Specifying the Neuropsychology of Affective Disorders: Clinical, Demographic and Neurobiological Factors

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Abstract Neuropsychological research in patients with affective disorders shows heterogeneous results with regard to the severity and profile of cognitive impairments. In this paper we hypothesize that the investigation of clinical (subtypes, comorbidity, traumatization, personality, severity, diurnal swings, course, duration, age of onset, biased processing, rumination, motivation, experience of failure, sleep, suicidal tendencies, computer attitudes), demographic (age, education, gender) and neurobiological factors (structural and functional brain changes, glucocorticoids, medication, ECT) that are related to cognitive performance has specified the understanding of severity and profile of neuropsychological impairments. We reviewed the literature pertaining to clinical, demographic and neurobiological factors following Pubmed and PsychInfo databases using different combinations of general key-terms including "Affective Disorder," "Depression," "Mania," "Neuropsychological," "Neurobiological," "Moderator," and "Review" as well as more specific demographic, clinical and neurobiological search terms. Findings from the literature show that the consideration of these factors has improved knowledge about the severity of neuropsychological impairments in patients with affective disorders whereas the neuropsychological profile is still poorly understood. Despite limited understanding, however, the existent results provide promising suggestions for the development of treatment programs.

Keywords Neurocognition · Depression · Mania · Neuroimaging · Intervention

Introduction

Affective disorders are highly prevalent with a lifetime prevalence of 15% for major depression disorder (MDD) within the general population (Wittchen 1994). Apart from symptoms of impaired mood, affective disorders are characterised by additional emotional, psychological, behavioural, physical, and cognitive symptoms such as neuropsychological dysfunction. According to the Diagnostics and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association A. P. 1994) and the International Classification of Diseases (ICD-10, WHO 1991), cognitive symptoms of MDD are characterised by reduced abilities to concentrate and impaired decision-making processes, and in the case of mania, flight of ideas, increased distractibility, and continuous change of plans and activities.

For more than 50 years, neuropsychologists have attempted to understand neuropsychological dysfunction in depression (Kiloh 1961; Madden et al. 1952). In particular, much research has focused on differentiating depression from dementia. In addition, neuropsychological profiling of mood disorders also has a close link to basic science in that patterns of neuropsychological dysfunction might closely relate to neurobiological dysfunction which
in turn could contribute to an improved understanding of mood disorders (Keefe 1995). More recently, authors emphasised that neuropsychological deficits contribute to the long-term functional outcome of patients with affective disorders. In fact, neuropsychological impairment of depressed patients has been associated with a reduced level of psychosocial and occupational functioning which remained when statistical analyses controlled for further depressive symptoms. This association has also been found among depressed patients in remission with persistent neuropsychological impairment (Baune et al. 2010; Jaeger et al. 2006; Martinez-Aran et al. 2007; Martino et al. 2009; Mur et al. 2009; Wingo et al. 2009). The association between neuropsychological dysfunction and psychosocial impairment appears to be more prominent in patients with mood disorders than in patients with schizophrenia (Brissos et al. 2008). Another clinical problem of untreated neuropsychological deficits in depressed patients is that these patients tend to show less compliance with antidepressant treatment (Martinez-Aran et al. 2009). Furthermore, patients with cognitive deficits may show an increased risk for suicide (Westheide et al. 2008). Given the high clinical relevance of neuropsychological deficits, effective neuropsychological treatment strategies are needed. The first interventional studies used treatment strategies that were originally developed for brain damaged patients (Elgamal et al. 2007; Naismith et al. 2010; Trebo et al. 2007). The results raised hope that cognitive deficits in affective disorders are successfully treatable. However, a better understanding of neuropsychological impairment in affective disorders may help to develop specific and more effective treatment programs.

By now, a huge number of studies have investigated neuropsychological performance in depressed patients. Studies using large neuropsychological test batteries document neuropsychological impairment in depressed patients primarily in the areas of attention, executive function, and memory (Beblo and Lautenbacher 2006). In the domain of attention, impairments of selective attention, divided attention, and vigilance have been reported. However, it is still a matter of debate whether depressed patients show cognitive slowing. Christensen et al. (1997) conclude from their meta-analysis that depressed patients show impaired performance on timed tasks, but it remains unclear whether this impairment is due to a slowing of cognitive processing or, alternatively, has to be regarded as a consequence of the increased rumination that is regularly reported among patients with depression. It has also been suggested that patients with MDD primarily show deficits in “effortful tasks” (Porter et al. 2007). As compared to automatic processing effortful processing requires increased attentional and executive resources (Hasher and Zacks 1979). However, results have been controversial (Christensen et al. 1997; Degl’Innocenti and Bäckman 1999; Den Hartog et al. 2003; Hammar et al. 2011).

Reduced executive functioning has been consistently reported in depression, with deficits particularly evident in the domains of cognitive flexibility and verbal fluency. With respect to word fluency, research shows that category naming (e.g. animals) is more heavily affected than letter fluency (e.g. words beginning with the letter “S”; Henry and Crawford 2005). Reduced cognitive flexibility has also been found to contribute to impaired decision-making processes (Cella et al. 2009) and to be closely related to impaired empathy (Shamay-Tsoory et al. 2009). In addition to deficits in cognitive flexibility, several studies have reported deficits in complex executive functions such as working memory, cognitive planning, problem-solving, and conceptualisation (Beblo and Lautenbacher 2006).

An additional domain of impaired cognitive function in depression is related to explicit memory function. These impairments do not only affect the reproduction of learned items since a reduced specificity of autobiographical memories, known as general autobiographical memories, has also been reported (Hermans et al. 2008). There have been several attempts to explain memory deficits as a result of impaired attention or impaired effortful processing; however, the general view is that memory deficits go beyond attention dysfunction. Furthermore, it remains somewhat unclear in the current research as to whether dysfunction of implicit memory and short-term memory form part of an impaired neuropsychological profile in depression. In addition to the already reported reduced abilities in attention, executive function and memory, studies have shown visuospatial deficits in depression; however, several researchers have suggested that these findings are less definite (Austin et al. 1992; Pälsson et al. 2000).

Estimations of the degree of cognitive impairments in depression indicate a statistically moderate magnitude of cognitive impairment. In a meta-analysis by Christensen et al. (1997), a deficit in cognitive function of, on average, −0.63 standard deviations below that of healthy controls has been reported in patients with depression. This degree of cognitive impairment in depressed patients is in line with studies from our group (e.g. Beblo et al. 1999, 2010; Lahr et al. 2007), in which we found that the most impaired cognitive performance (flexibility) was more than one standard deviation lower (z −1) than the healthy controls’ performance (Beblo et al. 1999). Gualtieri and Morgan (2008) found that patients with mood disorders may, on average, exhibit mild to moderate neuropsychological impairment. However, they report that 21% of patients with unipolar depression and 30%
of patients with bipolar disorder demonstrate severe and clinically relevant impairment (defined as test performance at least two standard deviations below normative values) in at least two cognitive domains which is only found in 4% of healthy controls.

While a large number of studies have been carried out to investigate neuropsychological deficits in depression, relatively little neuropsychological research has been conducted in mania. Although similar neuropsychological deficits occur in depression and mania (Murphy and Sahakian 2001), other researchers such as Gauggel et al. (Gruber et al. 2007; Rathgeber and Gauggel 2006) and Gunning-Dixon et al. (2008) demonstrated that patients with mania may suffer from more prominent neuropsychological deficits, especially in the area of executive function. Overall, the results of neuropsychological comparisons of manic and depressed patients are inconsistent since some studies also showed that performance of certain neuropsychological functions was worse in depressed patients compared to manic patients. Murphy et al. (1999) compared manic patients with bipolar type I disorder to patients with MDD and healthy controls. In a go/no-go paradigm, depressed patients showed increased reaction latencies when flexibility was required, as opposed to manic patients who showed an overall increase in the number of errors (reduced reaction inhibition) and omissions (impaired attention). Furthermore, both patient groups demonstrated a variety of non-specific neuropsychological deficits. Other studies confirmed prominent inhibition deficits among manic patients (Larson et al. 2005; McGrath et al. 1997).

