout the duration of the experiment in order to serve as a home cage control (CC) condition.

EEG validation of sleep deprivation

As has been done previously (e.g., Smith & Gisquet-Verrier, 1996), I performed EEG recordings on a small number of animals to confirm the efficacy of our system for replicating the well-known sleep depriving effects of the

platform method. Sleep-wake states were identified electrophysiologically in six rats (2 per experimental condition) across multiple days using chronically implanted EEG and EMG electrodes (Plastics One Co.). The method for recording sleep in the rat described below is similar to what has previously been described (Mistlberger et al., 1983, 1987; Pollock & Mistlberger, 2003). Rats were anesthesized with isoflurane for stereotaxic placement of electrodes. EEG electrodes consisted of stainless-steel jeweller's screws threaded into holes drilled through the skull at the following stereotaxic coordinates, in millimeters with respect to bregma; parietal cortex, 1.0 posterior, 2.5 lateral; hippocampus, 4.3 posterior, 2.0 lateral, 2.3 ventral; frontal cortex, 3.0 anterior, 2.0 lateral; occipital cortex, 1.0 anterior to Lambda, 3.5 lateral. Slow wave (1-3 Hz) and spindle (10-15 Hz) neocortical EEG activity were obtained by differential recordings from the electrodes positioned in the parietal and occipital cortices. Hippocampal theta rhythms (5-9 Hz) were obtained by differential recordings from two electrodes positioned in the dorsal hippocampus and, as a reference, the frontal cortex. EMG was recorded from two subcutaneous wire electrodes implanted contralaterally from each other and between the occipital bone and the neck muscle. A screw was also placed on the skull above the cerebellum to provide additional anchor support. The pins from all 6 electrodes were connected to a protective plastic headcap. The entire electrode assembly was then insulated and bonded to the skull with dental acrylic.

Following one week recovery from surgery, the rats were handled daily (15 min) for an additional week, during which sleep recordings were made to

habituate the rats to the recording conditions. Recordings were conducted in plexiglass chambers (37 x 35 x 53 cm) within electrically-shielded and sound-attenuating enclosures (Model E3125AA-3 Animal Chest, Grason-Stadler Co., West Concord, MA). Recording cables were connected to a commutator (Plastics One Co.) to allow free movement of the animal. An overhead passive infrared motion detector (Model 49-426, RadioShack Co.) was used to measure locomotor activity.

Following this adaptation period, rats were housed in the recording chambers for six consecutive days: one baseline day, four days of experimental conditions (with two rats per condition), and one recovery sleep day. On each recording day, rats were removed from their recording chambers for 30 min two hours after light onset (the beginning of their usual sleep phase) for food, water, and bedding change. Each animal was then reconnected to its recording cable and recordings carried out for the next 23.5 hours. The multiple platform method of sleep deprivation was the same as described above except, to keep recording cables from tangling, rats were tested individually with 3 platforms per chamber for the REMS deprivation condition.

Electrophysiological signals were amplified and bandpass filtered (0.3-35 and 30-300 Hz for EEG and EMG, respectively) by a polysomnograph (Grass Model 9, Grass Instruments Co.), then digitized (sampling rate of 250 Hz) and stored on a computer using SleepSign data acquisition software (Kissei Comptec Co.) for off-line analysis. Behavioral states were scored in 10 sec epochs with

each epoch classified as whatever state was predominant (see Table 23; Figure 7).

The forced swim test measure of immobility response

Rats were individually placed in tanks (60 cm high, 35 cm diameter) filled with fresh 25°C water to a depth of 30 cm. Rats from each of the three experimental groups were tested simultaneously, beginning 2-h after light onset, during the following consecutive days: one baseline day, four days of experimental conditions, and one recovery sleep day. Test sessions were 15 min on the baseline day and 5 min for all subsequent days. Overhead video cameras recorded behaviors in the tanks for subsequent analysis. As described by Lucki (1997), the following three behaviors were recognized and each 5 sec epoch scored as whichever of these behaviors was predominant: (1) immobility, consisting of floating with no additional activity other than that required to keep the head above water; (2) swimming, consisting of movement throughout the tank, easily identifiable by the waves it produced; and (3) climbing, consisting of active attempts to climb the wall of the pool with the forepaws. An increase in time spent immobile within and across sessions is taken as a measure of behavioral despair. An antidepressent effect of sleep deprivation is indicated by decreased time spent immobile, relative to control rats. After each test session, rats were dried under a 300 W heat lamp for 5 min before being returned to their experimental condition.

Statistical analyses

Average differences were evaluated by one-way ANOVAs with Newman-Keuls post hoc tests or *t* tests for planned comparisons. All alphas were set at 0.05 two-tailed.

A.1.3 Results and Discussion

EEG validation of the multiple platform method of sleep deprivation

Across the four days of sleep deprivation and relative to baseline, significant group differences were evident for changes in REMS ($F_{2,9} = 250.7$, $p < 0.0001$), non-REMS ($F_{2,9} = 56.66$, $p < 0.0001$), waking ($F_{2,9} = 132.3$, $p < 0.0001$), and locomotor activity ($F_{2,9} = 27.36$, $p = 0.0001$). Post-hoc testing revealed that sleep deprived rats had significantly greater decreases in REMS (-96%) and NREMS (-36%) and increases in waking (+55%) and locomotor activity (+100%) than either apparatus control or home cage control rats (see Figure 8). In contrast, apparatus control rats showed significant differences from home cage control rats in only changes of REMS (-40%) and locomotor activity (+27%) but not of NREMS (+9%) or waking (-3%).

The effects of sleep deprivation remained consistent throughout the days of experimental treatment (see Figure 9a-d). It can also be observed that the daily rhythms of wake, NREMS and locomotor activity were strongly attenuated in sleep deprived rats, but not in apparatus control rats, compared to home cage

control rats (see Figure 9e-h). During 24-h of recovery sleep, sleep deprived rats showed a significant rebound in total daily sleep relative to home cage control rats (+29%; t_2 = 5.40, p = 0.03), with trends towards increases in REMS (+100%; t_2 = 1.78, p = 0.11) and NREMS (+40%; t_2 = 2.61, p = 0.06). Similar effects of the multiple platform method as all of the above results have previously been reported (van Luijtelaar & Coenen, 1986; Suchecki et al., 2000; Machado et al., 2004).

Sleep deprivation prevents behavioral despair in the forced swim test model of antidepressant response

I found that sleep deprivation prevents behavioral despair in the modified version of the most commonly used and well-validated animal model of depression, the modified forced swim test (Lucki, 1997). In this test a reduction in passive behavior (immobility) and an increase in active behavior (swimming and/or climbing) are considered an antidepressant effect, and are sensitive to antidepressant treatments (Cryan et al., 2005). While home cage control rats exhibited across daily forced swim tests and relative to baseline the expected increase in immobility (+655%) and decrease in swimming (-35%) that is indicative of behavioral despair, sleep deprivation almost completely eliminated immobility (-89%) and instead increased swimming (+55%). Across the four days of sleep deprivation and relative to baseline, significant group differences were evident for changes in immobility ($F_{2,9}$ = 23.04, p = 0.0003) and swimming ($F_{2,9}$ = 96.53, p < 0.0001) but not climbing ($F_{2,9}$ = 0.07, p = 0.93). Thigmotaxic climbing is

considered an index of behavioral anxiety (Treit & Fundytus, 1988), and the fact that sleep deprived rats still showed the normal decrease (-71%) in its levels across daily forced swim tests indicates that other differences exhibited between sleep deprived and control rats are unlikely to be due to anxiety or a gross impairment in learning/memory.

Post-hoc testing revealed that sleep deprived rats had significantly lower amounts of immobility and higher amounts of swimming than both apparatus control and home cage control rats (see Figure 10). Apparatus control rats also had significantly lower amounts of immobility and higher amounts of swimming than home cage control rats, consistent with the intermediate level of effects seen upon their behavioral states (in particular REMS and locomotor activity) relative to the sleep deprivation and home cage control conditions (see Figure 8). By the first 24 hours of sleep deprivation, sleep deprived rats already showed significantly reduced immobility levels compared to home cage control (t_{10} = 5.06, p = .0005) and apparatus control (t_{10} = 3.45, p = .006) rats (see Figure 11), similar to the time course of antidepressant effects seen in depressed human patients. However, unlike in depressed human patients, the antidepressant effects of sleep deprivation were consistently seen in all sleep deprived rats on each day of sleep deprivation, indicating that the antidepressant effects seen in this animal model can only be generalized to mechanism involved in the response of responders and not to the susceptibility mechanism that determines differences between responders and nonresponders. After a full day of recovery sleep, the sleep deprived rats exhibited immobility scores comparable to the first

day of testing, indicating that sleep deprivation delays induction of behavioral despair, as opposed to masking it.

Table 1 - Unweighted and weighted versions of statistical formulas used

Statistic	Unweighted	Weighted
Within-subject response	$response = 1 - \frac{day2\ depression\ level}{day1\ depression\ level}$	
Cohen's *d* effect size	$d = \frac{\bar{x}_{responders} - \bar{x}_{nonresponders}}{\sqrt{\frac{(n_{responders}-1)s_{responders}^{\ 2} + (n_{nonresponders}-1)s_{nonresponders}^{\ 2}}{n_{responders}+n_{nonresponders}}}}$	
Distribution overlap	$overlap\% = 0.0043d^4 - 0.0525d^3 + 0.2766d^2 - 0.7816d + 0.9987$	
Conversion of Cohen's *d* effect size to Pearson product-moment correlation coefficient	$r = \frac{d}{\sqrt{d^2+4}}$	
Mean	$\bar{x} = \frac{\sum x_i}{n}$	$\bar{x}_w = \frac{\sum w_i x_i}{\sum w_i}$
Standard deviation	$s = \sqrt{\frac{\sum (x_i - \bar{x})^2}{n-1}}$	$s_w = \sqrt{\frac{\sum w_i (x_i - \bar{x}_w)^2}{\frac{(n-1)\sum w_i}{n}}}$
95% confidence interval on a mean	$95\%\ CI = \bar{x} \pm 1.96\left(\frac{s}{\sqrt{n}}\right)$	$95\%\ CI_w = \bar{x}_w \pm 1.96\left(\frac{s_w}{\sqrt{n}}\right)$

One-sample *t*-test	$t = \frac{\bar{x} - \mu}{\frac{s}{\sqrt{n}}}$	$t_w = \frac{\bar{x}_w - \mu}{\frac{s_w}{\sqrt{n}}}$
Two-sample *t*-test	$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$	$t_w = \frac{\bar{x}_{w1} - \bar{x}_{w2}}{\sqrt{\frac{s_{w1}^2}{n_1} + \frac{s_{w2}^2}{n_2}}}$
Pearson product-moment correlation coefficient	$r = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum (x_i - \bar{x})^2 \sum (y_i - \bar{y})^2}}$	$r_w = \frac{\sum w_i (x_i - \bar{x}_w)(y_i - \bar{y}_w)}{\sqrt{\sum w_i (x_i - \bar{x}_w)^2 \sum w_i (y_i - \bar{y}_w)^2}}$
Single measure one-way model intraclass correlation coefficient	$ICC = \frac{MS_{bs} - MS_{ws}}{MS_{bs} + (k-1)MS_{ws}}$	
Average measure one-way model intraclass correlation coefficient	$ICC = \frac{MS_{bs} - MS_{ws}}{MS_{bs}}$	
Orwin's fail-safe *N*	$N_{fail-safe} = \frac{N_{Observed}(\bar{d}_{Observed} - d_{Critical})}{d_{Critical} - d_{Null}}$	

Note: *bs* = Between-subjects; *d* = Cohen's effect size; *k* = Number of observation periods; *MS* = Mean square obtained by applying analysis of variance (ANOVA); *w* = Weight; *ws* = Within-subjects.

Table 2 - Antidepressant effects of sleep deprivation reported across studies

	$Mean_w$	$Stdev_w$	95% CI_w	*n* studies
Baseline day before night of sleep deprivation				
Responder vs. nonresponder differences in depression level				
Cohen's *d* effect size [a]	0.05	0.58	-0.14 to 0.24	36
Distribution overlap	96%			
Day after night of sleep deprivation				
Responders (% of patients)	49.4	14.1	46.9 to 51.8	127
Response (% decrease from baseline) [b]	32.7	11.1	30.4 to 35.0	88
All patients	55.4	10.1	52.2 to 58.6	38
Responders	7.3	8.7	4.4 to 10.2	35
Nonresponders				
Responder vs. nonresponder differences in depression level				
Cohen's *d* effect size [a]	-1.93	1.11	-2.33 to -1.52	29
Distribution overlap	20%			
Day after night of recovery sleep				
Relapsers (% of responders)	65.0	12.7	58.3 to 71.6	14
Response (% decrease from baseline) [b]	31.8	16.5	26.2 to 37.4	34
All patients	36.6	11.0	29.4 to 43.8	9
Responders	10.4	9.3	3.5 to 17.3	7
Nonresponders				
Responder vs. nonresponder differences in depression level				
Cohen's *d* effect size [a]	-0.47	0.45	-0.91 to -0.02	4
Distribution overlap	69%			
Day before night of sleep deprivation vs. day after night of sleep deprivation				
All patients				
Cohen's *d* effect size [c]	1.30	0.83	1.08 to 1.52	54
Distribution overlap	35%			
Responders				
Cohen's *d* effect size [c]	2.64	1.48	2.11 to 3.18	29
Distribution overlap	10%			
Nonresponders				
Cohen's *d* effect size [c]	0.44	0.71	0.18 to 0.69	30

Distribution overlap	71%			
Day before night of sleep deprivation vs. day after night of recovery sleep				
All patients				
Cohen's *d* effect size [c]	1.29	0.83	0.96 to 1.61	25
Distribution overlap	35%			
Responders				
Cohen's *d* effect size [c]	1.23	0.67	0.57 to 1.89	4
Distribution overlap	37%			
Nonresponders				
Cohen's *d* effect size [c]	0.11	0.22	-0.14 to 0.35	3
Distribution overlap	92%			
Day after night of sleep deprivation vs. day after night of recovery sleep				
All patients				
Cohen's *d* effect size [c]	0.14	0.42	-0.03 to 0.31	24
Distribution overlap	90%			
Responders				
Cohen's *d* effect size [c]	-1.08	0.29	-1.36 to –0.79	4
Distribution overlap	42%			
Nonresponders				
Cohen's *d* effect size [c]	0.09	0.06	0.02 to 0.16	3
Distribution overlap	93%			

Note: 95% CI = 95% confidence interval in which bounds the true mean of the population is likely to be with 95% probability; *n* studies = Number of studies contributing to each statistic; Stdev = Standard deviation; *w* = Weighted by the number of patients in each study.

