Tangled up in mood : predicting the disease course of bipolar disorder

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CHAPTER 5

Effects of mood state on divided attention in patients with bipolar disorder: evidence for beneficial effects of subclinical manic symptoms

Koenders MA, Spijker AT, Hoencamp E, Haffmans PM, Zitman FG, Giltay EJ (2014). Effects of mood state on divided attention in patients with bipolar disorder: evidence for beneficial effects of subclinical manic symptoms. Psychiatry Research; 220: 302-308.

Abstract

A relative small number of studies have been dedicated to the differential effects of the current mood state on cognition in patients with a bipolar disorder (BD). The aim of the current study was to investigate the effect of current mood state on divided attention (DA) performance, and specifically examine possible beneficial effects of the (hypo-) manic state. Over a maximum period of 24 months, medication use, divided attention test (a subtest of the Test for Attentional Performance (TAP)) was assessed every 6 months in 189 outpatients with BD. Data were analyzed with multilevel regression analysis (i.e. linear mixed models).

DA performance varied considerable over time within patients. Corrected for psychotropic medication a significant quadratic relationship between manic symptoms and DA performance was found, with mild hypomanic symptoms having a positive influence on divided attention scores and moderate to severe manic symptoms having a negative influence. No association between depressive symptoms and DA performance was found. In future research on mania and cognition as well as in the clinical practice both the beneficial and negative effects of mania should be taken into account.

5.1 Introduction

Bipolar disorder (BD) is an 'episodic illness' which is characterized by alternating episodes of depression and (hypo-) mania. Besides the recurrent mood disturbances numerous studies indicate that patients with bipolar disorder suffer from cognitive impairments (177-180). Attention problems, slowing of processing speed, and deficits in visual and working memory and executive functioning appear to be most consistently observed (36). A growing number of studies found evidence that cognitive impairments persevere in the euthymic state (37-39), giving rise to the ideas that cognitive impairments may represent a trait or an endophenotype of the disorder (40). However, it is also widely suggested that cognitive performance is affected by bipolar mood symptoms. Nevertheless, studies investigating this association are rather scarce and limited by cross-sectional designs and small sample sizes. We are aware of only two longitudinal studies on the effects of bipolar mood on cognition, performed by Malhi et al. (41) and Arts et al. (42). Mahli et al. investigated 25 bipolar I patients for a maximum of 30 months and found that compared to the euthymic state of the patients, verbal memory was more impaired during the depressive state. No significant effect of manic state (mean YMRS score > 10) on cognition was found after adjusting for confounders, but a manic state only occurred in 12 patients. Arts et al. (42) included a total of 76 bipolar I and II patients, who were neuropsychologically assessed every two months, for a period of 2 years. In this study cognitive functioning varied substantially over time and depressed mood had a negative impact on performance in several cognitive domains but no relation was found with mania.

It is rather remarkable that in the above described longitudinal studies no distinct association was found between (hypo) manic symptoms and cognitive performance, while a number of cross- sectional neuropsychological studies found cognitive impairment in (hypo) manic BD patients (181-183). The fact that longitudinal studies failed to find this association may be due to a) a lack of power because of the small number of currently (hypo)manic patients (41), or b) the occurrence of only subclinical or mild hypomanic symptoms, as seen in the study of Arts et al. (42) in which mean Young Mania Rating

Scale (YMRS) (60) scores were 1.6 during cognitive assessment. In contrast, the cross sectional studies (181-183) were able to examine cognitive functioning during mild to severe manic episodes (YMRS mean scores ranging from 18.2 to 23.6). Or c) that non-linear models better model the relationship between manic symptoms and cognitive functioning, as suggested by the findings of Kravariti et al. (43). In their cross-sectional study they found a non-linear association between mild manic symptoms and executive control and processing speed among 31 BD patients with mild manic symptoms. These results indicate that mild levels of mania are related to better cognitive functioning compared to moderate levels. This is in line with findings suggesting that low levels of manic symptoms are related to reports of mental alertness, goal directed activity, increased self-confidence and increased self-efficacy in non-clinical samples (44, 45). Further, creativity is known to be associated with hypomanic traits or hyperthymia (184), and hypomania (185), underlining the possibility of increased or special performance levels during hypomania. Recent studies found that adolescents developing BD premorbidly have already normal or even better than average cognitive abilities regarding intelligence quotient (IQ) and reading abilities compared to healthy controls (186, 187). It is widely suggested (188), but poorly investigated, that among talented people, BD is a well-known phenomenon. This suggests that manic symptoms may both enhance and worsen performance.

