Impact of (subclinical) mood symptoms on the IQ and cognitive performance of patients diagnosed with bipolar disorder type I and type II

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Table of contents

1. Abstract

Intellectual deficits have been known as a core feature of bipolar disorder for decades and are hypothesized to be responsible for the unfavorable psychosocial outcome and high unemployment rates. Those alterations seem to be permanent and are present not only during active- but also during euthymic phases. The focus of this study was on investigating a possible link between mood symptoms, assessed through the clinician-rated questionnaire YMRS and the self-rated QIDS, and the IQ together with cognitive abilities in four different domains. Measured was the performance of 50 recently diagnosed patients participating in the BINCO-study. Furthermore, the focus was on observing differences in scoring between different symptomatic states and the two types of disorder. The impact of confounders, including the intake of antipsychotic medication, benzodiazepines, and the educational level, were considered. While no significant association between depressive symptoms and the subscale-derived IQ could be detected, a quadratic relation was found between manic symptoms and SDIQ score, pointing towards lower scoring in patients with subclinical symptoms and higher performance in patients with mild to moderate symptoms. The QIDS-score significantly impacted the performance in the sub-scale „information", which provides the verbal comprehension index. The YMRS- score again showed a curvilinear association with the same subtest. The intake of antipsychotic medication seemed to show the greatest confounding effect on the dependent variable. Further research is needed to elucidate the effect of manic symptoms on IQ and verbal comprehension, as well as the role of antipsychotic medication. Also, larger sample sizes would determine the actual impact of each mood phase on the IQ.

2. Introduction

Being described for the first time in 1851 by Falret under the name of „folie circulaire" (Falret, J.P, 1851), the bipolar disorder, with its conflicting episodes of manic and depressive symptomatology, has been in the focus of interest and investigation for almost two centuries. Over time, scientific research has been able to answer a large number of questions regarding possible causes, expressions, consequences, and the efficiency of different treatment options. It became evident that during active phases of the disorder, extreme fluctuations in mood and energy affect several areas of the affected individual's functioning. Such might explain why bipolar disorder is nowadays ranked among the mental disorders with the most disability-adjusted life years and one of the highest burden of disease (World Health Organization, 2013). Between active phases, patients experience a state of symptomatic remission, called the euthymic phase, characterized by low mood symptoms which do not reach clinical significance. For a long time, affected individuals were expected to regain their baseline level of functioning during those episodes. Nevertheless, when looking at the psychosocial outcome of bipolar patients after illness onset, up to 60% fail to do so in occupational and social domains (MacQueen et al., 2001), and over 60% remain unemployed (Kupfer et al. 2002). Those results suggest that even during euthymic phases, patients still suffer from deficits compromising their functionality. While several studies investigated the causality of those persistent impairments by analyzing different illness variables, inter alia duration and the number of affective episodes, or the age of illness onset, results are still ambiguous and further research is needed to fully elucidate their individual impact.

One factor likely to interfere in the normal occupational and social functioning of bipolar patients is a cognitive deficit, which can be observed in up to 60% of patients suffering from the disorder (Martino et al., 2008). Especially during manic and depressive phases, impairments in executive function, verbal memory, psychomotor speed, sustained attention, and social cognition have become evident (Martinez-Aran et al., 2004). Some of those cognitive alterations persevere even when symptoms ease up, and further ones in other cognitive domains, including processing speed, visual memory, and verbal fluency, manifest (Malhi et al., 2007). Next to the cognitive performance, a decline in the overall intelligence quotient was seized by several researchers (Dickerson et al., 2004; Toulopoulou et al., 2006) which also seems to persist during asymptomatic episodes. A cross-sectional study by Vreeker et al. (2015)

comparing the intelligence quotient of bipolar patients with schizophrenic patients, healthy controls, and their first-degree relatives indicated that, regardless of the current phase, bipolar patients show significantly lower IQ scores than healthy controls but higher scores than schizophrenic patients. Surprisingly, similar patterns of cognitive alteration were not found in first-degree relatives, as previously was the case in individuals diagnosed with schizophrenia (Hughes et al., 2005). Those findings suggest that the observed impairments in different cognitive areas and IQ are not linked to family vulnerability. Furthermore, while in other psychological disorders, such as depression, schizophrenia, and anxiety disorders, it appears that subjects expressed lower IQ scores and experienced cognitive difficulties already during childhood (Koenen et al., 2009), in bipolar patients, the childhood IQ was actually above average, and higher educational performance was achieved when compared to controls and healthy relatives (Vreeker et al., 2015). Yet, these observations indicate that bipolar patients were cognitively highly functional before developing the first active episode of the disorder. Following this line of thought, characteristics proper to the disorder itself or secondary variables that accompany the diagnosis, such as the use of medication or repeated hospitalizations, may have enchained the decline in IQ and cognitive performance in this patient group. Which exact characteristics may account for the decline remains unclear (Torres et al., 2007).

Due to genetic overlap between bipolar and schizophrenic disorder (Purcell et al., 2009) and a partially shared disease pattern with major depression, investigation on these disorders might help understand the expression of cognitive impairment in individuals diagnosed with bipolar disorder. Cluster analysis by Potter et al. (2010) comparing three groups of schizophrenic patients with different levels of intellectual capacities showed that the level of symptoms of general psychopathology correlated negatively with the IQ. Intellectually compromised and intellectually deteriorated patients presented higher symptom levels and further negative symptoms than intellectually preserved patients. Sackeim et al. (1992) found a similar correlation in patients suffering from major depression: when compared to healthy controls, depressed individuals displayed significantly lower IQ scores the more pronounced their symptoms. Therefore, the intensity of the symptomatology seems to correlate directly with the IQ and cognitive performance. Applying these findings to bipolar disorder, clinical mood symptoms during active phases, and persistent residual mood symptoms during euthymic

phases could explain the alterations in the cognitive performance and the degradation in the intelligence quotient of this patient group.

Previous studies on the cognitive abilities of euthymic bipolar patients indicate a significant effect of subclinical symptoms on the performance during remission, which underlines the hypothesis of effects of mood symptoms on cognitive performance. Martinez Arán et al. (2004) found relations especially with the working memory, which could not be confirmed by Clark et al., who observed alterations in the areas of attentional set-shifting and verbal memory. Vreeker et al. (2015) located lower performance in the subtest assessing processing speed, but average performance in the other cognitive areas tested. Nonetheless, few studies are available on the effects of mood symptoms during active mood phases, due to assessment difficulties in severely manic or depressed patients. Assuming, that the symptom severity predicts the IQ scores and the level of cognitive impairment, patients whose symptom levels did not reach clinical significance are ought to achieve a higher scoring in cognitive assessment than patients who are experiencing an active episode. Moreover, regardless of the kind of symptoms, manic or depressive, it is hypothesized to observe stronger associations between mood and IQ in patients experiencing an acute phase of illness, while for euthymic patients, the mood might show little to no effect on IQ, as the symptom levels are less severe. Due to increased symptom severity (Solé et al. 2016) in patients experiencing simultaneously both kinds of mood, the performance of patients with mixed features is ought to be affected further than for patients who experience only one symptomatic state. Unfortunately, no studies are available yet to provide information on the effects of mixed features on cognitive performance or IQ.