In summary, neuropsychological studies with depressed and manic patients present heterogeneous results. Some patients demonstrated no or only slight impairment in neuropsychological function whereas other patients showed performances of more than two standard deviations below normative values in a variety of neuropsychological domains such as attention, executive functions, and memory. It is, therefore, not surprising that authors of reviews came to different conclusions. On the basis of a meta-analysis, Veiel (1997) outlined that patients with MDD show diffuse neuropsychological impairments with prominent deficits in cognitive flexibility. Castaneda et al. (2008) came to similar conclusions and suggested primarily executive dysfunctions in depressed patients. By contrast, Zihl and Münzel (2004) suggested that executive dysfunctions in general and impairments in cognitive flexibility in particular were rare in depressed patients. The results of Christensen’s quantitative review (Christensen et al. 1997) showed dominant impairments of depressed patients in the domains of perceptual-auditory tasks, memory and attention/ tracking. Drevets et al. (2008) and Porter et al. (2007) concluded that studies about the neuropsychology of affective disorders have produced discrepant results and Elderkin-Thompson et al. (2004) reasoned that patients with MDD do not exhibit specific neuropsychological impairments.

The heterogeneity of results of original research and the differing conclusions of recent reviews make clear that the attempt to establish a specific neuropsychological characterization of patients with affective disorders has failed. To overcome this failure, different authors (e.g. Beblo and Herrmann 2000; Porter et al. 2007) have suggested a more focused investigation of the relationship between affective disorders and neuropsychology by defining the specific factors that are found to influence cognitive performance. Some authors summarized evidence for the impact of single factors. Balanza-Martinez et al. (2010), for instance, focused on comorbidities and medication of patients with bipolar disorder. They pointed out that their neuropsychological performance is probably worsened by comorbid alcohol dependence, even in the remitted state, and by antipsychotic medication. Schlosser et al. (2011) suggested the hypothalamus–pituitary–adrenal (HPA) axis as an important neurobiological determinant of cognitive impairment in depression. Although many inconsistencies were reported, the authors stated that at least 70% of the studies reviewed indicated an association between excessive baseline secretion of glucocorticoids or reduced negative feedback and impairment in visual/verbal memory, working memory and executive function in patients with MDD. Only very few authors have tried to assemble the most relevant factors that may have an impact on cognitive functioning in patients with affective disorders. Porter et al. (2007) discussed clinical features (severity and diurnal variations, melancholia, patient status, psychosis, uni- vs bipolar depression, comorbidities, medication), age, and gender. In addition, they described factors with possible causal influence on cognitive functioning such as frontal-striatal abnormalities, HPA Axis functioning and hippocampus structure, as well as psychological factors (catastrophic reactions to failure, effortful processing, mood-related attentional bias). However, their review was limited to patients with MDD and some factors that are currently regarded as being of great importance were missing (e.g. rumination).

It is not clear from the research to what extent the consideration of factors that are related to cognitive dysfunctions have improved our knowledge about the neuropsychology of affective disorders. It is the aim of this paper to give an up-to-date review about those factors. We hypothesise that the investigation of these factors has specified the knowledge about the profile and severity of neuropsychological impairments in patients with affective disorders. In addition, we aimed at structuring and discussing the possible relations between these factors and provide implications for future research.
Methods

Pertinent literature search was identified and retrieved searching PubMed and PsycINFO databases covering articles from 1980 to 2011. The following selected keywords were used: “Affective Disorder,” “Depression,” “Mania,” “Neuropsychological,” “Moderator,” “Neurobiology,” “Review” as well as more specific terms such as “subtypes,” “comorbid,” “severity,” “diurnal variation,” “course,” “duration of illness,” “age,” “onset,” “bias,” “motivation,” “rumination,” “failure,” “MRI,” “PET,” “DTI,” “cortisol,” “default mode network,” ”structural brain changes,”  “functional brain abnormalities,” “connectivity,” “neuronal networks,” “medication,” “ECT.” Additional articles were identified by reviewing reference lists of reviews and research articles and, where appropriate, included in the review. These articles were evaluated for inclusion/exclusion according to relevance of specific moderators (diagnostic subtypes, symptom severity, age, psychological factors, medication and ECT, gender, suicidality, education, neurobiological factors) of neuropsychological performance in mood disorders (uni- and bipolar disorders) yielding 208 references finally included in this review.

Results

Clinical and Demographic Factors Being Related to Neuropsychological Performance

Several clinical and demographic factors are found to influence the profile and the severity of neuropsychological deficits of patients with mood disorders. A summary of such factors is presented in Table 1.

Subtypes of Mood Disorders and Co-morbidity

Subtypes The DSM-IV and ICD-10 classification systems of psychiatric disorders provide a system of diagnostic subtypes in order to capture the various differential presentations of mood disorders. It is not surprising that complex mood disorders tend to be associated with more severe neuropsychological deficits. For example, existing research demonstrates that bipolar disorder patients show stronger neuropsychological deficits compared to unipolar depressed patients (Burt et al. 2000). However, results are somewhat inconsistent among the literature as research has also shown that neuropsychological deficits are similar between bipolar and unipolar depressed patients or that differences in neuropsychological functioning rather relate to the profile of neuropsychological deficits (Taylor Tavares et al. 2007). Among bipolar patients, patients with bipolar disorder Type I demonstrated stronger neuropsychological impairment compared to patients with bipolar disorder Type II (Hsiao et al. 2009; Torrent et al. 2006). Along these lines, other studies have shown that patients with MDD have more severe neuropsychological deficits compared to those with dysthymia (e.g. Pálsson et al. 2000). The view that subtypes of depression with additional psychopathological symptoms are associated with poorer neuropsychological functioning, is also supported by research which demonstrates poorer neuropsychological functioning among MDD patients with the melancholic or psychotic sub-types of

### Table 1: Neuropsychological Relevance of Clinical and Demographical Variables for the Neuropsychological Performance of Patients with Affective Disorders

<table>
<thead>
<tr>
<th>Variables</th>
<th>Neuropsychological relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM IV subtypes</td>
<td>Deficits:</td>
</tr>
<tr>
<td></td>
<td>Bipolar &gt; unipolar</td>
</tr>
<tr>
<td></td>
<td>Bipolar I &gt; bipolar II</td>
</tr>
<tr>
<td></td>
<td>Major depression &gt; dysthymia</td>
</tr>
<tr>
<td></td>
<td>Melancholia &gt; no melancholia</td>
</tr>
<tr>
<td></td>
<td>Psychotic symptoms &gt; no psychotic symptoms</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>With additional alcohol abuse or anxiety more deficits than without</td>
</tr>
<tr>
<td></td>
<td>Borderline personality disorder, cannabis use: possibly irrelevant, attention-deficit hyperactivity disorder: possibly relevant</td>
</tr>
<tr>
<td>Severity/diurnal swings</td>
<td>More deficits in the morning, rather low associations between deficits and severity of a certain sub-type of the disorder</td>
</tr>
<tr>
<td>Course</td>
<td>Less deficits with remission but probably no complete recovery</td>
</tr>
<tr>
<td>Duration of disorder</td>
<td>More deficits with the duration and number of episodes and duration of hospitalization</td>
</tr>
<tr>
<td>Age</td>
<td>More deficits with increasing age</td>
</tr>
<tr>
<td>Onset</td>
<td>More deficits with late-onset than early-onset</td>
</tr>
<tr>
<td>Biased Processing</td>
<td>Depression: attentional and memory deficits with items of neutral or positive valence</td>
</tr>
<tr>
<td></td>
<td>Mania: possibly deficits with items of neutral or negative valence</td>
</tr>
<tr>
<td>Rumination</td>
<td>Negative impact</td>
</tr>
<tr>
<td>Experience of Failure</td>
<td>Negative impact</td>
</tr>
<tr>
<td>Motivation, Sleep, Education, Gender, Suicidal Tendencies, Attitude toward Computers, Traumatization, Personality</td>
<td>Possibly relevant</td>
</tr>
</tbody>
</table>
depression compared to patients with MDD without these sub-type specifiers (Fleming et al. 2004; Martinez-Aran et al. 2008; Michopoulos et al. 2008; Schatzberg et al. 2000). Withall et al. (2010) found for patients with melancholic compared to patients with non-melancholic subtypes of MDD not only poorer performance but also a longer time for neuropsychological recovery.

