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Review

The vigilance regulation model of affective disorders and ADHD

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ABSTRACT

According to the recently proposed vigilance model of affective disorders (vigilance in the sense of "brain arousal"), manic behaviour is partly interpreted as an autoregulatory attempt to stabilise vigilance by creating a stimulating environment, and the sensation avoidance and withdrawal in Major Depressive Disorder (MDD) is seen as an autoregulatory reaction to tonically increased vigilance. Indeed, using a newly developed EEG-based algorithm, hyperstable vigilance was found in MDD, and the contrary, with rapid drops to sleep stages, in mania. Furthermore, destabilising vigilance (e.g. by sleep deprivation) triggers (hypo)mania and improves depression, whereas stabilising vigilance, e.g. by prolonged sleep, improves mania. ADHD and mania have common symptoms, and the unstable vigilance might be a common pathophysiology. There is even evidence that psychostimulants might ameliorate both ADHD and mania. Hyperactivity of the noradrenergic system could explain both the high vigilance level in MDD and, as recently argued, anhedonia and behavioural inhibition. Interestingly, antidepressants and electroconvulsions decrease the firing rate of neurons in the noradrenergic locus coeruleus, whereas many antimanic drugs have opposite effects.

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1. Introduction

Major Depressive Disorder (MDD) as the most important unipolar depression, and Bipolar Disorders (BD) with both (hypo)manic and depressive episodes are severe and prevalent disorders considerably contributing to the disease associated burden worldwide (Collins et al., 2011). Depressive episodes are typically characterised by depressed mood, loss of pleasure in daily activities, weight loss, insomnia, agitation, fatigue, feelings of worthlessness or guilt, attentional problems, thoughts of death and suicidal ideation. Manic or hypomanic episodes occur mainly within BD and are characterised by abnormally elevated mood, inflated self-esteem, talkativeness, flight of ideas, distractibility, increase in goal-directed activity, decreased need for sleep, and excessive involvement in pleasurable activities. These impressive clinical syndromes can show a rapid onset in some patients within one or a few days, as found especially for bipolar compared to unipolar depression (Hegerl et al., 2008a), rapid improvements, as found e.g. with sleep deprivation in depression (Benedetti and Colombo, 2011), or rapid switches between manic and depressive states as observed in ultra-rapid cycling (Juckel et al., 2000; Wilk and Hegerl, 2010). These temporal patterns suggest the existence of a possibly circumscribed underlying neurobiological mechanism and justify optimism concerning a better understanding and better treatment of these disorders in the coming years. Up to now, however, the neurobiology of affective disorders has not been understood.

In this paper, a pathogenetic model of affective disorders will be presented, which interprets manic behaviour as an autoregulatory attempt to stabilise vigilance (vigilance in the sense of brain arousal) by creating a stimulating environment. Likewise, sensation avoidance and withdrawal in depression is interpreted as an autoregulatory reaction to a state of tonically increased vigilance. This model, which has been outlined earlier (Hegerl et al., 2009, 2010), differs from prevailing disease concepts. It opens new lines for research on the pathophysiology of affective disorders and has relevance for drug development and personalised treatment.

2. Regulation of vigilance and its measurement

2.1. EEG vigilance

Using EEG, different vigilance stages can not only be discerned during sleep but also during wakefulness. The term vigilance is used here in the sense of tonic neurophysiologic arousal, not as denoting a circumscribed attentional function (Oken et al., 2006). The precise regulation of vigilance and its adaptation to the environment is most important for all higher animals. This regulation of vigilance has been found to be intraindividually stable (Van Dongen et al., 2004) with, at the same time, considerable interindividual differences. Under resting conditions in an environment without major external stimulations, most subjects show more and more declines to lower vigilance stages with the passage of time. Some subjects exhibit an unstable vigilance regulation with rapid declines to low vigilance stages after only a few seconds, whereas others exhibit a hyperstable vigilance regulation without such declines to lower vigilance stages even after recording periods of 15 min or longer. This trait is modulated by many individual and environmental factors such as sleep deficits, vigilance enhancing substances, effort, motivation, and disease related factors.

2.2. VIGALL algorithm for assessment of EEG vigilance

Research on vigilance regulation (brain arousal) and on the role of this central neurophysiological mechanism in different psychiatric disorders has been hampered by the lack of valid and time economic tools to measure it. Until recently, the best available tool to study wakefulness regulation was the Multiple Sleep Latency Test (Carskadon and Dement, 1977; Sullivan and Kushida, 2008). A disadvantage of the MSLT is, however, the complex and time-consuming testing protocol, which requires four or five 20–40 min trials with 2 h between each trial. Furthermore, the MSLT only scores EEG-defined sleep onset, ignoring information about degree and fluctuations of wakefulness before sleep onset.

Recently, an EEG-based algorithm (Vigilance Algorithm Leipzig, VIGALL) has been developed and validated, which allows to objectively measure the regulation of vigilance. VIGALL automatically attributes to short EEG segments (1–3 s) a certain vigilance stage (Hegerl et al., 2008b; Olbrich et al., 2009, 2012a). This allows studying how vigilance is regulated during the recording period. The algorithm used in VIGALL takes into account both the frequency patterns as well as the cortical distribution of EEG activity using EEG source localisation approaches (Low Resolution Electromagnetic Tomography, LORETA; Pascual-Marqui et al., 2002). It is based on the former work of EEG changes in the transition period between wakefulness and sleep onset (Bente, 1964; Roth, 1961), which has been confirmed and further elaborated in more recent research (Benca et al., 1999; Cantero et al., 2002; Corsi-Cabrera et al., 2000; De Gennaro et al., 2001; De Gennaro and Ferrara, 2003; De Gennaro et al., 2004, 2005; Kaida et al., 2006; Marzano et al., 2007; Strijkstra et al., 2003; Tsuno et al., 2002). VIGALL differentiates the following vigilance stages, which can be observed during the transition from high alertness to relaxed wakefulness, to drowsiness up to sleep onset (for details see Olbrich et al. (2012b, c) and online supporting material Fig. S1):

- *Stage 0*: low amplitude, non-alpha activity during an activated state (e.g. mental effort);
- *Stage A* with dominant alpha activity corresponding to relaxed wakefulness (further divided into sub-stages A1, A2, A3 according to the degree of spreading of alpha activity from occipital to more anterior cortices);
- *Stage B* with low amplitude non-alpha (sub-stage B1) and increasing theta and delta activity including vertex waves corresponding to drowsiness (sub-stages B2 and B3);
- *Stage C* with sleep spindles or K-complexes characterising sleep onset.

