Associations between metabolic syndrome, immune dysregulation and cognitive functioning in bipolar disorder.

FF (Frederike) Kroll, S4093690

Master Behavioral and Cognitive Neurosciences (BCN), Faculty of Science and Engineering (FSE), University of Groningen

Minor thesis

Supervisor: Dr. BCM (Benno) Haarman, Department of Psychiatry, UMCG

Time of internship: 10.02.2020 – 30.06.2020

Date: 30.06.2020

Abstract

Bipolar disorder (BD) patients do not only suffer from mood symptoms but also show a variety of neurocognitive deficits in attention, memory, learning and social cognition. Many patients suffering from the disease do not benefit adequately from currently available treatment options and quality of life is often low. A possible way of improving cognitive impairments would be to treat prevalent inflammatory comorbidities, specifically metabolic syndrome and autoimmune disease, that may aggravate BD symptoms. The study population was provided by the *Lifelines* cohort study and included 494 adult BD subjects and 494 age-, sex- and education-matched controls with no psychiatric diagnoses. Metabolic syndrome was assessed based on the National Cholesterol Education Program Adult Treatment Panel III guidelines and autoimmune disease was defined by the American Autoimmune Related Diseases Association. Cognitive performance was tested using the Mini-Mental State Exam, the CogState Brief Battery and the Ruff Figural Fluency Test. Indeed, the prevalence of both metabolic syndrome (30.6% vs 14.2%) and autoimmune disorder (15.2% to 9.3%) is higher in the BD group compared to the controls. However, having a comorbidity did not significantly impair cognitive performance of the BD subjects. Nevertheless, BD patients should be screened for autoimmune disorder and metabolic syndrome regardless of its effects on cognitive performance to ensure the best possible treatment and highest quality of life outcomes.

Contents

Introduction

Bipolar disorder (BD) is a severe psychiatric affective disorder in which patients experience symptoms of (hypo)mania, depression or a mixed episode (Renes et al., 2014). In the Netherlands, the lifetime prevalence of BD is estimated to be 1.9% (ten Have et al., 2002). BD can be categorized into two subtypes: BD I, which manifests in at least one manic episode and can be accompanied by depressive episodes, and BD II, with at least one depressive and one hypomanic episode (Diflorio et al., 2010). The disease may manifest differently between sexes in that men with BD type I are generally more prone to manic episodes than their female counterparts, and some, but not all studies suggest that the prevalence of BD type II is higher in women than men (Diflorio et al., 2010). Smoking prevalence is around two to three times higher in BD patients compared to the general population (Heffner et al., 2011) and it is one of the contributing factors for the elevated risk of cardiovascular morbidity and mortality that can occur 10-25 years earlier than in healthy controls (Depp et al., 2016). Many patients suffering from the disease do not benefit adequately from currently available treatment options (Renes et al., 2014) and the quality of life is often low due to an insufficient recovery between episodes of mania or depression (ten Have et al., 2002).

Bipolar patients do not only display affective symptoms but also a variety of neurocognitive deficits, that only partially disappear during euthymia (Burdick et al., 2015). These include deficits in attention, verbal memory and learning, working memory and executive function (Burdick et al., 2015; Suwalska et al., 2014). Bipolar patients also show impaired social cognition as they are less able to assess intention of others (Latalova et al., 2011). A recent review suggests three neurocognitive subtypes among BD patients: those with normal cognitive performance, modest impairments, and lastly more severe impairments that impact several of the stated domains (Solé et al., 2017). There appears to be an influence of sex on cognitive performance, with females performing better than males in verbal memory and cognitive flexibility (Vaskinn et al., 2011) but worse in planning ability, attention and spatial working memory (Suwalska et al., 2014). Some research suggests that smoking may be associated with better short-term cognitive performance (Depp et al., 2016), but other studies present no significant differences in verbal learning and memory, associative learning and attention (Law et al., 2009).

Currently, the main treatment option for bipolar patients is the use of psychotropic medication such as lithium, antipsychotics, anticonvulsants and antidepressants (Szalach et al., 2019). At least some psychotropics are negatively linked to cognitive performance, accounting for up to a quarter of the total effect of BD on cognitive performance (Cullen et al., 2019). Lithium use is associated with subtle performance losses in verbal learning, short-term memory and psychomotor performance (Burdick et al.,

2015; Dias et al., 2012), however improvements in bipolar depression, particularly in attention and working memory, have been positively associated with lithium serum concentration as well (Dias et al., 2012; Steen et al., 2016). The evidence on antipsychotics is mixed; some may diminish cognitive responsiveness while others positively affect cognition (Burdick et al., 2015; Dias et al., 2012)., whereas anticonvulsants (Burdick et al., 2015; Steen et al., 2016) seem to only impair cognition. Even though the evidence suggests a negative effect of psychotropics on cognition, treatment-naïve BD patients show signs of cognitive impairment already, specifically in verbal memory (Mak et al., 2018).