**Comorbidity** This field of research generally indicates that co-morbid psychiatric disorders which have the ability to impair neuropsychological performance have an additional negative impact on neuropsychological functioning in depressed patients (Baune et al. 2009). Unipolar depression with a co-morbid anxiety disorder seems to be associated with additional neuropsychological impairment compared to depression without co-morbidity (Basso et al. 2007; DeLuca et al. 2005). Likewise, patients with bipolar depression and comorbid alcohol abuse or dependency show increased neuropsychological impairments (Balanza-Martinez et al. 2010). A study by Levy et al. (2008) indicated that not only bipolar patients with current alcohol dependence were more impaired than bipolar patients without alcoholism but also that bipolar patients in full remission from alcohol dependence displayed increased cognitive deficits. Sanchez-Moreno et al. (2009) found preliminarily inhibition deficits among euthymic bipolar patients with a history of alcoholism. The significance of alcoholism for the presentation of neuropsychological deficits even seems to outperform the significance of the affective disorder. Studies with patients who suffer from alcoholism with or without comorbidity depression showed that cognitive deficits of patients with alcoholism are not exacerbated by comorbid depression (Rosenbloom et al. 2005; Uekermann et al. 2003). Cannabis abuse may also contribute to neuropsychological dysfunctions in bipolar patients (Cahill et al. 2006), however, recent studies (Ringen et al. 2010; Secora et al. 2010) suggested no additional impairment associated with cannabis use in patients with bipolar disorder. Ringen et al. found in bipolar patients that cannabis abuse was related even to improved performance whereas the opposite was found for schizophrenic patients.

In a recent study, we compared patients with MDD with and without comorbid Borderline Personality Disorder (BPD; Beblo et al. 2011), patients with BPD only, and healthy control subjects. The patient groups showed only very little neuropsychological impairments and impairments did not add up in patients with both disorders. Likewise, Fertuck et al. (2006) failed to find additional neuropsychological impairments in MDD patients with comorbid BPD indicating that BPD might not be relevant for neuropsychological deficits in patients with affective disorders. Affective Disorders also often co-occur with attention-deficit hyperactivity disorder (ADHD) in children and adolescents. In a study of Rucklidge (2006), adolescents with bipolar disorder only, showed no serious neuropsychological impairments. By contrast, those with comorbid ADHD were particularly impaired in verbal memory and inhibition. In a similar sample, Gunther et al. (2011) found depressed patients with comorbid ADHD to perform worse in a few attentional measures as compared to patients with depression only. By contrast, patients with ADHD and depression did not perform worse than patients with ADHD only. However, the authors stated that the differences between the clinical groups were relatively small.

Taken together, affective disorders that imply additional symptoms as compared to affective disorders without these extra symptoms are associated with more severe neuropsychological deficits. Some psychiatric comorbidities such as alcoholism, anxiety disorders, and probably ADHD contribute to neuropsychological deficits in affective disorders whereas others, e.g. Borderline Personality Disorder or cannabis use, may have no or only little additional impact on cognitive functioning.

**Severity, Diurnal Swings, Course, and Duration of Illness**

While a meta-analysis by McDermott and Ebmeier (2009) concludes that some neuropsychological functions such as executive function, cognitive processing speed, and episodic memory are associated with the severity of the affective disorder, it generally appears that the severity of a certain sub-type of the disorder does not correlate strongly with neuropsychological test performance (Beblo and Lautenbacher 2006).

Some types of depression, such as melancholic subtype of MDD, are characterised by diurnal swings, with symptoms of depression reportedly worse in the morning compared to the evening. Research investigating neuropsychological function in these patients demonstrates neuropsychological profiles which reflect this diurnal pattern of depressive symptoms with poorer neuropsychological performance in the mornings compared to the evenings (Moffoot et al. 1994; Porterfield et al. 1997).

The reversibility of neuropsychological impairment among patients has been investigated in patients with euthymia (e.g. Clark et al. 2005) and prospective studies (e.g. Reppermund et al. 2009). During the course of an acute episode of depression, it has been reported that cognitive deficits improve with remission of the disorder, most likely among young patients (Savard et al. 1980; for review see Beblo and Lautenbacher 2006; Douglas and Porter 2009). However, these neuropsychological deficits commonly do not reverse completely and are, therefore, not
only regarded as a state but also as a trait-marker of the affective disorder. Although a clear profile of neuropsychological deficits of residual symptoms have not been clearly identified, some authors such as Douglas and Porter (2009) regard attention and complex executive functions as trait-markers of MDD. Several reasons have been discussed for persistent cognitive deficits. On the one hand, it has been suggested that neuropsychological deficits form part of residual symptoms of depression or part of a sub-threshold depression. On the other hand, some studies indicate that neuropsychological impairments may sum up over the course of the disorder. Gorwood et al. (2008) showed in a large sample of 8,229 MDD patients that memory performance diminished by 2–3% per previous episode of depression (calculated up to four episodes). Van Gorp et al. (1998) found in bipolar patients that lifetime months of mania and depression were negatively correlated with performance in verbal memory and several executive functions. Correlations between the duration of hospitalisation and severity of neuropsychological deficits support these findings (Christensen et al. 1997). Gorwood et al. (2008) conclude from their findings that neurotoxic effects on the hippocampus coming from stress and depression are responsible for diminished neuropsychological performance which is exacerbated with increasing numbers of depressive episodes. Their results and conclusions are also in agreement with the “kindling hypothesis” (Post 1992). This hypothesis suggests that depressive episodes become progressively independent of external triggers due to neurobiological changes as a consequence of repeated previous stressors and repeated previous episodes. However, Gorwood’s findings could also interpreted in a way that a longer history of depression indicates a more severe type of depression with more prominent cognitive deficits and more pronounced neurobiological abnormalities (please also see below “Structural Abnormalities and Cortisol”). In addition, Delaloye et al. (2010) found no cognitive deficits in a group of elderly euthymic depressed patients with early-onset. Duration of illness was neither related to brain abnormalities nor to neuropsychological performance. The authors speculate that not depression itself but associated factors such as comorbid substance abuse may lead to neurotoxic effects and to a progressive decline of neuropsychological functioning in the course of the disorder.

To sum up, while the subtype of affective disorder is correlated with cognitive deficits, these deficits are, surprisingly, not clearly associated with symptom severity of a certain sub-type of the disorder. However, deficits are related to diurnal swings with better performances of the patients in the evening, and the course of the affective disorder. Cognitive impairments improve with remission but some impairments may remain.

Age and Onset

Neuropsychological deficits associated with depression are observed predominantly in elderly patients (Beblo and Lautenbacher 2006; Christensen et al. 1997). Although these findings have been reported several times, it is unclear which domains of neuropsychological functions are primarily impaired. Porter et al. (2007) suggested a stronger impairment of executive function in elderly patients. By contrast, Thomas et al. (2009) reported memory deficits primarily in elderly, MDD patients, and Castaneda et al. (2008) reported executive function impairment primarily in younger MDD patients.

