What is diurnal mood variation?

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Abstract

Diurnal mood variation (DMV) is the change in mood over the course of the day, which is a characteristic in many depressed patients. There are two distinct forms of DMV, the classical form, with worse mood in the morning and an improvement towards the evening, and the reversed form, with a worsening of mood towards the evening. DMV is not just a response to environmental or behavioral conditions. Mood also follows an endogenous circadian rhythm. The lowest point in mood is observed during the night. DMV has been linked to a positive response to sleep deprivation. An explanation of why patients with DMV respond better to sleep deprivation has not yet emerged. Years of research have sought for an explanation what causes DMV. According to hypotheses that have been stated, DMV in depression can be understood from a weakened circadian function, or DMV is caused by increased susceptibility to stimuli. Patients who are more susceptible to stimuli tend to vary more in mood and have a higher chance of showing DMV. All these hypotheses treat the state of mood as a kind of black box. Specific regulatory relationships between brain areas and mood are not included in these studies. The direction of DMV seemed to be influenced by serotonin. Patients with a polymorphism in the promoter region of a serotonin transporter showed more reversed DMV than patients with classical DMV. Imaging studies showed that the balance between dorsal and ventral emotion neural systems is disrupted in DMV. In depressed patients, improvement of mood towards the evening is parallel with an increased metabolic activity in ventral limbic-paralimbic regions. These findings support the hypothesis, that limbic-paralimbic regions are involved in DMV. Further research is necessary to explain the exact mechanism underlying DMV. This knowledge is perhaps useful in designing personalized treatments for depression.

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Diurnal mood variation.

Mood has various dimensions, it relates to depression versus ecstasy, but also anger, stress and anxiety belong to mood. In this essay, mood is defined as an emotional state, happy or sad. Mood, like many other variables, shows a circadian rhythm. Unlike cortisol or melatonin levels, mood cannot be measured objectively. Mood is a subjective variable and needs a different approach than cortisol or melatonin. Common instruments for measuring mood are questionnaires. An example of a questionnaire is the adjective mood scale (AMS) developed by von Zerssen (1976). The AMS has been used in many investigations as a subjective way of measuring mood. Although this is a subjective measurement, an objective way to measure mood does not exist. Mood cannot be measured with a ruler or a thermometer. The AMS is validated for mood and an approved method for measuring mood. Many studies obtain results of mood status from a questionnaire, like the AMS, performed two or more times per day. In healthy subjects mood shows a circadian pattern of being low in the morning and improving towards the evening with relatively low amplitude (Murray 2007). Many depressed patients also demonstrate a circadian pattern of mood, but with much larger amplitude than in healthy subjects. Diurnal mood variation (DMV) is therefore, recognized as a specific characteristic of many depressed patients. DMV is defined as an improvement or worsening of mood over the course of a day (Gordijn et al. 1994).

DMV can be divided into two independent components: the positive affect (PA) and the negative affect (NA). PA is the extent by which a subject feels enthusiastic, delighted, active, and alert. NA includes distress, fear, anger, guilt, and disgust. These components differ between healthy subjects and depressed patients. Depressed patients show lower overall levels of PA, and higher overall NA levels.

Two types of DMV are distinguished in depression research: the ''classical'' DMV and reversed DMV. The most observed pattern of DMV in depressed patients is the classical DMV. Classical DMV refers to worse mood in the morning and an improvement of mood towards the afternoon or evening. Classical DMV is listed in the DSM-IV (American Psychiatric Association, 1994) as a characteristic of melancholic depression. Other symptoms of melancholic depression are loss of pleasure, weight loss and early awakening.

Reversed DMV is the worsening of mood in the afternoon or evening. It is less frequently observed than the classical form of DMV in depressed patients (Rusting and Larsen 1998). Mood worsening in the evening is associated with a symptom complex characterized by increased appetite, mood reactivity and hypersomnia. The study of Rusting and Larsen (1998) claims that in healthy subjects worsening of mood in the evening is associated with neuroticism, depressive mood, anxiety and feeling of hopelessness.