A different interpretation of the previously mentioned findings by Sackeim et al. (1992) and Potter et al. (2010) involves that the negative symptoms, which were more severe in the intellectually deteriorated schizophrenic patient groups and form the key symptomatic of the major depressive disorder, correlate directly with the IQ. In bipolar patients, literature regarding the association between the different mood states and performance in different cognitive areas aligns with this hypothesis and indicates further relation with depressive symptoms (Mahli et al., 2007; Arts et al., 2011). On the other hand, study results on the influence of (subclinical) mood symptoms on the performance in different WAIS subtests are scarce and contradictory.

While some studies (Roiser et al., 2009; Clark et al., 2002) were able to detect effects of depressive mood on several areas of cognitive performance, initial investigation on a possible correlation between negative symptoms and the IQ in this population did not find variations in the scores between illness phases (Coffmann et al., 1990; Donaldson et al., 2003). Nevertheless, those findings are to be treated with caution due to small sample sizes. In a larger study by Kravariti et al. (2012) a significant linear association between negative symptoms and the IQ could be found in patients with first-onset psychosis. Accordingly, whether there is a relationship between depressive mood and IQ or cognitive performance remains unclear.

Even though cognitive impairments were discovered to be present in bipolar patients also during (hypo-)manic phases (Murphy et al., 2001; Fleck et al., 2003), researchers failed to detect a direct association between the manic mood and those impairments (Mahli et al., 2007; Arts et al., 2011). Recent findings by Koenders et al. (2014) and Kravariti et al. (2012), therefore suggested a quadric association between those symptoms and the IQ. Low levels of mania could enhance the performance, which then decreases with increasing symptom severity. Kravariti et al. (2012) found here an association in an inverted U-shape between manic symptoms and cognitive functioning. In some patients, a positive relation between (hypo-)manic symptoms and the areas of cognitive functioning might therefore be discernible. Furthermore, secondary variables such as the use of antipsychotic medication, benzodiazepines, and the educational level, are expected to interfere in the association between mood and IQ. Based on findings by Thompson et al. (2005) and Mann-Wrobel et al. (2011), neuropsychological impairment should decrease as education increases. On the other hand, the use of antipsychotic medication predicts worse cognitive performance and a lower IQ scoring (Torrent et al., 2011; Donaldson et al., 2003). The intake of benzodiazepines should also show negative effects on performance (Stewart et al., 2005). Severely manic patients, who are prone to the administration of antipsychotics could therefore show impairments in cognitive performance and IQ, while patients with low or medium levels of manic symptoms might present increased performance.

Considering the classification of bipolar disorder in two forms: type II (BD-II) characterized by an attenuated form of manic symptomatology (hypomania) but further depressive phases, and type I (BD-I), characterized by a frequent need of hospitalization and in some cases psychotic symptomatology, significant differences between the types should be

evident. Nevertheless, study results regarding different cognitive profiles between type I and type II disorders have been contradictory. While Torrent et al. (2006) and Simonsen et al. (2008) suggest a different pattern of cognitive alteration between bipolar patients type I (BD-I) and type II (BD-II), showing more severe impairments in type I patients, Dittmann et al. (2008) were not able to confirm those findings and identified a similar pattern of alteration. Due to elevated mood symptomatology often accompanied by psychotic features and further need of antipsychotic medication, BD-I patients are expected to perform worse in the IQ assessment than BD-II patients (Martínez-Arán et al., 2008). The current discussion, whether bipolar disorder and schizophrenia might be a continuum rather than two separate disorders (Keshavan et al., 2011), and the discovery of qualitatively similar patterns of impairment in both patient populations (Daban et al., 2006), provides reasons to believe that there might be shared components between both disorders which affect the cognition. In the previously mentioned cross-sectional study by Vreeker et al. (2015), it became evident, that schizophrenic patients present a more severe level of cognitive impairment, expressed through lower IQ scores, than bipolar patients. The increased level of general psychopathology in schizophrenic patients, when compared to bipolar patients, could be an explanation for this observation. Following this hypothesis, bipolar I patients, whose symptomatic pattern resembles those of schizophrenic patients to a greater extent than bipolar II patients, might express more severe alterations.

At the current state of the investigation, the influence of (sub)clinical mood symptoms on cognitive abilities remains unclear. Associations with the IQ, as observed by Potter et al. (2010) and Sackeim et al. (1992), are unstudied, and results on a possible differential association with the type of the disorder or the current phase of illness have been contradictory. Therefore, this study will focus on investigating whether there is a correlation between (subclinical) mood symptoms and the IQ. Starting by comparing the IQ performance of BD-I and BD-II patients might highlight a possible confounding effect of the disorder type. In the next step, the relationship between depressive or manic mood and IQ will be elucidated. As emphasized by previous research, a possible quadratic association between manic symptoms and IQ will be investigated as well. Moreover, the effect of mood on different areas of cognitive functioning: including verbal comprehension, perceptual organization, processing speed, and working memory, will be studied in linear form for both mood states and quadratically for manic symptoms. The effect of several potential confounders: including the educational level,

the use of antipsychotic medication, and benzodiazepines will be considered. Finally, a differential association between mood phases and IQ-test performance will be explored. New insights in this domain could help to track the impact of the mood on the cognitive performance of bipolar patients, which may lead to understanding neurological and psychological processes in this population. Elucidating the way confounders act upon that association, depending on the symptomatic state, would enable future research to focus on adapting treatment methods regarding the current illness phase. Furthermore, investigation on this correlation could verify whether previous research findings can be replicated with a different sample.

3. Methods

3.1. Study Procedure

The current study is part of the larger Bipolar Netherlands Cohort (BINCO) study, a naturalistic longitudinal cohort study. The BINCO study mainly focuses on determining different parameters and their possible association with factors regarding the course of disease. Only recently diagnosed patients were included in the study. All participants signed informed consent before entering the study. The design consisted in a baseline, a six-month, and a one-year follow-up measurement, performed by clinicians at the outpatient center. Based on the collected data of the BINCO study, this study is going to use data related to intelligence and cognitive performance, mood symptoms, and disease course measured at baseline and six-month follow-up. The study protocol was approved by the local Ethical Committee and was carried out in accordance with the Declaration of Helsinki.

3.2. Participants

For the current study, the data of 50 participants of the BINCO study diagnosed with bipolar I or II disorder, will be used. The inclusion criteria for the participants of the BINCO study consisted of a bipolar diagnosis according to DSM-VI criteria and a recent diagnosis of bipolar disorder (<4 months). Recruitment went through the treating physician at the specialized bipolar outpatient department in Rotterdam, The Hague, and Leiden. Exclusion criteria included being below 18 years of age, not reading, speaking, or understanding the Dutch language, and being diagnosed with bipolar disorder NOS or cyclothymic disorder. Throughout

the study, all participants received specialized treatment at the outpatient department for bipolar disorders in PsyQ the Hague, Rotterdam, and Rivierduinen Leiden.