VIGALL has been validated by several studies, e.g. a simultaneous EEG-fMRI study (Olbrich et al., 2009), and a simultaneous EEG-FDG-PET study (Guenther et al., 2011). These studies show that decreasing vigilance stages are associated with increased metabolic activity in cortical but decreased activity in subcortical areas. A further study relating vigilance stages to autonomous functions showed that the lower the vigilance stages assessed with VIGALL the lower the heart rates and skin conductance levels are (Olbrich et al., 2012b).

Since the EEG shows a high intraindividual stability but a large interindividual variability, the algorithm used in VIGALL has to be adapted to the individual alpha peak and is not applicable for certain EEGs, e.g. those showing alpha variant rhythms or major modifications due to drugs (e.g. anticholinergic drugs) or certain diseases (e.g. severe Alzheimer's disease).

3. The vigilance regulation model of affective disorders

The vigilance regulation model of affective disorders takes into account that the level and the regulation of vigilance are not only influenced by the environment, but that we can create a more or less "arousing" environment by our behaviour. In an autoregulatory manner, a more or less stimulating environment can be actively

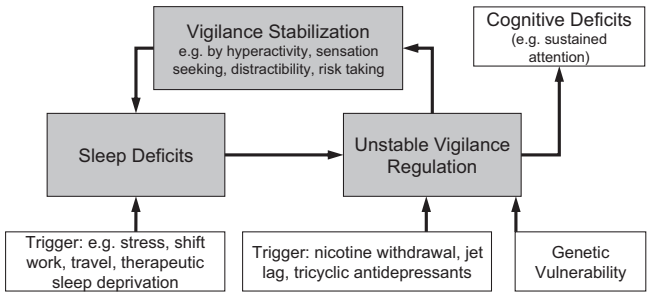

Fig. 1. The vigilance regulation model of mania. An unstable vigilance induces a pathogenetic circle with a vigilance stabilisation behaviour contributing to full-blown mania; figure constructed according to Hegerl et al. (2009).

created in order to stabilise or reduce vigilance levels. Such an autoregulatory attempt to stabilise vigilance by increasing external stimulation may be best exemplified by overtired children, who often develop a hyperactive, talkative and sensation seeking behaviour. In contrast, states of tonic hyperarousal are often associated with the tendency to withdraw and to avoid loud music, social interactions and other external stimulations.

The vigilance concept and the autoregulatory function of certain behavioural syndromes have already been proposed earlier (Bente, 1964; Ulrich, 1994), and related concepts have been presented concerning personality traits such as extraversion (Eysenck, 1990) and sensation seeking (Zuckerman, 1979). These personality traits were interpreted as autoregulatory behaviour in order to achieve an optimal level of arousal, and were suggested as reflecting vulnerability to affective disorders (Hensch et al., 2007).

We assume that in vulnerable subjects the physiological autoregulatory mechanisms can not only result in affective personality traits, but also go beyond these in clinically relevant behavioural syndromes. The heuristic value of this concept becomes especially apparent in manic and depressive states within affective disorders but also in attention deficit hyperactivity disorders (ADHD).

3.1. Vigilance regulation in mania

Fig. 1 summarises the suggested pathogenetic mechanisms in mania: In vulnerable subjects an unstable vigilance induces exaggerated autoregulatory behaviour as an attempt to stabilise vigilance. This autoregulatory behavioural syndrome comprises hyperactivity, talkativeness, sensation and novelty seeking, distractibility and impulsivity. The autoregulatory mechanism overrides the physiological tendency to seek sleep, thus aggravating the sleep deficits and as a consequence the instability of vigilance. A vicious circle is started, which then contributes to full-blown mania.

The pathogenetic concept presented in Fig. 1 is supported by different lines of evidence and provides an explanation for several seemingly paradoxical findings.

It has mostly been neglected in present theories on the pathophysiology of mania that many manic patients are indeed characterised by an unstable vigilance regulation (Van Sweden, 1986). This may be surprising, bearing in mind the highly energetic behaviour of manic patients who do not appear to be sleepy or tired. However, it is a robust finding that many manic patients, when studied in a quiet environment with low external stimulation and eyes closed, show rapid declines to low vigilance stages and micro sleeps with sleep spindles often already within the first seconds of EEG recording (Small et al., 1999; Ulrich, 1994; Van Sweden, 1986).

There is consistent evidence that this unstable vigilance regulation is not only a consequence of mania-induced sleep deficits but plays a causal role in the pathogenesis of mania:

- A large body of research shows that factors associated with sleep deficits are among the strongest triggers of mania and/or worsen manic behaviour (Harvey, 2008; Wehr, 1992). Sleep deprivation in bipolar depression can induce a switch into hypomania and mania in 10% or more of the patients (Wu and Bunney, 1990; Colombo et al., 1999; Kasper and Wehr, 1992) and sleep deprivation is used as an animal model of mania (Gessa et al., 1995). The causal relevance of sleep reduction (e.g. due to bereavement, newborn infants, shift work, travel, obstructive sleep apnoea) for triggering mania is reviewed in Plante and Winkelman (2008). A systematic review of manic and depressive prodromes revealed that sleep disturbance is by far the most robust early symptom of mania (median prevalence of 77%; Jackson et al., 2003), and it has been found that especially those life events which disturb sleep-wake-regulation can trigger or aggravate (hypo)manic syndromes (Barbini et al., 1996; Plante and Winkelman, 2008; Wehr, 1991).
- While sleep deficits can trigger mania, stabilisation of sleep-wake rhythm has become an established and important element in behavioural therapies for BD (Frank et al., 2005; Leibenluft and Suppes, 1999; Riemann et al., 2002). Also, extended bed rest and darkness as an add-on to the usual treatment of acute mania resulted in a faster decrease in Young Mania Rating Scale (YMRS; Young et al., 1978) in those patients with a recent (within 2 weeks) onset of mania (Barbini et al., 2005). Similar results have been reported by others (Nowlin-Finch et al., 1994; Wehr et al., 1998). Such interventions can be expected to interrupt the pathogenetic circle described in Fig. 1 by stabilising vigilance regulation.
- In smokers nicotine has vigilance stabilising properties. The withdrawal of nicotine causes EEG-signs of sedation (Fisher et al., 2012) and may trigger mania according to case reports (Benazzi, 1989; Labbate, 1992).
- Antidepressants, which reduce firing rate of locus coeruleus as outlined below, may be associated with an increased risk of inducing a switch into mania. It is interesting that this switch risk has been found, in some studies, to be higher in sedating antidepressants with anticholinergic and antihistaminic properties such as tricyclic antidepressants or trazodone than in SSRI (Gijsman et al., 2004; Jabeen and Fisher, 1991; Peet, 1994; Terao, 1993).