Another complicating factor in studying cognitive performance in patients with a bipolar disorder is the impact of medication use. There are indications that especially antipsychotics (189, 190), benzodiazepines (191), antidepressants (192), and the use of multiple types of medication (polypharmacy) (193) have a negative effect on cognition. The majority of the before mentioned studies failed to adjust for potential confounding by medication. However, separating the effects of mood fluctuation and (fluctuations in) medication use on cognitive performance in patients of whom almost all use some kind of psychotropic drug is a challenge.

In this current longitudinal study, we aimed to investigate the natural variability of divided attention (DA) performance in outpatients with bipolar disorder. In addition, we examined the association between mood state, including euthymia, depressive and (hypo)manic mood, with objectively as-

sessed DA performance adjusted for medication use.

There are several reasons studying DA in BD patients. First, DA is an essential component of everyday living (194) and is thought to be crucial for the ability to drive in traffic (195), to establish and maintain joint attention and to avoid confusion when confronted with unfamiliar situations. Second, with respect to bipolar and unipolar depression was found that the divided attention performance predicted response to treatment, remission of symptoms, and risk of relapse in depressed patients (196). Furthermore in longitudinal studies both impairments in executive functioning (197, 198) and attention (42) has been pointed out as possible endophenotypes of BD. Functional imaging research indicates that attending to both visual and auditory stimuli requires a recruitment of the frontal lobe (199). This means that the task involves besides attentional also executive processes. Deficits in these two domains are both frequently associated with BD (200). As part of executive function as well as attention, therefore, divided attention can be considered as a sensitive marker in mood disorders.

In the current study, we hypothesized that DA performance will be variable over time within patients, depending partly on the current fluctuating mood states, with increases of manic and depressive symptoms being associated with a decline in cognitive performance. Since low levels of manic symptoms could be associated with better performance, we also assessed potential non-linear relationships between level of manic symptoms and cognitive performance.

5.2 Methods

5.2.1 Study design

This is a 2-year prospective follow-up study among 189 bipolar outpatients with a diagnosis of BD I or BD II (also including BD not otherwise specified and cyclothymia) according DSM-IV-TR diagnostic criteria. All participants were older than 18 years. They were all treated in the Program for Mood Disorders at PsyQ in The Hague, The Netherlands. Exclusion criteria in this study were schizo-affective disorder, neurological disease and

substance abuse disorders. All participants gave full informed consent and this study was approved by the Medical Ethical Committee (METTIG) in Utrecht, The Netherlands, and was carried out in accordance with the declaration of Helsinki.

Diagnoses of BD and psychiatric co-morbidities were based on DSM-IV criteria and were assessed with a standardized diagnostic interview developed by Sheenan et al. (119) using the Dutch version of the MINI International Neuropsychiatric Interview Plus (version 5.00-R; MINI-PLUS) (120). The Questionnaire for Bipolar Illness, Dutch translation (23, 121) was used to specify subtypes of BD, its course over time and detailed information about age of onset of first symptoms regarding hypomanic, manic, and depressive episodes.

Of the total sample 90.2% of the patients (N=156) completed at least 1 year follow-up, eventually a cumulative number of 62 (32.8%) patients dropped out before the end of the study. The most common reasons for patients to quit prematurely were: being too unstable, being hospitalized, deeming the research too burdensome, discontinuing treatment at our outpatient clinic, and not showing up at an appointment more than 2 times. Patients missing more than one measurement were excluded from the current study. Figure 5.1 shows the number of patients who dropped out at the different time points. Between the group that participated until the end of the study (n=127) and the group that dropped out during the study (n=62) no significant differences in the demographic and clinical characteristics were found.

5.2.2 Assessment

After completing the baseline assessment, patients had face-to-face contacts with trained research assistants at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24- months follow-up. During these contacts, mood based functional impairment (Life Chart), medication use and social support were assessed (see Figure 5.1). The study protocol was approved by the local Ethical Committee, and was carried out in accordance with the Declaration of Helsinki.