Some studies showed that age of onset might be an additional factor that influences neuropsychological performance of elderly, depressed patients. The common point of view suggests structural brain abnormalities and associated cognitive deficits in patients with late-onset depression as compared to those with early-onset depression (Drevets et al. 2008; Laks and Engelhardt 2010). These onset-related deficits were found in memory functions (Delaloye et al. 2010; Dillon et al. 2009) as well as in executive functions and attention (Rapp et al. 2005). However, compared to patients with late-onset depression, Rapp et al. found increased memory problems in patients with recurring early-onset MDD.

There are several possible explanations for these findings. It has been speculated that late-onset geriatric depression presents a distinct type of affective disorders. Known risk factors for affective disorders such as personality abnormalities, a family history of psychiatric illness and dysfunctional past maternal relationships were found to be less relevant in late-onset MDD (Brodaty et al. 2001) whereas organic factors such as cerebrovascular disease and associated structural brain abnormalities are more prominent (Laks and Engelhardt 2010). However, structural brain abnormalities were also found in patients with early-onset depression. Hickie et al. (2005) and Ballmaier et al. (2008), for instance, reported hippocampal damage also for patients with early-onset depression—although to a smaller extend than in patients with late onset.

Alternatively, elderly patients with depression may suffer from more prominent cognitive deficits as part of a masked, undetected, early stage of dementia (Gaultieri and Johnson 2008). In fact, the risk of developing a senile dementia of the Alzheimer’s type is increased in patients with depression. Several factors which may contribute to this increased risk have been discussed. On the one hand, depressive disorders can be regarded as an early symptom of Alzheimer’s disease but on the other hand, neurobiological changes related to depressive disorders may increase the risk of Alzheimer’s disease. Neuroendocrino-
logical research has shown changes of the hypothalamic–pituitary-adrenal axis (HPA axis) in depressed patients as being associated with neurotoxic effects, especially in the hippocampus (Paizanis et al. 2007), predisposing to the development of Alzheimer’s disease (Sotiropoulos et al. 2008). Furthermore, physical and mental activity is protective against Alzheimer’s disease, most likely through the effect of an enhanced neuronal reserve based on increased neurogenesis (Elder et al. 2006; Mirochnic et al. 2009). This neuroprotective factor might not take effect in depression due to psychomotor-retardation.

In summary, older patients with affective disorders show more severe cognitive impairments than younger patients, especially those with late-onset depression. It is a still matter of debate which functions are primarily affected. In addition, possible mechanisms are still controversially discussed.

Psychological Factors: Biased Processing of Emotional Information, Motivation, Rumination, Response to Failure

**Biased Processing** Cognitive models of depression such as the model of Beck (1967) suggest that depressed patients show biased processing of emotional information favouring negative contents. Except for evidence from cognitive and clinical psychology, these assumptions were also confirmed by neuropsychological research. However, although many studies found a processing bias in the domains of perception/attention and memory, there were also conflicting results.

In a recent review, Gotlib and Joormann (2010) infer from the current literature that an attentional bias for negative information may primarily be evident in later stages of attentional processing. That is, depressed patients show problems to disengage from negative information but do not necessarily automatically orient their attention toward negative stimuli. Rinck and Becker (2005) showed that MDD patients were more easily distracted by negative words but did not detect negative words more easily in a visual search task. However, the authors explain these findings with methodological characteristics. Apart from attentional bias toward negative information, Leppanen (2006) summarized evidence for an attentional bias away from positive emotional stimuli.

Since memory performance depends on attention, it is not surprising that depressed patients may also exhibit an enhanced memory for emotionally negative material. Indeed, Koster et al. (2010) found that dysphoric subjects showed an attention bias for negative words, with the attention bias for negative words predicting free recall of negative words. Similar to the findings for attentional performance, however, a memory bias for negative information has not been found consistently in patients with depression. It has been speculated that the bias is more evident for explicit as compared to implicit memory (Colombel 2007; Gotlib and Joormann 2010). More generally, Gotlib and Joormann suggest the memory bias to be dependent on the elaboration of the stimuli that have to be studied, that is, memory bias may only occur with deeper processing. However, results may also be related to other factors. In a group of severely depressed MDD patients, Ellwart et al. (2003) found a memory bias for implicit memory but not for explicit memory performance. The authors speculated that results may depend on the severity of depression with severely impaired patients activating depression related information automatically without effortful processes.

While depressed patients process negative information more easily, manic patients show a processing bias toward positive information (Chamberlain and Sahakian 2006). In a study of Murphy et al. (1999) for instance, depressed patients had delayed responses for positive stimuli whereas manic patients had delayed responses for negative stimuli. However, since there are only a few studies with manic patients, more detailed conclusions about the attentional bias in manic patients appear to be premature.

**Motivation** Patients with depression very often report diminished drive and motivation which sometimes leads to the statement in the literature that neuropsychological deficits observed in patients with depression are partly due to reduced motivation. Contrary to this assumption, it has been observed that patients with depression are well motivated during neuropsychological testing. Moreover, patients put themselves under pressure and wish to meet the expectations of the neuropsychologist during neuropsychological testing. Based on these observations, reduced motivation and decreased neuropsychological functions are inconsistently associated in unipolar depression (Richards and Ruff 1989; Scheurich et al. 2008). However, motivational deficits seem to be more relevant for cognitive function for day-to-day tasks rather than in an artificial neuropsychological testing environment (Lahr et al. 2007). More research is clearly needed to estimate the impact of motivation on cognitive performance in depressed patients.

**Rumination** Rumination is a repetitive pattern of thoughts focussing on dysphoric symptoms, their causes and consequences. Rumination maintains and increases low mood in non-clinical samples and is related to the onset, severity and chronicity of depression (Donaldson and Lam 2004). Apart from its destructive potential for emotional processing, recently it became clearer that rumination also affects further cognitive processing by attracting attention (Donaldson et al. 2007). Indeed, several studies confirm that rumination has a negative impact on cognitive function, particularly on the specificity of the autobio-
graphic memory (Crane et al. 2007; Debeer et al. 2009; Raes et al. 2008), inhibition (Philippot and Brutoux 2008), cognitive flexibility (Watkins and Brown 2002), problem-solving (Donaldson and Lam 2004), working memory (Joormann and Gotlib 2008) and attention bias towards negative content (Donaldson et al. 2007).

Response to Failure

Relative to healthy subjects, MDD patients are more likely to fail in neuropsychological tasks if they failed in the precedent task. This effect may primarily be relevant for response accuracy but not for response latency (Elliott et al. 1996). It has been speculated that perceived failure trigger “ruminative” thoughts about failure which interfere with task performance or, alternatively, impair motivation (Beats et al. 1996; Elliott et al. 1996). However, in a consequent study Elliott et al. (1997b) demonstrated that depressed patients’ performance did not decreased following failure but it did not improve. By contrast, healthy subjects were able to improve their performance after having failed. Results of a recent study by Douglas et al. (2009) indicated that depressed patients may improve their performance after failure as well—but to a lesser extent than healthy participants. Furthermore, depressed patients’ reaction to failure may depend on the accuracy of feedback: In a study of Murphy et al. (2003) patients with depression showed normal performance when negative feedback is accurate and informative but an impaired performance when reinforcement contingencies are misleading or ambiguous.