Vigilance enhancing drugs like psychostimulants are seen as contraindicated in mania by many clinicians. However, according to the model presented here, vigilance stabilising drugs should be able to stop the manic vicious circle. Indeed, when reviewing the literature, there is a lack of empirical evidence for detrimental effects of psychostimulants in mania (Hensch et al., 2010) and even empirical data suggesting the opposite, namely rapid antimanic effects of psychostimulants (Beckmann and Heinemann, 1976; Bschor et al., 2001; Garvey et al., 1987; Max et al., 1995; Schoenknecht et al., 2010).

- If psychostimulants had a high risk to induce or worsen mania, then the broad use of stimulants in ADHD would be a considerable problem because of the high comorbidity between ADHD and BD: In pediatric samples, comorbidity of BD and ADHD is especially high; up to 85% of children with BD have also been found to have ADHD, and up to 22% of children with ADHD are also diagnosed BD (Singh et al., 2006). Given the differential diagnostic difficulties in distinguishing both diseases in children (Hensch et al., 2011), one can assume that many unrecognised or misdiagnosed pediatric manic patients have already received and are

receiving stimulants. A systematic reanalysis of randomised controlled trials (RCTs) using stimulants in ADHD by the Food and Drug Administration (FDA) revealed that psychotic or manic-like reactions occurred only quite rarely (in about 1 of 400 treated patients) and in the majority of cases (55 of 60) the symptoms resolved within 2 days (Gelperin and Phelan, 2006; Mosholder, 2006; Phelan, 2006b, 2006a; Ross, 2006). Furthermore, in a recent controlled trial in children with ADHD and severe mood dysregulation, even an improvement in Young Mania Rating Scale was observed under treatment with methylphenidate (Waxmonsky et al., 2008).

- Stimulants as an add-on to a mood stabiliser have already been given to bipolar patients, for example in order to treat comorbid ADHD or residual symptoms, such as sleepiness. In children and adolescents, open trials (Kowatch et al., 2003; Kummer and Teixeira, 2008) and three recent controlled trials (Findling et al., 2007; Scheffer et al., 2005; Zeni et al., 2009) showed that adding a stimulant did not worsen but often improved manic symptomatology. In adults, some uncontrolled studies (Carlson et al., 2004; El-Mallakh, 2000; Fernandes and Petty, 2003; Lydon and El-Mallakh, 2006; Nasr et al., 2006) and recent RCTs (Frye et al., 2007; Calabrese et al., 2010) also did not reveal higher (hypo)manic symptoms in bipolar depressed patients treated with stimulants in conjunction with mood-stabilisers.
- In several older case reports and case series antimanic effects were found when treating adult manic patients with psychostimulants (reviewed in Hegerl et al., 2009). A pronounced and rapid improvement of manic symptoms within 1 h was observed quite consistently in these studies, similar to the effect observed with psychostimulants in ADHD. For example, Garvey et al. (1987) reported a reduction of at least 50% of a mania scale in five of six patients, rated by clinicians blind to the d-amphetamine treatment. Similarly, Beckmann and Heinemann (1976) showed a pronounced decrease in mania ratings at the end of the 30 min d-amphetamine infusion in all of the six manic patients.
- In a pivotal study by Bschor et al. (2001) improvement of manic symptoms occurred about 2 h after oral intake of methylphenidate in a manic patient with signs of unstable EEG-vigilance regulation. Three months later, when the patient was admitted anew, again a rapid antimanic effect was shown after reexposition to methylphenidate. In contrast, no improvement was found in another manic patient without this EEG pattern.
- Our research group reported a rapid response of an acutely manic patient to monotherapy with vigilance stabilising drug modafinil (Schoenknecht et al., 2010). After five days the patient had clearly improved and after stopping modafinil, treatment was continued with lithium. Clinical improvement went along with a stabilisation of vigilance regulation.

3.2. Parallels between mania and ADHD

In line with the high comorbidity of BD and ADHD, mania and ADHD show striking similarities at the symptom level. Convincing evidence has accumulated suggesting that this is not only a superficial similarity but points to underlying common pathomechanisms (as reviewed in Hegerl et al., 2010). An unstable vigilance regulation is supposed to be of pathogenetic relevance in both disorders:

Unstable or low vigilance (hypoarousal) has been discussed for a long time as a pathogenetic factor in ADHD by several research groups (Arns and Kenemans, 2012; Barry et al., 2003). Similar to mania an unstable vigilance has also been found in ADHD using the Multiple Sleep Latency Test (MSLT; Cortese et al., 2009). Also, the findings of many EEG studies with increased slow EEG activity (theta and delta) and reduced alpha activity in ADHD (Barry et al., 2003) are likely to reflect an unstable vigilance regulation with more declines to the lower vigilance stages B1 and B2/3. These findings have been especially consistent for children, whereas for adolescents and adults a reduction of alpha activity has not been found in all studies (Hobbs et al., 2007; Koehler et al., 2009). Further support for lower vigilance in ADHD has recently been provided using VIGALL (Sander et al., 2010).

The unstable vigilance regulation provides a straightforward explanation for the attention deficits in ADHD, especially the well established deficits in continuous performance tasks (Nichols and Waschbusch, 2004). Furthermore, the vigilance model of ADHD explains the ADHD subtypes according to DSM-IV. In the predominantly inattentive subtype, the deficits are explained in a straightforward manner by the instability of the vigilance regulation. In the combined subtype with attention deficits and hyperactivity, additional autoregulatory aspects come into play with hyperactivity, sensation and novelty seeking as an attempt to stabilise vigilance (see also Weinberg and Brumback, 1990; Zentall and Zentall, 1983). The presented model also explains why the predominantly hyperactive-impulsive subtype is less frequently found (Hurtig et al., 2007): The unstable vigilance is a core pathogenetic factor. It always results in attention deficits, whereas hyperactivity is not a disorder of its own, but an autoregulatory response, which may or may not be present.

Sleep and circadian disorders are highly prevalent in ADHD, and it has been discussed that they might play a pathogenetic role in ADHD symptomatology (Arns and Kenemans, 2012; Yoon et al., 2012). In a consistent manner, all factors, which destabilise vigilance or induce sleep deficits, are found to aggravate ADHD, whereas interventions improving sleep quality and stabilising vigilance are helpful in ameliorating ADHD (Fallone et al., 2005; Gruber et al., 2009; Yoon et al., 2012; Gruber et al., 2011).