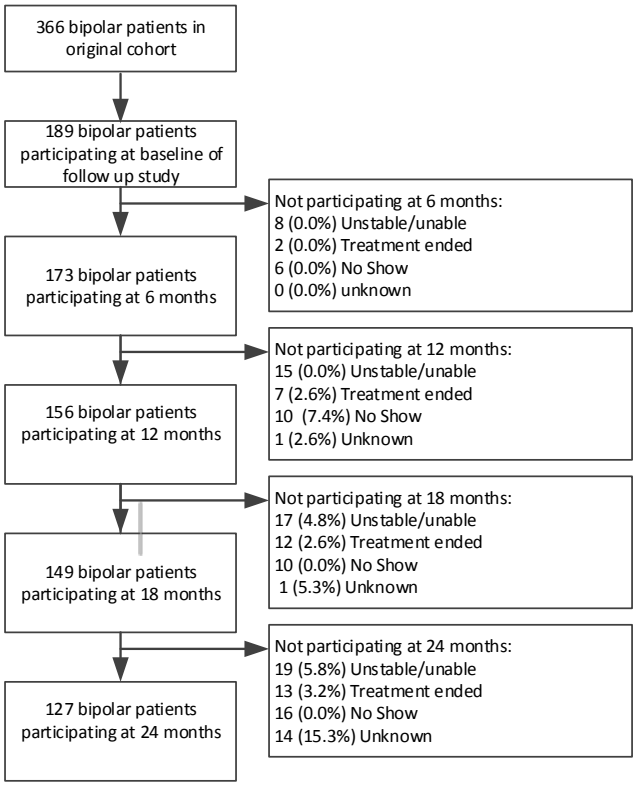

Figure 5.1 | Flow chart of cohort of bipolar patients during the study.

Divided attention test

Divided attention performance in this study was assessed by means of the TAP (Test for Attentional Performance, version 2.1) (201). The TAP is a widely used computer-based standardized test battery and easy to use in clinical practice (192, 202, 203). At baseline a total of 8 subtests of the TAP were assessed, including the divided attention (DA) subtest. During the follow-up only the DA test of the TAP was repeatedly assessed, and this test will be the focus of this study. The divided attention TAP subtest is a crossmodal task, with both visual and auditory input. During the task a visual and an auditory task must be processed in parallel. Four different visual stimuli are separately presented on the screen of which 2 are the target stimuli to which

the patient has to react by pressing a key. At the same time the patient hears high and low pitched tones alternately. When the high or low pitched tones emitted twice in succession the patient has to respond by pressing the key. Errors and omissions are the most important indicators for performance. To create a score for total performance, both errors and omissions are combined in one score. First, both variables were log-transformed because of their right-skewness. The log-transformed omission and error scores were then standardized as z-scores. Subsequently, the mean of those two z-scores was calculated, representing the overall performance on the divided attention test. This procedure resulted in one z-index-score for divided performance for every of the up to 5 waves, with a higher score indicating better performance

Assessment of mood states, clinical characteristics and medication use

All 189 patients who participated in the neurocognitive assessment at the baseline, were invited every 6 months for follow-up assessment during 24 months, at which divided attention was assessed, resulting in up to 5 time points. In those 6-monthly assessments, the current mood states were assessed using the self-report list: the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR) (http://www.ids-qids.org) and the observer based Young Mania Rating Scale (YMRS) (60). Mean QIDS scores can be interpreted as follows: no (0-5) or mild (6-10) depressive symptoms; QIDS scores >16 indicate severe or very severe (>20) depressive symptoms. For YMRS scores no formal classification of severity have been published, but could be interpretation as follows: scores <8 indicate no clinically significant symptoms; light symptoms of mania scores between 8-14; moderate and severe scores are respectively 14-24 and >24 (204, 205). Medication use over time was also monitored. Detailed information on current use of psychotropic medication was assessed at every 6-month wave, and coded according to the Anatomical Therapeutic Chemical Classification System (http://www.whocc.no/). Medication use was further dichotomized (1 = any use of the particular psychotropic medication; 0 = non-user) for lithium (ATC code: N05AN01), other mood stabilizers (i.e., anti-epileptics, ATC code: N03AF01, N03AG01, N03AX09), antipsychotic medication (ATC code:

N05Ax with exclusion of N05AN01), benzodiazepines (ATC codes: N05BA, N05CD, N03AE01, N05CF), and antidepressants (N06A). As lithium was regarded as drug of first choice, it was coded separately. At baseline sociodemographic and illness related data, like age, sex, illness subtype, substance use, age at onset and level of education, were collected with the Mini International Neuropsychiatric Interview (MINI, Dutch translation) (206) and the Questionnaire for Bipolar Illness (QBP) (207, 208).