BD is a neuro-progressive disorder, meaning that clinical deterioration can be seen over the years (Gama et al., 2013). There is a complex interaction between the immune system of the periphery and the central nervous system, and it is not yet established whether immune factors such as cytokines can transverse the blood brain barrier. However, clear associations can be observed between peripherally circulating cytokines in serum and the same cytokines being elevated in cerebrospinal fluid (Rosenblat, 2017). An immune dysfunction in BD may be the cause of excitotoxicity and enhanced oxidative stress (Barbosa et al., 2014; Perugi et al., 2015) which cause damage over time. Recent studies have found that BD patients have an increase in pro-inflammatory markers, specifically cytokines, complement factors, chemokines and T-cell-related activation markers (Anderson et al., 2015; Perugi et al., 2015). A clinical trial found that in men with elevated levels of multiple inflammatory markers, the onset of manic symptoms was particularly high (Becking et al, 2014). Serum c-reactive protein (CRP) levels, a robust measurement for inflammation, correlate with cognitive impairment in BD patients (Dickerson et al., 2013). When investigating inflammation-related monocyte gene expression in BD patients, it was found that immune activation could lead to an earlier age of onset and that during the course of the disease, there is an increased immune system dysregulation (Haarman et al., 2013). This immune dysregulation is thought to influence mood episodes, as a strong inflammatory state is found during mood episodes compared to depressive or euthymic states (Fiedorowicz et al., 2015). A recent review concluded that anti-inflammatory agents could be used to treat acute bipolar depression as well as improve manic symptoms (Rosenblat, 2019). This shows that the immune system may be a target for treatment of the disease additionally to conventional pharmacological treatment.

Additional evidence for an involvement of the immune system in BD is the high prevalence of inflammatory comorbidities. The conditions most often seen in bipolar patients are metabolic syndrome or its components and several autoimmune diseases (Perugi et al., 2015). Metabolic syndrome (MetS) is a multifactorial disease that is defined by having three or more of the following criteria: central obesity,

heightened serum triglycerides, high blood pressure, low HDL-cholesterol and high fasting glucose levels (Howard, 2006). The comorbidity of BD and MetS is high, as the prevalence of MetS is around twice as high in BD patients compared to the general population (Holt et al., 2010). The existence of MetS seems to be correlated not only to the onset, but also to the disease progression of BD. Comorbidity of the two are associated with more unfavorable response to pharmacological treatment and even a higher probability of suicide (Kesebir et al., 2018). Persistent low-grade levels of inflammation are common among MetS patients and having an immune dysregulation is thought to increase the risk of MetS in BD individuals (SayuriYamagata et al., 2017). There seems to be a reciprocal relationship between immune dysregulation and MetS: Pro-inflammatory cytokines may promote insulin resistance and thus type 2 diabetes, while in obesity higher leptin levels cause infiltration of macrophages and systemic inflammation. Research has shown that having MetS can impair cognition in otherwise healthy individuals. A study reported lower test scores in verbal fluency, construction recall, word list learning and attention in the MetS group compared to healthy controls (Oh et al., 2011). In a bipolar cohort, overweight patients scored significantly lower on psychomotor processing speed and verbal fluency, however these results were no longer significant when adjusted for age and years of education (Restrepo Moreno et al., 2019). Hypertension was significantly associated with more severe cognitive deficits, whereas investigating triglyceride levels and dyslipidemia provided mixed results (Bora et al., 2019). Global cognition, executive functions and social cognition are more impaired in BD patients suffering from MetS (Bora et al., 2019).

BD is also associated with a list of autoimmune diseases such as autoimmune thyroiditis (Kupka et al., 2002; Vonk et al., 2007), Crohn's disease (Eaton et al., 2010), rheumatoid arthritis (Hsu et al., 2014), multiple sclerosis (Cremaschi et al., 2017) and celiac disease (Carta et al., 2015). Likewise, patients with autoimmune disease have an increased risk of developing BD (Benedetti et al., 2020). Autoimmune disorders are defined as the presence of immune dysregulation where host tissue is falsely recognized as pathogenic, which triggers an inflammatory response and the release of pro-inflammatory cytokines (Rosenblat, 2017). It is hypothesized that in BD, this chronic low-grade inflammation is thought to disrupt the hypothalamic-pituitary-adrenal axis and contribute to the progression of the disease (Ferreira et al., 2016). BD patients show a reduction in T-regulatory lymphocytes ($CD4^+CD25^+Foxp3^+$) which are related to the inhibition of developing autoimmune diseases (Barosa et al., 2014). There have been no studies investigating the effect of autoimmune disorders on cognitive performance in bipolar patients yet. Given their pro-inflammatory nature and evidence that high CRP levels correlate with cognitive impairment (Dickerson et al., 2013), autoimmune disorders may well contribute to the cognitive deficits that can be seen in bipolar patients.

In conclusion, MetS and autoimmune diseases both seem to be correlated to BD and could potentially feed into the chronic inflammation in BD and be partially responsible for cognitive impairments in patients. The available drugs for BD do not treat the inflammatory comorbidities associated with it, but on the contrary, can even accelerate them (Barbosa 2014). If a link between BD, inflammatory comorbidities and cognitive decline could be established, anti-inflammatory agents could be used additionally to the current treatment. Therefore, it is important to investigate whether demographic (age, sex, education, smoking behavior) and clinical (use of psychotropics) variables are associated with having either of these comorbidities. If so, diagnosis and treatment of MetS and autoimmune disorders simultaneously with the management of psychiatric aspects of BD could be considered to delay BD onset and decelerate its progression. It could also be used to predict and modify cognitive performance.

This study aims to answer what the prevalence of metabolic syndrome and immune dysregulation is in BD subjects compared to healthy controls. We will investigate whether age, sex, education, smoking behavior, MetS components, individual autoimmune disorders and use of psychotropics are correlated with the prevalence of these comorbidities, as well as whether they impact measures of functioning in BD. We first hypothesize that the prevalence of metabolic syndrome as well as autoimmune disorder will be higher in the BD group. Second, we hypothesize that age, sex, education, smoking behavior and the use of psychotropics will be able to predict the occurrence of these comorbidities. Last, we hypothesize that cognitive function is negatively impacted by having either metabolic syndrome or autoimmune disorder additionally to BD.