[a] Effect sizes, reported in terms of Cohen's *d*, are for group differences in depression levels between responders versus nonresponders where more positive *d* values indicate greater depression levels in responders relative to nonresponders and, conversely, more negative *d* values indicate lower depression levels in responders relative to nonresponders.

[b] Response based on clinician-rated measurements of depression.

[c] Effect sizes, reported in terms of Cohen's *d*, are for differences in depression levels between the two days indicated where more positive *d* values indicate greater depression levels on the previous day (e.g., day before the night of sleep deprivation) relative to the day that comes after (e.g., day after the night of sleep deprivation) and, conversely, more negative *d* values indicate lower depression levels on the previous day relative to the day that comes after.

Table 3 - Mean$_w$ antidepressant effects for studies that used total and partial sleep deprivation methods[a]

Sleep deprivation method	% Rspdrs	Response after night of sleep deprivation[b]			% Rlpsrs	Response after recovery night[b]			Effect size for group differences in depression[c]		
		All patients	Rspdrs	Nrspdrs		All patients	Rspdrs	Nrspdrs	Before sleep dep	After sleep dep	After rec sleep
Total	48.8 (90)	33.2 (63)	55.7 (24)	8.2 (23)	61.7 (9)	38.4 (20)	35.0 (3)	19.0 (2)	0.00 (24)	-2.16 (18)	-1.10 (1)
Partial - 2nd half of night	51.3 (31)	32.6 (21)	53.9 (12)	6.2 (10)	68.1 (5)	23.3 (11)	36.8 (5)	5.7 (4)	0.22 (11)	-1.56 (10)	-0.27 (3)
Partial - 1st half of night	**20.7 (3)**	**16.9 (3)**	63.2 (1)	-9.7 (1)		31.5 (3)	52.6 (1)	-7.3 (1)			

Note: Mean$_w$ = Average weighted by the number of patients in each study; Rec sleep = Recovery sleep; Sleep dep = Sleep deprivation. A blank cell indicates a lack of available studies to calculate that average.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. Significant differences (with alpha set at .05 and after correcting for family-wise error rate, $p < .005$ two-tailed) from total sleep deprivation are presented in bold font.

[b] Effect sizes, reported in terms of Cohen's *d*, are for group differences in depression levels between responders versus nonresponders where more positive *d* values indicate greater depression levels in responders relative to nonresponders and, conversely, more negative *d* values indicate lower depression levels in responders relative to nonresponders.

[c] Response based on clinician-rated measurements of depression.

Table 4 - Correlations (r_w) across studies that used the 2nd half of the night sleep deprivation method between the timing of the start of the sleep deprivation and its antidepressant effects[a]

	% Rspdrs	Response after night of sleep deprivation[b]			Effect size for group differences in depression[c]		% Rlpsrs	Response after recovery night[b]		
		All patients	Rspdrs	Nrspdrs	Before sleep dep	After sleep dep		All patients	Rspdrs	Nrspdrs
r_w	.11	-.05	-.70	.76	.43	-.17	.80	-.54	-.83	.92
(n)	(31)	(21)	(12)	(10)	(11)	(10)	(5)	(11)	(5)	(4)

Note: HDRS = Hamilton Depression Rating Scale; Nrspdrs = Nonresponders; Rlpsrs = Relapsers; Rspdrs = Responders; Recov night = Recovery night; r_w = Pearson product-moment correlation coefficient weighted by the number of patients in each study (see Table 1 for formula); Sleep dep = Sleep deprivation.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. Significant correlations (with alpha set at .05 and after correcting for family-wise error rate, $p < .005$ two-tailed) are presented in bold font.

[b] Antidepressant response was the percentage decrease in depression level from baseline based on clinician-rated measurements of depression.

[c] Effect sizes are for group differences in depression levels between responders versus nonresponders. The positive/negative directions of the correlation coefficients have been reversed so that positive correlations between sleep deprivation timing and this effect size indicate that as the start of the sleep deprivation becomes later differences in depression levels between responders and nonresponders become larger while, conversely, negative correlations indicate that as the start of the sleep deprivation becomes later differences in depression levels between responders and nonresponders become smaller.

Table 5 – Sample characteristics of the studies used in the analysis on the antidepressant effects of sleep deprivation

Variable	$Mean_w$	$Stdev_w$	Range	*n* studies
Date of publication (year)	1994.3	8.5	1974-2010	166
Depressed patients	42.9	36.4	1-145	166
Sleep deprivations	47.6	46.0	1-296	166
Age of patients (years)	46.4	6.6	15.0-72.0	150
Age at onset of depression (years)	34.2	4.9	14.7-52.7	37
Previous depressive episodes	4.3	1.5	0-7.1	37
Duration of current depressive episode (weeks)	20.0	30.6	1.5-286	45
Male (% of patients)	36.2	20.1	0-100	151
Bipolar (% of patients)	33.7	38.4	0-100	116
Psychotic (% of patients)	6.2	13.7	0-100	50
Antidepressant medication (% of patients currently taking)	32.7	42.3	0-100	152
Mood stabilizers[a] (% of patients currently taking)	3.5	13.3	0-100	134
Severity of depression at baseline				
21-item HDRS score	24.7	2.6	14.2-32.0	56
17-item HDRS score	20.8	2.8	16.4-25.5	18

Note: HDRS = Hamilton Depression Rating Scale; *n* studies = Number of studies contributing to each statistic; Stdev = Standard deviation; *w* = Weighted by the number of patients in each study.

[a] Mood stabilizers included lithium, valproate, and carbamazepine.

Table 6 – Correlations between demographic/clinical variables and the antidepressant response to sleep deprivation[a]

Variable	Studies reporting a significant effect[b]	Mean effect size[c] (*r*)	Variability accounted for[d] (r^2)
Age	8.3% (36)	.01 (22)	0% (22)
Age at onset of depression	0% (3)		
Previous depressive episodes	14.3% (7)	.36 (1)	13% (1)
Duration of current depressive episode	0% (7)	.27 (1)	7% (1)
Male	0% (22)		
Bipolar	25% (8)		
Psychotic	100% (1)	.27 (1)	7% (1)
Antidepressant medication	0% (7)	-.03 (1)	0% (1)
Mood stabilizer	0% (1)	.22 (1)	5% (1)
Severity of depression at baseline	18.8% (32)	-.08 (9)	1% (9)

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.
[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.
[c] Mean effect size is expressed as a correlation coefficient (*r*) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates that higher levels of this variable are associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates that higher levels of this variable are associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated across primary studies either from reported correlations or, when these were unavailable, from Cohen's *d* effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in the variable between responder and nonresponder groups.

[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

Table 7 – Correlations (r_w) across studies between sample characteristics and the antidepressant effects of sleep deprivation[a]

Variable	% Rspdrs	Response after night of sleep deprivation[b]			Effect size for group differences in depression[c]		% Rlpsrs	Response after recovery night[b]		
		All patients	Rspdrs	Nrspdrs	Before sleep dep	After sleep dep		All patients	Rspdrs	Nrspdrs
Date	.04	.22	.38	.25	.15	.21	.42	.03	-.16	-.21
	(127)	(88)	(38)	(35)	(36)	(29)	(14)	(34)	(9)	(7)
Age	-.06	.05	.19	-.31	-.15	.04	.33	-.32	-.36	-.53
	(115)	(80)	(35)	(32)	(33)	(28)	(12)	(32)	(7)	(5)
Age at onset of depression	.23	-.17	-.08	-.79				-.33		
	(18)	(19)	(7)	(5)				(11)		
Previous depressive episodes	.08	-.12	.38					.27		
	(17)	(18)	(5)					(12)		
Duration of current depressive episode	-.25	-.48	.47	-.36	.00	-.46		-.55		
	(23)	(23)	(7)	(7)	(5)	(5)		(12)		
Male	.05	.01	-.12	.27	-.03	**.58**	-.58	-.26	-.37	.46
	(118)	(81)	(37)	(35)	(36)	**(29)**	(11)	(30)	(8)	(7)
Bipolar	.17	.20	-.20	-.09	.12	-.07	-.12	**.62**	.36	
	(88)	(65)	(33)	(30)	(29)	(25)	(6)	**(23)**	(6)	
Psychotic	-.05	-.25	-.52	-.52	.07	-.52		-.02		
	(34)	(32)	(10)	(10)	(8)	(6)		(20)		
Antidepressant medication	-.19	.07	.20	.21	-.04	.36	-.40	.03	.51	.69
	(116)	(82)	(35)	(32)	(34)	(27)	(11)	(29)	(7)	(5)
Mood stabilizer	-.03	.09	.08	-.09	.06	-.34	-.23	.08	.74	.83

	(103)	(76)	(32)	(30)	(32)	(25)	(11)	(29)	(7)	(5)
Severity of depression at baseline										
21-item HDRS score	.21 (46)	.32 (26)	-.26 (13)	.46 (12)	-.09 (14)	.14 (9)	-.53 (7)	.02 (10)	-.55 (6)	.25 (6)
17-item HDRS score	.31 (12)	-.31 (13)						.54 (6)		

Note: HDRS = Hamilton Depression Rating Scale; Nrspdrs = Nonresponders; Rlpsrs = Relapsers; Rspdrs = Responders; Recov night = Recovery night; r_w = Pearson product-moment correlation coefficient weighted by the number of patients in each study (see Table 1 for formula); Sleep dep = Sleep deprivation. A blank cell indicates an insufficient number of studies (< 5) to calculate that correlation.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. Significant correlations (with alpha set at .05 and after correcting for family-wise error rate, $p < .005$ two-tailed) are presented in bold font.

[b] Antidepressant response was the percentage decrease in depression level from baseline based on clinician-rated measurements of depression.

[c] Effect sizes are for group differences in depression levels between responders versus nonresponders. For convenience in comparing to other correlations in this table, the positive/negative directions of the correlation coefficients for these effect sizes have been reversed in this table so that positive correlations between any variable and this effect size indicate that as the variable increases differences in depression levels between responders and nonresponders become larger while, conversely, negative correlations indicate that as the variable increases differences in depression levels between responders and nonresponders become smaller.

Table 8 – Influence of environmental variables during sleep deprivation on the antidepressant response to sleep deprivation[a]

Variable	Studies reporting a significant effect[b]	Mean effect size[c] (r)	Variability accounted for[d] (r^2)
Bright light	0%	-.36	13%
	(2)	(1)	(1)
Confinement to bed	0%	-.05	0%
	(1)	(1)	(1)

[a] Numbers in brackets refer to the number of studies (n) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.
[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.
[c] Mean effect size is expressed as a correlation coefficient (r) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates the variable is associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates the variable is associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated from Cohen's d effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in antidepressant response between experimental conditions.
[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

Table 9 – Correlations between spontaneous behavior variables and the antidepressant response to sleep deprivation[a]

Timing relative to sleep dep	Variable	Studies reporting a significant effect[b]	Mean effect size[c] (*r*)	Variability accounted for[d] (r^2)
Night before night of sleep dep	Actometer activity counts	0% (1)		
Day before night of sleep dep	Actometer activity counts	50% (2)	.63 (1)	40% (1)
	Frequency of body touching	100% (1)	.49 (1)	24% (1)
	Frequency of object touching	100% (1)	.49 (1)	24% (1)
	Frequency of "yes" nodding	0% (1)	-.31 (1)	10% (1)
	Frequency of looking at the head of the interviewer	0% (1)	-.28 (1)	8% (1)
	Eye-blink rate	0% (1)	0.21 (1)	4% (1)
	Frequency of gesturing	0% (1)	-.18 (1)	3% (1)
	Frequency of "no" shaking	0% (1)	-.08 (1)	1% (1)
	Frequency of speaking	0% (1)	.04 (1)	0% (1)
	Frequency of head movements	0% (1)	-.02 (1)	0% (1)

Night of sleep dep	Actometer activity counts	25% (4)		
Day after night of sleep dep	Actometer activity counts	50% (2)		
Day after night of sleep dep	Eye-blink rate	100% (1)	.28 (1)	8% (1)
Change from day before to day after night of sleep dep	Increased eye-blink rate	100% (1)	.75 (1)	56% (1)

Note: Sleep dep = Sleep deprivation.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.

[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.

[c] Mean effect size is expressed as a correlation coefficient (*r*) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates that higher levels of this variable are associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates that higher levels of this variable are associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated across primary studies either from reported correlations or, when these were unavailable, from Cohen's *d* effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in the variable between responder and nonresponder groups.

[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

Table 10 – Correlations between psychological variables and the antidepressant response to sleep deprivation[a]

Timing relative to sleep dep	Variable	Studies reporting a significant effect[b]	Mean effect size[c] (*r*)	Variability accounted for[d] (r^2)
Day before night of sleep dep	Activation/energy/vigor	0% (1)		
	Anxiety/strain/stress/tension	0% (3)	-.09 (2)	1% (2)
	Fatigue/tiredness	50% (2)	-.33 (2)	11% (2)
	Vigilance on continuous performance test	50% (2)	.32 (2)	10% (2)
	Pain threshold	0% (1)		
	Expectations about therapeutic effects of sleep deprivation	0% (3)		
Day after night of sleep dep	Activation/energy/vigor	0% (1)	.31 (1)	10% (1)
	Anxiety/strain/stress/tension	0% (3)	-.23 (2)	5% (2)
	Fatigue/tiredness	0% (4)	-.22 (4)	5% (4)
	Vigilance on continuous performance test	0% (2)	.33 (2)	11% (2)
	Pain threshold	0% (1)		

Change from day before to day after night of sleep dep	Increased activation/energy/vigor	100% (1)	.76 (1)	58% (1)
	Decreased anxiety/strain/stress/tension	50% (2)	.32 (2)	10% (2)
	Increased fatigue/tiredness	0% (1)	-.12 (1)	1% (1)

Note: Sleep dep = Sleep deprivation.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.