5.2.3 Statistical analysis

Sociodemographic and baseline characteristics were summarized as means (standard deviation [SD]) for continuous variable and as numbers (proportions) for categorical variables. To estimate the potential variability of DA performance within patients over the two-year period, we used intra-class correlation analyses (ICC) for absolute agreement with a two way random effect model for single measures. These analyses were performed on unstructured DA data, that is, for errors and omission data separately.

Because the up to 5 waves (i.e. baseline through 24 months) were dependent (repeated measurements within an individual) and missings occurred because of dropouts, multilevel regression analysis (i.e. linear mixed models) with a compound symmetry covariance matrix was used to investigate the cross-sectional associations of mood states with TAP results. Associations were first assessed in a crude model. Subsequently, we repeated the multilevel regression analyses adjusting first for age, sex, and level of education (Model 1). In Model 2, we additionally adjusted for variables that previously have been associated with cognitive disturbances: substance abuse (209) (smoking, alcohol use, drug abuse), BD diagnosis (210) , and medication use (192, 211, 212) (using 5 dichotomous groups).

A history of psychosis in BD patients is associated with worse cognitive performance (213), and in the current study data on history of psychosis was collected as well. However, since psychosis didn't appeared to be associated with DA performance during follow up (beta=.06, P=.496) this covariate was not included in the multivariate model.

Next, to test whether the association had the shape of a curve instead of

a straight line, a quadratic term of the QIDS and YMRS scales was added as predictor variable. Data are presented as standardized beta coefficients. All tests were two-tailed with $p<0.05$ denoting statistically significance. The software used was SPSS version 17.0 (SPSS Inc., Chicago, Ill).

5.3 Results

Table 5.1 shows the socio-demographic and health characteristics of the 189 participants with complete data for the main outcome variables on at least one time point. In total there were 687 data points with complete data during 24 months of follow-up. The included subjects had a mean age of 49.4 years and were predominantly female (61%). Most participants (79%) had at least secondary education.

Smoking was current for 43%, alcohol use for 64% (with 10% 3 or more units per day) and drug abuse for 7% of all patients. A bipolar I disorder was diagnosed in 73%. Over all 5 time points, mean QIDS scores fluctuated between 6.7 (SD=4.6) to 7.1 (SD=4.8), indicating on average mild depressive symptoms, with 52.7% (n=362) reporting mild to moderate depressive symptoms (QIDS 6-16) and 7.4% (n=51) reporting severe depressive symptoms (QIDS > 16). Mean scores on the YMRS during follow up fluctuated between 1.1 (SD=2.6) to 1.5 (SD=3.9), indicating only mild overall subclinical manic symptoms. During follow up 10.9% (n=75) reported subclinical manic symptoms (YMRS 4-7), 5.8% (n=40) reported mild manic symptoms (YMRS 8-14) and at 2.6% of the time points (n=18) severe manic symptoms (YMRS > 15) were reported; indicating that the majority of the sample having no clinically significant manic symptoms during follow-up (YMRS < 8).