Psychostimulants reduce the slow wave activity as has to be expected from a drug with vigilance stabilising properties (Bresnahan et al., 2006). Additionally, stimulants reduce attention deficits, sensation seeking behaviour and hyperactivity in patients with ADHD (Pietrzak et al., 2006; Riccio et al., 2001; Spencer et al., 2005). The first effects of medication are usually rapid (within 30–45 min for methylphenidate, Greydanus et al., 2007), similar to the rapid antimanic effects observed in case reports and case series. In line with the model proposed for mania, these therapeutic effects of psychostimulants in ADHD can be explained by their vigilance stabilising effects, which interrupt the autoregulatory hyperactivity and sensation seeking behaviour.

3.3. Vigilance regulation in depression

While the behavioural syndrome in mania may stabilise an unstable vigilance regulation by creating a stimulating environment, the opposite may be true in depression. Depressed patients tend to withdraw themselves from all interactions and show sensation avoidance behaviour, possibly as a reaction to a hyperstable vigilance regulation. Several lines of evidence support this view.

In contrast to the unstable vigilance regulation in mania, a hyperstable vigilance regulation can often be observed during depressive episodes (Ulrich, 1994; Ulrich and Fuerstenberg, 1999). Our research group found in unmedicated depressed patients ($n = 30$) compared to healthy controls ($n = 30$) a significantly more stable vigilance regulation over the recording period of 15 min (Hegerl et al., 2012; Fig. 2). This hyperstable vigilance is in line with the prolonged sleep onset latency found in depressive patients (Armitage, 2007; Tsuno et al., 2005), their inner restlessness and tension, and the hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis in depression (Holsboer and Ising, 2010; Pariante and Lightman, 2008). The tendency in depression to have tonically high vigilance stages explains the seemingly paradoxical finding that the worse the night time

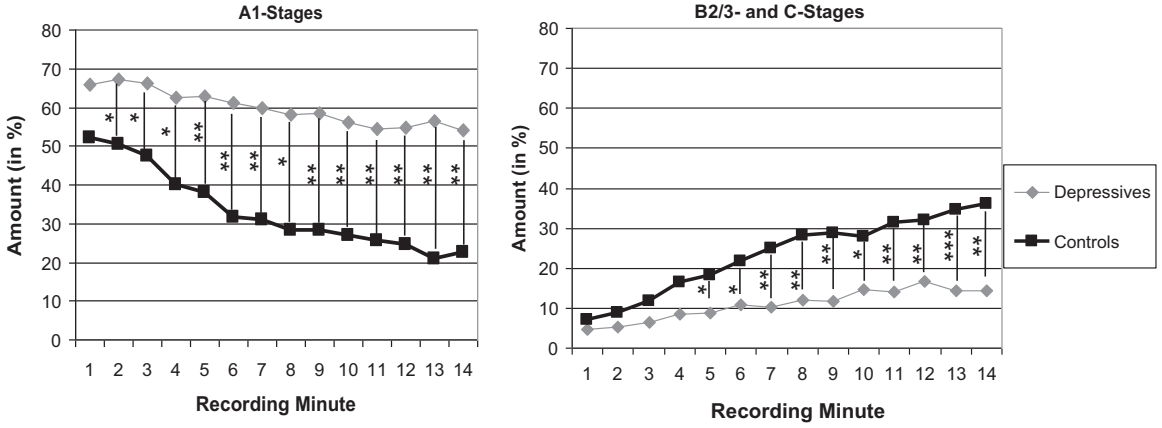

Fig. 2. Changes in percentage of stage A1 (left side) and stages B2/3 and C (right side) over time in unmedicated patients with unipolar depression compared to healthy controls. Differences between depressives and controls were tested by Mann–Whitney *U* test: $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$; figure constructed according to Hegerl et al. (2012).

sleep, the longer the daytime sleep latency on the MSLT (Kayumov et al., 2000).

Sleep deprivation (SD) is a well-established treatment in depressive episodes. Staying awake during the second half of the night results in a pronounced reduction of the depressive symptoms in more than 50% of the patients (Benedetti and Colombo, 2011). This is paradoxical at first glance; especially for the patients who have the deep desire to find sleep and who suffer from sleep disturbances. Unfortunately, recovery sleep and even short naps can be followed by the immediate return of the previous depressive symptomatology. The vigilance model of affective disorders provides a simple explanation for these effects: SD might increase sleep propensity and break up the hyperstable vigilance regulation found in depressed patients and by that reduce the autoregulatory behaviour with withdrawal and sensation avoidance. Some further preliminary support for this hypothesis comes from studies showing that patients with higher sustained attention in a continuous performance test or higher subjective arousal ratings benefit more from sleep deprivation (Bouhuys et al., 1995; Wu et al., 1992).

While SD can trigger mania and has antidepressant effects, sleep can be depressiogenic in vulnerable subjects. During depressive episodes within MDD and BD, many patients clearly describe their depression as most severe in the morning becoming less severe during the course of the day and the late evening. Sleep may reduce sleep propensity and aggravate the hyperstable vigilance regulation, whereas being awake may increase sleep propensity and by that reduce this vigilance dysregulation during the course of the day. In line with this reasoning, switches from mania to depression tend to occur during the second half of the night, whereas switches from depression to mania tend to occur during the afternoon and evening (Feldman-Naim et al., 1997; Wilk and Hegerl, 2010).

The relationship between changes in sleep and changes in mood has been studied within a longitudinal, prospective design in 59 patients with BD (Bauer et al., 2006). Cross correlations between self reported sleep or bed rest and mood showed that in the majority of patients with a significant cross correlation an increase in sleep or bed rest was followed by an increase in depression, whereas a reduction of sleep or bed rest was followed by hypomania or mania. Relationships between reduced sleep and (hypo)mania as well as increased sleep and depressive symptoms have also been reported by other research groups (Leibenluft et al., 1996; Wehr et al., 1982).

According to preclinical studies, all standard antidepressants and electroconvulsive treatment have in common that they *decrease* the tonic as well as phasic firing rate of the locus coeruleus (LC), where most of the noradrenergic neurons are located (see below, Section 4.3). This is an intriguing finding bearing in mind the importance of this system for the regulation of vigilance.