Methods

Database

Data of the study population was provided by the *LifeLines* cohort study. *LifeLines* is a large, multigenerational study that included over 167,000 participants from the North of the Netherlands. The present study used cross-sectional data from the baseline (2017) measurement. The LifeLines cohort study was approved by the Medical Ethics Committee of the University Medical Center Groningen.

Subjects

The study population included 494 adult (18+) subjects with a self-reported diagnosis of bipolar disorder as well as 494 age-, sex- and education-matched controls with no psychiatric diagnoses. Duration of disease and medication use was not relevant for inclusion in the BD group.

Study variables

Age, sex, highest education level, smoking exposure, autoimmune disorders and psychotropic use were self-reported by subjects. Age category was defined by the first number of the subject's age, meaning that 18-19 years were put in category 1, 20-29 years in category 2 and so on; eight categories were established. Metabolic syndrome was classified according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines (Howard, 2006) as having at least three of the metabolic abnormalities listed in Table 1, measured by the general practitioner (GP). Autoimmune disorder was defined as having one or more autoimmune disorders listed by the American Autoimmune Related Diseases Association ("Autoimmune Disease List • AARDA", 2020).

Table 1: Metabolic abnormalities characterizing metabolic syndrome, according to the NCEP ATP III guidelines.

Clinical Measure	**NCEP ATP III (2001): at least three of the five criteria below**
Waist circumference	>40 inches for men, >35 inches for women
Triglycerides	>=150 mg/dl or drug treatment for elevated triglycerides
Fasting glucose	>=100mg/dl or drug treatment for elevated blood glucose
HDL cholesterol	<40 mg/dl for men, <50 mg/dl for women or drug treatment for low HDL cholesterol
Blood pressure	>130 mmHg systolic or >85 mmHg diastolic or drug treatment for elevated blood pressure

Cognitive functioning was measured in 40 BD subjects and 32 healthy controls using the Mini-Mental State Exam (*MMSE*) which included 30 questions testing orientation, attention, memory, language and visual-spatial skills (Folstein et al., 1975). *MMSE* scores required for passing the test were adjusted for each subject according to their highest level of education reached. Additionally, 297 BD and 298 healthy participants completed the Ruff Figural Fluency Test (*RRFT*) (Ruff, 1996). The *RFFT* is a paper and pencil test measuring non-verbal fluency, specifically non-verbal capacity for initiation, planning, and divergent reasoning. The test consists of five 60-second parts, each with a different stimulus presentation, in which the subjects draw as many unique designs as possible by connecting dots in different patterns ("PAR | RFFT | Ruff Figural Fluency Test", 2020). The total number of unique designs is the outcome measure of the *RFFT*. Cognitive functioning was also assessed with the CogState Brief Battery (*CBB*) (Fredrickson et al., 2010) test in 194 BD subjects and 205 healthy controls. The CBB has good test-retest reliability, construct and criterion validity and the sensitivity of the CBB subtests have been established in literature ("Featured Batteries - Cogstate Ltd", 2020). In this study the One Card Learning task, a continuous visual recognition learning task assessing learning and attention, was selected. Reaction time, measured as

mean of the log10 transformed reaction time for correct responses and accuracy, measured as arcsine square root hit rate (correct responses divided by total responses) were the outcome measures.

Statistical analysis

For statistical analysis, the software SPSS version 25 was used. To explore the subject characteristics, a descriptive analysis of age (mean±SD) and sex (%) in BD subjects and healthy controls was carried out. The prevalence of metabolic syndrome and autoimmune disease was determined and differences in prevalence between the groups were tested using X^2 test. Differences in demographic (age, sex, education, smoking behavior) and clinical (MetS components, individual autoimmune disorders, use of psychotropics) variables were examined using X^2 test for categorical variables and independent t-tests for continuous variables. To investigate the influence of different independent variables on the dichotomous dependent variables MetS and immune dysregulation (yes/no) for both BD subjects and controls, a binary logistic regression was performed using the backward method. A X^2 test for the *MMSE* and independent t-tests for the *CBB* and *RFFT* were used to test group differences between BD subjects and healthy controls. Independent t-tests were used to investigate differences in cognitive performance in the BD group between those with no comorbidities and those with either MetS or autoimmune disease. Predictors of cognitive performance for the *CBB* and *RFFT* were assessed with linear logistic regression using the backward method. For all analyses, a p-value of <0.05 was considered as statistically significant.

Results

Subject characteristics

The study population includes 493 BD subjects and 493 controls, both of which have an average age of 46.7 years (SD=10.8) with ages ranging from 19 to 83 years. Both groups were made up of 193 (39.1%) males and 300 (60.9%) females.

Prevalence of immune dysregulation

The prevalence of metabolic syndrome was significantly higher in BD subjects (151 cases, 30.6%) compared to the control group (70 cases, 14.2%), X^2 (df=1, N=986) = 38.26, $p < 0.001$. Table 2 summarizes the characteristics for MetS per group. BD subjects had on average a significantly higher waist circumference, $t(984) = 4.16$, $p < 0.001$, higher fasting glucose levels, $t(982) = 2.64$, $p < 0.05$ and higher triglyceride levels, $t(623) = 3.91$, $p < 0.001$ but lower HDL cholesterol levels, $t(984) = -3.35$, $p < 0.001$ and lower systolic blood pressure, $t(984) = -2.22$, $p < 0.05$. Diastolic blood pressure did not differ significantly

between groups, $t(975) = 1.4$, $p = 0.16$. Similar to the prevalence of metabolic syndrome, there were more cases of having at least one autoimmune disorder in the BD group (75 cases, 15.2%) than in the healthy controls (46 cases, 9.3%), X^2 (df=1, N=986) = 7.92, $p < 0.05$.