DMV occurs in all day life of depressed patients according to the subtype of depression. To demonstrate that DMV is not just a response to environmental conditions (such as time of day) or behavioral conditions (such as timing in the sleep cycle), but that mood follows an endogenous circadian rhythm, two different protocols can be used. One protocol is to unmask the circadian oscillation by applying sleep deprivation (this is called a constant routine protocol), and the other is to decouple the sleep wake cycle from the circadian pacemaker (a forced desynchrony protocol). In the constant routine protocol subjects stay awake for 25 to 40 hours under very constant conditions. They stay in a supine posture, and receive iso-caloric snacks, to provide a constant energy supply. Subjects are exposed to dim light, to unmask the underlying circadian oscillation. In the forced desynchrony protocol subjects are instructed to live on a scheme of longer or shorter days than 24 hours. This is to decouple the sleep wake cycle from the circadian pacemaker. In a study of Koorengevel, the protocol consisted of 6 days of 20 hours (13.5 hour wakefulness in dim light and 6.5 hours of darkness) (Koorengevel et al. 2003). It was shown in that study that the sleep-wake cycle and pacemaker play part in the course of mood. The interaction between the circadian clock and sleep homeostat, have been shown to influence mood in depressed patients and healthy subjects alike (Boivin et al. 1997). It was concluded that the influences of the

pacemaker and sleep-wake cycle on the mood curves in seasonal affective disorder(SAD) patients do not differ enough from the curves of mood in healthy subjects to be detected (Koorengevel et al. 2003).
In a study of Wirz-Justice in 2008, 11 SAD subjects were kept in a constant routine protocol of 40 hours. The circadian rhythm of mood in controls could be contrasted with the overall lower mood in the depressed patients (figure1). A circadian rhythm of mood can be seen with the lowest point of mood during the night. In the group of SAD patients mood starts to deteriorate in the first half of the experiment around 7 PM. At 4 AM mood is at the lowest point and starts improving, at 10 AM the next day an improvement in mood is observed in respect to the first half of the experiment (Wirz-Justice 2008).

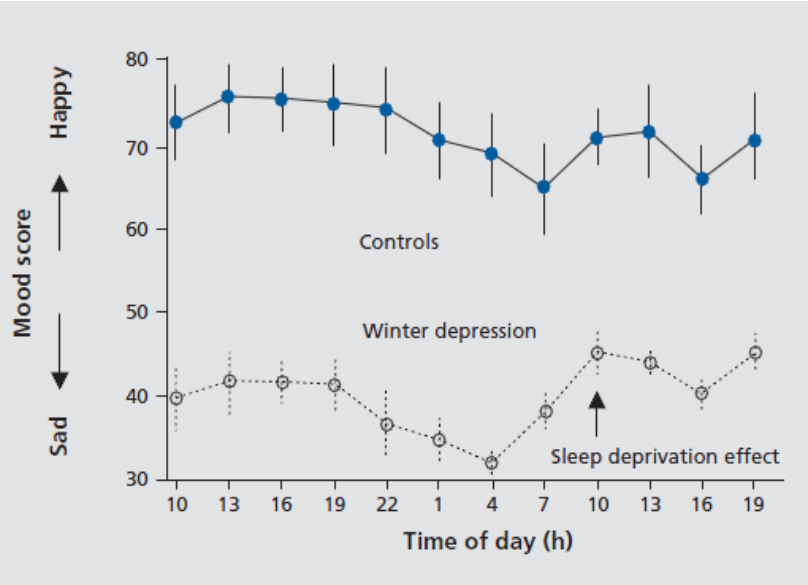

Figure 1. Mood changes (100-mm visual analogue scale) across a 40-hour
constant routine protocol (= total sleep deprivation) in control middle-aged women (N=8) and women with winter depression (N=11). Both groups show a circadian rhythm; in addition, patients improve on the second day after sleep deprivation.
(Wirz-Justice 2008)

Years of research have tried to explain what causes diurnal variation of mood, but a clear explanation has not yet emerged. Several studies showed that mood, like other variables, such as core body temperature, and hormone levels are regulated by a circadian clock interacting with a sleep homeostat (Wirz-Justice 2008). In several mood disorders, it has been demonstrated that the circadian amplitudes of these variables decrease (Murray 2007) (Levitan 2007). DMV in depression can be usefully understood from a weakened circadian function.