Due to the energising properties of psychostimulants seen in healthy subjects, it has been tempting to study their possible antidepressant effect. However, depressive symptoms only superficially suggest sleepiness and a lack of drive, symptoms which might respond to psychostimulants. Rather, many patients with typical depression do not suffer from sleepiness (tendency to fall asleep), but from insomnia and decreased sleep drive during the day (prolonged sleep latencies) despite feelings of tiredness and exhaustion. They also do not suffer from lack of drive, but rather from *inhibition* of drive (retardation) combined with high inner tension. Thus, if many depressive patients are characterised by increased arousal/hyperstable vigilance, psychostimulants are unlikely to be helpful in general. In line with this assumption, evidence for an antidepressant effect of stimulants in patients with typical MDD is indeed lacking up to today.

A recent meta-analysis by Candy et al. (2008) analysed randomised-controlled trials from the last six decades testing antidepressant effects of stimulants as monotherapy or add-on in depression. Concerning clinical response, no significant effects could be shown. Concerning the second outcome variable, reduction in depression symptoms, only one of the subanalyses by Candy revealed a significant effect based on three trials. However, two of the trials were on patients with serious concomitant medical conditions, namely traumatic brain injury and HIV with hypersomnia. The third trial comprised 20 outpatients with "moderate depression" and "apathy, fatigue, [and] lack of energy" (Elizur et al., 1979). No diagnostic details are specified, but given the symptom of apathy, one might suspect atypical depression in this group. Further RCTs, which have been published since the analyses by Candy et al. (2008), also failed to show an antidepressant effect of stimulants as add-on (Beck et al., 2010; Dunlop et al., 2007; Ravindran et al., 2008), with the exception of one small short-term trial with modafinil add-on (Abolfazli et al., 2011; $N = 46$; 6 weeks).

In *bipolar* depression two trials showed some add-on effect of (ar)modafinil (Frye et al., 2007; Calabrese et al., 2010). Thus, one may assume that, in contrast to unipolar depression, bipolar patients may show some profit from stimulant add-on. This assumption is waiting for replication in other large add-on trials soon to be completed.

In conclusion, in unipolar depression there is no evidence for an antidepressant effect of stimulants as monotherapy, and no strong evidence for any add-on effect. However, depression is a heterogeneous condition (Baumeister and Parker, 2011), and the vigilance theory may help to identify subgroups of patients, who respond

to stimulants: according to uncontrolled studies there might be an antidepressant effect of stimulants in *secondary depression* (Masand et al., 1991). Such secondary depressive syndromes may be characterised by sleepiness, anergic states and lack of drive. Similarly, in *atypical depression*, which is likely characterised by unstable vigilance regulation (see Section 5), stimulants show some possible benefit. Furthermore, in *bipolar depression*, which may also be characterised by a more unstable vigilance (see Section 5), preliminary evidence also suggests some antidepressant effect of stimulant add-on.

4. The role of central noradrenergic activity in vigilance and affective disorders

Concerning the neurobiological bases of the vigilance regulation model of affective disorders, two important questions have to be addressed:

(1) What are the neurobiological processes underlying the unstable vigilance regulation in mania and/or ADHD as well as the hyperstable vigilance regulation in major depression?
(2) What are the neurobiological processes mediating the autoregulatory hyperactive, sensation and novelty seeking behaviour in mania and ADHD as well as the sensation and novelty avoidant and retarded behaviour in depression?

A deeper understanding of these mechanisms could become the key for the development of new (pharmaco)therapeutic strategies.

Concerning the first question, the research of the last two decades has deepened our understanding of the complex processes regulating vigilance and sleep–wakefulness. Many interacting neurochemical systems have been found to be involved (Saper et al., 2010; Siegel, 2009). One of them is of special interest in the context of the presented model, namely the central noradrenergic system. The activity of this neuromodulatory system not only increases and stabilises vigilance but can also mediate the autoregulatory behavioural inhibition and retardation in depression.

4.1. Central noradrenergic activity and vigilance

The relevance of the noradrenergic system for maintenance of vigilance and phasic arousal reactions is well established (Berridge and Waterhouse, 2003; Berridge, 2008; Valentino and Van, 2008). The firing rate of neurons in the LC runs not only in parallel with tonic changes of arousal (i.e. decrease of firing rate with decreasing vigilance stages) but also with short phasic reactions to external or internal arousing events as found in studies with monkeys (Rajkowski et al., 1994). LC neurons displayed continuous activity in alert waking, but prolonged pauses in drowsiness, and the pauses occurred 1–3 s before slow wave EEG appeared. In addition, LC activation preceded by up to 3 s desynchronised EEG and LC neurons responded phasically and selectively to unexpected meaningful sounds (Rajkowski et al., 1994; see also Berridge and Foote, 1991). Recently, Carter and De Lecea (2011) could confirm the causal role of LC activity in wakefulness using optogenetics, which allows neurons to be turned "on" and "off" with light of given frequencies. The functional dynamic of the noradrenergic system is in line with the findings that vigilance can rapidly fluctuate, e.g. within milliseconds following an arousing event, as shown in studies with EEG, skin conductance and introspection.

4.2. Central noradrenergic system and depression

Several findings, such as high cerebrospinal fluid levels of NE and its primary metabolite, point to hyperactivity of the central noradrenergic system, in particular the LC, in typical depression (see for references Gold et al., 2005; West et al., 2010b; Itoi and Sugimoto, 2010). In an animal model it was shown that many behavioural symptoms of depression are accompanied by increased firing of LC neurons (Simson and Weiss, 1988; Weiss et al., 2005). More recently it has been convincingly shown that high noradrenergic activity can go in line with inhibition of behaviour, a core symptom of depression (Stone et al., 2011). These inhibitory effects are possibly mediated via postsynaptic galaninergic and adrenergic receptors, and via the release of CRH (Stone et al., 2011). Besides noradrenergic afferents to CRH neurons, mostly from the noradrenergic A1 and A2 groups (Stone et al., 2011), converging evidence suggests that the activity of LC neurons is activated by CRH afferents. CRH is therefore a likely mediator of stress-elicited LC activation (reviewed by Valentino and Van, 2008) and links the stress-related activity of the HPA axis to LC activity. It is of interest that LC activity is increased by early adverse life events: a long separation (180 min) of rat pups from dam during early life (postnatal days 2–14) was associated with a tonic activation and a doubling of the firing rate in later life (days 22–35) compared to that of control rats as well as those with only a short separation (15 min) (Swinny et al., 2010).