*Table 2: Characteristics of metabolic syndrome (waist circumference, systemic/diastolic blood pressure, fasting glucose levels, HDL cholesterol, triglycerides) for BD subjects and healthy controls. Results are givenin mean ± standard deviation. * p < 0.05.*

	BD subjects	**Healthy controls**
Waist circumference	94.64 ± 14.05*	91.12 ± 12.45
Systemic blood pressure (mmHg)	124.09 ± 14.6*	126.22 ± 15.59
Diastolic blood pressure (mmHg)	74.05 ± 9.03	74.89 ± 9.9
Glucose (mmol/L)	5.19 ± 1.02*	5.02 ± 1.02
HDL cholesterol (mmol/L)	1.41 ± 0.41*	1.49 ± 0.42
Triglycerides (mmol/L)	1.56 ± 1.93*	1.2 ± 0.71

Table 3 summarizes the counts of each autoimmune disorder per group. Fibromyalgia and rheumatoid arthritis occurred significantly more often in the BD group, X^2 (df=1, N=986) = 4.49, $p < 0.05$ and X^2 (df=1, N=986) = 7.01, $p < 0.05$, while there was no significant difference in psoriasis prevalence between groups, X^2 (df=1, N=986) = 2.61, $p = 0.11$. Celiac disease, endometriosis, lupus, Meniere's disease, psoriatic arthritis and Raynaud's phenomenon were only detected in the BD group whereas chronic Lyme disease occurred only in healthy controls.

*Table 3: Counts of individual autoimmune diseases in BD subjects and healthy controls- *p<0.05.*

Autoimmune disease	**Count in BD subjects**	**Count in healthy controls**
Celiac disease	7	0
Chronic Lyme disease	0	2
Endometriosis	1	0
Fibromyalgia	34*	19
Lupus	1	0
Menière's disease	1	0
Multiple sclerosis	3	3
Psoriasis	25	15
Psoriatic arthritis	1	0
Raynaud's phenomenon	1	0
Rheumatoid arthritis	27*	11

Demographic and clinical variables associated with immune dysregulation

The ratio of males to females, mean age, the maximally reached education level, smoking behavior and psychotropic use categorized by not having any comorbidities, having MetS or autoimmune disorder can be seen in Table 4: Summary of demographic and clinical variables in the BD group. Given are sex and mean age +- SDTable 4.

*Table 4: Summary of demographic and clinical variables in the BD group. Given are sex and mean age +- SD, education level ([2]=LTS, LEAO, LHNO, VMBO, [3]=MAVO, MULO, MBO-short, VMBO-t, [4]=MBO-long, Gymnasium, VWO, Atheneum, INAS, [5]=HAVO, VWO, Atheneum, gymnasium, HBS, MMS, [6]=HBO, HTS, HEAO, doctoral university education, Bachelor's), smoking exposure and psychotropic use per subgroup.BD = bipolar disorder, MetS = metabolic syndrome, AD = autoimmune disease. *p < 0.05.*

	BD + no MetS + no AD	**BD + METS**	**BD + AD**
Sex			
Male	125 (41.9%)	56 (37.1%)	19 (25.3%)
Female	173 (58.1%)	95 (62.9%)	56 (74.7%)
Age			
Mean ± SD	45 ± 11	49±11	48±9
Education			
No education	3 (1%)	4 (2.6%)	3 (4%)
Primary school	18 (6%)	6(3.9%)	2 (2.7%)
Lower or preparatory secondary vocational education[1]	45 (15.1%)	36 (12.1%)	11 (14.7%)
Junior general secondary education[2]	32 (10.7%)	20 (13.2%)	11 (14.7%)
Secondary vocational education or work-based learning[3]	73 (24.5%)	45 (29.8%)	24 (32%)
Senior general secondary or pre-university education[4]	37 (12.4%)	9 (5.9%)	8 (10.7%)
Higher vocational education[5]	69 (23.2%)	18 (11.9%)	11 (14.7%)
University education	16 (5.4%)	6 (3.9%)	2 (2.7%)
Smoking			
Yes	88 (29.5%)	62 (41.1%)	22 (29.3%)
No	92 (30.9%)	43 (28.5%)	22 (29.3%)
Past	100 (33.6%)	43 (28.5%)	31 (41.3%)
Parents smoked during childhood			
Yes	194 (65.1%)	117 (77.5%)	63 (84%)
No	69 (23.2%)	18 (11.9%)	7 (9.3%)
Psychotropic use			
Antipsychotics	50 (16.7%)	17 (15.3%)	10 (13.3%)
Benzodiazepines and other hypnotics/sedatives	61 (20.5%)	40 (26.5%)	21 (28%)
Antidepressants	39 (13.1%)	22 (14.6%)	10 (13.3%)
Psychostimulants	1 (0.3%)	2 (1.3%	0 (0%)
Lithium	90 (30.2%)	34 (22.5%)	13 (17.3%)

After correction for the confounders sex, age, smoking behavior and psychotropic use the binary logistic regression revealed that a higher age category ($p < 0.05$) and smoking behavior ($p < 0.05$) was significantly associated with having MetS in BD subjects, χ^2 (df=9, N=472) = 26.11. There was a significant association between being female ($p < 0.001$) and lithium use ($p < 0.05$) with having an autoimmune disorder and BD, χ^2 (df=10, N=472) = 34.55.