Implication of diurnal mood variation.

Since the beginning of treating major depressive disorders (MDD), it is attempted to find predictors for the outcome of treatment (Haug 1992; Reinink et al. 1993). Several characteristics have been associated with a positive outcome to antidepressant medication. Characteristics like severity of depression, greater social support and later age at onset have been associated with a positive outcome to antidepressant treatment (Morris et al. 2007). DMV have been associated with a positive outcome of total sleep deprivation (TSD). A study performed by Elsenga and van den Hoofdakker in 1987 with 44 endogenously depressed patients concluded that the response to TSD in patients with DMV was significantly higher. They concluded that a morning worsening in mood may predict antidepressant response of TSD. Later a study of Reinink et al. 1990 showed that the direction of DMV is of importance for the response to TSD. Patients with the classical DMV of feeling better towards the evening benefitted more from TSD than other patients. Patients with DMV of worsening of mood towards the evening may even feel worse after TSD (Reinink et al. 1990). An explanation for this observed effect is that patients with classical DMV have a phase advance of the lowest point in mood after TSD. The

lowest point of mood is shifted to the night, what results in a positive influence on subjective mood state during the day. According to these findings the direction of DMV should be a good indicator for the prediction of the outcome of TSD.
In a study carried out by Gordijn in 1994, it was found that the direction of DMV was not the most important parameter for the outcome of TSD. If the response to TSD was caused by a phase advance of the trough in mood, patients with reversed DMV should experience a worsening of mood earlier in the day after TSD. This is not the case; it was found that patients with reversed DMV also responded positively to TSD (Gordijn et al. 1994). So it can be concluded that a positive response to TSD is not due to a phase advance of the lowest point in mood. Further investigation showed, that the strongest correlation with the TSD response was the standard deviation of the mood fluctuation, measured with the AMS (Gordijn et al. 1994).
The question then arises, why patients with DMV do respond better to TSD than patients without DMV. A hypothesis stated by Gordijn is: the hypothesis of increased susceptibility in patients with DMV.
Patients who are more susceptible to stimuli tend to vary in mood and have a higher chance to show DMV (Gordijn et al. 1994). It is not known what causes this increased susceptibility in these patients. Suggested is that the instability of brain state in depressed patients is involved (Van Den Burg et al. 1992). Patients with DMV respond better to antidepressant medication (Carpenter et al. 1986) which is a stimulus, TSD is also a stimulus, hence the hypothesis: Patients with DMV are more susceptible to stimuli. The problem with this hypothesis is that it does not explain why there are more patients with the classical form of DMV than there are with reversed DMV.
Another hypothesis was formulated by van den Burg et al (1992). This hypothesis states that the antidepressive response to TSD results from disinhibitory process induced by increased 'cerebral fatigue' due to prior wakefulness (Van Den Burg et al. 1992). The increased cerebral fatigue could play a key role in antidepressant effects of TSD. This hypothesis could be an explanation for the predominance of classical DMV. Bouhuys 1989 demonstrated that the clinical response to TSD can be predicted by high levels of arousal (Bouhuys et al 1989). A study of Clark 2006 supported this hypothesis. It was shown in that study that depressed patient had elevated baseline limbic activity compared to healthy subjects. After TSD the limbic activity decreased in these patients. These findings are consistent with the hypothesis of over-arousal (Clark et al. 2006).

Diurnal mood variation and chronotype.

For the diagnosis of MDD it is not necessary to show DMV, although it is seen in many patients, it is not a requirement for the diagnosis. During prior healthy intervals virtually all patients will not have demonstrated DMV. When hospitalized for MDD, the majority of patients will develop the classical form of DMV (Graw et al. 1980). The predominance of the classical form of DMV could be due to a phase delay of the mood rhythm. This is explained as follows: Patients with MDD often are late chronotype (Wood et al. 2009). In late chronotype, all circadian rhythms appear to be shifted to a later time. Therefore, late chronotypes experience the lowest point in mood, not in the night, but the interval of low mood is delayed towards the morning. A study by Wood in 2009 found that bipolar depressed patients are more likely to be evening types. It was also shown that the severity of depression and the rating of being a late chronotype correlated positively.