4.3. LC activity and antidepressive treatments

Most antidepressants and electroconvulsive seizures reduce the firing rate of LC neurons in a pronounced manner. This has been found in preclinical studies for different SSRI, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, MAO inhibitors, the norepinephrine-dopamine reuptake inhibitor nomifensine and the selective norepinephrine reuptake inhibitor reboxetine. Furthermore, this has been found for acute as well as for chronic applications (2 weeks), and for the spontaneous firing rate as well as the sensory evoked burst-firing of the neurons in the LC (reviewed by Szabo and Blier, 2001; West et al., 2009). Even mirtazapine, when chronically given in sufficient dose, reduces the firing rate of noradrenergic neurons, despite the fact that this drug has antagonistic effects on alpha-2-receptors, which could increase the firing rate via its effects on presynaptic autoreceptors. This decrease of LC firing rate under antidepressant treatment might explain drowsiness and somnolence, which is frequently a side effect of SSRI, SNRI and other antidepressants (e.g. O'Hanlon et al., 1998; Riedel et al., 2005; Cascade et al., 2009; Bull et al., 2002). In contrast to the reduction of LC firing rate by antidepressants in adult rats, West et al. (2010a, 2010b) could demonstrate an increase of LC activity under short-term treatment with paroxetine and venlafaxine in young rats. It was suggested that this unusual increase of LC activity early in the course of drug administration in young animals could explain the counter-therapeutic reaction with an increase in depressive symptomatology and suicidal ideation sometimes seen in adolescents treated with these drugs (Liberzon and George, 2010; West et al., 2010a, b).

In line with a reduced firing rate of LC neurons following application of antidepressants and electroconvulsive seizures, it was found that in rats different antidepressants and electroconvulsive seizures decreased the expression of tyrosine hydroxylase in LC (Nestler et al., 1990; Rovin et al., 2012). Because tyrosine hydroxylase is an activity-dependent peptide, a decrease is in line with a decreased LC activity. Consistent with this are findings in humans that treatment with antidepressants reduced the cerebrospinal fluid concentration of the NE metabolite MHPG across 16 studies (3-Methoxy-6-Hydrocyphenylglycol; Grant and Weiss, 2001).

Thus, it appears that a reduction of the firing rate of LC neurons could be an important element or even one final common pathway not only in pharmacological but also in non-pharmacological (electroconvulsion) antidepressant treatment mechanisms. The decrease in LC firing rate could contribute to a normalisation of the

hyperstable vigilance and, as a consequence, reduce the autoregulatory behavioural pattern.

It should be noted that, of course, other antidepressant mechanisms may also play a role, the more so, given the pharmacological diverseness of antidepressant drugs. According to first data, two antidepressants do not seem to permanently reduce LC firing rate: the serotonin antagonist and reuptake inhibitor trazodone, which additionally impacts several other receptors, such as alpha and histaminergic receptors (Ghanbari et al., 2012), and bupropion, which has some stimulant properties and a pharmacological profile different from other available antidepressants (Moreira, 2011). A study by El Mansari et al. (2008) showed that the decrease of the noradrenergic firing rate under bupropion was only transitory and recovered after two weeks. In line with this, bupropion is associated with less somnolence than standard antidepressants and produces equal or even less somnolence compared with placebo (Moreira, 2011). Thus, one can hypothesise that bupropion is especially suited for those subgroups of depressed patients characterised by unstable vigilance regulation, and that EEG vigilance regulation might predict differential treatment response to bupropion compared with other antidepressants. Accordingly, bupropion has been suggested for treatment of depression with ADHD comorbidity (Bond et al., 2012) and depression with sleepiness (Papakostas et al., 2006).

Finally it should be mentioned that other mechanisms besides LC firing rate reduction have also been suggested as common final pathways of antidepressants, most notably the neurotrophic hypothesis of depression. This theory is based on the fact that chronic stress and depression are associated with reduced expression of BDNF in the hippocampus and reduced hippocampus volume, whereas chronic antidepressant treatments reverse these effects and increase BDNF (Autry and Monteggia, 2012). The vigilance theory of affective disorders does not contradict the BDNF hypothesis, because dampening a hyperactive stress system by antidepressants would imply both reduction in hypervigilance and BDNF increase. Rather, the vigilance hypothesis offers an additional explanation for some symptoms in affective disorders and their treatment, including rapid treatment effects, such as by anticholinergic drugs (see Section 4.5), which can not be explained by more long-term neurotrophic effects.

4.4. LC and antimanic drugs

If unstable vigilance is a central pathogenetic factor in mania, then antimanic drugs should increase the firing rate of neurons in the LC. This is also in line with what has been reported.

Several atypical neuroleptics, which possess antimanic properties, increase the firing rate of NE-neurons and/or tyrosine-hydroxylase-levels in the LC. This has been found for olanzapine (Ordway and Szebeni, 2004; Seager et al., 2005), asenapine (Franberg et al., 2009), quetiapine (Yamamura et al., 2009a) and zotepine (Yamamura et al., 2009b). Concerning the first-generation neuroleptic haloperidol, there are also, albeit equivocal, findings of an increase of LC firing rate (Nilsson et al., 2005; Piercey et al., 1994).

The antiepileptic drugs carbamacepine and valproate, which also have some antimanic properties, are supposed to exert their antiepileptic effects via inhibition of GABA transaminase and thus inhibition of GABA catabolism (Van den Berg et al., 1993). A different mechanism might be responsible for the antimanic effects, which occur slower than the antiepileptic effects. Valproate significantly increases (chronic application: 25%) tyrosine hydroxylase mRNA expression, which is correlated with the activity of LC neurons (Sands et al., 2000). Carbamazepine was found to clearly increase the firing rate of LC neurons (>100% in rats). In this study, such an effect was not found for other anticonvulsants (phenobarbital, ethosuximide, diphenylhydantoin) but also not for valproate (Olpe and Jones, 1983).

Lithium has numerous effects on different neurotransmitters including changes in NE transmission. Studies which analysed the effects of lithium on NE transmission in animals, healthy subjects and patients are controversial, although some of the studies found an increase in central NE transmission (Ozerdem et al., 2004; Sastre et al., 2005) and an increase of tyrosine hydroxylase levels (Chen et al., 1998; Rastoge and Singhal, 1977; Terao et al., 1992) with lithium treatment.

In summary, it is quite a consistent finding that antidepressant treatment is associated with a decrease in LC activity, whereas antimanic treatment seems to be associated with an increase of the activity of noradrenergic neurons. These changes could counteract the hyperstable vigilance in depression and the unstable vigilance in mania.