[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.

[c] Mean effect size is expressed as a correlation coefficient (*r*) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates that higher levels of this variable are associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates that higher levels of this variable are associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated across primary studies either from reported correlations or, when these were unavailable, from Cohen's *d* effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in the variable between responder and nonresponder groups.

[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

Table 11 – Correlations between evoked potential variables and the antidepressant response to sleep deprivation[a]

Timing relative to sleep dep	Variable	Studies reporting a significant effect[b]	Mean effect size[c] (*r*)	Variability accounted for[d] (r^2)
Day before night of sleep dep	P1 amplitude	100% (1)	-.73 (1)	53% (1)
	N1 amplitude	100% (2)	-.58 (2)	34% (2)
	P2 amplitude	0% (1)		
	N2 amplitude	0% (1)		
	P300 amplitude	0% (1)		
	N1-P2 amplitude	0% (1)	.16 (1)	2% (1)
	N1 latency	0% (2)	-.11 (1)	1% (1)
	P2 latency	0% (2)	.03 (1)	0% (1)
	P300 latency	0% (1)		
	Change in P1 amplitude with increasing stimulus intensities	100% (1)	-.49 (1)	24% (1)
	Corneo-fundal potential peak to light adaptation	0% (1)	-.12 (1)	2% (1)
	Corneo-fundal potential trough to	0%	.04	0%

	dark adaptation	(1)	(1)	(1)
Day after night of sleep dep	N1-P2 amplitude	0%	.07	1%
		(1)	(1)	(1)
	N1 latency	0%	.00	0%
		(1)	(1)	(1)
	P2 latency	0%	.13	2%
		(1)	(1)	(1)
Change from day before to day after night of sleep dep	Increased N1 amplitude	100%	.67	45%
		(1)	(1)	(1)
	P2 amplitude	0%		
		(1)		
	N2 amplitude	0%		
		(1)		
	Decreased P300 amplitude	100%	-.57	32%
		(1)	(1)	(1)
	Decreased N1 latency	100%	-.56	32%
		(1)	(1)	(1)
	P2 latency	0%		
		(1)		
	N2 latency	0%		
		(1)		
	P300 latency	0%		
		(1)		
	Increased corneo-fundal potential peak to light adaptation	100%	.60	36%
		(1)	(1)	(1)
	Increased corneo-fundal potential trough to dark adaptation	0%	.22	5%
		(1)	(1)	(1)

Note: Sleep dep = Sleep deprivation.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.

[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.

[c] Mean effect size is expressed as a correlation coefficient (*r*) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates that higher levels of this variable are associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates that higher levels of this variable are associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated across primary studies either from reported correlations or, when these were unavailable, from Cohen's *d* effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in the variable between responder and nonresponder groups.

[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

Table 12 – Correlations between sleep variables and the antidepressant response to sleep deprivation[a]

Timing relative to sleep dep	Variable	Studies reporting a significant effect[b]	Mean effect size[c] (r)	Variability accounted for[d] (r^2)
Night before night of sleep dep	Total sleep amount	0% (8)	.03 (7)	0% (7)
	Time spent in bed	0% (4)	.20 (4)	4% (4)
	Sleep efficiency	0% (8)	-.07 (7)	0% (7)
	Waking amount during sleep period	17% (6)	-.04 (5)	0% (5)
	Waking amount during early morning	0% (3)	.20 (3)	4% (3)
	Stage 1 sleep amount	0% (5)	-.01 (4)	0% (4)
	Stage 2 sleep amount	0% (5)	-.07 (4)	0% (4)
	SWS amount	13% (8)	.13 (7)	2% (7)
	REMS amount	0% (8)	-.11 (7)	1% (7)
	Sleep latency	0% (8)	.09 (7)	1% (7)
	REMS latency	38% (8)	-.11 (7)	1% (7)
	rem density in REMS	14%	-.08	1%

		(7)	(7)	(7)
	Delta power	0%	.27	7%
		(3)	(1)	(1)
	SWS amount in 1st NREMS episode	33%	.19	4%
		(3)	(2)	(2)
Day before night of sleep dep	Microsleep amount	100%	-.63	40%
		(1)	(1)	(1)
Sleep period awoken from for "2nd half of the night" sleep dep	Total sleep amount	0%		
		(1)		
	Time spent in bed	0%		
		(1)		
	Sleep efficiency	0%		
		(1)		
	Stage 1 sleep amount	0%		
		(1)		
	Stage 2 sleep amount	0%		
		(1)		
	SWS amount	0%		
		(1)		
	REMS amount	0%		
		(1)		
During & day after night of sleep dep	Microsleep amount	100%	-.52	27%
		(2)	(2)	(2)
Nap after night of sleep dep	Total sleep amount	0%	-.02	0%
		(4)	(3)	(3)
	Sleep efficiency	0%	.19	4%
		(2)	(2)	(2)

	Waking amount during sleep period	0%	-.15	2%
		(3)	(2)	(2)
	Stage 1 sleep amount	0%	.19	4%
		(3)	(3)	(3)
	Stage 2 sleep amount	0%	.20	4%
		(3)	(3)	(3)
	SWS amount	0%	-.03	0%
		(3)	(3)	(3)
	REMS amount	67%	-.40	16%
		(3)	(3)	(3)
	Sleep latency	0%	-.10	1%
		(2)	(2)	(2)
	REMS latency	0%	.19	4%
		(2)	(2)	(2)
	rem density in REMS	67%	-.27	7%
		(3)	(2)	(2)
Rec night	Total sleep amount	0%	.04	0%
		(5)	(5)	(5)
	Time spent in bed	0%	-.06	0%
		(2)	(2)	(2)
	Sleep efficiency	0%	.04	0%
		(5)	(5)	(5)
	Waking amount during sleep period	0%	-.11	1%
		(4)	(4)	(4)
	Waking amount during early morning	0%	.14	2%
		(2)	(2)	(2)
	Stage 1 sleep amount	0%	.08	1%
		(3)	(3)	(3)
	Stage 2 sleep amount	0%	-.17	3%
		(3)	(3)	(3)

	SWS amount	17% (6)	.24 (6)	6% (6)
	REMS amount	17% (6)	-.15 (6)	2% (6)
	Sleep latency	0% (5)	-.18 (5)	3% (5)
	REMS latency	0% (5)	-.01 (5)	0% (5)
	rem density in REMS	20% (5)	-.09 (5)	1% (5)
	Delta power	100% (1)	.47 (1)	22% (1)
	SWS amount in 1st NREMS episode	100% (1)	.50 (1)	25% (1)
Change from day before to day after night of sleep dep	Waking theta power	100% (1)	.69 (1)	48% (1)
Change from night before night of sleep dep to rec night	Total sleep amount	0% (1)		
	Sleep efficiency	0% (2)		
	Waking amount during sleep period	0% (2)		
	Stage 1 sleep amount	0% (2)		
	Stage 2 sleep amount	0% (2)		
	Increased SWS amount	33%	.60	36%

	(3)	(1)	(1)
Decreased REMS amount	50%		
	(2)		
Sleep latency	0%		
	(3)		
REMS latency	0%		
	(2)		
rem density in REMS	0%		
	(1)		
Delta power	0%		
	(1)		

Note: NREMS = Non-REM sleep; Sleep dep = Sleep deprivation; Rec night = Recovery night; rem density = Rapid eye movement density; REMS = Rapid eye movement sleep; SWS = Slow wave sleep.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.

[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.

[c] Mean effect size is expressed as a correlation coefficient (*r*) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates that higher levels of this variable are associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates that higher levels of this variable are associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated across primary studies either from reported correlations or, when these were unavailable, from Cohen's *d* effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in the variable between responder and nonresponder groups.

[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

Table 13 – Correlations between functional brain imaging variables and the antidepressant response to sleep deprivation[a]

Timing relative to sleep dep	Brain region of activity	Studies reporting a significant effect[b]			Mean effect size[c] (r)			Variability accounted for[d] (r^2)		
		Left	Right	Both[e]	Left	Right	Both[f]	Left	Right	Both[f]
2 days before night of sleep dep	Anterolateral prefrontal cortex (upper parts)	100% (1)	100% (1)		-.80 (1)	-.74 (1)	-.77 (1)	64% (1)	55% (1)	59% (1)
	Anterolateral prefrontal cortex (lower parts)	0% (1)	0% (1)		-.67 (1)	-.47 (1)	-.57 (1)	45% (1)	22% (1)	32% (1)
	Orbitofrontal cortex	100% (1)	100% (1)		.72 (1)	.78 (1)	.75 (1)	51% (1)	60% (1)	56% (1)
	Inferior temporal cortex	0% (1)	0% (1)		.29 (1)	.56 (1)	.42 (1)	8% (1)	31% (1)	18% (1)
	Hippocampus	0% (1)	100% (1)		.31 (1)	.81 (1)	.56 (1)	10% (1)	65% (1)	31% (1)
Day before night of sleep dep	Whole brain			0% (1)						
	Cortical surface			0% (1)			.40 (1)			16% (1)
	Frontal pole	0% (1)	0% (1)							
	Inferior prefrontal gyrus	100% (1)	0% (1)		-.34 (1)			12% (1)		
	Cingulate	100% (1)	100% (1)	100% (1)	.43 (1)	.41 (1)	.53 (2)	19% (1)	17% (1)	29% (2)
	Anterior cingulate	0%	100%		.30	.61	.48	9%	37%	23%

	(2)	(2)		(1)	(2)	(1)	(1)	(2)	(1)
Dorsal anterior cingulate &	0%	0%		-.09	.11	.01	1%	1%	0%
medial prefrontal	(1)	(1)		(1)	(1)	(1)	(1)	(1)	(1)
Dorsal anterior cingulate		0%			.23			5%	
		(1)			(1)			(1)	
Ventral anterior cingulate	100%	0%		.52	-.01	.25	27%	0%	6%
	(1)	(1)		(1)	(1)	(1)	(1)	(1)	(1)
Subgenual cortex	0%	0%	100%			.38			15%
	(1)	(1)	(1)			(1)			(1)
Orbitofrontal cortex/basal	50%	100%		.25	.80	.52	6%	64%	28%
cingulate	(2)	(2)		(2)	(2)	(2)	(2)	(2)	(2)
Medial cortex			0%			.46			22%
			(1)			(1)			(1)
Parietal cortex	0%	0%		-.14	-.18	-.16	2%	3%	2%
	(1)	(1)		(1)	(1)	(1)	(1)	(1)	(1)
Insula	0%	0%							
	(1)	(1)							
Temporal cortex	0%	0%		-.26	-.27	-.27	7%	8%	7%
	(1)	(1)		(1)	(1)	(1)	(1)	(1)	(1)
Superior temporal cortex	50%	0%		.36	.06	.14	13%	0%	2%
	(2)	(2)		(2)	(1)	(1)	(2)	(1)	(1)
Inferior temporal cortex	0%	50%		-.16	.18	-.15	3%	3%	2%
	(2)	(2)		(1)	(2)	(1)	(1)	(2)	(1)
Occipital cortex	0%	0%							
	(1)	(1)							
Basal ganglia			0%			.48			23%
			(1)			(1)			(1)
Striatum	0%	0%							
	(1)	(1)							
Putamen	0%	0%							
	(1)	(1)							

	Limbic system			100% (1)			.59 (1)			34% (1)
	Amygdala	100% (1)	100% (1)	50% (2)	.52 (1)	.77 (1)	.64 (1)	27% (1)	59% (1)	42% (1)
	Hippocampus	0% (2)	50% (2)	0% (1)	.44 (1)	-.03 (2)		20% (1)	0% (2)	
	Thalamus			0% (1)			.48 (1)			23% (1)
	Midbrain	0% (1)	100% (1)	0% (1)		-.40 (1)	.42 (1)		16% (1)	17% (1)
	Cerebellum	0% (1)	0% (1)	0% (1)	-.17 (1)	-.22 (1)	.04 (2)	3% (1)	5% (1)	0% (2)
	White matter			0% (1)			.36 (1)			14% (1)
Day after night of sleep dep	Cortical surface			0% (1)			.08 (1)			1% (1)
	Anterolateral prefrontal cortex (upper parts)	0% (1)	0% (1)		-.65 (1)	-.58 (1)	-.61 (1)	42% (1)	33% (1)	37% (1)
	Anterolateral prefrontal cortex (lower parts)	0% (1)	0% (1)		-.05 (1)	.10 (1)	.03 (1)	0% (1)	1% (1)	0% (1)
	Cingulate			0% (1)						
	Dorsal anterior cingulate & medial prefrontal	0% (1)	0% (1)		-.44 (1)	-.21 (1)	-.33 (1)	20% (1)	4% (1)	11% (1)
	Dorsal anterior cingulate		0% (1)			-.16 (1)			2% (1)	
	Ventral anterior cingulate	0% (1)	0% (1)		-.30 (1)	-.05 (1)	-.18 (1)	9% (1)	0% (1)	3% (1)
	Orbitofrontal cortex	0% (2)	0% (2)		.18 (2)	.26 (2)	.22 (2)	3% (2)	7% (2)	5% (2)

	Medial cortex			0% (1)			.10 (1)			1% (1)
	Parietal cortex	0% (1)	0% (1)		.29 (1)	-.09 (1)	.10 (1)	8% (1)	1% (1)	1% (1)
	Temporal cortex	0% (1)	0% (1)		-.07 (1)	.40 (1)	.16 (1)	1% (1)	16% (1)	3% (1)
	Superior temporal cortex	0% (1)	0% (1)		-.01 (1)	-.25 (1)	-.13 (1)	0% (1)	6% (1)	2% (1)
	Inferior temporal cortex	50% (2)	0% (2)		.31 (2)	.30 (2)	.31 (2)	10% (2)	9% (2)	9% (2)
	Basal ganglia			0% (1)			.03 (1)			0% (1)
	Limbic system			0% (1)			.18 (1)			3% (1)
	Amygdala	0% (1)	0% (1)	0% (1)	.38 (1)	.38 (1)	.38 (1)	14% (1)	14% (1)	14% (1)
	Hippocampus	0% (1)	0% (1)	0% (1)	.50 (1)	-.10 (1)	.20 (1)	25% (1)	1% (1)	4% (1)
	Thalamus			0% (1)			.10 (1)			1% (1)
	Midbrain			0% (1)			.08 (1)			1% (1)
	Cerebellum	0% (1)	0% (1)	0% (1)	.14 (1)	.20 (1)	.02 (2)	2% (1)	4% (1)	0% (2)
	White matter			0% (1)			.17 (1)			3% (1)
Change from day before to day after night of sleep dep	Decreased anterior cingulate	100% (1)			-.35 (1)			12% (1)		
	Decreased dorsal anterior	0%	0%		.40	.35	.38	16%	12%	14%

cingulate & medial prefrontal	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)
Decreased dorsal anterior cingulate		100% (1)		.42 (1)			17% (1)	
Decreased ventral anterior cingulate	100% (1)	0% (1)	.46 (1)	.04 (1)	.25 (1)	21% (1)	0% (1)	6% (1)
Increased temporal cortex	100% (1)							
Decreased amygdala	0% (1)	100% (1)	.12 (1)	.53 (1)	.33 (1)	2% (1)	28% (1)	11% (1)

Note: Sleep dep = Sleep deprivation.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.