Cognitive performance

MMSE

The percentage of people who passed the MMSE was significantly higher in the control group compared to the BD subjects, X^2 (df=1, N=72) = 6.203, $p < 0.05$. Within the BD group however, subjects with MetS or autoimmune disorder did not perform significantly worse on the MMSE, X^2 (df=1, N=40) = 0.505, $p = 0.477$ and X^2 (df=1, N=40) = 0.061, $p = 0.805$, respectively.

CBB

The accuracy measurement did not significantly differ between healthy controls and BD subjects, t(403) = -0.161, p = 0.872, as well as it did not differ within the BD group based on having autoimmune disorder, t(193)=0.126, p = 0.9 or having MetS, t(193) = 0.907, p = 0.366. After controlling for the confounders age, sex, psychotropic use and smoking behavior, the only variable associated with worse performance of BD subjects on the accuracy test was lithium use, ß = -0.105, t(186) = -2.24, $p < 0.05$.

Similar findings were obtained in the speed measurement. Reaction speed did not significantly differ between groups, t(397) = -1.019, p = 0.309, and neither those with MetS or autoimmune disorder within the BD group performed worse than those with only BD, t(192) = -0.261, p = 0.794 and t(192) = -0.339, p = 0.735, respectively. Again, only lithium use was associated with an increase in reaction time of BD subjects after controlling for confounders, ß = 0.095, t(185) = 2.706, $p < 0.05$.

RFFT

The number of unique designs significantly differed between groups, with healthy controls coming up with more designs than the BD subjects, t(593) = 2.791, $p < 0.05$. However, within the BD group there was no difference between those with and without MetS, t(295) = -0.932, p = 0.352, and those with and without autoimmune disorder, t(295) = 1.513, p = 0.13. A linear regression revealed that within the BD subjects, a higher age category,ß = -0.919, t(282) = -3.504, $p < 0.01$, lower education level, ß = 0.907, t(282)

= 5.451, $p < 0.01$ and lithium use, ß = -1.776, $t(282) = -2.705$, $p < 0.01$ were associated with thinking of less unique designs.

Discussion

The current study aimed to answer what the prevalence of MetS and autoimmune disorder is in BD subjects compared to healthy controls. As hypothesized, the prevalence of both MetS (30.6% vs 14.2%) and autoimmune disorder (15.2% to 9.3%) is higher in the BD group compared to the controls. It was investigated whether age, sex, education, smoking behavior and use of psychotropics could be correlated to higher prevalence of these disorders in the BD subjects. After correcting for confounders, only age category and smoking behavior were identified as predictors for having metabolic syndrome. Being female and using lithium as mood stabilizer significantly predicted having an autoimmune disorder additionally to BD. Finally, it was tested whether cognitive performance would be negatively associated with having MetS or autoimmune disorder. The *MMSE* passing rates were significantly higher in the healthy controls, but results did not significantly differ between BD subjects with or without one of the comorbidities. Both accuracy and speed measured by the *CBB* were not influenced by having MetS or autoimmune disorder, and the use of lithium use was identified as sole predictor of poorer accuracy and higher reaction time. The results indicate that smoking, level of education, sex and psychotropic use did not influence speed and accuracy measurements. There was no difference in unique designs between BD subjects with or without MetS or autoimmune disorder, however the regression analysis revealed a higher age category predicting lower non-verbal fluency and having autoimmune disorder predicting higher non-verbal fluency scores.

The prevalence of both MetS and autoimmune disorder is higher in the BD group, confirming the hypothesis. This is in line with the idea that the immune system is over-reactive in at least some subjects with BD. Having MetS, as a BD subject, was predicted by being in a higher age category and being a smoker. These results agree with the study of Hildrum et al. (2007) observing a drastic increase of MetS with age, as well as a review stating that tobacco smoking is associated with an elevated risk of dyslipidemia, higher waist circumference and insulin resistance (Balhara, 2012). In line with previous research showing a sex effect in autoimmune disorder prevalence (Ngo et al., 2014), within the BD group being female significantly predicted being more affected by autoimmune disorder. Unexpectedly, lithium use was a second predictor for having an autoimmune disorder in the BD cohort. There are no similar studies revealing an association between lithium and autoimmune disorder as of now, which limits the generalizability of this result to the general population.

The significant difference in MMSE passing rates as well as the lower performance in non-verbal fluency in BD subjects compared to controls was in line with previous research confirming a cognitive impairment, specifically in attention and working memory, in BD patients (Burdick et al., 2015; Suwalska et al., 2014). In contrast to previous research describing lower attention (Oh et al., 2011) and worse executive functions (Bora et al., 2019) in subjects suffering from MetS, having MetS did not impair any of the cognition measures in the BD subjects. This may be due to differences in the cognitive tests used, as the results cannot be directly compared when using various test batteries. Measures of reaction speed and accuracy were not influenced by having an autoimmune disorder additionally to BD. Since this is the first study investigating the potential effect of autoimmune disorder in BD, there are no studies validating these results.

There was no effect of sex on cognitive performance, contradicting the result of Vaskinn et al. (2011) and Suwalska et al. (2014) highlighting differences in cognitive flexibility and attention. The results of the regression analysis on speed, accuracy and non-verbal fluency contradict the claims of Depp (2016) which state that current smokers show worse cognitive performance compared to non-smokers. In the current study, smoking behavior was not a predictor of cognitive performance. The results also oppose previous studies describing a detrimental effect of psychotropics on cognitive performance. Besides lithium, neither psychotropic medication was a predictor for loss in cognitive function, although the literature describes effects for antipsychotics (Burdick et al., 2015; Dias et al., 2012) and anticonvulsants (Burdick et al., 2015; Steen et al., 2016). This may be evidence supporting the findings of Mak et al. (2018) that suggest cognitive impairment is already present in treatment-naïve BD patients and is at least not entirely due to medication effects. The observed negative effect of lithium use on accuracy and reaction time is in line with research illustrating performance losses in psychomotor performance (Dias et al., 2012). However, another possible explanation for the observed effect may be that in patients with long-term BD who suffer from more severe cognitive decline, lithium use is more prevalent. This would mean that there is no direct link between lithium use and cognitive decline, but rather between severity of disease and cognitive decline. As several studies point out the protective effects of lithium on cognition (Dias et al., 2012; Steen et al., 2016), no definite conclusion should be drawn from this result.