4.5. Interactions of LC firing rate with other transmitters

Having discussed the role of LC activity in vigilance, in affective disorders and their treatment, the following section will discuss other neurotransmitters, which interact with LC activity and are involved in wakefulness regulation. These neurotransmitters may contribute to both the regulation of vigilance and mood (see Fig. 3).

4.5.1. Dopaminergic system

The hyperactive LC neurons may explain not only behavioural inhibition (see above) but also possibly the symptom of anhedonia in depression. It was suggested that anhedonia might be a consequence of hyperactive LC neurons imposing an inhibitory effect on ventral tegmental dopamine neurons. This inhibitory effect is supposed to be caused by galanin, which is co-localised with NE in LC cells, and which is released especially by increased burst firing of LC neurons from terminals on LC axons in ventral tegmental area (Weiss et al., 2005; West and Weiss, 2011). The reduction of the firing rate of LC neurons under treatment with antidepressants might therefore increase the firing of these dopaminergic neurons which are relevant for reward and hedonic processes (Weiss et al., 2005; West and Weiss, 2011). In line with this galanin hypothesis of antidepressants' effects on dopamine is a recent study by West and Weiss (2011). The authors found that, with the exception of the MAO-inhibitor phenelzine, all tested antidepressants, and also electroconvulsive shock, increased the spontaneous firing rate of dopaminergic neurons in the ventral tegmental area.

4.5.2. Cholinergic system

It has been discussed whether or not the noradrenergic effects on vigilance occur directly, or in part indirectly, via the cholinergic system in the basal forebrain. This system is considered to be the final common pathway for the sleep and arousal modulating effects of multiple neurochemical systems. This view is supported by the fact that antimuscarinic substances (atropine, scopolamine) can block the activating effects of the LC on the cortex (Dringenberg and Vanderwolf, 1998). In line with this, activating effects of cholinergic drugs on the EEG have been described (Graef et al., 2011). Thus, increasing vigilance by increasing cholinergic activity in the basal forebrain might have similar depressiogenic effects as modulating LC activity. Indeed, older as well as more recent studies point in this direction. Depression has been related to an excess of cholinergic transmission because cholinesterase inhibitors, such as physostigmine, exacerbated depressive symptoms in MDD and induced depressive symptoms in currently manic patients or in healthy subjects (Burt et al., 1999; Dagyte et al., 2011; Janowsky et al., 1972). Anticholinergic drugs, in contrast, should alleviate depression and/or cause (hypo)manic states according to the vigilance theory of affective disorders. In line with this, euphoria has been associated with short-term administration of anticholinergics (Fleischhacker et al., 1987; Knable, 1989), and in a NIMH study scopolamine

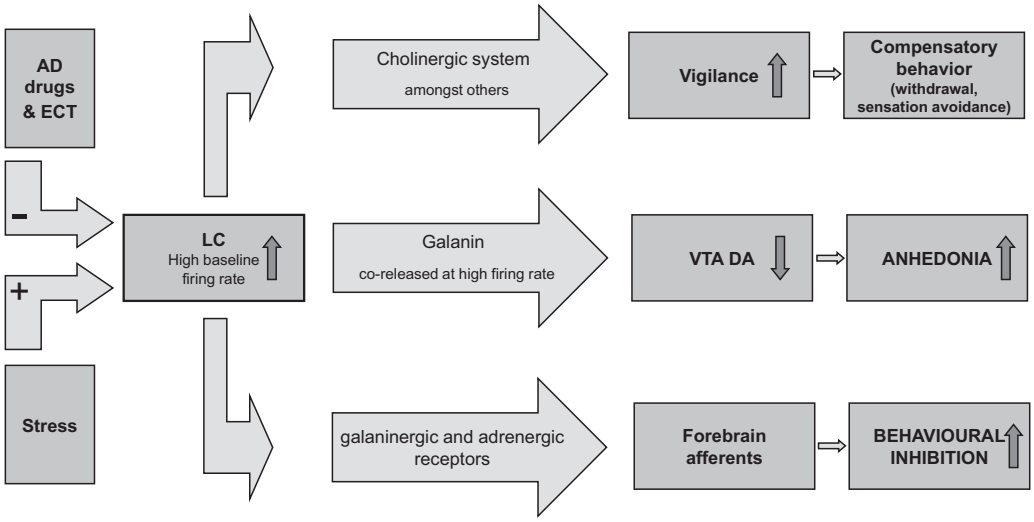

Fig. 3. Influence of LC in interaction with other transmitter systems on vigilance, anhedonia and behavioural inhibition in depression (see Section 4 for explanation). *Legend*: AD antidepressant drugs; ECT electroconvulsive therapy, LC locus coeruleus, VTA ventral tegmental area.

produced rapid and robust antidepressant effects (Furey and Drevets, 2006). The patients reported marked improvement by the evening of or the morning after scopolamine administration, and effects persisted after change to placebo within the cross-over design of this study. A recent placebo-controlled cross-over trial replicated this antidepressant effect of scopolamine in MDD (Drevets and Furey, 2010). Furthermore, the nicotinic acetylcholine receptor antagonist mecamylamine has shown antidepressant effects (Philip et al., 2010), and it was suggested that the anticholinergic effects of all classical antidepressants contribute to their anti-depressant effects (Shytle et al., 2002). Partial nicotinic acetylcholine agonist may have the same antagonistic effects as receptor antagonists, because they are much more potent in desensitising, i.e. inactivating, than in activating nicotinic acetylcholine receptors (Rollema et al., 2009a). In this line, varenicline, a partial agonist of $\alpha 4\beta 2$ nicotinic acetylcholine receptors, has successfully been tested in preclinical trials for treating depression (Rollema et al., 2009a, 2009b). However, it might be difficult to predict the net effect of activation and desensitisation of acute or chronic application in different brain regions in an individual subject. In this respect, it should be noted that partial agonist varenicline has also been associated with significant increases in suicidal behaviour in smoking cessation (Moore et al., 2011). Concerning nicotine, abrupt withdrawal, which may destabilise vigilance regulation, was associated with mania in case reports (Benazzi, 1989; Labbate, 1992).

In summary, the findings of depressiogenic and anti-manic effects of vigilance-increasing cholinergic drugs and the antidepressive effects of anticholinergic drugs are well in line with the vigilance theory of affective disorders.

5. Conclusion and perspectives

The presented vigilance model of affective disorders provides an explanation for several clinically surprising or paradoxical phenomena such as response to psychostimulants in ADHD and mania, the antidepressant and mania-triggering effects of sleep deficits, and the depressiogenic and antimanic effects of prolonged sleep. The heuristic value of the vigilance theory of affective disorders lies in the possibility to derive testable hypotheses concerning treatment response, thereby possibly contributing to the ambitious goal of predicting individual treatment response.