Body temperature and mood.

Circadian rhythms in behavior and physiology might well be interrelated. It is, for instance, reasonable to expect that it is easier to perform at the peak of the body temperature rhythm than at the trough. Such relationships have also been studied with respect to the circadian rhythm of mood.

Boivin et al (1997) demonstrated that the circadian rhythm of mood in healthy subjects is parallel with the circadian variation of body temperature (Boivin et al. 1997).Koorengevel et al (2003) extended these observations to show that the course of mood is parallel to body temperature both in healthy subjects and patients with SAD (Koorengevel et al. 2003). In figure 2 the sleep-wake cycle-related and pacemaker-related variation of mood and core body temperature are plotted. Measurements were performed both in summer and winter. The average course of AMS scores are z-transformed to account for differences between patients and healthy subjects. A negative score means an improvement in mood. Since the pacemaker's period length and phase position did not differ between conditions, the temperature data were averaged across all forced desynchrony experiments.

A mathematical procedure has disentangled the influence of the circadian pacemaker from the influence of the sleep-wake cycle. So the effect of prior sleep is that mood starts at a low value, gradually increases until about 4 hours later, and then gradually declines in the rest of the wake interval. In depressed patients mood improved just before bedtime. This improvement of mood was not observed in healthy subjects. The effect of the circadian pacemaker is that mood more or less follows the circadian influence of the pacemaker on body temperature (Koorengevel et al. 2003).

The study of Murray in 2002 investigated the 24h cycle of mood. The aim of the study was to investigate if the self-reported PA has a circadian component and that NA does not. The study found support for this hypothesis (Murray et al. 2002). It was shown that the PA rhythm is parallel to the body temperature rhythm. This confirms the expectation that a peak in temperature coincides with a peak in mood.