At baseline 108 (57%) patients used 2 or more different psychotropics. Of all patients, 72% of the patients used lithium, during follow-up this percentage varied between 70% and 77%. At baseline 22% used anti-epileptics, in the next 24 months this varied between 12% and 21%. At baseline 35% used antidepressants, 25% used antipsychotics and 25% used benzodiazepines. During follow-up these percentages ranged respectively between 30% and 42% (antidepressants) with a remarkable decrease in the last 6 months; 24%-38% (antipsychotics) with an increasing pattern over 24 months; and 16%-25%

Variable name	N or mean
Male sex – n (%)	74 (39.2%)
Age – mean ± SD (yr)	49.4 ± 11.3
Age – range (yr)	19 – 81
Level of education: – n (%)	
- primary	40 (21.2%)
- secondary	59 (31.2%)
- higher	90 (47.6%)
Current smoker – n (%)	81 (42.9%)
Alcohol use: – n (%)	
- none	69 (36.5%)
- 1-2 units/day	101 (53.4%)
- ≥3 units/day	19 (10.1%)
Drugs abuse – n (%)	13 (6.9%)
Primary diagnosis: – n (%)	
- bipolar I disorder	138 (73.0%)
- bipolar II disorder or NAO	51 (27.0%)
Age of onset – mean ± SD (yr)	26.8 ± 9.8
Medication use: - n(%)	
- lithium	132 (71.7%)
- other mood stabilizer	39 (21.2%)
- antidepressant	64 (34.8%)
- antipsychotic	45 (24.5%)
- benzodiazepine	45 (24.5%)
QIDS – mean (SD)	7.7 ± 5.1
YMRS – mean (SD)	1.8 ± 3.1

Table 5.1 | Baseline sociodemographic characteristics in 189 participants with bipolar disorder.

(benzodiazepines) with a decreasing pattern over 24 months.

Table 5.2 shows the stability of for either errors and omissions of the DA over time for the unstructured data. ICCs between different time points varied between 0.20 and 0.75 indicating low to moderate stability over time. There was no clear pattern that consistency increased in case of shorter time intervals between DA measurements. The overall mean ICC of 0.58 for errors and 0.46 for omissions indicated that there was considerable variability in DA performance within patients over time.

Table 5.3 and Figure 5.2 present the results of the multilevel analyses on the association between mood states and divided attention performance. The results showed no significant association between depressive symptoms and divided attention performance, neither when linear nor when quadratic (non-linear) associations were tested. Yet, visual inspection of the figure seemed to indicate that a threshold existed for depressive symptoms above which divided attention performance was adversely affected.

	6 months		**12 months**		**18 months**		**24 months**	
	ICC (CI)	P-value (N)	ICC (CI)	P-value (N)	ICC (CI)	P-value (N)	ICC (CI)	P-value (N)
DA errors								
Baseline	.20 (0.04-0.35)	.009 146	.44 (0.29-.57)	<0.001 129	.75 (0.66-.82)	<0.001 123	.75 (0.65-0.83)	<0.001 103
6 months			.46 (0.30-0.59)	<0.001 122	.33 (0.16-0.49)	<0.001 113	.43 (0.26-0.58)	<0.001 100
12 months					.34 (0.17-0.50)	<0.001 115	.54 (0.38-0.67)	<0.001 96
18 months							.54 (0.38-.67)	<0.001 93
DA omissions								
Baseline	.43 (0.29-0.55)	<0.001 146	.52 (0.38-0.63)	<0.001 129	.39 (0.22-0.53)	<0.001 123	.36 (0.18-.52)	<0.001 103
6 months			.61 (.48-.71)	<0.001 121	.41 (0.25-0.56)	<0.001 113	.56 (0.41-0.68)	<0.001 100
12 months					.50 (0.35-0.62)	<0.001 115	.50 (0.33-0.64)	<0.001 96
18 months							.49 (0.31-0.63)	<0.001 93

Data (unstructured errors and omission) are intraclass correlation coefficient (ICC) with a two way random effect model for single measures (with 95% confidence intervals between brackets) and p-values. When using all time points for 72 patients with no missing data on any time point, the ICC for errors was 0.58 (95% CI: 0.47-0.68; P<0.001) and the ICC for omissions was 0.46 (95% CI: 0.35-0.58; P<0.001).

Table 5.2 | Stability of divided attention in bipolar patients over up to two years of follow up.