3.3. Measures

3.3.1. Clinical characteristics

The patients' diagnosis was confirmed using the Composite International Diagnostic Interview (CIDI) 2.1 Lifetime Dutch version (Section E, depression, Section F, mania) in the BINCO sample at baseline. Information regarding the use of medication and the educational level were collected during an interview at the baseline assessment. For the medical intake, only the use of antipsychotic drugs and benzodiazepines will be considered. Whether a participant is administered more than one type of medication is also relevant. The educational level is determined using information regarding the patient's school records. As most of the participants grew up in the Netherlands the Dutch school system will serve as a reference for educational performance. In the Netherlands, children receive primary education from age 4 to age 12. Subsequently, during secondary education, they are being separated into different levels: low, intermediate, high preparatory, and pre-university. In tertiary education, intermediate professional education, higher professional education, or university can be pursued. Using the study of Vreeker et al., (2015) as a reference, the participants will be divided into different categories: Level 1: Low (no education, primary education, and low secondary education), Level 2: Intermediate secondary education, Level 3: Intermediate professional education, Level 4: High preparatory vocational and pre-university, Level 5: Bachelor's degree, Master's degree, Ph.D. or higher professional education.

3.3.2. Mood severity and mood episodes

Depression severity was measured using the Quick Inventory of Depressive Symptomatology – self-report (QIDS-SR) (Rush et al., 2006). The QIDS consists of 16 items, scored on a scale from 0 to 3 which assess the nine DSM-IV symptom domains that are affected in a depressive episode: sad mood, poor concentration, self-criticism, suicidal ideation, anhedonia, energy, sleep disturbance, decrease/increase in appetite/weight, and psychomotor agitation/retardation (American Psychiatric Association, 2013). In psychometric evaluations, the QIDS has proven acceptable psychometric properties to assess the severity of depressive symptoms in bipolar patients (Trivedi et al., 2004). In this study, depressive symptoms were considered clinically

significant when reaching a score above 10 in the QIDS. Scores from 0 to 4 were interpreted as no depressive symptoms, from 5 to 10 as subclinical symptoms, from 11 to 16 as mild to moderate symptoms, and over 16 as severe depressive mood. Mania severity was measured through the Young Mania Rating Scale (YMRS) (Young et al., 1978), a clinician-rated interview assessing the severity of a (hypo-) manic episode. It consists of an eleven-item scale, which is scored on a scale from 0 to 4 for seven items, and on 0 to 8 for four items. High internal reliability for this test has been reported (Young et al., 1978). It has also been proven to be a valid assessment method across different cultures. We can say that a patient experiences clinically significant manic symptoms when a score above 5 is reached. With a score of 0 patients were considered experiencing no manic symptoms. A score between 1 and 6 indicated subclinical mood symptoms, between 6 and 11 mild to moderate manic symptoms, and a score over 11 pointed towards severe symptoms. If in both tests the scores remain below the mentioned cut-off, the patient is considered not experiencing clinically significant mood symptoms. A patient is classified as experiencing mixed features when the cut-off in both, the QIDS and YMRS, is reached.

3.3.3. Intelligence and cognitive performance

To estimate the patients' IQ, the subtests information, block design, arithmetic, and digit symbol coding of the Wechsler Adult Intelligence Scale (WAIS, Blyler et al., 2000) were conducted. The subtest „Information" assesses the degree of general knowledge through different questions about culturally acquired information. It provides the Verbal Comprehension Index. In the „Block Design" subtest, the participant reproduces patterns from a picture with colored blocks. Performance in this subtest indicates the Perceptual Organization Index. The Processing Speed Index is assessed through the subtest „Digit Symbol Coding" which consists in matching a previously assigned symbol to the corresponding number. In the subtest „Arithmetic" participants solve mathematic problems or equations which assesses the Working Memory Index (Wechsler et al., 1981). While the subtests Information and Arithmetic are part of the verbal IQ, Digit Symbol Coding and Block Design belong to the performance IQ. To obtain an estimate of the IQ through the four subtests, the participants are assigned a scaled score, based on their performance, which is corrected regarding their age. The mean of the scaled scores obtained in each subtest is summed. The sum of the scaled scores is then multiplied by 11, which is the total number of subtests available, and then divided by four,

which is the number of tests used to assess the IQ. The obtained score will be called the subset-derived IQ (SDIQ) and has proven to provide an accurate estimate of the actual IQ assessed through all 11 subtests of the WAIS (Vreeker et al., 2015; Blyler et al., 2000). Using only four subtests is especially beneficial when assessing patients in acute phases of mental illness, as it takes less time and therefore reduces the patients' effort.

3.4. Statistical analyses

In a first step, it is examined whether the type of disorder acts as a confounder by comparing the SDIQ scores of patients diagnosed with Bipolar I Disorder to those diagnosed with Bipolar II Disorder, using independent samples t-tests. Then, a multiple linear regression analysis will be carried out to investigate whether manic and depressive mood severity is related to performance on the IQ tests. In both analyses: the crude model assesses the impact of manic or depressive symptom severity on SDIQ performance; the adjusted model takes into consideration the confounder “educational level”; the fully adjusted model accounts also for the use of antipsychotic medication and of benzodiazepines next to the educational level. Additionally, the association between the YMRS and the SDIQ is also analyzed through curvilinear regression analyses to investigate possible increased performance when mild symptoms are present. Subsequently, the impact on the performance in different cognitive domains, determined by the scale scores in each subtest, will be analyzed through the same multiple linear regression models as mentioned. Again, the association will also be considered quadratically for (hypo-)manic symptoms. Finally, it will be investigated whether the SDIQ is differentially associated with full mood episodes compared to no/subclinical mood episodes based on the QIDS and YMRS scoring. Different states include “current depressive episode”, “current manic episode”, “euthymic episode” or “with mixed features”. The association between mood state and the SDIQ is analyzed with an ANCOVA. It will also be controlled for the effect of confounders. Statistical analyses are conducted through SPSS 27.0.1.

4. Results

4.1. Sample characteristics

The data of 50 participants of the BINCO study was analyzed in this study. Subjects were between 17 and 59 years old, and the average age was 36. While 28 of the participants were

female, 18 were male. Out of the total number of participants, 13 were diagnosed with BD-I and 32 with bipolar BD-II disorder. For four patients, there was no data regarding the type of disorder available. Means and standard deviations of the studied variables are presented in Table 1. The WAIS-R assessment was complete for 49 out of 50 patients at the 6-month follow-up assessment. The participants obtained SDIQ scores that ranged from 57,75 to 145,75 (M = 102.93, SD = 20.75). The distribution of the scores among the observed population is illustrated in Figure 1. In a general population, the mean IQ scores are around 100 with 68% of people obtaining scores within one standard deviation of 15 below and above the mean. In the assessed population, 53.06% fell into this category. Within two standard deviations above or below the mean of a general population were 10 patients, who obtained SDIQ scores below 85, and 13 patients who obtained scores above 115. No differential association regarding gender could be detected. SDIQ scores were consistent over the educational levels, except for participants who quit after intermediate secondary education and those who completed high preparatory vocational education or pre-university. Here, the achieved scoring remained under 100. SDIQ scores by educational level are displayed in Figure 3. Comparing the means of WAIS-R scoring obtained from patients diagnosed with bipolar I disorder to those diagnosed with bipolar II disorder, type I patients show lower IQ scores (M = 98.153, SD = 18.79) than type II patients (M = 105.273, SD = 20.42). Nevertheless, no significant group differences could be detected (t = –1.083, P = .285). The disorder type could therefore be excluded as a confounder on the association between mood and IQ.