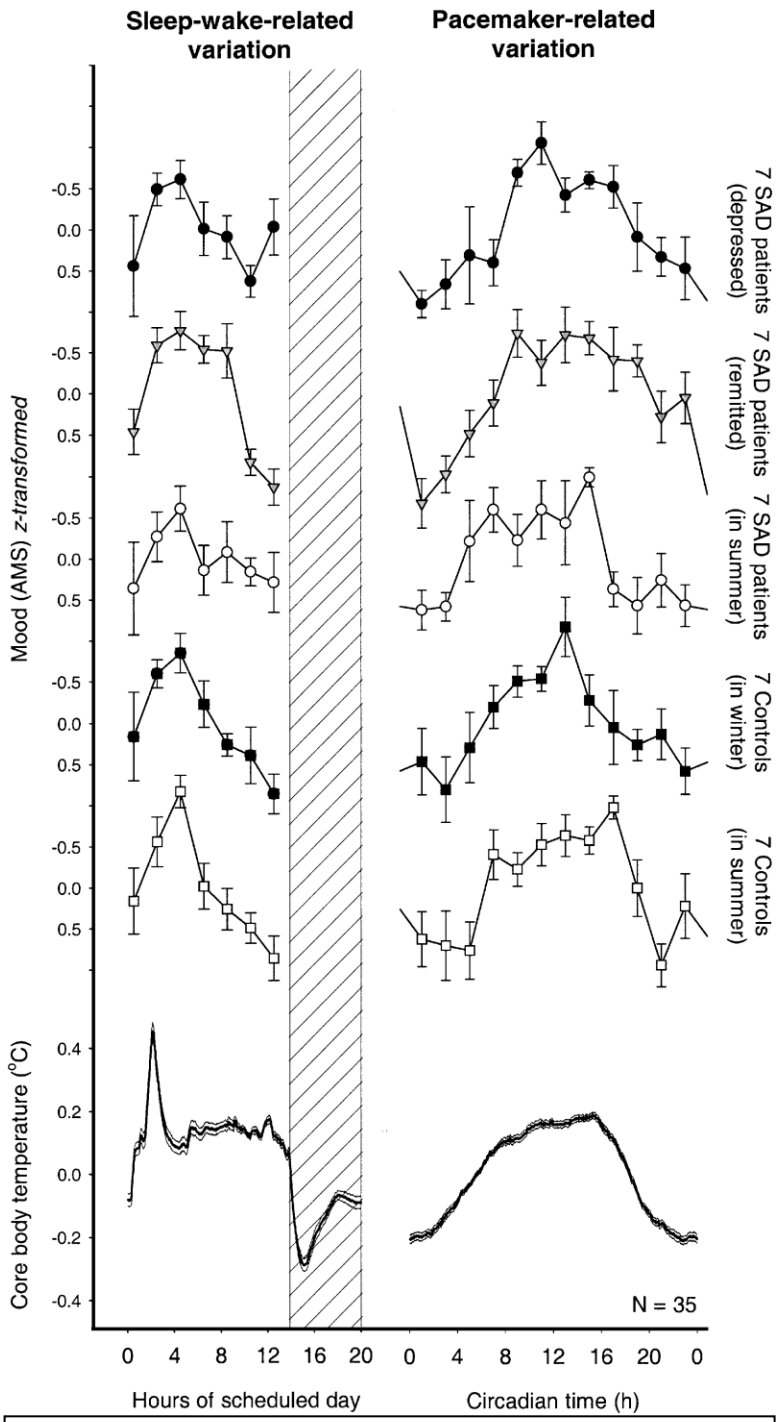

Figure 2: Sleep–wake cycle related and pacemaker-related modulation of mood and core body temperature (mean -+S.E.M.) in SAD patients and matched controls. The course of mood measured with the AMS z-transformed in a forced desynchrony protocol. (Koorengevel et al. 2003)

Serotonergic influence in diurnal mood variation.

Serotonin is a neurotransmitter involved in many different processes in humans. A functional decrease of serotonergic neurotransmission has been associated with depression and sleep alterations (Adrien 2002). This functional decrease in serotonergic neurotransmission is a good target for pharmacological treatment of depression. Antidepressant drugs such as selective serotonin reuptake inhibitors (SSRI) target this functional decrease. In a recent study of Joyce et al a patient group of 195 depressed patients was examined. 80 patients had no DMV; 53 had classical DMV; and 62 had reversed DMV. The response to the antidepressant drug of fluoxetine, a SSRI, or nortriptyline, a tricyclic antidepressant, was examined (Joyce et al. 2005). Patients with reversed DMV responded better to the tricyclic antidepressant nortriptyline than to the SSRI. Further investigation showed that reversed DMV was associated with a higher tryptophan:large neutral amino acid (Trp:LNAA) ratio, and a higher frequency of the polymorphisms in the promoter region of serotonin transporter (5-HTTLPR) (Joyce et al. 2005). This polymorphism in genotype of 5-HTTLPR has been associated with a poorer or slower response to serotonergic antidepressants (Zanardi et al. 2000). These findings raise the possibility of a serotonergic influence in patients with DMV. According to a later study, the antidepressant effect of TSD can be accounted for by serotoninergic mechanisms as those described for pharmacological treatments (Adrien 2002). In contrast to earlier work by Gordijn et al (1994), this suggests that the direction of DMV is an important factor for the response to TSD.

Diurnal mood variation physiology.

All the aforementioned theories and hypotheses treat the state of mood as a kind of black box. Specific regulatory relationships between brain areas and mood are not included. What happens in the brain when a patient is suffering from DMV? DMV in depressed patients may relate to functional changes in components of the ventral and dorsal emotion neural system (Phillips et al. 2003). The ventral emotion neural system includes the amygdala, ventral anterior cingulate and orbitofrontal cortex, ventral striatum and insula. The dorsal emotion neural system includes the hippocampus, dorsal cingulate and prefrontal cortex. Functional abnormalities in one or both neural systems underlie abnormal emotion regulation. Previous research in depressed and healthy subjects support the hypothesis that, in DMV, these neural systems are functionally changed (Drevets et al. 2002).