[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.

[c] Mean effect size is expressed as a correlation coefficient (*r*) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates that higher levels of this variable are associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates that higher levels of this variable are associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated across primary studies either from reported correlations or, when these were unavailable, from Cohen's *d* effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in the variable between responder and nonresponder groups.

[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

[e] Significant results reported in studies that statistically examined the combined activity of this structure on both the left and right hemispheres.

[f] For studies that reported results separately for the left and right hemispheres, the average across both hemispheres was calculated for that study and this was then used in the average across studies.

Table 14 – Correlations between neurochemical variables and the antidepressant response to sleep deprivation[a]

Timing relative to sleep dep	Variable	Studies reporting a significant effect[b]	Mean effect size[c] (r)	Variability accounted for[d] (r^2)
Several days or weeks before night of sleep dep	Dopamine metabolite (HVA)	0% (1)	-.20 (1)	4% (1)
3 days either before or after night of sleep dep†	Sensitivity to dopamine changes (prolactin response to D2 receptor antagonism)	0% (1)	-.03 (1)	0% (1)
2 days before night of sleep dep	Dopamine metabolite (HVA)	0% (1)	-.18 (1)	3% (1)
	D2 dopamine receptor vacancies in the left basal ganglia	0% (1)	.12 (1)	2% (1)
	D2 dopamine receptor vacancies in the right basal ganglia	100% (1)	.51 (1)	26% (1)
	Norepinephrine/epinephrine metabolite (MHPG)	0% (1)	-.02 (1)	0% (1)
	Norepinephrine/epinephrine metabolite (VMA)	50% (2)	-.74 (1)	55% (1)
	Melatonin at night	0% (1)		
Day before night of sleep dep	Dopamine metabolite (HVA)	50% (2)	-.41 (2)	17% (2)
	Norepinephrine/epinephrine	20%	.32	10%

	metabolite (MHPG)	(5)	(3)	(3)
	Serotonin metabolite (5HIAA)	0%	-.04	0%
		(2)	(1)	(1)
	Imipramine binding to blood platelets	0% (1)		
	Sensitivity to serotonin changes (prolactin response to serotonin agonist)	100% (1)	-.41 (1)	17% (1)
	Melatonin at night	0%	-.50	25%
		(1)	(1)	(1)
	Calcium	0%	-.04	0%
		(1)	(1)	(1)
	Choline compounds MR spectroscopy in the pons	100% (1)	.85 (1)	72% (1)
	Choline compounds MR spectroscopy in the left prefrontal cortex	0% (1)	-.23 (1)	5% (1)
	Creatine MR spectroscopy in the pons	0% (1)	.10 (1)	1% (1)
	Creatine MR spectroscopy in the left prefrontal cortex	0% (1)	-.50 (1)	25% (1)
	N-acetylaspartate MR spectroscopy in the pons	0% (1)	.28 (1)	8% (1)
	N-acetylaspartate MR spectroscopy in the left prefrontal cortex	0% (1)	-.62 (1)	38% (1)
During night of sleep dep	Dopamine metabolite (HVA)	0%	-.13	2%
		(1)	(1)	(1)
	Norepinephrine/epinephrine metabolite (MHPG)	33% (3)	-.25 (1)	6% (1)

	Norepinephrine/epinephrine metabolite (VMA)	0% (2)	-.33 (1)	11% (1)
	Melatonin at night	0% (1)	-.35 (1)	12% (1)
Day after night of sleep dep	Dopamine metabolite (HVA)	0% (3)	-.06 (2)	0% (2)
	D2 dopamine receptor vacancies in the left basal ganglia	0% (1)	-.27 (1)	7% (1)
	D2 dopamine receptor vacancies in the right basal ganglia	100% (1)	-.55 (1)	30% (1)
	Sensitivity to dopamine changes (prolactin response to D2 receptor antagonism)	0% (1)	.44 (1)	19% (1)
	Norepinephrine/epinephrine metabolite (MHPG)	0% (4)	-.11 (3)	1% (3)
	Norepinephrine/epinephrine metabolite (VMA)	0% (1)	.36 (1)	13% (1)
	Serotonin metabolite (5HIAA)	0% (2)	-.18 (1)	3% (1)
	Imipramine binding to blood platelets	0% (1)		
	Melatonin at night	0% (1)	-.51 (1)	26% (1)
	Calcium	0% (1)	-.14 (1)	2% (1)
	Choline compounds MR spectroscopy in the pons	0% (1)	-.20 (1)	4% (1)
	Choline compounds MR spectroscopy in the left prefrontal cortex	0% (1)	.00 (1)	0% (1)

	Creatine MR spectroscopy in the pons	0% (1)	-.40 (1)	16% (1)
	Creatine MR spectroscopy in the left prefrontal cortex	0% (1)	-.17 (1)	3% (1)
	N-acetylaspartate MR spectroscopy in the pons	0% (1)	-.06 (1)	0% (1)
	N-acetylaspartate MR spectroscopy in the left prefrontal cortex	0% (1)	.11 (1)	1% (1)
Day after rec night	Norepinephrine/epinephrine metabolite (MHPG)	100% (1)	-.43 (1)	18% (1)
Change from day before to day after night of sleep dep	Increased dopamine metabolite (HVA)	0% (2)	.58 (1)	34% (1)
	Decreased D2 dopamine receptor vacancies in the left basal ganglia	0% (1)	.35 (1)	12% (1)
	Decreased D2 dopamine receptor vacancies in the right basal ganglia	100% (1)	.83 (1)	70% (1)
	Increased norepinephrine/ epinephrine metabolite (MHPG)	50% (2)	.37 (2)	14% (2)
	Increased norepinephrine/ epinephrine metabolite (VMA)	100% (1)	.72 (1)	52% (1)
	Serotonin metabolite (5HIAA)	0% (1)		
	Sensitivity to serotonin changes (prolactin response to tryptophan)	0% (1)		
	Increased BDNF	100% (1)	.46 (1)	21% (1)
	Choline compounds MR spectroscopy in the left prefrontal cortex	0% (1)		

	Creatine MR spectroscopy in the left prefrontal cortex	0% (1)		
	N-acetylaspartate MR spectroscopy in the left prefrontal cortex	0% (1)		
	Glutamine MR spectroscopy in the left prefrontal cortex	100% (1)	.59 (1)	35% (1)
	Glutamate, glutamine, & GABA combined MR spectroscopy in the left prefrontal cortex	0% (1)		
	Myo-inositol MR spectroscopy in the left prefrontal cortex	0% (1)		
Change from 3 days either before or after night of sleep dep to day after night of sleep dep†	Increased sensitivity to dopamine changes (prolactin response to D2 receptor antagonism)	100% (1)	.76 (1)	57% (1)

Note: 5HIAA = 5-Hydroxyindole-3-acetic acid; HVA = Homovanillic acid; MHPG = 3-Methoxy-4-hydroxyphenylglycol; MR = Magnetic resonance; Rec night = Recovery night; Sleep dep = Sleep deprivation; VMA = Vanillylmandelic acid.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.

[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.

[c] Mean effect size is expressed as a correlation coefficient (*r*) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates that higher levels of this variable are associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates that higher levels of this variable are associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated across primary studies either from reported correlations or, when these were unavailable, from Cohen's *d* effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in the variable between responder and nonresponder groups.

[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).
† In the one study (Ebert et al., 1993) that examined dopamine sensitivity by measuring prolactin response to the D2 dopamine receptor antagonist sulpiride, baseline was separated apart by 3 days from sleep deprivation, with half of patients getting baseline after sleep deprivation and the other half before sleep deprivation. Although results were not reported separately for these two methods, no significant differences (with alpha at .10) were seen between them.

Table 15 – Correlations between genetic variables and the antidepressant response to sleep deprivation[a]

Variable	Studies reporting a significant effect[b]	Mean effect size[c] (r)	Variability accounted for[d] (r^2)
Angiotensin-converting enzyme gene	0% (1)	-.12 (1)	2% (1)
Dopamine d2 receptor gene	0% (1)	.05 (1)	0% (1)
Dopamine d3 receptor gene	0% (2)	.06 (1)	0% (1)
Dopamine d4 receptor gene	0% (1)		
Glycogen synthase kinase 3-β gene	100% (1)	.32 (1)	10% (1)
Serotonin transporter gene	50% (2)	.30 (1)	9% (1)
Serotonin 5-HT2A receptor gene	0% (1)	.16 (1)	2% (1)

[a] Numbers in brackets refer to the number of studies (n) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.
[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.
[c] Mean effect size is expressed as a correlation coefficient (r) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates the variable is associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates the variable is associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated across primary studies either from reported correlations or, when these were unavailable, from Cohen's d effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in the variable between responder and nonresponder groups.
[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

Table 16 – Correlations between hormonal variables and the antidepressant response to sleep deprivation[a]

Timing relative to sleep dep	Variable	Studies reporting a significant effect[b]	Mean effect size[c] (*r*)	Variability accounted for[d] (r^2)
Several days before night of sleep dep	Cortisol	0% (1)		
	Sensitivity of cortisol response to dexamethasone	40% (5)	-.67 (1)	44% (1)
	Prolactin	0% (1)	-.03 (1)	0% (1)
Day before night of sleep dep	Beta-endorphin	0% (1)	-.27 (1)	8% (1)
	Cortisol	0% (5)	.06 (3)	0% (3)
	Sensitivity of cortisol response to dexamethasone	0% (1)		
	Dehydroepiandrosterone (DHEA)	100% (1)	.42 (1)	18% (1)
	Estradiol	0% (1)		
	Follicle-stimulating hormone	0% (1)		
	Growth hormone	0% (1)		
	Interleukin-6	100% (1)	-.66 (1)	44% (1)

	Luteinizing hormone	0% (1)		
	Prolactin	0% (3)	.03 (1)	0% (1)
	Progesterone	0% (1)		
	Progesterone metabolite (3α,5α-THP)	100% (1)	.54 (1)	29% (1)
	Progesterone metabolite (3α,5β-THP)	100% (1)		
	Progesterone metabolite (3β,5α-THP)	0% (1)		
	Testosterone		.54 (1)	29% (1)
	Thyroid-stimulating hormone (thyrotropin)	0% (8)	.03 (5)	0% (5)
	Thyroid hormone (T3)	0% (5)	-.36 (1)	13% (1)
	Thyroid hormone uptake (T3U)	100% (2)	-.59 (2)	35% (2)
	Thyroid hormone (fT3)	0% (3)	.16 (2)	3% (2)
	Thyroid hormone (rT3)		.68 (1)	46% (1)
	Thyroid hormone (T4)	20% (5)	.06 (5)	0% (5)
	Thyroid hormone (fT4)	0% (6)	.18 (4)	3% (4)
During night of sleep dep	Cortisol	33% (3)	.08 (3)	1% (3)

	Prolactin	0% (1)	-.24 (1)	6% (1)
	Thyroid-stimulating hormone (thyrotropin)	50% (2)	.30 (2)	9% (2)
	Thyroid hormone (T4)	0% (1)	.02 (1)	0% (1)
Day after night of sleep dep	Beta-endorphin	0% (1)	-.40 (1)	16% (1)
	Cortisol	0% (2)	.05 (2)	0% (2)
	Sensitivity of cortisol response to dexamethasone	0% (1)		
	Dehydroepiandrosterone (DHEA)	100% (1)		
	Growth hormone	0% (2)	.56 (1)	31% (1)
	Prolactin	0% (1)	-.16 (1)	2% (1)
	Progesterone	0% (1)		
	Progesterone metabolite (3α,5α-THP)	0% (1)		
	Progesterone metabolite (3α,5β-THP)	100% (1)		
	Progesterone metabolite (3β,5α-THP)	0% (1)		
	Thyroid-stimulating hormone (thyrotropin)	50% (2)	.05 (2)	0% (2)
	Sensitivity of thyrotropin response to thyrotropin-releasing hormone	100% (1)	.32 (1)	10% (1)

	Thyroid hormone (T3)		-.01 (1)	0% (1)
	Thyroid hormone (fT3)		.12 (1)	2% (1)
	Thyroid hormone (T4)		-.40 (1)	16% (1)
	Thyroid hormone (fT4)		.28 (1)	8% (1)
During rec night	Prolactin	0% (1)	-.07 (1)	1% (1)
	Thyroid-stimulating hormone (thyrotropin)	0% (1)	.07 (1)	1% (1)
Day after rec night	Cortisol	0% (1)	-.02 (1)	0% (1)
	Dehydroepiandrosterone (DHEA)	100% (1)		
	Growth hormone	0% (1)		
	Progesterone	0% (1)		
	Progesterone metabolite (3α,5α-THP)	0% (1)		
	Progesterone metabolite (3α,5β-THP)	100% (1)		
	Progesterone metabolite (3β,5α-THP)	0% (1)		
Several days after night of sleep dep	Adrenocorticotropic hormone	0% (1)	-.17 (1)	3% (1)

	Cortisol	100% (1)	-.32 (1)	10% (1)
	Sensitivity of cortisol response to dexamethasone	0% (2)	.36 (2)	13% (2)
Change from day before to day after night of sleep dep	Increased beta-endorphin	100% (1)	-.50 (1)	25% (1)
	Increased cortisol	0% (3)	-.25 (1)	6% (1)
	Estradiol	0% (1)		
	Follicle-stimulating hormone	0% (1)		
	Luteinizing hormone	0% (1)		
	Decreased prolactin	0% (3)	.10 (1)	1% (1)
	Testosterone	0% (1)		
	Increased thyroid-stimulating hormone (thyrotropin)	33% (10)	-.02 (5)	0% (5)
	Increased thyroid hormone (T3)	14% (7)	.26 (2)	7% (2)
	Thyroid hormone uptake (T3U)	0% (2)		
	Increased thyroid hormone (fT3)	25% (4)	.48 (2)	23% (2)
	Thyroid hormone (rT3)	0% (1)		
	Increased thyroid hormone (T4)	13% (8)	-.20 (2)	4% (2)

	Increased Thyroid hormone (fT4)	0% (7)	.06 (1)	0% (1)
Change from day after night of sleep dep to day after rec night	Cortisol	0% (2)		
	Prolactin	0% (2)		
	Thyroid-stimulating hormone (thyrotropin)	0% (2)		
	Thyroid hormone (T3)	0% (1)		
	Thyroid hormone (fT3)	0% (1)		
	Thyroid hormone (T4)	0% (1)		
	Thyroid hormone (fT4)	0% (1)		

Note: 3α,5α-THP = 3α,5α-tetrahydroprogesterone; 3α,5β-THP = 3α,5β-tetrahydroprogesterone; 3β,5α-THP = 3β,5α-tetrahydroprogesterone; fT3 = Free triiodothyronine; fT4 = Free thyroxine; Rec night = Recovery night; rT3 = Reverse triiodothyronine; Sleep dep = Sleep deprivation; T3 = Triiodothyronine; T3U = Triiodothyronine uptake; T4 = Thyroxine.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.