As for the current mood state of the participants, 19 reached the cut-off (>10) in the QIDS for clinically significant depressive symptomatology. Scores ranged from 1 to 30. The mean of M = 10.15 (SD = 7.0) indicates that the average participant was experiencing depressive symptoms at the assessment point. No depressive symptoms were experienced by 21.28% of the participants. Subclinical symptoms were seized in 36.17% of the participants, 25.53% experienced mild to moderate-, and 17.02% severe symptoms. For the YMRS, 18 participants reached the cut-off for clinically significant manic symptoms. Scores ranged from 0 to 16. With a mean of M = 4.10, most participants did not experience clinically significant manic symptoms at the assessment point. Out of the 48 patients assessed, 37.5% were experiencing subclinical manic symptoms, 35.42% mild to moderate symptoms, and 2.08% severe symptoms. 25% were experiencing no manic symptoms. It can therefore be said that a

similar number of participants considered in this study were suffering from manic and depressive symptoms. The cut-off in both assessments was reached by eight participants, who can be classified as experiencing mixed features. Patients who reached neither cut-off were considered euthymic. This applied to a total of 16 participants. Between BD-I and BD-II patients the mean for the manic and depressive symptomatology differed. Those differences were insignificant for depressive mood (P = .32) but reached significance for the manic mood (P = .06). BD-I patients presented higher YMRS scoring, indicating greater manic symptom severity (M = 5.9) than BD-II patients (M = 4.2). Results of the t-test assessing group differences between the two types of bipolar disorder are displayed in Table 5.

The educational levels of the participants ranged from level 1, Primary Education, to level 5: Successful completion of University or Higher professional education achieved. The number of participants in each level is represented in Figure 2. A total of 28% of the participants in the study obtained a university degree or achieved higher professional education. Around 32% completed high preparatory vocational education or pre-university, while 26% terminated after intermediate professional education. Nearly 4% quit after intermediate secondary education, and 6% did not continue after primary education. Furthermore, 41 participants were taking psychopharmaceutics at the assessment point, including mood stabilizers (n=27), Benzodiazepines (n=15), and antipsychotic medication (n=14). Types of mood stabilizers included mainly Lithium and Priadel. Benzodiazepines included Diazepam, Lorazepam, Oxazepam, and Temazepam. Out of the patients taking Benzodiazepines, four were taking two different types. Out of the 14 patients taking antipsychotic medication, also four were administered two or more different types. Types of antipsychotic medication included Quetiapine, Promethazine, Olanzapine, and Haldol. Data regarding the intake of antipsychotic medication was missing for two patients and regarding the intake of benzodiazepines for three patients regarding antipsychotic medication.

4.2. Mood symptoms and IQ

Starting with the crude model, the linear analysis of the association between depressive symptomatology and the SDIQ did not reach statistical significance (F = 1.66, P = .20), neither between manic symptoms and the SDIQ (F = .01, P = .91). The associations are represented in Table 2. Accordingly, neither the depressive nor the manic symptomatology significantly

impacted the IQ when considered sole. Also, in the adjusted and fully adjusted models, no significant association was found between manic or depressive symptom severity and SDIQ. Regression analysis of the effect of (hypo-)manic symptomatology, expressed through YMRS scores, on the SDIQ showed that the predictability increased significantly (R^2 = .13, P = .01) when considering a quadric relationship between the variables. The association remained significant after adjusting for confounders. While most participants did indeed show lower SDIQ scores when experiencing (hypo-)manic symptoms, two participants obtained exceptionally high scores, while experiencing rather severe symptoms. This can be observed in Figure 4: low to medium levels of manic symptomatology were significantly associated with lower IQ scores, which increase with rising symptom severity.

4.3. Mood symptoms and cognitive performance

Associations of mood with the different subtests are depicted in Table 3. Linear regression analyses of the YMRS with the four subscales of the WAIS-R used to assess different areas of cognitive performance showed no statistically significant association. Investigating the impact of the confounders on the association between the YMRS and the different subscales used to assess cognitive performance, an increase in the β-weight could be observed for the associations with the subscale "Arithmetic" and "Information" after adjusting for "educational level", "Intake of antipsychotic medication", and "Intake of benzodiazepines", without reaching significance. A significant quadratic association was found between manic symptoms and the performance in the subtest "Information", providing the Verbal Comprehension Index (β = .05, P = .03). The effect persisted after controlling for confounders. The curve followed a U-shape, indicating lower scoring in patients with subclinical symptoms and improved performance with increasing symptom severity. Again, one patient achieved exceptionally high scoring while having an above-average SDIQ, which could impact the curve progression.

The QIDS-C scores were also significantly associated (F = 3.32, P = .08) with the scoring in the subtest "Information". As illustrated in Figure 5, a higher scoring in the QIDS-C is associated with worse performance in the subtest "Information" indicating negative effects of depressive symptomatology on the patient's verbal comprehension. The previously detected effect of the QIDS scores on the performance in the subscale "information" was not significant anymore after controlling for confounders (β = –.09, P = .16).

4.4. Differences between symptomatic states

Differences in IQ performance between the four groups representing different symptomatic states (depressive, (hypo-)manic, euthymic and mixed), were assessed through an ANCOVA after confirming that the covariance is consistent across groups and that homogeneity of regression slopes was given. Results are displayed in Table 4. It became evident that no significant group differences are present in the sample. After adding the covariates, the association becomes slightly more significant, without reaching statistical relevance, but the effect size decreased. Therefore, no differential association between symptomatic state and IQ was to be detected, suggesting similar performance in IQ assessment between symptomatic states.

5. Discussion

Nowadays, it is known that a high percentage of people diagnosed with bipolar disorder suffer from deteriorations in IQ and cognitive abilities. Over the past years, several factors that could affect cognitive performance have been analyzed, without reaching explicit conclusions. The impact of the patients' mood symptomatology has been investigated by few researchers and mainly as a possible confounder variable, where it appeared that an observed effect would often disappear after controlling for (sub-)clinical mood symptoms (Clark et al. 2002, Ferrier et al. 1999). This points towards a direct relation between cognition and mood. Furthermore, it became evident that in each symptomatic state, different cognitive areas are affected and the association with IQ differed (Kravariti et al. 2012). Thus, the aim of this current study consisted in analyzing whether mood symptoms might be directly linked to the observed deterioration in IQ and cognitive performance.

Within the studied group, variations in IQ depending on different state and trait factors were expected to be observed. Results showed that no significant group differences between bipolar I and bipolar II patients were present in the sample and no effect of depressive mood symptoms on the SDIQ could be observed. Nonetheless, manic symptoms were quadratically associated with the performance in the WAIS-R, showing worse performance in patients with subclinical mood symptoms, which then improves with increasing symptom severity. Also, the QIDS showed a significant linear effect on the performance in the subscale "Information",

providing the Verbal Comprehension Index, which disappeared after controlling for confounders. The YMRS, on the other hand, showed a quadratic association with this same subtest. Last, no differences in the IQ performance between the groups presenting different symptomatic states, or types of disorder could be observed.