Taken together, there is evidence for biased information processing in patients with depression and mania. However, for depression an attentional bias for negative stimuli is primarily detectable for later stages of processing. In addition, depressed patients recall negative information more easily than neutral or positive information. This bias may increase with the conscious elaboration of the material. It is still a matter of debate whether motivational deficits account for neuropsychological deficits in depression. By contrast, there is clear evidence that rumination impairs performance in different neuropsychological domains. There are also congruent results pertaining to an impaired performance after failing the preceding task relative to healthy controls. Rumination and motivational deficits were primarily discussed as possible mechanisms behind these findings.

Additional Factors

Some studies found an association between suicidality and impaired executive function in unipolar depressed patients (Dombrovski et al. 2008; Westheide et al. 2008). This finding has implications for the prevention of suicide attempts, although inconsistent results across studies remain (Roskar et al. 2007). Sleep disturbances often reported by patients with mood disorders have been suggested to account for neuropsychological deficits as reduced sleep is known to negatively affect cognitive performance (Goder et al. 2007; Naismith et al. 2009). Furthermore, Savitz et al. (2008) found a negative impact of early emotional and sexual trauma on cognitive performance in patients with bipolar disorders. This finding is in line with the study by Vythilingam et al. (2002) who reported a reduced hippocampus volume only in traumatised, MDD patients.

Other factors such as education and gender have also been shown to be associated with neuropsychological functioning in patients with mood disorders (Barrett et al. 2008). Depressed patients with lower levels of education tend to perform disproportionately worse in neuropsychological testing compared to education matched control subjects (Avila et al. 2009). It has been speculated that patients with higher levels of education are in a better position to compensate for depression-associated neuropsychological dysfunction. The relation between gender and neuropsychological performance may be moderated by personality traits. Van den Heuvel et al. (1996) found in elderly women that depression was related to cognitive dysfunction primarily in women with a weak internal locus of control. In men, the association between depression and cognitive dysfunction was moderated by neuroticism. The authors concluded that low neuroticism or high internal locus of control act as protective factors against depressive reactions when experiencing cognitive dysfunction.

Furthermore, variables related to computer-based tasks have been identified to impact neuropsychological function. Among a sample of depressed patients, Weber et al. (2002) found that a negative attitude towards computers was related to an increased level of nervousness, as well as a reduced level of neuropsychological performance when using computer-based attention tasks. Such a finding, if confirmed, would implicate the (at least additional) use of paper-pencil test for assessing depressed patients.

In sum, apart from the above described clinical and demographic factors, there are more variables that may influence the relation between affective disorders and neuropsychological performance. However, given the small number of related studies, it is too early to draw definite conclusions. Nevertheless, first results demonstrate the complexity of the neuropsychology of affective disorders.

Neurobiological Factors Being Related to Neuropsychological Performance

Alterations of Brain Structure and Function

It is undisputed that psychological processes, including cognitive function, have a neuronal representation. Several
Structural and functional alterations in patients with mood disorders have been documented. In some of these studies, structural and functional changes were related to neuropsychological impairments. Given the relatively unspecific neuropsychological deficit profile of patients with mood disorders, it is not surprising that the research findings on neuronal alterations have also been heterogeneous and somewhat non-specific so far.

Few studies have reviewed the similarities and variations between unipolar and bipolar mood disorder in relation to cognitive dysfunction and their neurobiological correlates. The literature suggests that mood disorders may share common cognitive impairments in areas such as executive function, memory, attention, and social perception as well as common biological features primarily relating to lack of development or atrophy in the prefrontal cortex (Marvel and Paradiso 2004; Melcher et al. 2008; Strakowski et al. 2002). Further, these PFC abnormalities appear to lead to a loss of capacity to modulate the limbic system resulting in either emotional cycling (BD) or depression (UD) depending upon the subcortical abnormalities uniquely present to each disorder (Strakowski et al. 2002). The neurobiological differences between unipolar and bipolar depression associated with cognitive function are shown in Table 2.

**Structural Abnormalities and Cortisol** Apart from elderly patients with a late-onset of depression and patients suffering from depression with psychotic symptoms (for review see Drevets et al. 2008; Lorenzetti et al. 2009), global structural abnormalities such as cerebral atrophy are not typical of mood disorders. Atrophy is reported to be present in the prefrontal cortex (PFC), the cingular cortex with prominent changes in the left subgenual cingular cortex (Drevets et al. 1997), the temporal cortex, and the basal ganglia. Within the PFC, the orbital, medial, and dorsolateral parts are affected. In addition to grey matter changes, white matter damage has also been documented (Drevets et al. 2008). Among patients with bipolar disorder, the posterior cingular cortex also shows a reduced volume (Drevets et al. 2008). Several studies which investigated the temporal cortex with particular focus on the hippocampal volume, demonstrated atrophy in this brain structure. Investigations into the volume of the amygdala show inconsistent findings; atrophy as well as increased amygdala volumes, particularly among patients with bipolar disorder have been reported (Davidson et al. 2002). In addition to findings which demonstrate atrophy within the basal ganglia (Baumann et al. 1999), other research has also demonstrated increased volume of the basal ganglia among patients with bipolar disorder (Marchand and Yurgelun-Todd 2010). Some of the inconsistencies among these findings might also be related to a number of other factors such as gender, and severity and duration of the mood disorder (Lorenzetti et al. 2009).

Several biological mechanisms may contribute to these structural abnormalities in mood disorders. One area of interest relates to the glucocorticoid receptors which are rich in the hippocampus. It is suggested from experimental research in highly stressed animals that cortisol can damage the hippocampus (Sapolsky 1996). Since pathological abnormalities of the hypothalamic-pituitary-adrenal axis (HPA) in conjunction with an increased excretion of cortisol in depression have been described, the abnormalities of the HPA axis following stress may lead, or at least contribute, to the structural changes such as those evident in the hippocampus. In support of these findings are previous studies which have established an association between duration of the mood disorder/numbers of episodes (McKinnon et al. 2009; Sheline et al. 1996) and early traumatisation (Vythilingam et al. 2002), respectively, and the degree of hippocampal damage. In addition, the effect of stress on the hippocampus appears to be modulated by genetic factors (Fred et al. 2008). On the other hand, it should be considered that the structural abnormalities represent a vulnerability factor for the development of mood disorders and hypercortisolism (Lorenzetti et al. 2009). Another important finding from the past few years is the observation that the human hippocampus has the ability to generate new neurons over the whole life span (Paizanis et al. 2007) with research suggesting that physical and mental activity (Mirochnic et al. 2009) and certain drugs (Wang et al. 2008) may stimulate this process. This is of importance since mood disorders may counteract this life-long process (Becker et al. 2009).