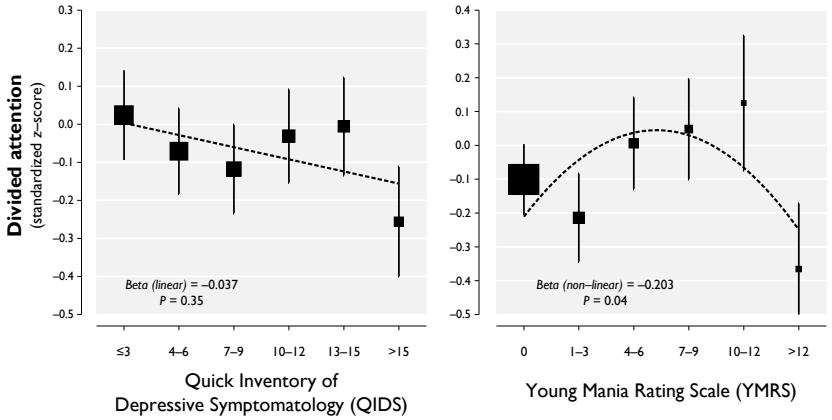

Figure 5.2 | Plots of the association between disease severity scores on the QIDS and YMRS and the standardized score of the divided attention. Categorized QIDS and YMRS scores are depicted on the x-axis to aid interpretability.These values were treated as continuous variables in all statistical analyses. The size of each square is proportional to the number of participants. Vertical lines indicate standard errors. Scores are adjusted for time, sociodemographic factors (gender, age, education), smoking, alcohol use, drug abuse, BD diagnosis, and medication use (5 dichotomous groups) in multilevel regression (i.e., mixed) models.

When dichotomizing patients according to their score on the QIDS, those patients with scores over 15, representing severe depression, had a lower mean divided attention score than those patients with scores of 15 or lower, representing mild or light depression, that approached significance (-0.26 SE 0.14 vs. -0.05 SE 0.10; P=0.07).

Manic symptoms were not linearly associated with divided performance, however a non-significant trend was found, with more manic symptoms leading to better performance on the divided attentions test (Table 5.3). However, the non-linear association appears to be significant, indicating this to be a more suitable model than the linear model (Table 5.3 and Figure 5.2). The non-linear model shows that in the range of YMRS scores between 4-12, reflecting mild manic symptoms, the scores on the DAT were increasing, however, with scores above 12, scores on the DAT were dramatically lower.

Scale	Term	Beta	p-value
QIDS linear:			
Crude	Linear	–0.050	0.21
Model 1	Linear	–0.041	0.29
Model 2	Linear	–0.037	0.35
YMRS linear:			
Crude	Linear	0.008	0.83
Model 1	Linear	0.010	0.78
Model 2	Linear	–0.005	0.90
QIDS nonlinear:			
Crude	Linear	–0.107	0.39
	Quadratic	0.059	0.63
Model 1	Linear	–0.083	0.49
	Quadratic	0.044	0.71
Model 2	Linear	–0.033	0.78
	Quadratic	0.004	0.97
YMRS nonlinear:			
Crude	Linear	0.171	0.047
	Quadratic	–0.213	0.037
Model 1	Linear	0.162	0.056
	Quadratic	–0.199	0.048
Model 2	Linear	0.151	0.077
	Quadratic	–0.203	0.044

Data are beta-coefficients (p value).
Crude: adjusted for time in multilevel regression (i.e., mixed) models.
Model 1: additionally adjusted for sociodemographic factors (gender, age, education).
Model 2: additionally adjusted for smoking, alcohol use, drug abuse, BD diagnosis, and medication use (5 dichotomous groups).

Table 5.3 | Linear and nonlinear associations between disease severity scores and the divided attention (standardized z-scores) in 189 participants with bipolar disorder.

5.4 Discussion

In this study we aimed to elucidate the influence of the current mood state on cognition. In this prospective longitudinal study data were available from a total of 189 patients with bipolar disorder with a total of 687 data points collected every 6 months during 24 months. All results were adjusted for the use of psychotropic medication use. First, we found that divided attention performance was rather variable over time within patients. Our results suggested that fluctuations in current mood state affected divided attention. The most apparent finding was that mild manic scores (between 4-12 on the

YMRS) predicted a better score on the divided attention task, while more severe mania led to significantly poorer divided attention scores. With respect to the association between depressive mood and DA performance, the findings only approached statistical significance levels.