[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.

[c] Mean effect size is expressed as a correlation coefficient (*r*) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates that higher levels of this variable are associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates that higher levels of this variable are associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated across primary studies either from reported correlations or, when these

were unavailable, from Cohen's *d* effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in the variable between responder and nonresponder groups.

[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

Table 17 – Correlations between circadian rhythm variables and the antidepressant response to sleep deprivation[a]

Timing relative to sleep dep	Variable	Studies reporting a significant effect[b]	Mean effect size[c] (r)	Variability accounted for[d] (r^2)
Average of several days before night of sleep dep	Amplitude of mood rhythm	100% (3)	.56 (3)	32% (3)
	Frequency of mood rhythm occurrence	100% (2)	.64 (2)	41% (2)
1-2 months before night of sleep dep	Duration of melatonin phase	100% (1)	.75 (1)	56% (1)
2 days before night of sleep dep	Amplitude of mood rhythm	50% (2)	.17 (2)	3% (2)
Day before night of sleep dep	Amplitude of mood rhythm	50% (10)	.30 (6)	9% (6)
	Amplitude of cortisol rhythm	100% (1)		
	Amplitude of rectal temperature rhythm	100% (1)		
During and day after night of sleep dep	Amplitude of cortisol rhythm	0% (1)		
Change from before to during and/or to day after night of	Decreased amplitude of rectal temperature rhythm	0% (1)	.31 (1)	10% (1)

sleep dep				
	Increased minimum in rectal temperature rhythm	100% (1)	.40 (1)	16% (1)
	Maximum in rectal temperature rhythm	0% (1)		
	Decrease in duration of melatonin phase	50% (2)	.48 (2)	23% (2)
	Shift in offset time of melatonin rhythm	50% (2)	-.43 (2)	18% (2)
	Shift in peak time of cortisol rhythm	0% (1)	.02 (1)	0% (1)
	Shift in peak time of prolactin rhythm	50% (2)	.63 (1)	40% (1)
	Shift in peak time of thyrotropin rhythm	0% (2)		

Note: Sleep dep = Sleep deprivation.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.

[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.

[c] Mean effect size is expressed as a correlation coefficient (*r*) between the variable and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates that higher levels of this variable are associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates that higher levels of this variable are associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the variable and the antidepressant response. The mean effect size was calculated across primary studies either from reported correlations or, when these were unavailable, from Cohen's *d* effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences in the variable between responder and nonresponder groups.

[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

Table 18 – The most powerful correlates of the antidepressant response to sleep deprivation[a]

Before sleep deprivation Variable	r^2	*n* studies	Change from before to after sleep deprivation Variable	r^2	*n* studies
Increased choline compounds in the pons	72%	1	Decreased D2 receptor vacancies in r. BG	70%	1
Increased r. orbitofrontal activity	63%	3	Increased psychological activation	58%	1
Decreased b. upper anterolateral prefrontal activity	59%	1	Increased prolactin response to D2 antagonism	57%	1
Increased r. amygdala activity	59%	1	Increased eye-blinks	56%	1
Duration of melatonin phase	56%	1	Increased VMA	52%	1
Decreased P1 amplitude	53%	1	Increased waking EEG theta power	48%	1
Increased rT3	46%	1	Increased N1 amplitude	45%	1
Decreased l. lower anterolateral prefrontal activity	45%	1	Increased light adaptation potential	36%	1
Decreased interleukin-6	44%	1	Increased glutamine in the l. prefrontal cortex	35%	1
Increased diurnal rhythms of mood	41%	2			
Decreased microsleeps	40%	1			
Increased r. anterior cingulate activity	37%	2			
Decreased T3U	35%	2			
Decreased N1 amplitude	34%	2			
Increased b. limbic system activity	34%	1			

Note: b. = Bilateral; BG = Basal ganglia; D2 = D2 subtype of the dopamine receptor; l. = Left; N1 = Negative polarity event-related potential that occurs approximately 100 milliseconds after the presentation of a stimulus; P1 = Positive polarity event-related potential that occurs approximately 100 milliseconds after the presentation of a stimulus; r. = Right; rT3 = Reverse triiodothyronine; T3U = Triiodothyronine uptake; VMA = Vanillylmandelic acid.

[a] This table only includes variables which, in the majority of studies that examined them, were reported to be significantly related to the antidepressant response to sleep deprivation and by which at least a third of the variance in antidepressant response across patients is accounted for ($r^2 \geq 33\%$; which is also equivalent to saying the overlap in distributions of the variable between responders and nonresponders is less than a third).

Table 19 – Correlations between variables and the relapse that follows response to sleep deprivation[a]

Timing relative to sleep dep	Variable	Studies reporting a significant effect[b]	Mean effect size[c] (r)	Variability accounted for[d] (r^2)
Pre-existing	Angiotensin-converting enzyme gene	100% (1)	.41 (1)	17% (1)
	Dopamine d2 receptor gene	0% (1)	.01 (1)	0% (1)
	Dopamine d3 receptor gene	0% (2)	.03 (1)	0% (1)
	Dopamine d4 receptor gene	0% (1)	.16 (1)	3% (1)
	Glycogen synthase kinase 3-β gene	0% (1)	.30 (1)	9% (1)
	Serotonin transporter gene	0% (2)		
	Serotonin 5-HT2A receptor gene	100% (1)	.29 (1)	9% (1)
Day before night of sleep dep	Diurnal variation of mood	0% (1)	-.20	4% (1)
Day after night of sleep dep	Degree of antidepressant response to sleep dep	100% (1)	.82 (1)	67% (1)
Nap after night of sleep dep	Occurrence of a nap	50% (4)	.30 (3)	9% (3)

	Time of day of nap	0% (2)	.25 (1)	6% (1)
	Total sleep amount	40% (5)	.46 (5)	21% (5)
	Total NREMS amount	100% (1)	.75 (1)	56% (1)
	Stage 1 sleep amount	0% (1)		
	Stage 2 sleep amount	100% (1)	.75 (1)	56% (1)
	SWS amount	0% (3)	.23 (3)	5% (3)
	REMS amount	50% (1)	.25 (1)	6% (1)
Rec night	Time of night when sleep occurred	0% (2)		
	Total sleep amount	0% (2)		
	Sleep efficiency	0% (1)		
	Waking amount during sleep period	0% (1)		
	Total NREMS amount	0% (1)		
	Stage 1 sleep amount	100% (1)	-.44 (1)	19% (1)
	Stage 2 sleep amount	0% (1)		
	SWS amount	0% (2)		

	REMS amount	0% (1)		
	Sleep latency	100% (1)	-.57 (1)	32% (1)
3 days after night of sleep dep	Adrenocorticotropic hormone	0% (1)		
	Cortisol	0% (1)		
	Sensitivity of cortisol response to dexamethasone	0% (1)		
Change from day following night of sleep dep to day following rec night	Increased amplitude of rectal temperature rhythm	0% (1)	.13 (1)	2% (1)
	Lower minimum in rectal temperature rhythm	100% (2)	.45 (2)	20% (2)
	Maximum in rectal temperature rhythm	0% (1)		
	Decreased psychological activation	100% (1)	.73 (1)	53% (1)
	Increased psychological stress	100% (1)	.80 (1)	64% (1)

Note: NREMS = Non-REM sleep; Sleep dep = Sleep deprivation; Rec night = Recovery night; rem density = Rapid eye movement density; REMS = Rapid eye movement sleep; SWS = Slow wave sleep.

[a] Numbers in brackets refer to the number of studies (*n*) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic. Relapse was measured either following a nap after a night of sleep deprivation or following a night of recovery sleep.

[b] The percentage of studies that reported this variable to be significantly ($p < .05$) related to the the relapse that follows response to sleep deprivation out of the total number of published studies that statistically examined this relationship.
[c] Mean effect size is expressed as a correlation coefficient (r) between the variable and the relapse that follows response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates that higher levels of this variable are associated with an elevated degree of relapse, a negative effect size (maximum possible is -1.00) indicates that higher levels of this variable are associated with an attenuated degree of relapse, and an effect size of zero indicates no relationship between the variable and the relapse. The mean effect size was calculated across primary studies from reported correlations.
[d] Percentage of variability between subjects in the relapse that follows response to sleep deprivation accounted for by the variable, calculated by the coefficient of determination (r^2).

Table 20 – The most powerful correlates of the relapse that follows response to sleep deprivation[a]

	After sleep deprivation & before relapse			Change from after sleep deprivation to after relapse	
	Variable	r^2		Variable	r^2
1	Increased antidepressant response	67%	1	Increased psychological stress	64%
2	Increased NREMS amount during a nap	56%	2	Decreased psychological activation	53%
3	Increased Stage 2 sleep amount during a nap	56%			

Note: NREMS = Non-REM sleep; Sleep dep = Sleep deprivation.

[a] This table only includes variables which, in the majority of studies that examined them, were reported to be significantly related to the relapse that follows response to sleep deprivation and by which at least a third of the variance in relapse across patients is accounted for ($r^2 \geq 33\%$).

Table 21 – Ability of neurochemical treatments to affect the response to sleep deprivation[a]

Neurochemical treatment	Studies reporting a significant effect[b]	Mean effect size[c] (r)	Variability accounted for[d] (r^2)
Antidepressant medication	0% (7)	.04 (1)	0% (1)
Caffeine	0% (1)	.21 (1)	4% (1)
Cholinergic antagonist	0% (1)	.04 (1)	0% (1)
Dopaminergic agonist	0% (2)	.12 (1)	1% (1)
GABA-benzodiazepine antagonist	0% (1)	-.03 (1)	0% (1)
Lithium	0% (1)	.22 (1)	5% (1)
Modafinil	0% (1)	.04 (1)	0% (1)
Tryptophan-depletion challenge	0% (1)		

[a] Numbers in brackets refer to the number of studies (n) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.
[b] The percentage of studies that reported this treatment to be significantly ($p < .05$) affect the antidepressant response to sleep deprivation out of the total number of published studies that statistically examined this relationship.
[c] Mean effect size is expressed as a correlation coefficient (r) between the treatment and the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates the treatment is associated with an enhanced antidepressant response, a negative effect size (maximum possible is -1.00) indicates the treatment is associated with an attenuated antidepressant response, and an effect size of zero indicates no relationship between the treatment and the antidepressant response. The mean effect size was calculated across primary studies from Cohen's d effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences between treatment and control conditions.
[d] Percentage of variability between subjects in antidepressant response to sleep deprivation accounted for by the treatment, calculated by the coefficient of determination (r^2).

Table 22 – Ability of treatments to maintain the response to sleep deprivation beyond a single night of recovery sleep[a]

Treatment	Treatment timing relative to night of sleep deprivation	End point of treatment observations[b]	Studies reporting a significant effect[c]	Mean effect size[d] (r)	Variability accounted for[e] (r^2)
Tryptophan-depletion challenge	Day after	Day after night of recovery sleep	100% (1)	0.65 (1)	43% (1)
Serotonergic 5-HT1A autoreceptor antagonist	For 9 days in combination with 3 sleep deprivations	9 days after first night of sleep deprivation	100% (1)	0.64 (1)	41% (1)
Melatonin in the evening	For 6 days after first sleep deprivation	1 week after first night of sleep deprivation	0% (1)	-.43 (1)	18% (1)
Physical exercise under bright light	For 1 week after first sleep deprivation	1 week after first night of sleep deprivation		.38 (2)	15% (2)
Lithium	Started from day after to several months prior	3 days to a month after night of sleep deprivation	60% (5)	0.39 (3)	15% (3)
Light therapy	For 1 week after first sleep deprivation	1 week after first night of sleep deprivation	67% (3)	0.21 (4)	4% (4)
GABA-benzodiazepine antagonist	During	Day after night of recovery sleep	100% (1)	.20 (1)	4% (1)
Sleep phase advance	For 1 to 6 nights after	From day after recovery night to 2 weeks later	67% (3)		

[a] Numbers in brackets refer to the number of studies (n) used in each analysis. A blank cell indicates an insufficient number of studies to calculate that statistic.