Depression severity has been shown to correlate positively with blood flow and glucose metabolism in the amygdala and negatively with blood flow or glucose metabolism in prefrontal cortex, cingulate cortex and temporoparietal cortex (Drevets et al. 2002). In healthy subjects sadness is associated with an increased blood flow in ventral cerebral regions and reduced blood flow in frontal and partial regions (Phan et al. 2002). Depressed patients who improved in mood rating after treatment have been associated with changes in blood flow and glucose metabolism in the amygdala, dorsolateral frontal cortices, anterior cingulate cortex and orbital frontal cortex (Drevets et al. 2002). The hypothesis can be stated as followed: changes in cerebral metabolic activity in components of the dorsal and ventral emotion neural system may parallel mood changes and therefore may be associated with DMV in depressed patients.

A study conducted by Germain et al (2007) examined depressed patient with DMV and healthy subjects. Measurements where performed with positron emission tomography scans. The patient group consisted of 12 depressed patients, and there were 13 matched controls. One patient was excluded from the study due to unknown reasons. Five patients self-rated with classical DMV, six patients with no DMV and one patient with reversed DMV.

The regional cerebral metabolic rate of glucose (rCMRglc) was measured with positron emission tomography (PET) in the morning and evening. In depressed patients rCMRglc was significantly greater during scans performed in the evening compared with morning scans in two areas (figure 3). These areas are the left amygdala, anterior cingulate cortex and posterior hypothalamus. There was no comparison performed between patients with classical DMV, reversed DMV, or no DMV.

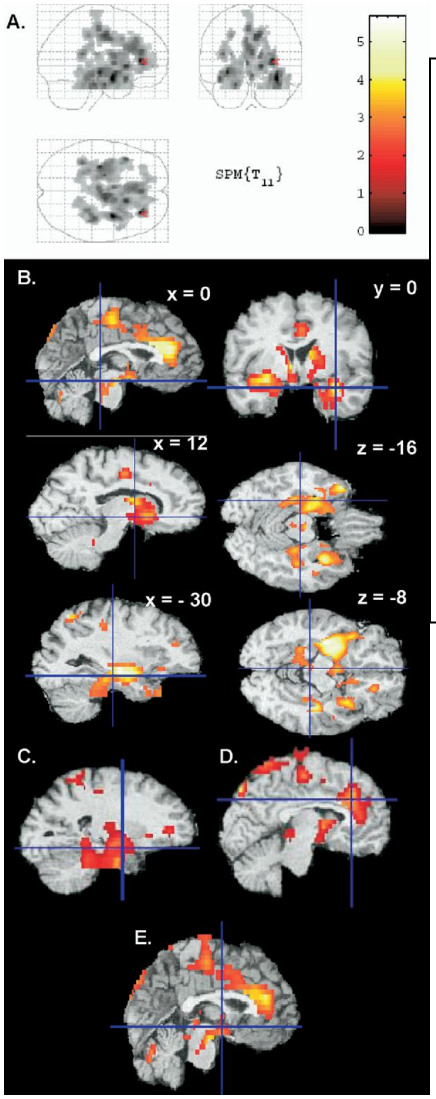

Figure 3. Areas with greater relative glucose metabolism during evening scans than morning scans in the depressed sample only (*p*_.05 at the corrected cluster level), projected onto a 3D transparent brain **(A)** and transverse sections **(B)**. The volumes of interest corresponding to left amygdala **(C)**, anterior cingulate cortex **(D)**, and posterior hypothalamus **(E)** are also presented. The color scale on the right depicts t values for evening-morning contrast (Germain et al. 2007).