5.1. Mood and IQ

While previous study results pointed towards an overall alteration in IQ in patients suffering from bipolar disorder (Vreeker et al. 2015), the SDIQ of the studied individuals corresponded to an average IQ when looking at normal distributions. Nonetheless, no improved scoring could be observed with increasing educational levels. Alterations in the first two levels could be due to a low number of participants belonging to these groups. For the largest group of patients, who finished high preparatory vocational education or pre-university, the mean SDIQ score remained under 100, while most of the other groups obtained scores above. Low SDIQ scores in level four educated participants might point towards a general alteration in IQ of the participants, as scoring would be expected to be higher regarding the educational level. Differences in IQ between groups could explain why a relatively large number of participants obtained SDIQ scores within more than one standard deviation from the mean, indicating exceptionally high or low scoring. A possible explanation for the observed phenomenon relies on the staging model by Kapczinski et al. (2009). The model proposes five different stages, that bipolar patients undergo. While during the latent phase individuals are at risk for developing the disorder without showing any symptoms, at stage four, patients are severely cognitively and functionally impaired, and consequently unable to live autonomously. A marked impairment in cognition and functioning becomes only evident at stage three. Kapczinski et al. (2009) suggest, that the degradation could be due to increased stress caused by multiple episodes and a progressive degradation in the ability to use effective coping skills. Due to a recent diagnosis, the cognitive capacities of the studied subjects might not have been identically compromised by different trait or state factors hypothesized to affect bipolar individuals in later stages of the illness. As participants might situate in different stages, cognitive abilities could be affected to a different degree, which explains the variations in the WAIS-R scoring.

The mood initially expected to constitute one possible state factor causing alterations in IQ did not show any significant linear association with the WAIS-R scoring. Based on

previously discussed findings by Kravariti et al. (2012), Potter et al. (2010), and Sackeim et al. (1992), who found a significant effect of negative symptoms on IQ in patients with first-onset psychosis, schizophrenia, and major depression, these effects were expected to become evident as well in bipolar patients. Consequently, the null finding does not align with mentioned observations in other patient populations. Also, relying on findings by Sackeim et al. (1992), who found discrepancies between the verbal IQ (VIQ) and performance IQ (PIQ) in patients suffering from major depression, the four subtests used in this study might have been insufficient to detect discrepancies between verbal and performance IQ. As a result, no direct effect on the overall IQ could be detected, while the two IQ subtypes might have been affected differently.

The null finding for the impact of manic symptomatology can be attributed to the absence of a linear relationship between mood and IQ. As previously detected by Koenders et al. (2014) and Kravariti et al., (2012) manic symptoms seem to have a non-linear association with the IQ. While Kravariti et al. and Koenders et al. found here increased performance at low to medium symptom levels, which then decreases with rising severity, current results point towards lower performance at subclinical symptom levels which then increases with rising severity. In this study, only one patient reached the cut-off for severe manic symptoms, which might explain why the curve does not follow similar patterns as it did in previously mentioned studies, while the increased performance, which can be observed in mild to moderate symptom severity, aligns with those findings. Moreover, the two patients who achieved high SDIQ scores and were suffering from more severe manic symptoms could have been outliers. Their impact on the curve progression is therefore to consider with caution and might not be representative.

Another explanation for the unusual curve shape could be, that the drop in performance, which was detected in severely manic patients (Koenders et al., Kravariti et al., 2012), might not be attributed to increased symptom severity but to adverse factors. As suggested in the staging model by Kapczinski et al. (2009)., secondary factors, such as further intake of antipsychotic medication, repeated psychotic episodes, recurrent need for hospitalization, and an increasing amount of stress, might account for the degradation in cognitive abilities over the stages. In the current sample, the recent diagnosis and relatively low levels of manic mood could have prevented this effect, and patients might have been still in the initial stages of the

disorder. The intake of antipsychotic medication, for example, showed little effect on the quadratic association between manic mood and IQ. Indeed, only 14 out of the 50 participants were even administered antipsychotic medication at the assessment point. While Donaldson et al. (2003) found the use of antipsychotic medication as being one of the most significant predictors of the IQ in BD-I patients, and Arts et al. (2010) who found a significant correlation with basic information processing and psychomotor speed, those observations could not be made in the current sample.

A third possible interpretation points towards a reversed association between IQ and manic symptoms, indicating an increased risk for manic symptomatology in patients with a higher IQ. Aligning with the discovery of Koenen et al. (2009) and Smith et al. (2015), that a higher childhood IQ predicted a higher risk of mania at the adult age, the only recently diagnosed participants in this study might have developed manic symptoms as a result of an increased childhood IQ. This theory is underlined by the findings of Gale et al. (2012), who observed an elevated risk of being admitted with bipolar disorder in male patients with high IQ scores. Koenders et al. and Kravariti et al. detected intellectual impairments in severely manic symptoms could again be attributed to previously mentioned processes hypothesized by several researchers as possibly harming the IQ over time. Nevertheless, this hypothesis could not be investigated, as no data on pre-illness IQ was available.

When observing group differences between the four detected symptomatic states, it becomes evident that the performance in the IQ assessment does not differ between groups. As previously discussed, those results could also be attributed to relatively low levels of symptom severity in the symptomatic groups. As a result, the three symptomatic groups might not have significantly differed from each other based on levels of clinical symptoms. Nonetheless, failure to detect differences between symptomatic and euthymic patients does not necessarily stand opposed to previously discussed research results (Vreeker et al., 2015; Dickerson et al., 2004; Toulopoulou et al., 2006), which were mainly performed with currently symptomatic patients or where differences in the performance between symptomatic states were not investgated. The study results point towards a global pattern of alteration in IQ among bipolar patients, regardless of the current symptomatic state, but further investigation including more representative groups for each different symptomatic state is needed to reach a conclusion.

5.2. Mood and IQ subtest performance

As expected, a significant effect of both symptomatic states on one cognitive area could be detected. A linear association of depressive mood on the performance in the subtest "Information", responsible for assessing verbal comprehension, was seized. The interpretation implies that the presence of depressive symptoms affects negatively verbal comprehension. Yet, the effect disappeared after controlling for confounders, which indicates that other factors were responsible for the alterations in this cognitive domain. The YMRS on the other hand showed a persistent significant quadratic association with the same subtest. While at low level to moderate levels of symptom severity the performance in the "Information" subtest was impaired, scoring increased with further symptom severity, following a similar pattern as it did for the overall SDIQ score. The results show that higher levels of manic symptoms might actually improve performance in this cognitive domain. Again, it can be observed that specifically one participant with a high SDIQ showed increased performance in the assessment. The score might be an outlier, and its impact on the curve is to be considered with caution. Nonetheless, the fact, that both mood types were significantly associated with this same subtest indicates that verbal comprehension might be the cognitive area that is affected the most by mood symptoms. Several studies have investigated the impact of mood symptoms on cognitive performance but findings in the different areas differ. When measuring the impact of mood on cognitive performance in euthymic patients: effects on attention, working memory, and learning became evident, while the executive functioning of the patient group remained intact (Ferrier et al. 1999). The depressive mood has been confirmed to correlate with dysfunction in speed and attention (Van der Werf-Elderling et al., 2010). In this study, only a few different types of cognitive performance were assessed, and performance was not significantly altered by the mood in three out of four. Results of one of the few studies using the same subtest (Vreeker et al., 2015; Kravariti et al., 2012), discovering an association of manic symptoms with processing speed, could not be confirmed. Also, no significant differences in the performance in VIQ or PIQ related subtests could be observed between depressive and (hypo-)manic symptomatology but observed effects might be attributed to the small number of subtests used, which cannot provide a full-scaled performance or verbal IQ.