Associations between neuropsychological performance, cortisol and hippocampus volume are highly complex and additionally complicated in mood disorders (Schlosser et al. 2011). Although the results are not fully conclusive at this stage, a study by O’Brien et al. (2004) indicates that cognitive deficits in depressed patients are most likely associated with a decreased volume of the hippocampus, rather than with the secretion of cortisol. However, there is a paucity of research that has explored the structural neurobiology-cognitive impairment relationship. Table 2 shows the structure-cognition findings that are robust however, this evidence is primarily from earlier studies and, in light of the existing inconclusive data as well as improved assessment and imaging technologies, warrant renewed investigation. The findings indicate that structural abnormalities that relate to cognitive function are besides of the hippocampus—primarily found in the dorsolateral prefrontal cortex (DLPFC). This is consistent with what could be expected given the putative functions of these regions and the impaired cognitive outcomes with which they are associated, namely executive function, attention/
<table>
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<tr>
<th>Cognitive domains</th>
<th>Structural abnormalities</th>
<th>Functional abnormalities</th>
<th>Common in unipolar and bipolar depression</th>
<th>Exclusive in unipolar depression</th>
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<th>Common in unipolar and bipolar depression</th>
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<td></td>
<td>LV: ↑v (Hartberg et al. 2011)</td>
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<td>EntC: ↓v (Furtado et al. 2008; Marvel and Paradiso 2004; Benes et al. 1998)</td>
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<td>Left OFC: ↓a (Kronhaus et al. 2006)</td>
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<td>Attention/working memory</td>
<td>DLPFC: ↓v (Marvel and Paradiso 2004)</td>
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<td>Social cognition</td>
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<td>IFG: ↑a (Chen et al. 2011)</td>
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<td>Amygdala: ↑a (Almeida et al. 2010; Chen et al. 2011; Siegle et al. 2002; Ebmeier et al. 2006)</td>
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<td>Lingual gyrus: ↓a (Chen et al. 2011)</td>
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| LH of VPFC: ↑a (Blumberg et al. 2003; Melcher et al. 2008) |
| VMPFC: ↑a (Ebmeier et al. 2006; Rose et al. 2006) |
| TL: ↓a (Strakowski et al. 2002; Melcher et al. 2008) |
| Cerebellum: ↓a (Strakowski et al. 2002; Melcher et al. 2008) |
| Putamen: ↓a (Strakowski et al. 2002; Melcher et al. 2008) |
| Left OFC: ↑a (Kronhaus et al. 2006) |
| Medial TL: ↑a (Chen et al. 2011) |
| Putamen: ↑a (Chen et al. 2011) |
| Pallidum: ↑a (Chen et al. 2011) |
| HC: ↑a (Chen et al. 2011; Whalley et al. 2009) |
| PCC: ↓a (Chen et al. 2011; Chen et al. 2010) |
| OFC: ↑a (Chen et al. 2011; Chen et al. 2010; Bermpohl et al. 2010) |

↑ increased; ↓ reduced; ↑a hyperactivation; ↓a hypoactivation; ↑v increased volume; ↓v decreased volume; ACC anterior cingulate cortex; bf blood flow; dens density; DLPFC dorsolateral prefrontal cortex; EntC entorhinal cortex; ESVA extrastriate visual areas; HC hippocampus; IFG inferior frontal cortex; LV left ventricle; MPFC medial prefrontal cortex, none no findings exclusive to unipolar and bipolar disorder in relation to specific cognitive domains; OFC orbitofrontal cortex; PCC posterior cingulate cortex; PHC parahippocampal; RVPFC rostroventral prefrontal cortex; TL temporal lobes; VMPFC ventromedial prefrontal cortex; vol volume; VPFC ventral prefrontal cortex
working memory, and declarative memory. Furthermore, some correlational studies demonstrated associations between neuropsychological deficits and structural abnormalities of the orbital frontal cortex (Taylor et al. 2003) left cingulate cortex (Yuan et al. 2008), and the basal ganglia (Naismith et al. 2002) as well as white matter lesions (Hickie et al. 2007) in patients with MDD.

Taken together, relations between neuropsychological deficits and structural brain abnormalities in affective disorders are complex and further related to other factors such as cortisol. Furthermore, etiological mechanisms are controversially discussed. Structural damage was interpreted as both, consequence and cause of the affective disorder.

**Functional Abnormalities** In several functional studies, researchers assessed the association between neuronal activation and neuropsychological function. Overall, previous findings are somewhat inconsistent (Rogers et al. 2004). In a positron emission tomography (PET) emission study, Elliott et al. (1997a) investigated patients with unipolar depression while performing the Tower of Hanoi task. In comparison to healthy controls, patients with depression demonstrated reduced planning abilities, as well as reduced activation of the prefrontal cortex and the striatum. On the contrary, Bremner et al. (2004) reported a reduced activity of the right hippocampus and ACC during a learning task; however, the MDD patients showed no learning deficits. Moreover, Videbech et al. (2003) demonstrated reduced cognitive performance in MDD patients completing a word fluency task; however, these patients showed no abnormalities in brain activation. Finally, Barch et al. (2003) found that patients with MDD had neither performance deficits in a working memory task nor an abnormal activation of the PFC.

Several studies indicate that patients with mood disorders compared to healthy controls show an increased activation while performing cognitive tasks. Fitzgerald et al. (2008) and Harvey et al. (2005) found no cognitive deficits in a working memory task (“n-back”) in MDD patients, while they showed a stronger activation of the prefrontal cortex and the ACC compared to healthy controls. The authors interpret this brain activation as a compensatory mechanism of additional brain regions. Wagner et al. (2008) were able to show in their case control study that healthy subjects demonstrated a deactivation of the rostral ACC in the classical colours Stroop paradigm relative to patients with unipolar depression. The authors interpreted these findings to suggest that brain activity which was irrelevant to the neuropsychological task was suppressed. In a functional magnetic resonance imaging (fMRI) study, Mitterschiffthaler et al. (2008) investigated the activation pattern of the rostral ACC during the processing of emotionally relevant information in MDD patients. Using the emotional Stroop test, depressed patients took longer to identify the colour of negative items. An increased attentional bias towards emotionally negative stimuli was associated with a hyper-activation of the rostral ACC. From these findings, the authors suggest that that a strong activation of the rostral ACC might hinder effective task processing of emotionally relevant information.

Connectivity analysis using MRI is a research tool which has been used more frequently in the past few years. Connectivity analysis measures the correlation of activation patterns between different brain regions and provides important information on abnormalities of neuronal networks in patients with mood disorders. Research using this research tool has demonstrated findings which support the notion that neuronal networks correlate more closely with symptoms of depression than single brain structures. The attentional bias has often been associated with the activation of the amygdala when patients were exposed to emotional and anxiety-related stimuli in particular (Drevets et al. 2008). Beyond these findings, Hamilton and Gotlib (2008) were able to show that patients with MDD demonstrated a stronger connectivity between the amygdala and hippocampus/basal ganglia during processes of encoding emotionally negative pictures. Frodl et al. (2010) investigated the attentional bias in a face-recognition task using connectivity analysis. The authors demonstrated increased as well as decreased connectivity between various brain regions and concluded that the increased connectivity between the DLPFC and the orbital frontal cortex could serve as a neuronal correlate of the attentional bias towards negative stimuli of MDD patients.

In this research context, the concept of default mode networks (DMN; Raichle et al. 2001) has gained more importance in the recent past. The DMN is regarded as a network of brain structures that reflects self-referential processes that are deactivated during non self-referential goal-oriented tasks (Brody et al. 2009; Sheline et al. 2009). Sheline et al. investigated the DMN of emotional modulation in patients with MDD and healthy subjects. Watching negative compared to neutral pictures, depressed patients showed reduced deactivation in widespread areas of the DMN such as the anterior cingulate cortex, ventromedial cortex, lateral temporal and lateral parietal cortex. The authors also found an increased activation of amygdala, parahippocampus, hippocampus and dorsal medial prefrontal cortex. Similar patterns were found for reappraising the pictures indicating that changes of DMN activation occur for automatic and active emotion regulation. The authors conclude that these DMN changes may reflect ruminative processes in depression. Bluem et al. (2009) reported
abnormalities of the DMN in a resting state in depressed patients in that there was a reduced connectivity between the precuneus/posterior cingulate cortex and the basal ganglia, whereas the connectivity between emotionally relevant brain structures in another study reported by Greicius et al. (2007) was increased. These authors found an increased integration of the subgenual ACC in the DMN activity and they therefore suggested that the DMN is altered in MDD.