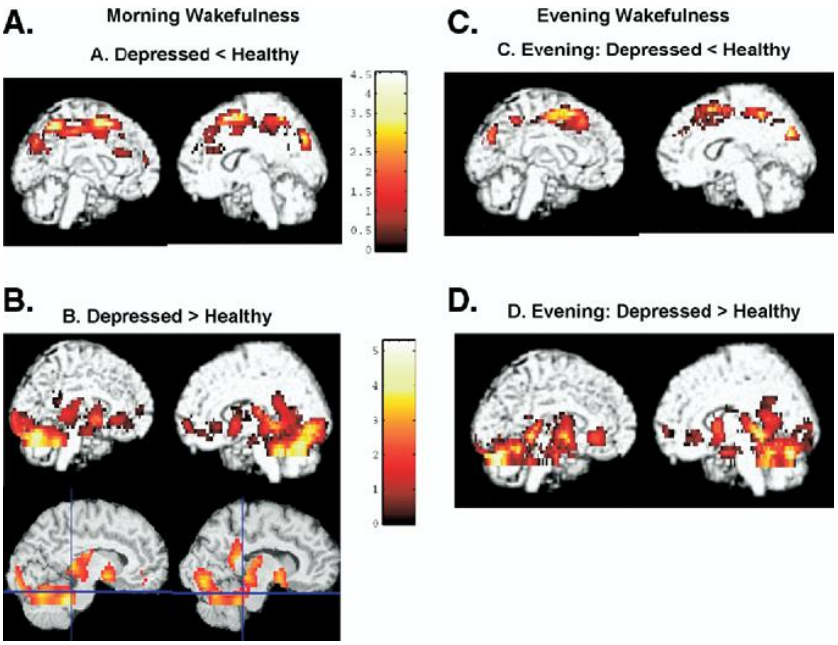

Figure 4. Between-group differences during morning and evening wakefulness.
Areas where rCMRglc is greater or smaller in depressed patients compared
with healthy subjects during morning wakefulness presented onto
rendered images. (Germain et al. 2007)

Figure 4 shows that depressed patients had hypermetabolism in the limbic-paralimbic region, hypometabolism in the frontal and parietal cortex at both times of day compared with healthy subjects. In evening wakefulness there was no significant difference in rCMRglc found in any of the volumes of interest between depressed patients and healthy subjects.
Depressed patients showed a greater increase in central, parietal and temporal cortices compared to healthy subjects. Post hoc analysis showed that patients remained hypometabolic in these areas during the day, compared to healthy subjects (Germain et al. 2007). However this increase in metabolism during evening wakefulness when patients mood is improved could reflect partial normalization.
This study suggests that DMV in depression may relate to changes in rCMRglc across time of day. The findings are consistent with the hypothesis that a dysfunctional limbic-cortical network underlies depression (Germain et al. 2007).
Hypometabolism in basal ganglia has been associated with depression and hypermetabolism in the cerebellum has been associated with sadness in healthy subjects. Hypermetabolism in the cerebellum is also observed in depressed patient during resting states (Videbech et al. 2002). The response to antidepressants is associated with changes in blood flow and metabolism in the cerebellum. Evening mood improvement is parallel with the increase in rCMRglc in parietal and temporal cortices, basal ganglia, and cerebellum (Germain et al. 2007). It would be interesting to see if rCMRglc has the same pattern in reversed DMV but then an increase in the morning.

Directions for further research

DMV have been studied for many years now, DMV as a predictor for the efficacy of antidepressants, DMV as an early predictor in the outcome of chronotherapy, but the specific mechanisms causing DMV remain unknown. The imaging techniques have come a long way since the first description of DMV. The time is there to further investigate DMV and its predicting value in treatment.
Previous studies have shown that response to antidepressant treatment is associated with changes in metabolic activity in the brain (Holthoff et al. 2004). A study of Germain et al (2007) showed that depressed patients with evening mood improvement had smaller increases in rCMRglc during evening relative to morning in lingual, fusiform cortices and midbrain and greater increases in rCMRglc in parietal and temporal cortices compared with healthy subjects. This increase, in parietal and temporal

cortices is associated with a partial normalization of activity in these regions (Phillips et al. 2003). The parietal and temporal cortices may be involved in preserving emotional homeostasis (Mayberg 2003). These imaging studies provided support for the hypothesis that depression is a multidimensional disorder. This disorder is characterized by a disbalance between ventral and dorsal emotion neural system. The ventral and dorsal emotion neural system fail to maintain a stable balance under stress. The specific mechanism what causes this disbalance remains unknown. The observed increase in limbic-paralimbic metabolic activity in evening wakefulness, compared to morning wakefulness in depressed patients, suggests that increased activation in this ventral network may maintain frontal activation and mood improvement (Mayberg 2003).
The question arises if a reversed pattern can be observed in patients with reversed DMV. The study by Germain et al (2007) did not allow a comparison between patients with classical DMV and reversed DMV. There was only one patient with a self-rated pattern of reversed DMV. For further research, it would be interesting to make a comparison between brain metabolism in patients with reversed DMV and classical DMV patients.