[b] The length of time following the first night of sleep deprivation that the treatment was begun and for which time point treatment observations were used as a comparison against the other treatments listed in this table. The lack of common time points across studies for measuring maintenance of response made it impossible to use a single consistent time point for comparisons.
[c] The percentage of studies that reported this treatment to significantly ($p < .05$) maintain the antidepressant response to sleep deprivation beyond a single night of recovery sleep out of the total number of published studies that statistically examined this relationship.
[d] Mean effect size is expressed as a correlation coefficient (r) between the treatment and the ability to maintain the antidepressant response to sleep deprivation. A positive effect size (maximum possible is 1.00) indicates the treatment is associated with an enhanced maintenance of the antidepressant response, a negative effect size (maximum possible is -1.00) indicates the treatment is associated with an attenuated maintenance of the antidepressant response, and an effect size of zero indicates no relationship between the treatment and maintenance of the antidepressant response. The mean effect size was calculated across primary studies from Cohen's d effect sizes (converted to correlation coefficients; see Table 1 for the formula) for differences between treatment and control conditions. Depression measurements at the endpoint of treatment were used for these comparisons.
[e] Percentage of variability between subjects in maintenance of the antidepressant response to sleep deprivation accounted for by the treatment, calculated by the coefficient of determination (r^2).

Table 23 – Behavioral states and the correlates used to define them in animal studies

Relative magnitudes are denoted as follows: high (+), medium or lower (±), or only low (-). Empty cells indicate correlates not required for the classification of that behavioral state.

BEHAVIORAL STATE		MOTION	EMG	SLOW WAVES	SPINDLES	THETA RHYTHMS
Waking	Locomotor	+				
	Active		+			
	Quiet	-	±	-	-	
NREM sleep	Slow wave	-	±	+		
	Transitional	-	±		+	
	Low-amplitude	-	-	-	-	-
REM sleep		-	-	-	-	+

Figure 1 - Dates of articles that met criteria for inclusion in the present analyses on the antidepressant response to sleep deprivation and were used in Table 2

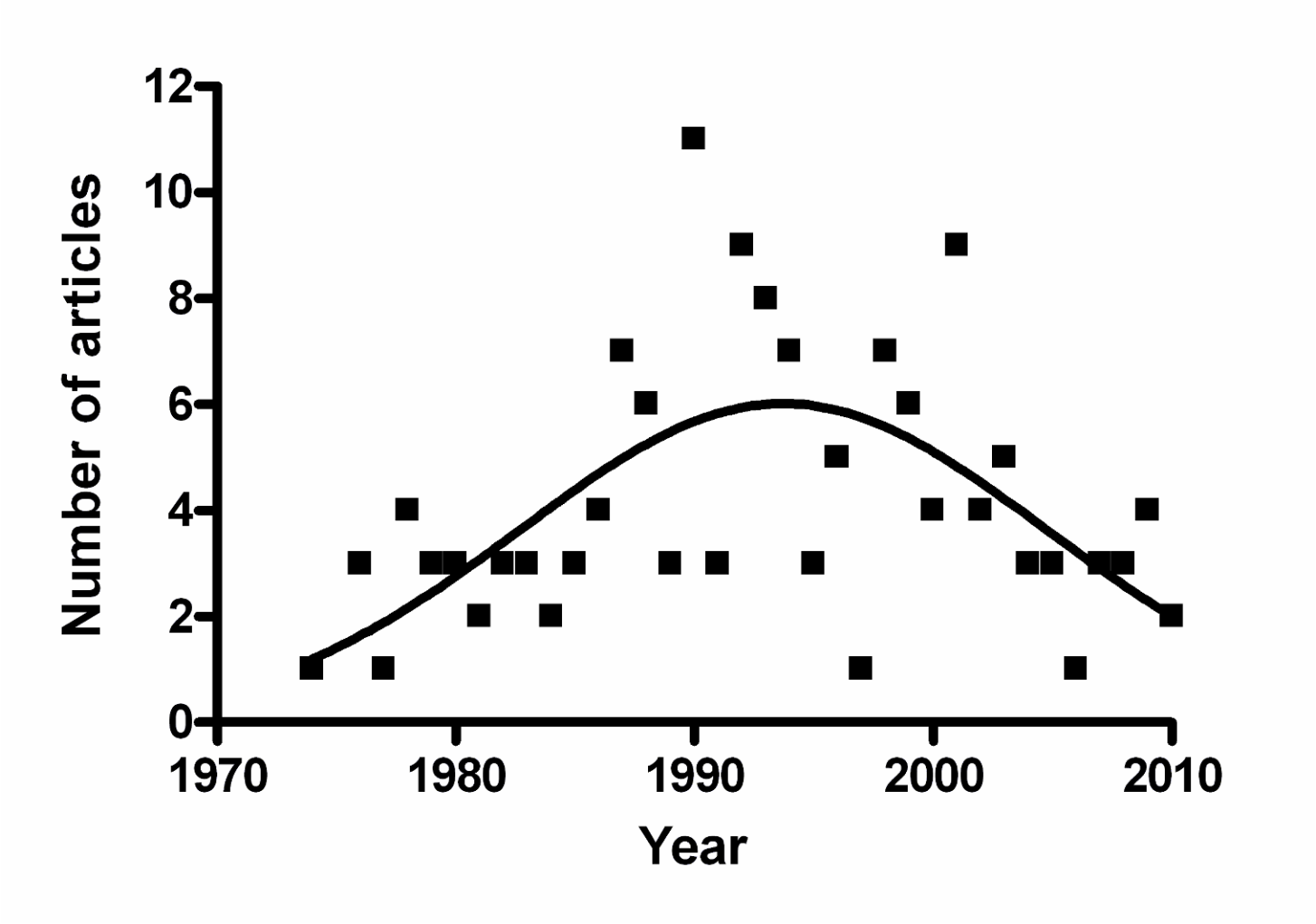

Figure 2 - The timing of changes in depression of responders and nonresponders to sleep deprivation in three studies

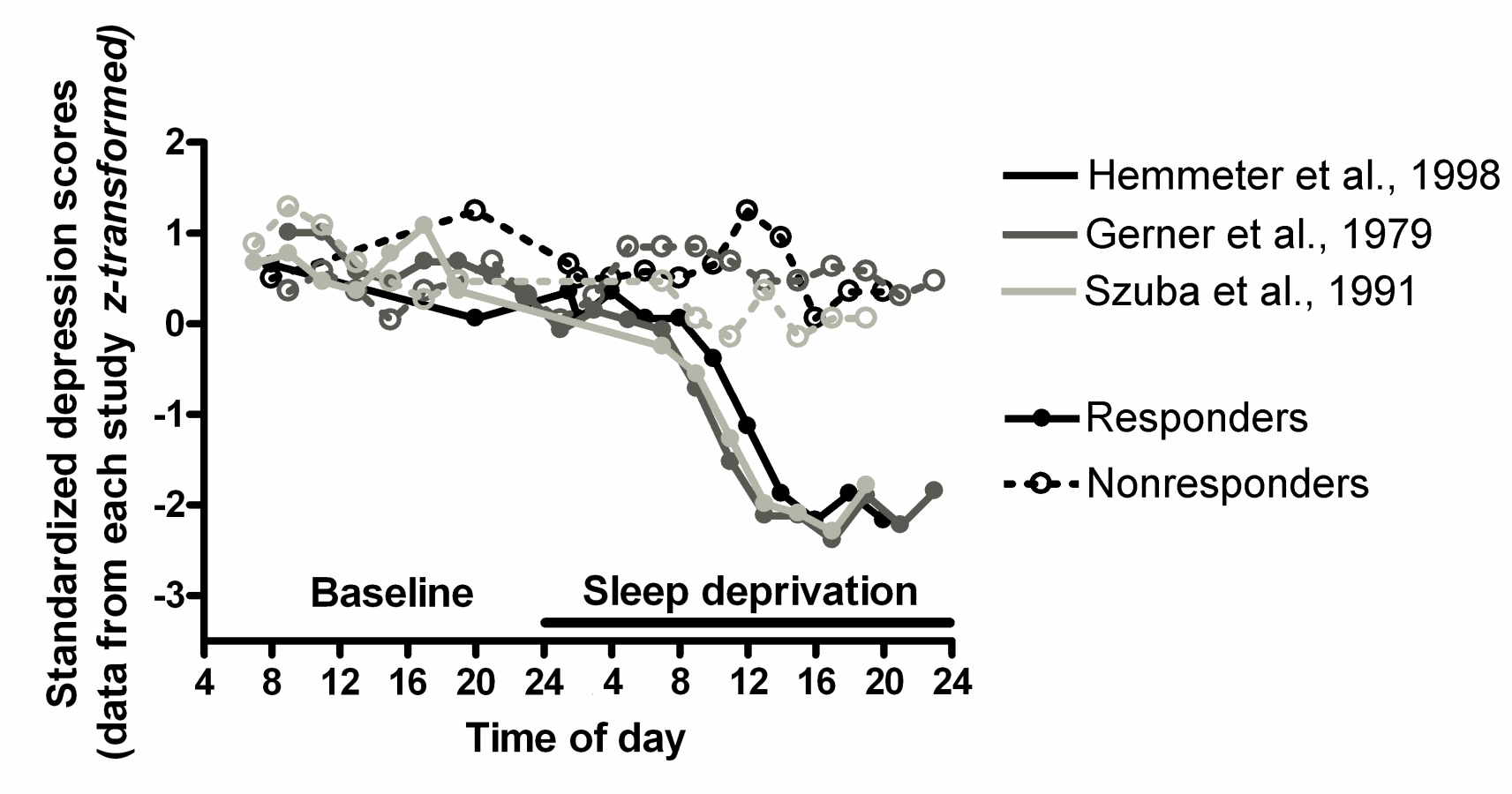

Figure 3 - The timing of response measurement and the antidepressant effects of sleep deprivation across studies that recorded response measurement at only a single time of day

Asterisks indicate outliers. Regression line equation: Y=65.11+2*(65.11-87.91)/(1+10^((((X-7+ABS(X-7))/2)*0.4255)))

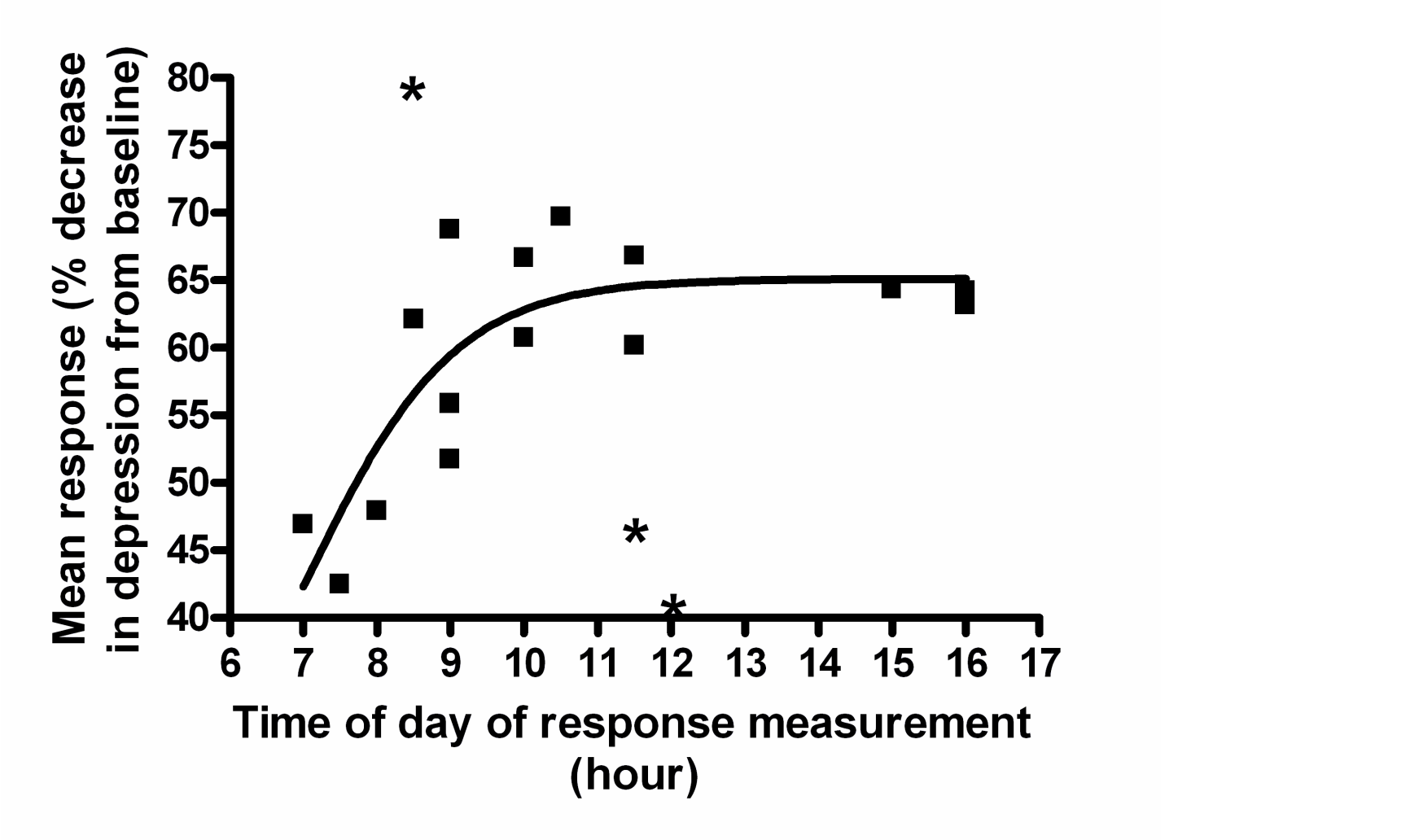

Figure 4 - Sample characteristics showing significant relationships with antidepressant effects of sleep deprivation across studies