5.3. IQ differences between BD-I and BD-II patients

Due to increased overall symptom severity and further positive symptoms, which also promote the intake of antipsychotic medication, BD-I patients were hypothesized to perform significantly worse than BD-II patients. Nonetheless, this hypothesis could not be confirmed by the results. BD-I patients indeed showed lower SDIQ scores when comparing the means of both groups, but no statistical significance was reached. Findings could be attributed to significant differences in the manic symptoms between those groups. Manic mood, which was initially hypothesized to show a negative effect on IQ, did actually increase the performance. BD-I patients were expected to perform worse than BD-II patients due to more severe manic symptomatology, might have instead experienced a favorable effect of their symptomatology. Another interpretation implies that secondary factors accompanying the increased symptom severity did not apply to the current sample. As mentioned previously, the participants in this study might not have reached a stage where first cognitive impairments become evident, and the levels of antipsychotic medication intake were relatively low. Nonetheless, this was not assessed in the current study, as a possible impact of chronicity could not be determined. The absence of group differences between BD-I and BD-II patients does not align with previous research detecting more severe levels of impairments in BD-I patients (Torrent et al., 2006; Simonsen et al., 2008). Nevertheless, mentioned studies concentrated on cognitive performance and not directly on IQ, as was the case in this study. While the cognitive profiles between BD-I and BD-II patients therefore might indeed differ, this was not assessed in this study.

5.4. Limitations

Several limitations might have compromised the validity of this study. First, the cross-sectional design of the study forbids investigating the causes and effects of the cognitive alterations. Several hypotheses regarding the findings could therefore not be followed up on, as no information about the previous course of illness was available. Moreover, a relatively low number of participants provided sufficient data at the assessment point to be included in the analysis. As the BINCO study is ongoing, data was only available for 50 patients at the time this study took place. The relatively small number of participants could have led to an overinterpretation of outlier scores, which impacted significantly curve progressions. Furthermore, the sample might lack representability, as all participants were from the Netherlands, recently diagnosed, and treated at only three different outpatient centers.

Consequently, it is to be suspected, that all participants share a similar socio-demographic background. Also, Berkson's bias might apply here, as participants were willing to participate in the study and following treatment during assessment (Regeer et al. 2009). Findings therefore only apply to a very restricted range of bipolar patients, who share both personal and illness characteristics with the study sample. Findings might not be representable for bipolar individuals with varied cultural affiliations or socio-demographic environments. Moreover, patients presenting severe manic or depressive symptoms were likely to be excluded from the current study, as the probability for reluctance to participate in an investigation or treatment dropout increases with increasing symptom severity (Oflaz et al., 2015, Baines et al., 2012, Brown et al., 2001). Correspondingly, no general assumptions about patients with severe mood symptoms could be made, as only a few individuals presenting with those symptoms were included in this study.

Second, the study lacks a control group, including individuals without any mood symptoms. There were relatively few euthymic patients included in the sample and the majority were experiencing subclinical mood symptoms, which is why this group was barred as a potential control group. Moreover, most of the patients were recently diagnosed or experiencing a first active episode of the disorder. As bipolar disorder often manifests between the age of 20 and 30, some participants might have not been able to finish their education, which is why the educational level could be an insignificant measure, providing only the patients' current state of education. This would also explain the low confounding effects observed. Other potential confounders that were hypothesized by other researchers to affect IQ and cognitive performance were not considered because the information was obtained through recall or self-report, which might have been compromised by personal experiences. Undetected confounding effects of those variables could have led to an overestimation of the effects of mood on IQ in manic and depressed patients. Next to the sample, the restricted range of assessments for cognitive performance restrained assumptions about the cognitive performance of bipolar patients. Previous studies reported impairments especially in the areas of executive functioning, verbal learning, and psychomotor speed, which were not assessed in this study.

Also, the mood assessment was performed using two different methods: one self-rated system for the depressive symptomatology and a clinician-rated one for the manic

symptomatology. This might have affected the scoring, as patients could evaluate the symptom severity differently from the clinician. Nonetheless, Hershenberg et al. demonstrated in 2020 that the agreement between the patient and the clinician-rated assessment was moderate to strong in patients suffering from treatment-resistant depression. Those findings might apply to participants who presented depressive symptoms at the assessment point, and scoring should be equivalent to a clinician-rated assessment. Last, a wide range of statistical tests were performed to obtain an overview of the multiple effects of mood on IQ and cognitive performance. This might have led to a Type I error due to multiple comparisons.

5.5. Implications for future research

The results obtained in this study provide indications of how the symptomatology in bipolar patients affects IQ and cognitive performance. Most effects did not reach statistical significance, which could be due to small sample sizes or to the study design. Replications with a cohort study and a larger number of participants would therefore allow further insight into symptomatic impacts and especially the evolution of the cognitive abilities over time. Of particular interest is the quadratic relation between manic symptomatology and IQ. While in previous studies by Kravariti et al. and Koenders et al. more severe levels of symptoms were associated with lower performance, this was not the case in this study, where performance increased with increasing symptom severity. Nonetheless, the findings are hypothesized to be attributed to the small number of participants presenting severe (hypo-)manic symptoms. A larger study including further patients with severe manic symptomatology is needed to explore in-depth their impact. Through a cohort study design, impairments could be tracked along the different stages of illness, elucidating whether the general level of IQ alteration increases and which factors might account for the deterioration.

As indicated in research by Potter et al. (2010) and Sackeim et al. (1992) the cognitive performance in schizophrenic and depressed patients is further associated with negative symptoms. Nonetheless, no such association could be determined in the studied sample. Replicating the trial including bigger sample sizes and a control group would be useful to investigate furhter the impact of depressive mood on IQ in bipolar patients. A significant compromising effect of mood on verbal comprehension in bipolar patients could open new paths for research, focusing on this specific cognitive field.

The absence of group differences between symptomatic and euthymic patients is also to be considered in future research, as it contradicts several previous studies on the topic. Again, bigger sample sizes and a control group of asymptomatic bipolar patients might emphasize the full impact of mood on IQ in bipolar patients. Discovering how mood interacts with IQ and cognitive abilities, and how other variables might compromise this interaction, could improve our understanding of neurological aspects of the disorder but also expand treatment methods, begetting a beneficial effect for patients and clinicians.

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7. Appendices

Table 1.

Baseline sociodemographic characteristics in 50 participants with bipolar disorder.