The current study has several limitations. Firstly, the prevalence of bipolar disorder and autoimmune disease were self-reported by the subjects, and only the components of metabolic syndrome were assessed by their GP. This may imply that some subjects did in fact not have a valid diagnosis, or that other potential subjects may have been overlooked due to not completing the health questionnaire. The

questionnaire also did not distinguish between bipolar I and II, which may have affected the cognitive impairment analyses. A previous study found that although an impairment can be seen in both classifications of the disease, there is evidence that the impairment in bipolar I or in patients with a history of psychosis is higher (Burdick et al., 2015). The lack of evidence for a cognitive impairment caused by having MetS or autoimmune disorder could also be explained by the mental state of the subjects which was not recorded in the current study. A previous study demonstrated that depressed patients show more severe cognitive impairments compared to euthymic and hypomanic patients (Malhi et al., 2007). Since BD is a neuro-progressive disorder, the duration of disease is much relevant for measuring cognition. Variables including age at the onset of the first mood episode, duration of the current episode and illness course characteristics were not recorded although it is established that BD patients with a more severe illness may have more pronounced cognitive impairment (Law et al., 2009). Also not recorded were the dosages of medication, which may explain why the results could not confirm the evidence that cognition is impaired by psychotropic use (Cullen et al., 2019; Burdick et al., 2015; Steen et al., 2016). Lastly, not all subjects participated in the cognitive tests which limits the generalizability of the results, especially for the MMSE with only 72 participants.

Further research is needed to establish whether BD patients without inflammatory comorbidities show the same immune marker profile as the ones with metabolic syndrome or autoimmune disorder. Elevated peripheral inflammatory markers may be the main cause of cognitive impairment and should be included in upcoming studies. Future studies should take into account the current mental state of patients, as cognition may vary greatly depending on whether the patient is experiencing depression, mania or euthymia. Clinical trials investigating the effects of anti-inflammatory medication on mood symptoms in BD patients should also record possible improvements in cognition.

Conclusion

In conclusion, both metabolic syndrome and autoimmune disease affect a significant amount of BD subjects, underlining the possible involvement of the immune system in the pathophysiology of bipolar disorder. There are some differences in cognitive performance, specifically in attention, memory and non-verbal fluency between BD subjects and healthy controls, however these differences could not be explained by having either of the inflammatory comorbidities. Nevertheless, BD patients should be screened for autoimmune disorder and metabolic syndrome regardless of its effects on cognitive performance to ensure the best possible treatment and highest quality of life outcomes. Using anti-

inflammatory agents as opposed to lithium, which has repeatedly been shown to impair cognition, may pose a new strategy to tackle the complexity of bipolar disorder.

References

Anderson, G., & Maes, M. (2015). Bipolar disorder: Role of immune-inflammatory cytokines, oxidative and nitrosative stress and tryptophan catabolites. *Current Psychiatry Reports, 17*(2), 8-8. https://doi.org/10.1007/s11920-014-0541-1

Autoimmune Disease List • AARDA. AARDA. (2020). Retrieved 14 March 2020, from https://www.aarda.org/diseaselist/.

Balhara, Y. (2012). Tobacco and metabolic syndrome. *Indian Journal Of Endocrinology And Metabolism*, *16*(1), 81. https://doi.org/10.4103/2230-8210.91197

Barbosa, I. G., Machado-Vieira, R., Soares, J. C., & Teixeira, A. L. (2014). The immunology of bipolar disorder. *Neuroimmunomodulation*, *21*(2-3), 117–122. https://doi.org/10.1159/000356539

Becking, K., Boschloo, L., Vogelzangs, N., Haarman, B., Riemersma-van der Lek, R., Penninx, B., & Schoevers, R. (2013). The association between immune activation and manic symptoms in patients with a depressive disorder. *Translational Psychiatry*, *3*(10), e314-e314. https://doi.org/10.1038/tp.2013.87

Benedetti, F., Aggio, V., Pratesi, M., Greco, G., & Furlan, R. (2020). Neuroinflammation in Bipolar Depression. *Frontiers In Psychiatry*, *11*. https://doi.org/10.3389/fpsyt.2020.00071

Bora, E., McIntyre, R., & Ozerdem, A. (2018). Neurococognitive and neuroimaging correlates of obesity and components of metabolic syndrome in bipolar disorder: a systematic review. *Psychological Medicine*, *49*(5), 738-749. https://doi.org/10.1017/s0033291718003008

Burdick, K., Ketter, T., Goldberg, J., & Calabrese, J. (2015). Assessing Cognitive Function in Bipolar Disorder: Challenges and Recommendations for Clinical Trial Design. *The Journal Of Clinical Psychiatry*, *76*(03), e342-e350. https://doi.org/10.4088/jcp.14cs09399

Carta, M. G., Conti, A., Lecca, F., Sancassiani, F., Cossu, G., Carruxi, R., Boccone, A., Cadoni, M., Pisanu, A., Francesca Moro, M., & Demelia, L. (2015). The Burden of Depressive and Bipolar Disorders in Celiac Disease. *Clinical practice and epidemiology in mental health : CP & EMH, 11*, 180–185. https://doi.org/10.2174/1745017901511010180

Cremaschi, L., Kardell, M., Johansson, V., Isgren, A., Sellgren, C., Altamura, A., Hultman, C. & Landén, M. (2017). Prevalences of autoimmune diseases in schizophrenia, bipolar I and II disorder, and controls. *Psychiatry Research*, 258, pp.9-14.