Our study results indicated that very mild manic symptoms may have a positive effect on the cognition function of divided attention, while more severe symptoms may be impairing. This association only became visible when the data were analyzed using non-linear models, which is in line with the findings by Kravariti et al. (43). The existence of this specific association may at least partly explain the failure to find an association between mania and cognition in previous longitudinal studies (41, 42). These findings underline the importance of a non-linear approach of manic symptoms, implicating the need of using different statistic methods. Furthermore, analyzing mood as a continuous or categorized variable, rather than as a dichotomous variable (e.g. depressed/not depressed, manic/not manic), may help to uncover information about the diverging effects of subclinical mood symptoms on cognition.

Second, in our cohort the number of patients scoring >14 on the YMRS was limited. The scores below 14 however, could reflect a non-pathological "hyperthymic mood state" with clinical phenomena like cheerfulness, being overoptimistic, self-assured, eloquent, having high energy levels, highly explorative and low harm avoidance as proposed by Akiskal and Akiskal (214). The authors hypothesized in their review that this temperament could represent the most common phenotypic group with the genetic loading, vulnerability, for bipolar disorder. The development towards a pathological state, bipolar disorder itself, could be the aberrant end of the spectrum (214). In line with this "spectrum" approach, is the recently introduced bipolar spectrum disorder as separate diagnosis (205). Clinically it is relevant to realize that this "hyperthymic mood state" may be an asset in daily functioning for the patient and partner. The use of medication may suppress this active and positive phase and hence might be one of the reasons for medication non-adherence (215, 216). Besides, slight improvement in cognitive functioning may be an important indicator for the patient to be at risk of becoming (hypo-) manic. Poor divided attention is known to be associated

with diminished performance in more complex daily life tasks, for instance driving a car, which may have serious safety consequences for patients (217, 218) and as a consequence, with respect to medication use a complex trade off exists.

5.4.1 Depressive episodes and divided attention

In our sample, mean QIDS scores were between 6 and 8 during 2 years, indicating no or mild depressive symptoms. Our findings show that in the overall model there was no significant association between depression symptoms and DA performance. However, a borderline significant trend was found with patients with a severe depression (QIDS > 15) performing worse on the DA test compared to patients with a mild depression (QIDS < 15). The non-significant findings are likely due to the relatively low number of patients with higher QIDS scores who participated at any one time point. Our findings are contradictory to previous research, in which depressed mood was consistently associated with cognitive impairments. However, in the recent study by Arts et al. (42) impairments in sustained attention were found to be stable over time, irrespective of mood symptoms.

5.4.2 Strengths and limitations

A strength of this study is the prospective design over a 24 months period with a large cohort of 189 patients in a real life outpatient setting, making it possible to include 687 data points and hence increase the reliability of our findings. Second, we adjusted for psychotropic medication use to take the potential confounding effects into account. Third, we used a different statistical approach to investigate the association between mania and cognitive performance. However, several limitations have to be noted. First, the results can only be applied to relatively stable bipolar outpatients, as the number of time points of severely depressed as well as severely manic patients was low. Dropout may have selectively occurred in the more severe cases leading to withdrawal from the study or admissions, resulting in some selection bias. Second the rating of severity of mania was assessed with the YMRS, of which no strict classification of severity is provided for interpret-

ing the scores. Moreover, interpretation of YMRS scores is further hampered by cultural differences, as scores differ in study locations (219) and interviewers nationality (220). Third, we tested only one cognitive domain. Although divided attention is known as a combination between attention and executive functioning more elaborate cognitive batteries such as the more recently developed cognitive battery of the International Society of Bipolar Disorder (ISBD) (221) may be more appropriate. Fourth, since we did not compare cognitive performance over time with a healthy control group, it is unclear whether divided attention was on average already reduced in euthymic BD patients.

5.4.3 Conclusive remarks

Bipolar disorder is known as a severe mood disorder, characterized by manic or hypomanic as well as depressive episodes. Hypomanic symptoms can put patients at risk for developing severe mood episodes (12). However, hypomanic or hyperthymic states can also include increased creativity driven by executive function, speed of thought and higher alertness. Therefore, increased performance on an executive function task like divided attention has to be seen as subclinical state, indicating the two sides of the disease: severely ill, as well as the possibility of being in a "supranormal" or "hyperthymic" mood state with regard to some of the cognitive abilities. Therefore, in future research both sides of the hypomanic mood state should be taken into account when studying its relation to cognition.