Variable Name	N or mean
Gender Female n (%)	28 (60.87)
Age mean (SD)	35.67 (12.01)
Bipolar Type-I n (%)	13 (28.89)
Educational Level mean (SD)	3.75 (1.12)
Level 1 n (%)	3 (6)
Level 2 n (%)	2 (4)
Level 3 n (%)	13 (26)
Level 4 n (%)	16 (32)
Level 5 n (%)	14 (28)
Psychopharmaca Use n (%)	39 (82.98)
Mood stabilizers n (%)	27 (57.45)
Antidepressants n (%)	11 (23.40)
Stimulants n (%)	4 (8.51)
Antipsychotic Medication n (%)	14 (29.16)
Benzodiazepine Use n (%)	15 (31.91)
SDIQ mean (SD)	102.92 (20.75)
Block design scale mean (SD)	9.28 (3.31)
Arithmetic scale mean (SD)	9.24 (2.60)
Information scale mean (SD)	10.38 (2.54)
Digit symbol scale mean (SD)	8.78 (2.57)
QIDS score mean (SD)	10.15 (7.00)
YMRS score mean (SD)	4.10 (4.02)

Table 2.

Linear and nonlinear associations between symptom severity scores and SDIQ in 50 participants with bipolar disorder

Scale	Term	Beta	p-value
QIDS linear:			
Crude	Linear	–.56	.20
Model 1	Linear	–.46	.33
Model 2	Linear	–.13	.80
YMRS linear:			
Crude	Linear	.09	.91
Model 1	Linear	.21	.79
Model 2	Linear	.71	.41
YMRS nonlinear:			
Crude	Linear	–4.61	.03
	Quadratic	.42	.01
Model 1	Linear	–4.43	.03
	Quadratic	.41	.02
Model 2	Linear	–3.57	.09
	Quadratic	.38	.03

Note. Crude: impact of symptom severity on SDIQ score

Model 1: additionally adjusted for Educational Level

Model 2: additionally adjusted for use of Benzodiazepines and antipsychotic medication

Table 3.

The association of mood scores with the cognitive performance

	Block Design	Arithmetic	Information	Digit Symbol Coding
QIDS linear				
Crude	–.05 (*.47*)	–.05 (*.39*)	–.10 (*.08)**	–.01 (*.10*)
Model 1	–.04 (*.64*)	–.05 (*.43*)	–.10 (*.09*)*	–.01 (*.11*)
Model 2	.01 (*.87*)	.01 (*.88*)	–.09 (*.16*)	.02 (*.82)*
YMRS linear				
Crude	–.04 (*.73*)	.05 (*.61*)	.03 (*.79*)	–.04 (.70)
Model 1	–.02 (*.89*)	.05 (*.60*)	.04 (*.64*)	–.03 (.76)
Model 2	.04 (*.77*)	.13 (*.24*)	.09 (*.41*)	–.01 (.93)
YMRS nonlinear				
Crude	.03 (*.31*)	.03 (*.13*)	.05 (*.03*)**	.03 (.13)
Model 1	.03 (*.33*)	.03 (*.13*)	.05 (*.03*)**	.03 (.14)
Model 2	.02 (*.53*)	.03 (*.19*)	.04 (*.04*)**	.03 (.16)

Note. Data are Beta coefficients (*P-value*)

*$p < .1$

**$p<.05$

Table 4.

Group differences between symptomatic states (ANCOVA)

Model	*Sum of squares*	*F*	*p-value*	*Partial ETA squared*
Crude	165.30	.12	.95	.01
Model 1	196.34	.14	.94	.01
Model 2	565.50	.42	.74	.03

Note. Crude: differences in the impact of symptomatic states on SDIQ score

Model 1: additionally adjusted for Educational Level

Model 2: additionally adjusted for use of Benzodiazepines and antipsychotic medication

Table 5.

Independent samples t-test for bipolar type I and type II disorder

						95% CI	
Variable		*F*	*p*	*t*	*df*	*LL*	*UL*
SDIQ	Equal variances assumed	.30	.59	−1.08	43	−20.38	6.14
	Equal variances not assumed			−1.12	24.12	−20.21	5.97

Figure 1.

Histogram illustrating the distribution of SDIQ scores

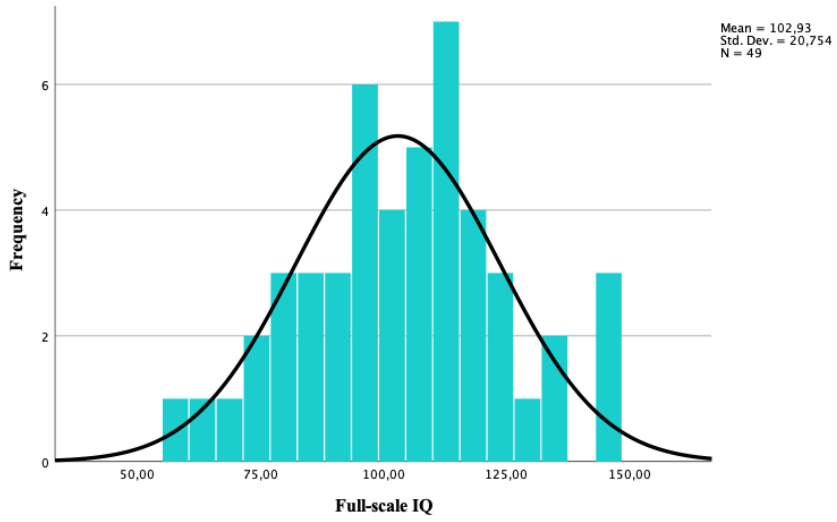
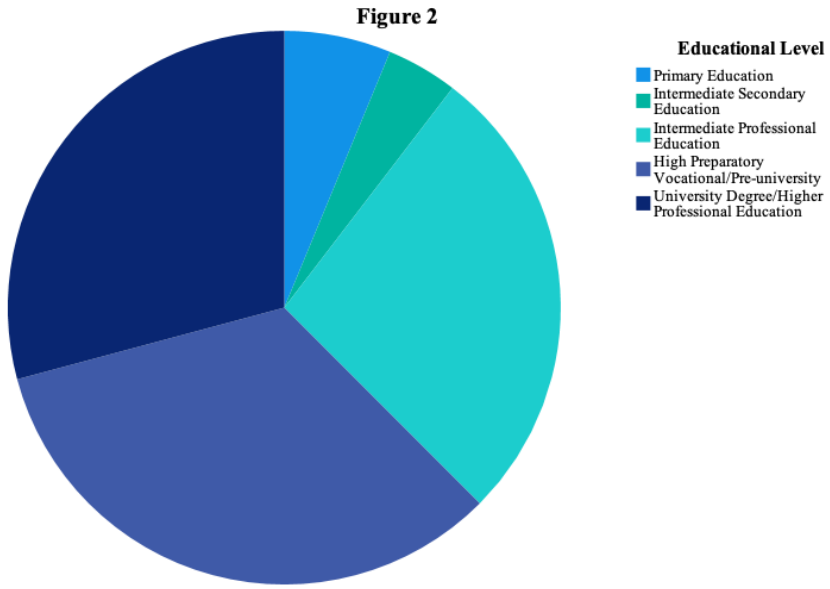


Figure 2.