Cullen, B., Smith, D., Deary, I., Pell, J., Keyes, K., & Evans, J. (2019). Understanding cognitive impairment in mood disorders: mediation analyses in the UK Biobank cohort. *British Journal Of Psychiatry*, *215*(5), 683-690. https://doi.org/10.1192/bjp.2019.188

Depp, C. A., Bowie, C. R., Mausbach, B. T., Wolyniec, P., Thornquist, M. H., Luke, J. R., McGrath, J. A., Pulver, A. E., Patterson, T. L., & Harvey, P. D. (2015). Current smoking is associated with worse cognitive and adaptive functioning in serious mental illness. *Acta psychiatrica Scandinavica*, *131*(5), 333–341. https://doi.org/10.1111/acps.12380

Dias, V., Balanzá-Martinez, V., Soeiro-de-Souza, M., Moreno, R., Figueira, M., Machado-Vieira, R., & Vieta, E. (2012). Pharmacological approaches in bipolar disorders and the impact on cognition: a critical

overview. *Acta Psychiatrica Scandinavica*, *126*(5), 315-331. https://doi.org/10.1111/j.1600-0447.2012.01910.x

Dickerson, F., Stallings, C., Origoni, A., Vaughan, C., Khushalani, S., & Yolken, R. (2013). Elevated C-reactive protein and cognitive deficits in individuals with bipolar disorder. *Journal Of Affective Disorders*, *150*(2), 456-459. https://doi.org/10.1016/j.jad.2013.04.039

Diflorio, A., & Jones, I. (2010). Is sex important? Gender differences in bipolar disorder. *International Review Of Psychiatry*, *22*(5), 437-452. https://doi.org/10.3109/09540261.2010.514601

Eaton, W. W., Pedersen, M. G., Nielsen, P. R., & Mortensen, P. B. (2010). Autoimmune diseases, bipolar disorder, and non-affective psychosis. *Bipolar disorders*, *12*(6), 638–646. https://doi.org/10.1111/j.1399-5618.2010.00853.x

Featured Batteries - Cogstate Ltd. Cogstate.com. (2020). Retrieved 16 March 2020, from https://www.cogstate.com/clinical-trials/computerized-cognitive-assessment/featured-batteries/.

Ferreira, B. I., Abreu, J. L., Reis, J. P., & Figueiredo, A. M. (2016). Psoriasis and Associated Psychiatric Disorders: A Systematic Review on Etiopathogenesis and Clinical Correlation. *The Journal of clinical and aesthetic dermatology*, *9*(6), 36–43.

Fiedorowicz, J. G., Prossin, A. R., Johnson, C. P., Christensen, G. E., Magnotta, V. A., & Wemmie, J. A. (2015). Peripheral inflammation during abnormal mood states in bipolar I disorder. *Journal of affective disorders*, *187*, 172–178. https://doi.org/10.1016/j.jad.2015.08.036

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189-198.

Fredrickson, J., Maruff, P., Woodward, M., Moore, L., Fredrickson, A., Sach, J., & Darby, D. (2010). Evaluation of the Usability of a Brief Computerized Cognitive Screening Test in Older People for Epidemiological Studies. *Neuroepidemiology*, *34*(2), 65-75. https://doi.org/10.1159/000264823

Gama, C., Kunz, M., Magalhães, P., & Kapczinski, F. (2013). Staging and Neuroprogression in Bipolar Disorder: A Systematic Review of the Literature. Revista Brasileira De Psiquiatria, 35(1), 70-74. https://doi.org/10.1016/j.rbp.2012.09.001

Haarman, B., Riemersma-Van der Lek, R., Burger, H., Netkova, M., Drexhage, R., & Bootsman, F. et al. (2013). Relationship between clinical features and inflammation-related monocyte gene expression in bipolar disorder - towards a better understanding of psychoimmunological interactions. *Bipolar Disorders, 16*(2), 137-150. https://doi.org/10.1111/bdi.12142

Heffner, J., Strawn, J., DelBello, M., Strakowski, S., & Anthenelli, R. (2011). The co-occurrence of cigarette smoking and bipolar disorder: phenomenology and treatment considerations. *Bipolar Disorders*, *13*(5-6), 439-453. https://doi.org/10.1111/j.1399-5618.2011.00943.x

Hildrum, B., Mykletun, A., Hole, T., Midthjell, K., & Dahl, A. (2007). Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: the Norwegian HUNT 2 study. *BMC Public Health, 7*(1). https://doi.org/10.1186/1471-2458-7-220

Holt, R., Abdelrahman, T., Hirsch, M., Dhesi, Z., George, T., Blincoe, T., & Peveler, R. (2010). The prevalence of undiagnosed metabolic abnormalities in people with serious mental illness. *Journal of Psychopharmacology, 24*(6), 867-73. https://doi.org/10.1177/0269881109102788

Howard, W. (2006). Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Yearbook Of Endocrinology, 2006*, 113-114. https://doi.org/10.1016/s0084-3741(08)70316-0