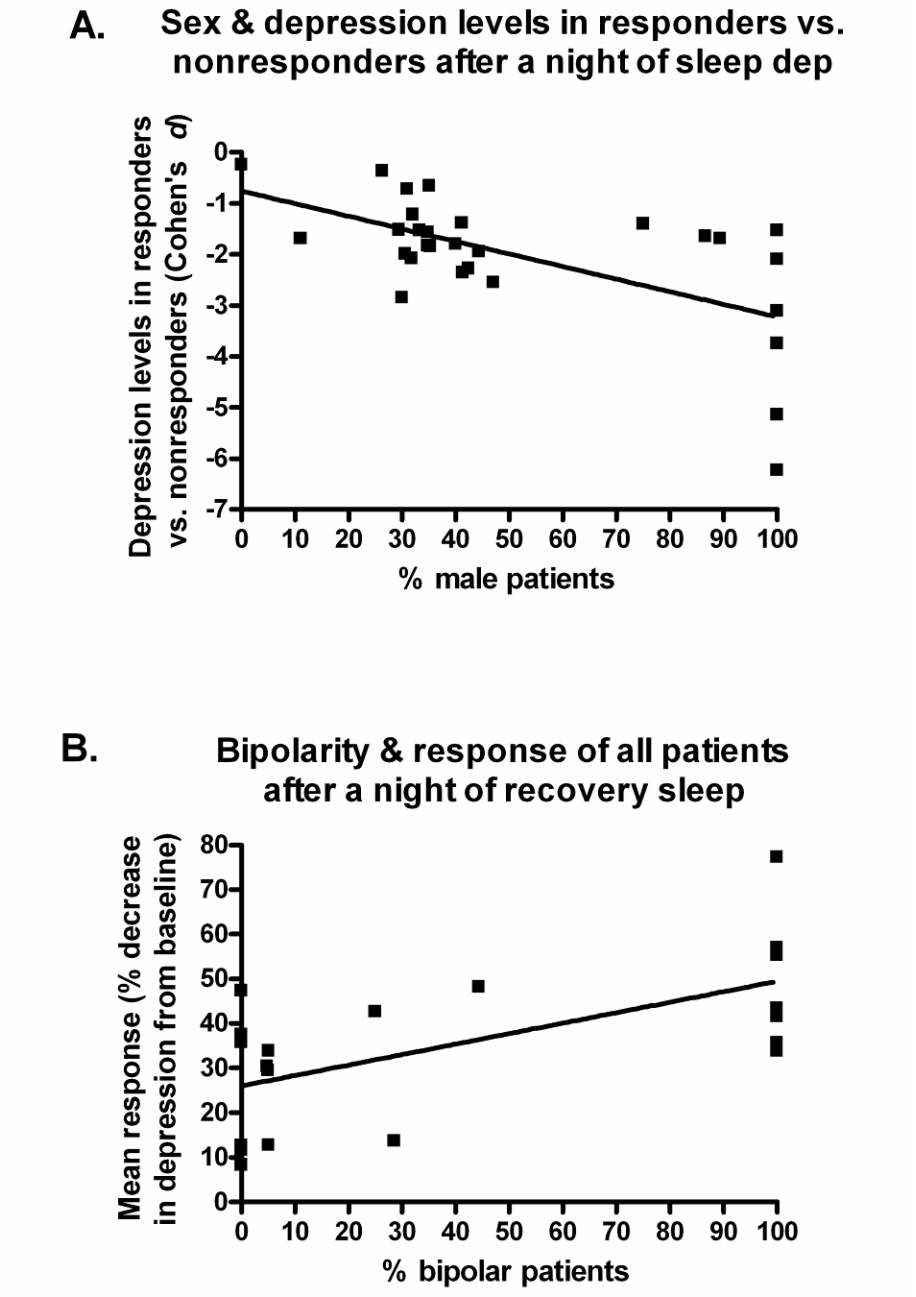

Figure 5 - Summary of the factors related to either the susceptibility to response to sleep deprivation or to this response itself

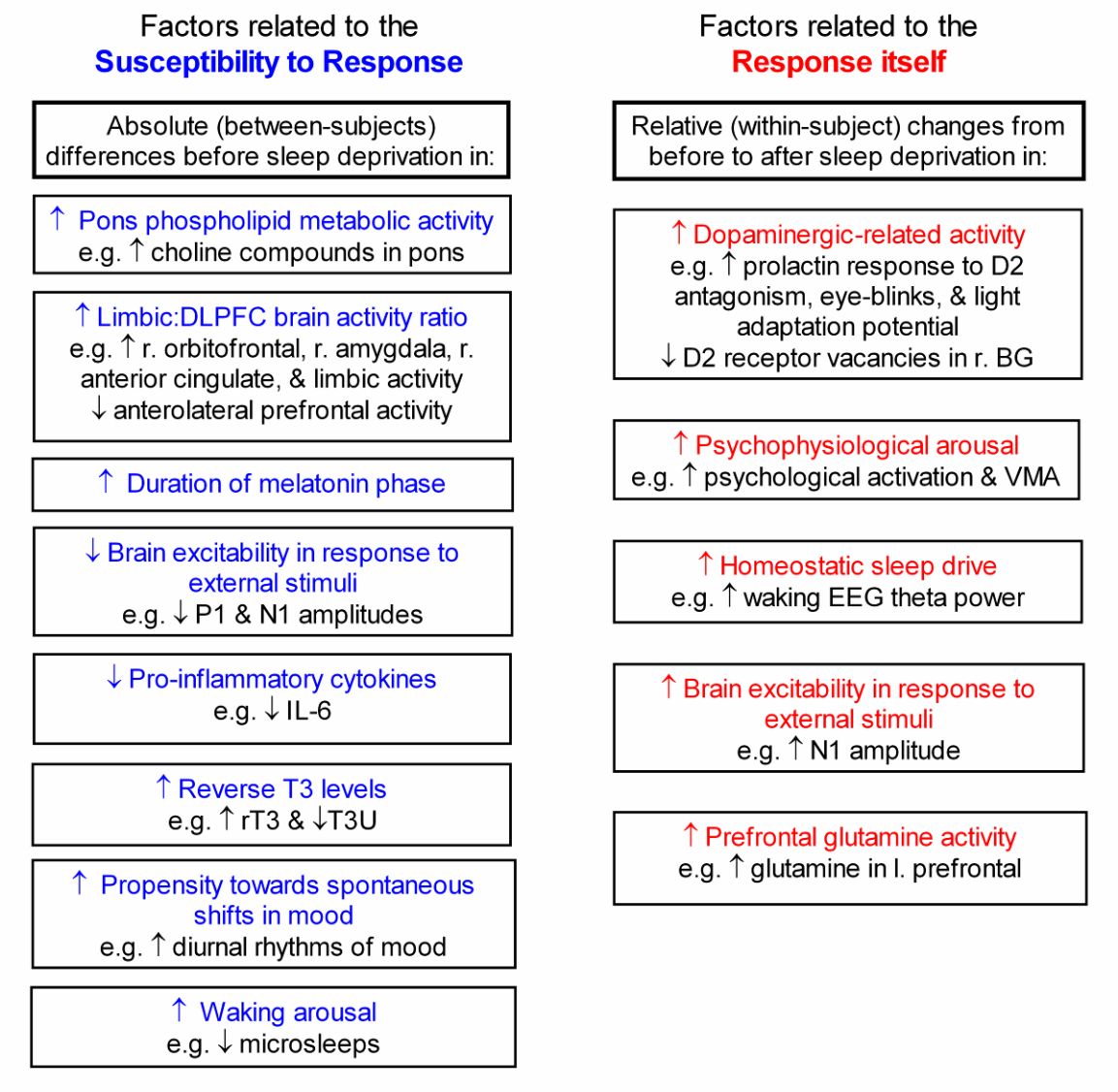

Figure 6 - The multiple platform apparatus

Illustrated below is the layout of platforms for the sleep deprivation group (panel A, left half of pool) and the wire floor for the apparatus control (panel A, right half of pool). The positions of the rats, feeders and drinking bottles are illustrated in panels B-D.

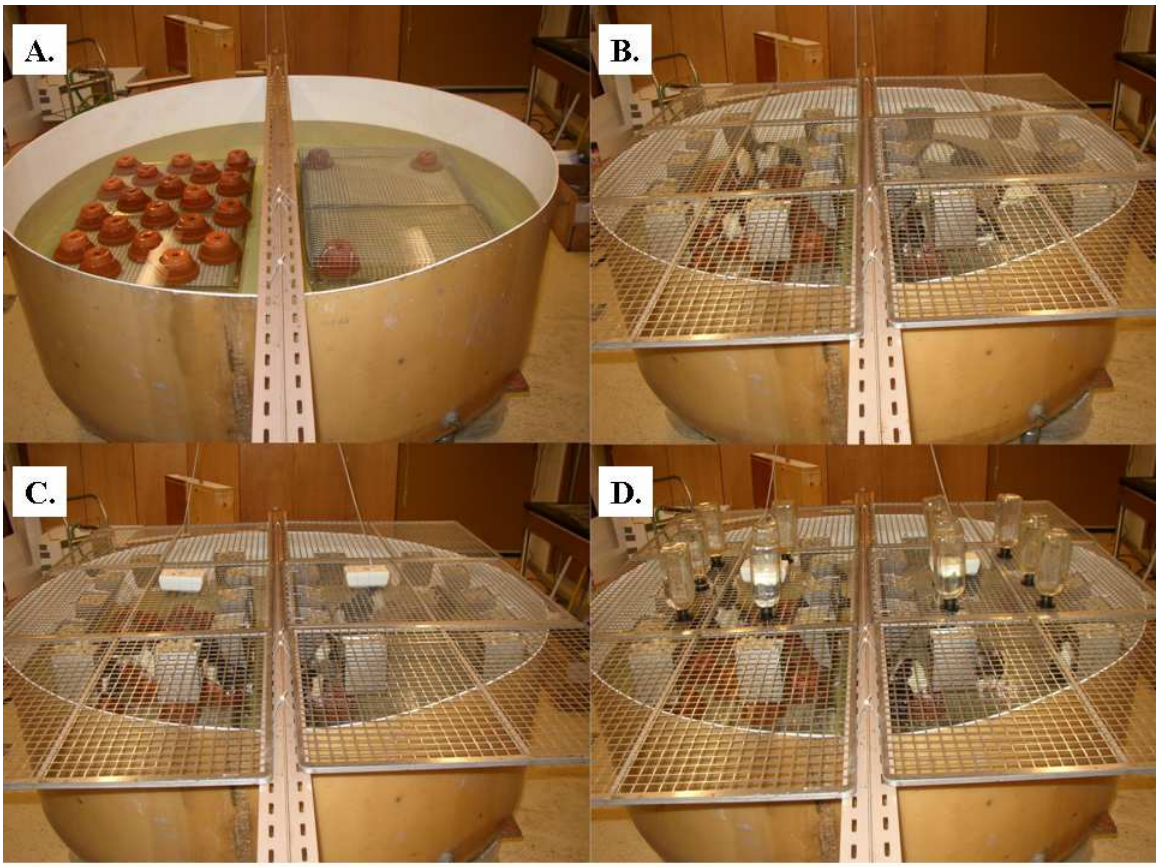

Figure 7 - Examples of electrophysiological recordings and associated behavioral states with rats

Shown below are four polygraphic examples demonstrating the different behavioral states analyzed: wakefulness without movement (W), wakefulness with movement (M), slow-wave sleep (SWS), transitional sleep (TS), rapid-eye-movement sleep (REMS), and low-amplitude sleep (LS). Each example shows, in order, the following four channels: EEG derived from the two lateral electrodes, EEG derived from the two midline electrodes, nuchal EMG, and motion detector signals. The code for the wave form recognition boxes is as follows: light blue boxes surround slow waves, dark blue boxes surround spindles, pink boxes surround theta rhythms, and yellow boxes surround motion detection signals.

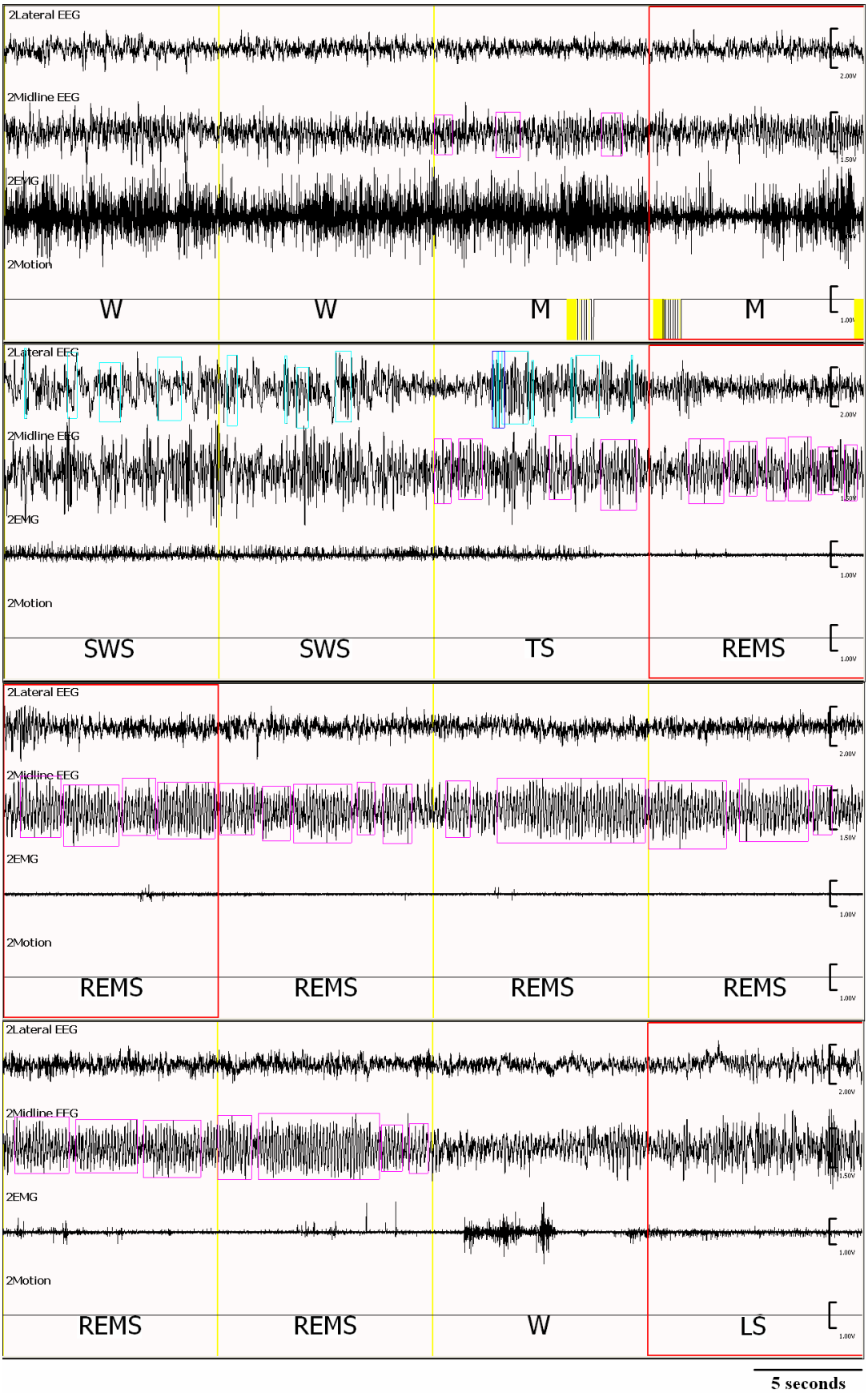
2Lateral EEG
2Midline EEG
2EMG
2Motion
W
W
M
M
2Lateral EEG
2Midline EEG
2EMG
2Motion
SWS
SWS
TS
REMS
2Lateral EEG
2Midline EEG
2EMG
2Motion
REMS
REMS
REMS
REMS
2Lateral EEG
2Midline EEG
2EMG
2Motion
REMS
REMS
W
LS
5 seconds

Figure 8 - Percentage change from baseline in behavioral states averaged (± SEM) across days of sleep deprivation with rats
SD = Sleep deprivation condition; AC = Apparatus control condition; CC = Home cage control condition.