Pie chart illustrating the distribution of educational levels



Note. The number of participants in each educational level is represented ascendant from level 1 to level 5.

Figure 3.

SDIQ scores by Educational Level

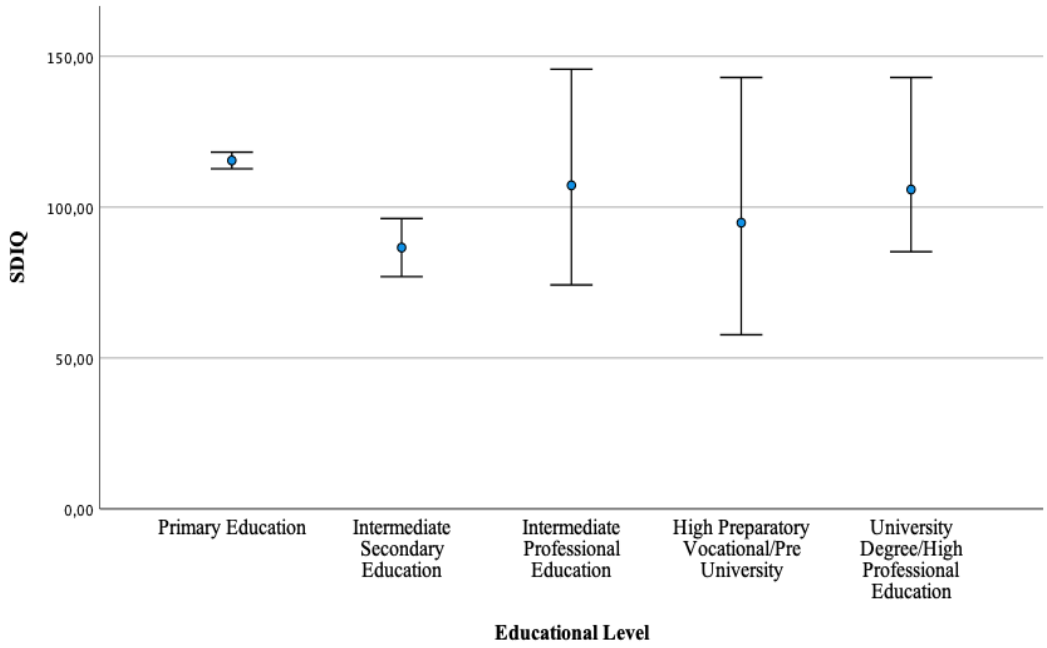


Figure 4.

Curvilinear regression analysis

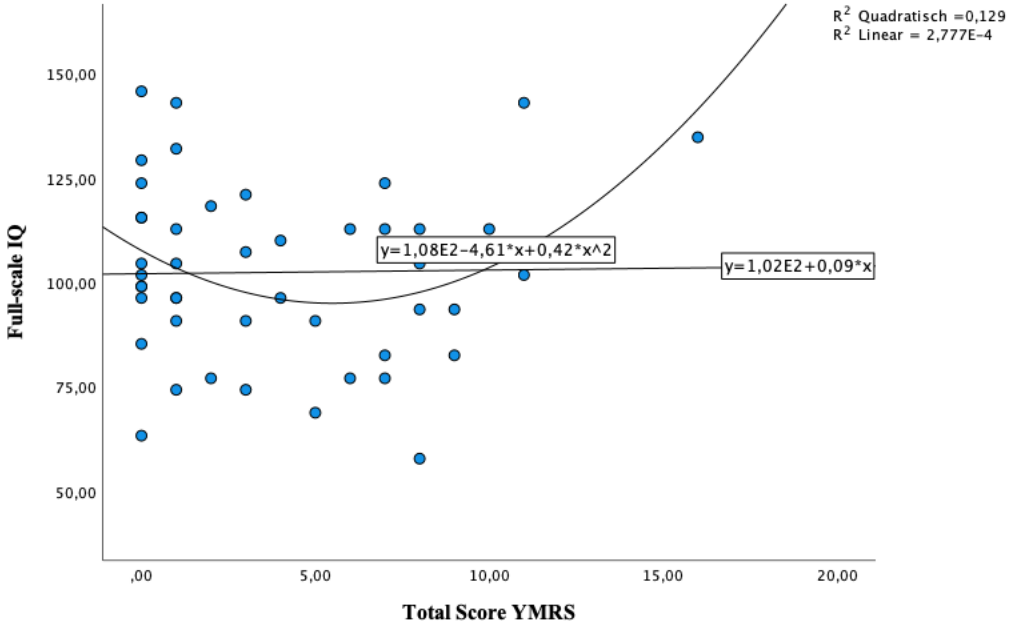


Figure 5.

Linear regression between the QIDS-C score and the performance in the subtest "Information"

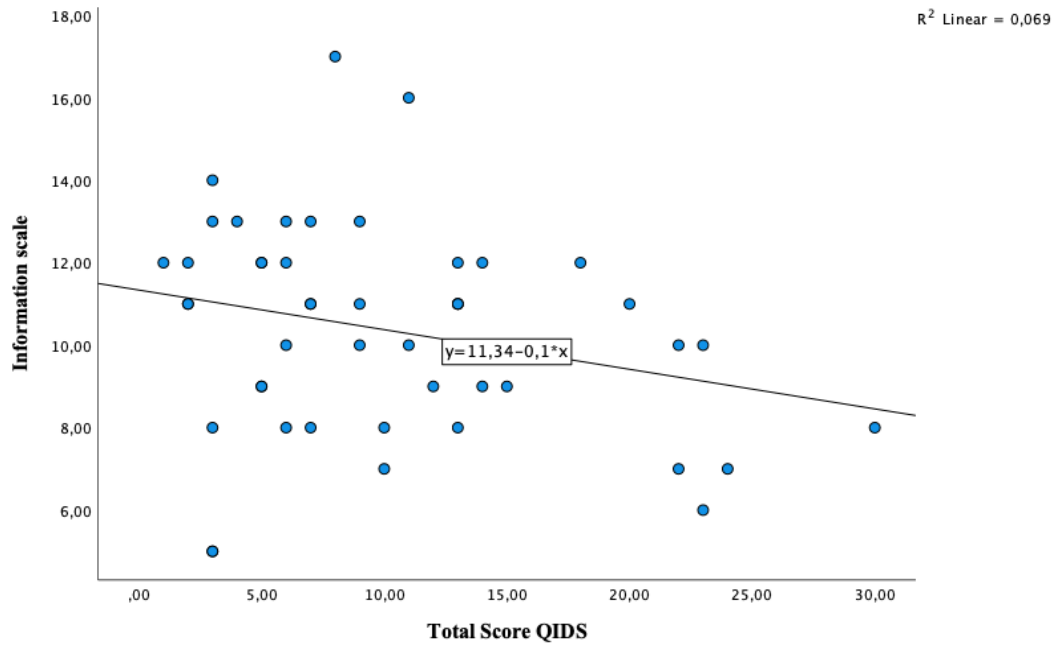


Figure 6.

Curvilinear regression between the YMRS score and the performance in the subtest „Information"