Clinically most relevant is the possible antimanic effect of psychostimulants. We would expect an antimanic effect of stimulants in those patients who are characterised by an unstable EEG vigilance. This hypothesis is presently tested in an international placebo-controlled randomised trial.

For treatment of MDD, a highly heterogeneous phenotypical category (Baumeister and Parker, 2011), differential prediction is even more important given the high non-response rate to the first applied antidepressant (Warden et al., 2007). Patients with hyperstable vigilance (hyperarousal) can be expected to be responders to treatments, which reduce LC firing rate, such as standard antidepressants or electroconvulsive therapy (ECT), whereas patients with unstable vigilance (hypoarousal) may be expected to be non-responders to standard antidepressants. Former quantitative EEG studies already point in this direction: high theta activity (possibly indicating unstable vigilance regulation) was associated with lower treatment response to antidepressants (Iosifescu et al., 2009; Knott et al., 1996, 2000). Most interestingly, scattered evidence points to the possibility that such patients with high theta might show some treatment response to psychostimulants (DeBattista et al., 2011; Suffin and Emory, 1995).

There are at least two phenotypically defined subgroups of depressed patients, who may, in contrast to typical depression, be characterised by unstable vigilance: atypical depression and bipolar depression.

- Atypical depression is characterised by hypersomnia, hyperphagia and leaden paralysis, and the biological correlates seem to be in contrast to those of typical depression, namely reduced HPA axis activity, CRH deficiency and low NE activity (Asnis et al., 1995; Gold and Chrousos, 2002).
- Bipolar patients also show more atypical depressive symptoms according to some studies (Agosti and Stewart, 2001; Detre et al., 1972; Mitchell et al., 2008; Perugi et al., 1998; Robertson et al., 1996), including the more frequently reported symptom of hypersomnia (Kaplan and Harvey, 2009; Kaplan et al., 2011). However, more studies applying EEG are needed to separate subjective anergia from real sleepiness in bipolar depressed patients, because a study by Nofzinger et al. (1991) did not find pathological sleepiness applying MSLT in hypersomnic depressed bipolar patients. Nonetheless, together with some further signs of possible noradrenergic hypofunction in BD (Schatzberg and Schildkraut, 2000; Wiste et al., 2008), one can hypothesise a more unstable vigilance in (a subgroup of) BD. A trait-like vigilance instability in BD would also explain findings of higher scores in

Table 1
Vegetative/neurobiological features and drug-response in depression subgroups.

Typical Depression[a]	Atypical Depression	Bipolar Depression
HPA hyperfunction[b]	HPA hypofunction[b]	HPA hyperfunction[c]
Hyperstable vigilance[d]	Normal or unstable vigilance[e]	Unstable vigilance > UPD[e]
Insomnia[f]	Hypersomnia[g]	Hypersomnia > UPD[h,i]
Loss of appetite/weight[g]	Hyperphagia/weight increase[g]	Hyperphagia > UPD[i]
Motor retardation or agitation[g]	Leaden paralysis[g]	Psychomotor retardation > UPD[i]
Response	Response	Response to antidepressants
- to antidepressants	- better to MAO-I than TCA[j,k]	Questionable[l]
- to ECT	- SSRI possibly less effective than in typical depression[m,j]	

> or <: symptom more/less frequent; UPD: unipolar depression; HPA: hypothalamic-pituitary-adrenal; ECT: electroconvulsive therapy; TCA: tricyclic antidepressants; MAO-I: monoamine oxidase inhibitors; SSRI: selective serotonin reuptake inhibitors.

[a] Typical depression is no DSM-IV-TR episode specifier, but overlaps with melancholic depression specifier (Parker et al., 2010; Baumeister and Parker, 2011).
[b] Antonijevic (2008), Gold and Chrousos (2002), Stetler and Miller (2011), Thase (2009).
[c] Daban et al. (2005).
[d] Hegerl et al. (2012).
[e] Still to be tested.
[f] Baumeister and Parker (2011).
[g] DSM-IV TR.
[h] Kaplan and Harvey (2009), Kaplan et al. (2011).
[i] Mitchell et al. (2008), Rybakowski et al. (2007).
[j] Davidson (2007), Henkel et al. (2010), Stewart et al. (2010).
[k] Liebowitz et al. (1988), Stewart et al. (2009).
[l] Amit and Weizman (2012), Azorin and Kaladjian (2009), Gijsman et al. (2004), Rybakowski (2012), Sachs et al. (2007).
[m] Number of available studies limited/Findings may only apply to a subgroup (Stewart et al., 2002).

personality traits such as Sensation Seeking or impulsivity, irrespective of current psychopathological mood state (Brocke et al., 2000; Najt et al., 2007; Swann et al., 2001) and impairment in sustained attention, which has also been documented in strictly euthymic states and first degree relatives (Maalouf et al., 2010).

Data on the efficacy of pharmacological treatments in atypical and bipolar depression would be in line with the assumption of a more unstable vigilance in both: There is no clear evidence that bipolar patients respond to antidepressant monotherapy (Azorin and Kaladjian, 2009; Gijsman et al., 2004; Rybakowski, 2012; Sachs et al., 2007), and it has been speculated that several of the so called "treatment resistant" patients with major depression might just be unrecognised bipolar patients (Correa et al., 2010; Shapiro and Sharma, 2010). Patients with atypical depression also respond less well to tricyclic antidepressants and possibly also SSRI, although concerning the latter, data are too limited to draw final conclusions (Davidson, 2007; Henkel et al., 2006, 2010; Stewart et al., 2010).

Table 1 summarises differences between typical unipolar depression, atypical depression and bipolar depression concerning neurobiological phenotypes and drug response to antidepressants. Within DSM-IV-TR an episode with atypical depression is separated from three other episode specifiers, i.e. melancholia, psychotic depression, and anxious depression. "Typical depression" is not a DSM-IV-TR episode specifier but is used here as a contrast to a depressive episode with atypical features. The DSM-IV-TR concept of melancholia, however, strongly resembles "typical depression" (Baumeister and Parker, 2011). It should be noted that even atypical depression is still a heterogeneous group (Thase, 2009) with many but not all atypical patients showing HPA hypofunction (Stewart et al., 2005). This once again underlines the importance of EEG vigilance and other endophenotypes to disentangle such heterogeneity, thereby improving treatment response and etiological research.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2012.10.008.

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