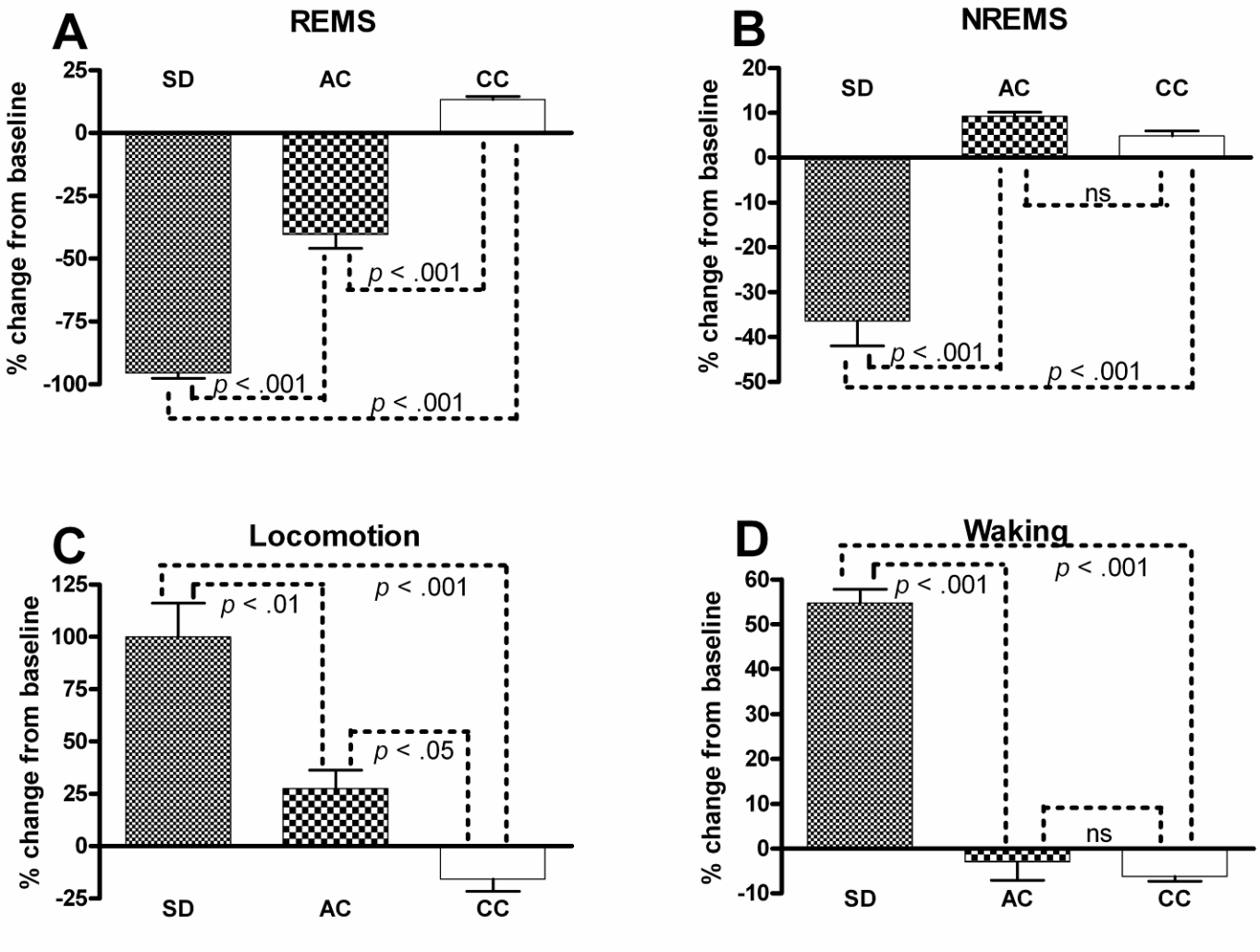

Figure 9 - Group mean (± SEM) changes in behavioral states across and within days with rats

Panels A-D show daily mean (± SEM) percentages of REMS, NREMS, waking, and locomotor activity on baseline (B), sleep deprivation (SD1-4), and recovery (R) days in sleep deprived (SD, solid red lines), apparatus control (AC, dashed blue lines) or home cage control (CC, dotted black lines) rats. Panels E-H show daily rhythms of REMS, NREMS, waking, and locomotor activity averaged across the 4 days of sleep deprivation. The time of daily lights-off (1200-2400h) is denoted by the heavy black bar at the top of the figures.

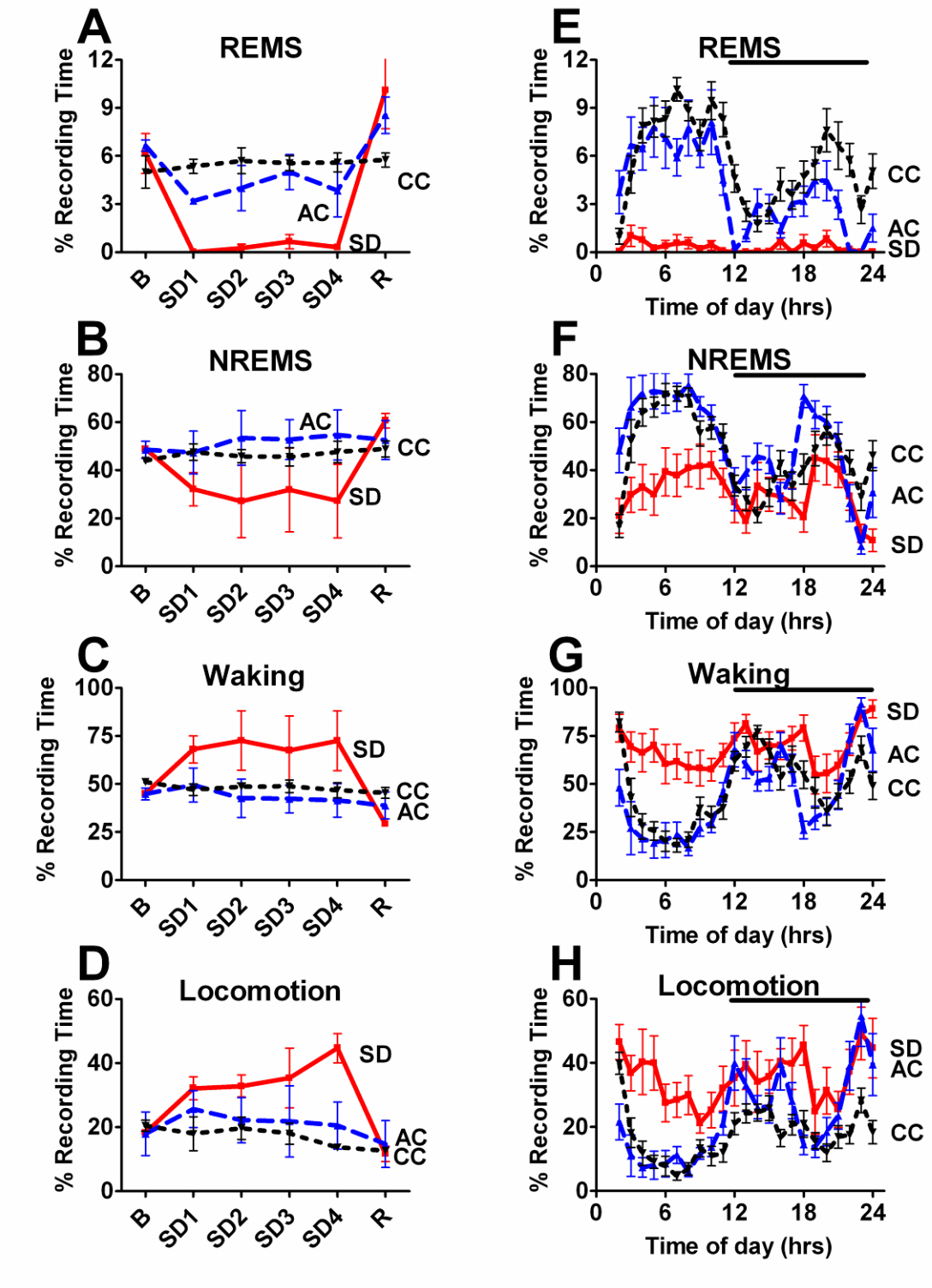
A
REMS
% Recording Time
12
9
6
3
0
CC
AC
SD
B
SD1
SD2
SD3
SD4
R
E
Time of day (hrs)
0
6
12
18
24
B
NREMS
80
60
40
20
F
C
Waking
100
75
50
25
G
D
Locomotion
60
40
20
H

Figure 10 - Percentage change from baseline in forced swim test measures averaged (± SEM) across days of sleep deprivation with rats

SD = Sleep deprivation condition; AC = Apparatus control condition; CC = Home cage control condition.

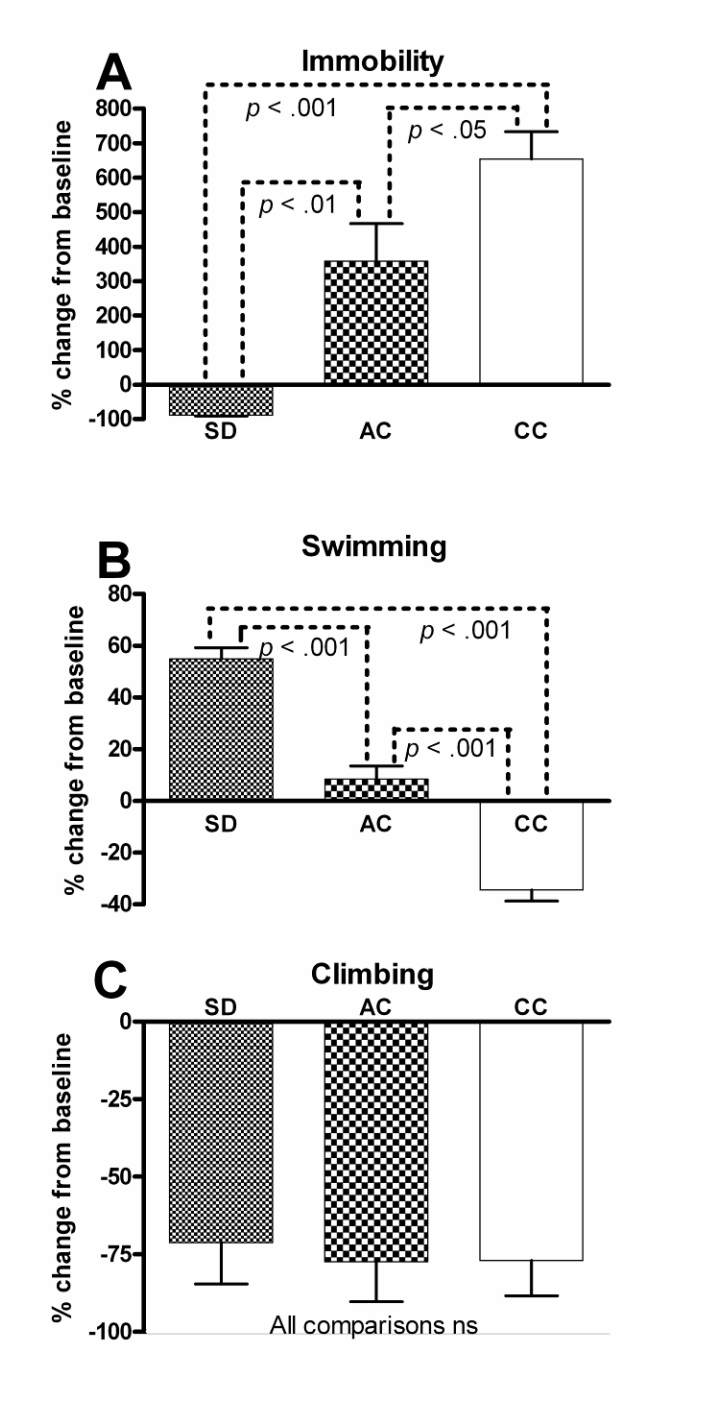

Figure 11 - Group mean (± SEM) changes in forced swim test measures across days with rats

Panel A-C show immobility, swimming, and climbing, respectively, during a daily 5 min forced swim test on a baseline day (hour 0), four days (hours 24, 48, 72, & 96) of sleep deprivation, and one recovery day. SD = Sleep deprivation condition; AC = Apparatus control condition; CC = Home cage control condition. Asterisks indicate days showing significant differences ($p < .05$) between CC and SD conditions.