Design for further research

Further investigation is necessary to find out which mechanisms are involved in DMV. Studies to compare differences in rCMRglc during morning and evening wakefulness in depressed patients are needed to clarify the specific systems involved in mood improvement and mood worsening.
Patient groups:
Two groups of patients, both suffering from a major depressive episode according to DSM-IV and suffering from either classical DMV or reversed DMV (American Psychiatric Association, 1994). The two groups need to be matched for age, sex, and average severity of depression. An exact match for age, sex, and severity of depression is an ideal situation. In this ideal situation, reaching significance, a sample size of 6 classical DMV and 6 reversed DMV is required. An ideal situation is never the case in studying humans. Therefore a large group of patients is needed. The study of Germain et al (2007) used 12 depressed patient compared to 13 healthy subjects. It was concluded in that study that a larger sample was required to further elaborate on possible clinical correlations. In this study a comparison will be made between two groups of depressed patients. Expected is that these two groups differ more from one another in rCMRglc patterns, than depressed patients compared to healthy subjects. The power to find differences in rCMRglc patterns is greater, therefore the group size is preferably in the range between 10 and 15 patients.
Measuring brain metabolic patterns:
rCMRglc patterns need to be studied in these two groups, rCMRglc could be measured using [*18*F]-fluoro-deoxyglucose PET scans. Scans need to be performed in the morning when mood is high in reversed DMV and worse in the classical DMV group, and scans need to be performed in the evening. Subjective mood questionnaires need to be filled out prior to PET scan. These questionnaires are necessary to determine if patients showed a pattern of DMV on that specific day. Areas of interest are the ventral limbic-paralimbic system and, parietal and temporal cortices. A brain glucose metabolism pattern for evening mood improvement has already been established in the study of Germain et al (2007). Due to the relatively small sample size and the in group differences, these results are preliminary. There is no comparison available in rCMRglc patterns, between evening mood improvement and morning mood improvement. Expected of the comparison is that morning PET scans of patients with classical DMV show the same pattern as the evening PET scans of patients with reversed DMV. If this is the case, it supports the hypothesis that the limbic-paralimbic system and, parietal and temporal cortices are involved in diurnal mood variation.

Concluding

Depression has been known to influence human life: suffering from a depression makes it hard to enjoy life to the fullest. Treating depression with pharmacological intervention is one of the most costly expenses in our healthcare system. Such interventions received a lot of attention, one of them being lithium treatment. There are many studies conducted trying to find out how lithium works, but this is still not clear. Treating depression with drugs has been done for many years, for most if not all antidepressant drugs the specific mechanisms remain unknown. Treating depression with antidepressant drugs takes some time before an effect is achieved, if there is any effect. Non-pharmacological interventions are becoming more popular in this day and age. Non-pharmacological interventions are cheap and are fast acting. Sleep deprivation and bright light therapy seem to have effect on depressive symptoms. Historically these interventions are approached in the form of a black box. There is a behavior, there is an intervention, and after the intervention there is a different behavior observed. It was shown in those "black box" studies that patients with DMV respond positive to the intervention. It is not clear why patients with DMV respond better to this cheap, non-pharmacological intervention. More recent studies show a serotonergic influence in DMV, but an exact mechanism underlying DMV has not yet emerged. Imaging techniques have improved a lot since the first black box studies. Now we live in a time where we can look into the brain to see what is going on. It is possible to study the exact mechanism causing DMV in depression. The exact knowledge of the mechanism enables more specific clinical interventions and might help to improve a patients life with depression.

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