Regarding the distinction between uni- and bipolar depression some particularities have to be mentioned (for details see Table 2). While unipolar depression is characterised by more diffuse hypofrontal activation and localised limbic hyperactivation (Almeida et al. 2010; Furtado et al. 2008; Marvel and Paradiso 2004; Melcher et al. 2008; Siegle et al. 2002; Wagner et al. 2006) neurobiology in bipolar depression appears to be associated with cognitive impairment that can be surmised functionally as involving localised hypoactivation of frontal regions and a more widely distributed hyperactivation of the limbic structures (Chen et al. 2011). This supports the existing models of bipolar disorder which suggests that emotion dysregulation and executive functions are associated with impulse control and performance monitoring features (Green et al. 2007; Phillips et al. 2008). The cognitive outcomes converge in the limbic-cortical dysregulation created in both neurobiological profiles. This dysregulation results in the simultaneous activation or deactivation of otherwise synchronised regions resulting in reduced capacity for information processing and behaviour formation through functional deficits in regions responsible for the cognitive and affective interactions between evaluation, regulation, and inhibition.

There is increasing evidence that elements of the functional neurobiology of both conditions is trait-based and therefore independent of mood-state (Blumberg et al. 2003; Chen et al. 2011; Kronhaus et al. 2006; Melcher et al. 2008; Wagner et al. 2006). However, the cognitive deficits in both conditions have been largely correlated with symptom severity and therefore might be state-dependent as well (Chen et al. 2011; Marvel and Paradiso 2004; Melcher et al. 2008). There is a paucity of research that has sufficiently controlled for symptomatic state-specific performance and further investigation is required to identify state-independent cognition-biology correlations in order to identify those factors that may be more closely related to pathophysiology rather than mood-state.

In sum, patients with affective disorders show both, increases and decreases of neuronal activation while performing neuropsychological tasks. Bipolar patients as compared to patients with unipolar depression may show more widely distributed hyperactivation of limbic structures. Hypoactivation is regarded as insufficient recruitment of neuronal networks. By contrast, hyperactivation is interpreted as compensatory mechanism or, alternatively, as reduced deactivation of DMN structures. Connectivity analyses further support the notion that neuropsychological abnormalities are more closely related to neuronal networks than single brain structures.

**Neuropsychological Dysfunction and Neurobiological Models of Depression**

The aforementioned structural and functional alterations relevant to neuropsychological function in depression should be interpreted in the context of neurobiological models of depression which suggest the involvement of abnormal neuronal networks. Over the past few years, several empirically supported neurobiological models of mood disorders have been developed. According to Mayberg’s Model (Mayberg 1997) primarily developed on findings with MDD patients, alterations of the rostral ACC play an important role in the mediation between the ventral and dorsal brain structures. A reduced activation of dorsal brain areas (DLPFC, dorsal ACC, posterior cingular cortex, inferior parietal cortex) possibly underlies neuropsychological dysfunction in depression and an activation of ventral areas (ventral PFC, subgenual ACC, anterior-insular, hypothalamus) probably forms the neuronal basis of vegetative and somatic symptoms of depression. On the basis of previously reported fronto-striatal models of depression (Drevets and Raichle 1992; Swerdlow and Koob 1987) and newer empirical findings, a dysfunctional neuronal network, including a hyperactivated positive feedback loop between the amygdala, medial dorsal thalamus and the medial PFC is postulated (see Fig. 1; Drevets et al. 2008). These authors suggest a reduced inhibiting input of this hyperactivated positive feedback loop in depression through other feedback loops which involve the basal ganglia. As a result, activation patterns of further subcortical structures such as the bed nucleus of the stria terminalis, hypothalamus and the peri-aqueductal grey change, too. Drevets et al. (2008) suggested abnormalities in the Nucleus Basalis of Meynert, with it cholinergic projections, in particular, to be an important basis of neuropsychological deficits in depressed patients.

Collectively, a variety of structural and functional alterations have been associated with neuropsychological impairments of mood disorders and depression in particular. Etiological models of depression involving abnormal brain network functions such as fronto-striatal models of depression (Drevets et al. 2008) integrate those findings and suggest associations with neuropsychological dysfunction in depression.
Antidepressant Medication and Electroconvulsive Therapy (ECT)

Antidepressants modify neurotransmitter systems and cognitive performance. Tricyclic antidepressants (TCAs) inhibit the neurotransmitter acetylcholine and thereby may induce severe cognitive side-effects, potentially leading to a delirium, particularly among elderly patients with depression. On the contrary, selective serotonin reuptake inhibitors (SSRIs) have either no or very mild anticolinergic effects. Most studies have shown that SSRIs have a substantially greater positive effect on cognitive function compared to TCAs (Peretti et al. 2000). It has been speculated that serotonin norepinephrine reuptake inhibitors (SNRIs) may have even greater positive effects on cognitive performance in MDD patients (Herrera-Guzman et al. 2009). Positive effects on cognition have also been described for Mirtazapine (Borkowska et al. 2007), whereas lithium appears to have a diminishing effect on cognitive performance (Wingo et al. 2009). Holmes et al. (2008) found that medicated (with lithium of valproic acid) bipolar patients were cognitively more impaired that non-medicated patients. These impairments were related to attentional performance including an attentional bias away from positive stimuli but the impairments were not related to memory. Balanza-Martinez et al. (2010) refer to several studies that have shown the short-term neurotoxic effects of lithium; however, they also emphasise that the long-term intake of lithium might have neuroprotective effects as well.

Evaluating the effects of medication on cognitive performance should also include the effects of withdrawal of antidepressants which could lead to a decreased cognitive performance (Hindmarch et al. 2000).

Although it has been established that ECT have significant neuropsychological side-effects, memory deficits in particular, these effects may be limited to the first days after treatment. In a recent review, Semkowska and McLoughlin (2010) conclude that in the first 3 days after ECT treatment patients show medium-large deficits in the domains of memory and executive functions. Processing speed, spatial and global cognition showed small subacute effects. During the subsequent 2 weeks, however, neuropsychological deficits resolved. Similarly, Smith et al. (2010) compared memory effects of ECT versus pharmacotherapy (nortriptyline and lithium) in MDD patients and concluded that both treatments have similar (even positive) long-raging effects on memory. However, there are only very few long-term studies that have prospectively investigated the effects of ECT on neuropsychological performance. In a study by Johanson et al. (2005), it was reported that patients still had mild to moderate memory deficits 24 years after ECT treatment, however, they could not be clearly attributed to the ECT treatment. Falconer et al. (2010) found deficits in spatial recognition memory 1 month post treatment in MDD patients.

The effects of ECT on cognitive functioning also depend on other factors. Unilateral ECT may have a lower risk for cognitive side effects than bilateral ECT (O’Connor et al. 2010).
In addition, greater cognitive reserves may protect against adverse effects of ECT on cognition (Legendre et al. 2003). Effects of ECT may also depend on stress hormone levels. In a study of Neylan et al. (2001) elevated basal cortisol levels were associated with a greater decrease of cognitive functioning after ECT in MDD patients.

Taken together, psychotropic medication and ECT influence the neuropsychological performance of patients with affective disorder. Positive and negative effects have been described depending on additional factors such as the specific type of antidepressants, type of ECT, cognitive reserves and cortisol levels. Furthermore, short-term effects have to be separated from long-term effects.

Discussion

In agreement with our expectations, we found clinical, demographic and neurobiological factors to be associated with the severity of neuropsychological impairments in patients with affective disorders. In particular, patients with more severe diagnoses, some comorbid mental disorders such as alcohol abuse, anxiety disorders, and possibly ADHD, higher age, and late onset, psychological processes such as rumination and processing bias, and potentially, sleep disturbances, lower education, suicidal tendencies, traumatization, and negative attitude toward computers (only computer tasks) are more severely impaired. Some factors such as gender and personality may interact with these factors. In addition, changes of brain structure and function, neuroendocrinological and neurochemical deviations are associated with neuropsychological impairments in affective disorders. Antidepressant anticholinergic medication and ECT treatment (rather short-lasting effects) are relevant external neurobiological factors with potentially destructive effects on cognition. Most studies included depressed patients. For patients in the manic state too few studies have been conducted for definite conclusions about relevant factors that influence the neuropsychological outcome.

Behaviourally, both factors that are directly related to the disorder (subtype and single symptoms) as well as independent factors (“moderators”) contribute to the neuropsychological performance (Fig. 2). Since neurobiological factors represent a different level of consideration, it is hard to say whether those factors (with the exception of medication and ECT) have to be regarded as correlates of the affective disorder, clinical and demographic factors, the neuropsychological performance itself, or alternatively, whether they could be regarded as independent contributors. For instance, increased cortisol levels may be interpreted as correlate of the melancholic subtype of MDD, as a correlate of traumatization, or increased cortisol levels may have predictive value for the neuropsychological performance beyond diagnosis and traumatization.

Figure 2 also illustrates the complexity of causal relations. Some experimental studies shed light on causal psychological mechanisms. Crane et al. (2007) induced rumination in subjects with a history of MDD. The induced
rumination resulted in reduced autobiographical memory specificity in the patient group. Likewise, Murphy et al. (2003) investigated the influence of negative feedback on task performance in MDD. Compared to healthy control subjects, depressed patients performed worse in maintaining response sets when confronted with misleading negative feedback. By contrast, like healthy control subjects they were able to increase task performance after negative but correct feedback. However, with regard to several factors causal mechanisms are yet not fully understood. As reported above, for instance, it has been found that the duration of MDD is associated with hippocampus shrinkage (Sheline et al. 1996). In accordance with these findings, Gorwood et al. (2008) showed that memory performance diminished by 2–3% per previous episode of MDD (calculated up to four episodes). They conclude from their findings that stress and depression related neurotoxic effects on the hippocampus are responsible for reduced memory performance. However, it can also be postulated that a longer history of depression or mania indicates a more severe type of affective disorder with more prominent cognitive deficits and a reduced hippocampus volume. Some studies indeed suggest a converse causality with a reduced hippocampal volume being the cause or correlate of mental disorders instead of being the consequence (e.g. Lyons et al. 2001). Gilbertson and coworkers (2002) investigated monozygote twins. More severe symptoms in patients with PTSD were associated with smaller hippocampi of both the patients and the patients’ trauma-unexposed identical co-twin. In addition, twin pairs with one twin showing a severe PTSD and the patients’ trauma-unexposed identical co-twin. In addition, twin pairs with one twin showing a severe PTSD had smaller hippocampi than non-PTSD pairs.

While the factors discussed in this paper are related to the severity of neuropsychological impairment in patients with affective disorders, no clear conclusions could be drawn with respect to the neuropsychological profile. For instance, patients in a euthymic state of their disorder, younger patients, or patients with a milder affective disorder, tend to perform relatively better, but study results do not clearly show which functions are primarily affected. Several reasons may account for this ambiguity. Firstly, some studies indicate that the factors here discussed are complexly interrelated. Van den Heuvel et al. (1996) found that depressive symptoms were related to cognitive dysfunction in female elders who exhibit a weak internal locus of control. In men, by contrast, the association between depression and cognitive dysfunction was moderated by neuroticism. Thus, the relation between depression, gender, and neuropsychological performance was further moderated by personality traits. Investigating the memory bias for emotionally relevant stimuli in MDD, Ellwart et al. (2003) found a memory bias for implicit memory but not for explicit memory performance. This finding contrasts with other findings where memory bias was evident in explicit memory performance. The authors speculated that the factor “biased information processing” may not generally be related to memory performance in depressed patients but depend additionally on the symptom severity. Unfortunately, possible interactions are clearly unmanageable given the high number of factors that are known to influence neuropsychological performance in patients with affective disorders. However, guided by clear hypothesis, future studies should include different factors.

Secondly, the expectation to find specific neuropsychological deficits in patients with affective disorders comes from studies with neurological patients with distinct brain dysfunctions. By contrast, Hasler and colleagues (2004, 2006) regard mood disorders as an aggregation of various psychopathological and biological clusters. These clusters (“endophenotypes”) are genetically and phenomenologically more homogenous and might act as a promising basis for the formulation of etiologically-based sub-types of mood disorders. However, it seems possible that not only affective disorders are too broadly conceptualised to be related to distinct brain regions and distinct neuropsychological domains but that the clinical and demographical factors discussed here do not have a distinct neural and neuropsychological correlate either. Rumination, for instance, unfolds its destructive effects on cognitive performance by occupying and biasing processing capacities. Thus, rumination may affect all neuropsychological domains that depend on these capacities. Furthermore, rumination is related to broad brain networks. Cooney et al. (2010) suggested that rumination in MDD patients is associated with enhanced recruitment of limbic and medial and dorsolateral prefrontal regions. As already mentioned above, Sheline et al. (2009) related rumination to a changed regulation of default mode network structures during cognitive tasks. Subjects had to look at negative pictures and reappraising them. In particular, depressed patients exhibited a failure to reduce activity in the ventromedial prefrontal cortex prefrontal cortex (BA 10), anterior cingulate (BA 24/32), lateral parietal cortex (BA 39), and lateral temporal cortex (BA 21) and an accelerated activity in amygdala, parahippocampus, hippocampus, and dorsal medial prefrontal cortex.

Apart from theoretical aspects, some of the factors discussed here have important clinical impact and may stimulate the development of effective neuropsychological treatment strategies. If, for instance, cortisol is a major destructive agent of cognitive performance, both psychotherapeutic and psychopharmacological treatment strategies that are known to regulate HPA axis functioning may be further developed and applied. If sleep disturbances contribute to cognitive impairments, treatment strategies, from the neuropsychological point of view, should also focus on sleep. With regard to rumination, mindfulness
based intervention is a promising treatment strategy. A mindful mindset brings rumination into consciousness and enables the person concerned to orientate attention back to what is relevant in the present moment. Indeed, Deyo et al. (2009) showed that mindfulness-based stress reduction (MBSR; Kabat-Zinn 1990) increased wellbeing and reduced rumination in a sample of individuals seeking support from MBSR for various medical and psychological problems. In addition, symptoms of depression improved. In a sample of patients with life time mood disorders, Ramel et al. (2004) showed that MBSR reduced rumination even after controlling for reductions in affective symptoms and dysfunctional beliefs. Furthermore, training intensity was correlated with decreased rumination. With a comparable program, Zylowska et al. (2008) found pre-post improvements in decreased rumination. With a comparable program, ling for reductions in affective symptoms and dysfunctional showed that MBSR reduced rumination even after control-

Experimental studies and prospective studies are needed to
impairments is the coincidental consideration of different
research should imply manic patients, too. In addition, a
 promising approach to further specify these impairments is the additional consider-
ation strategies for patients with affective disorders, future
with the development of effective neuropsychological treat-
ment of failure, sleep, suicidal tendencies, computer attitudes),
demographic (age, education, gender) and neurobiological
factors (structural and functional brain changes, glucocorti-
coids, medication, ECT) that are known to be related to
cognitive performance. Studies have demonstrated that these
factors have an impact on the severity of cognitive impairment
but findings regarding the neuropsychological profile remain
heterogeneous. Nevertheless, some of the factors discussed
here have an important clinical impact and the knowledge
about those factors may help to further improve effective
neuropsychological treatment strategies for patients with
affective disorders. This is a very relevant goal since
neuropsychological deficits contribute to long-term functional
outcome, and patients concerned with deficits may show less
compliance and an increased risk for suicide. In connection
with the development of effective neuropsychological treat-
ment strategies for patients with affective disorders, future
research should imply manic patients, too. In addition, a
 promising approach to further specify neuropsychological
impairments is the coincidental consideration of different
factors that are known to influence cognitive performance.
Experimental studies and prospective studies are needed to
better understand etiological mechanisms. Such studies may
then allow identifying etiologically-defined clusters con-
sisting of psychopathological, neuropsychological and
biological characteristics.

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