Hsu, C. C., Chen, S. C., Liu, C. J., Lu, T., Shen, C. C., Hu, Y. W., Yeh, C. M., Chen, P. M., Chen, T. J., & Hu, L. Y. (2014). Rheumatoid arthritis and the risk of bipolar disorder: a nationwide population-based study. *PloS one, 9*(9), e107512. https://doi.org/10.1371/journal.pone.0107512

Kesebir, S. (2018). Epigenetics of metabolic syndrome as a mood disorder. *Journal of Clinical Medicine Research, 10*(6), 453-460. https://doi.org/10.14740/jocmr3389w

Kupka, R. W., Nolen, W. A., Post, R. M., McElroy, S. L., Altshuler, L. L., Denicoff, K. D., Frye, M. A., Keck, P. E., Jr, Leverich, G. S., Rush, A. J., Suppes, T., Pollio, C., & Drexhage, H. A. (2002). High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. Biological psychiatry, 51(4), 305–311. https://doi.org/10.1016/s0006-3223(01)01217-3

Latalova, K., Prasko, J., Diveky, T., & Velartova, H. (2011). COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER. *Biomedical Papers*, *155*(1), 19-26. https://doi.org/10.5507/bp.155.2011.003

Law, C., Soczynska, J., Woldeyohannes, H., Miranda, A., Brooks, J., & McIntyre, R. (2009). Relation between cigarette smoking and cognitive function in euthymic individuals with bipolar disorder. *Pharmacology Biochemistry And Behavior*, *92*(1), 12-16. https://doi.org/10.1016/j.pbb.2008.10.002

Mak, A., Lau, D., Chan, A., So, S., Leung, O., & Wong, S. (2018). Cognitive Impairment In Treatment-Naïve Bipolar II and Unipolar Depression. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-20295-3

Malhi, G., Ivanovski, B., Hadzi-Pavlovic, D., Mitchell, P., Vieta, E., & Sachdev, P. (2007). Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. *Bipolar Disorders*, *9*(1-2), 114-125. https://doi.org/10.1111/j.1399-5618.2007.00324.x

Ngo, S., Steyn, F., & McCombe, P. (2014). Gender differences in autoimmune disease. *Frontiers In Neuroendocrinology, 35*(3), 347-369. https://doi.org/10.1016/j.yfrne.2014.04.004

Oh, H., Kim, S., Kang, S., Park, S., & Song, S. (2011). The Relationship between Metabolic Syndrome and Cognitive Function. *Korean Journal Of Family Medicine*, *32*(6), 358. https://doi.org/10.4082/kjfm.2011.32.6.358

PAR | RFFT | Ruff Figural Fluency Test. Parinc.com. (2020). Retrieved 16 March 2020, from https://www.parinc.com/Products/Pkey/360.

Perugi, G., Quaranta, G., Belletti, S., Casalini, F., Mosti, N., Toni, C., & Dell'Osso, L. (2015). General medical conditions in 347 bipolar disorder patients: Clinical correlates of metabolic and autoimmune-allergic diseases. *Journal Of Affective Disorders, 170*, 95-103. https://doi.org/10.1016/j.jad.2014.08.052

Renes, J., Regeer, E., Van der Voort, T., Nolen, W., & Kupka, R. (2014). Treatment of bipolar disorder in the netherlands and concordance with treatment guidelines: Study protocol of an observational,

longitudinal study on naturalistic treatment of bipolar disorder in everyday clinical practice. *Bmc Psychiatry, 14*(1). https://doi.org/10.1186/1471-244X-14-58

Restrepo Moreno, S., García Valencia, J., Vargas, C., & López-Jaramillo, C. (2019). Cognitive performance in patients with bipolar disorder and metabolic syndrome. *RevistaColombiana De Psiquiatría (English Ed.)*, *48*(3), 149-155. https://doi.org/10.1016/j.rcpeng.2017.10.004

Rosenblat, J. D., & McIntyre, R. S. (2017). Bipolar Disorder and Immune Dysfunction: Epidemiological Findings, Proposed Pathophysiology and Clinical Implications. *Brain sciences*, *7*(11), 144. https://doi.org/10.3390/brainsci7110144

Rosenblat, J. (2019). Targeting the immune system in the treatment of bipolar disorder.*Psychopharmacology, 236*(10), 2909-2921. https://doi.org/10.1007/s00213-019-5175-x

Ruff, R.M. (1996). Ruff Figural Fluency Test: Professional Manual. Lutz (United States): Psychological Assessment Resources, Inc.

SayuriYamagata, A., Brietzke, E., Rosenblat, J., Kakar, R., & McIntyre, R. (2017). Medical comorbidity in bipolar disorder: The link with metabolic-inflammatory systems. *Journal of Affective Disorders, 211*, 99-106. https://doi.org/10.1016/j.jad.2016.12.059

Solé, B., Jiménez, E., Torrent, C., Reinares, M., Bonnin, C., & Torres, I. et al. (2017). Cognitive Impairment in Bipolar Disorder: Treatment and Prevention Strategies. *International Journal Of Neuropsychopharmacology*, *20*(8), 670-680. https://doi.org/10.1093/ijnp/pyx032

Suwalska, A., & Łojko, D. (2014). Sex Dependence of Cognitive Functions in Bipolar Disorder. *The Scientific World Journal*, *2014*, 1-10. https://doi.org/10.1155/2014/418432

Szałach, Ł., Lisowska, K., & Cubała, W. (2019). The Influence of Antidepressants on the Immune System. *Archivum Immunologiae Et Therapiae Experimentalis*, *67*(3), 143-151. https://doi.org/10.1007/s00005-019-00543-8

Ten, H., Vollebergh, W., Bijl, R., & Nolen, W. (2002). Bipolar disorder in the general population in the netherlands (prevalence, consequences and care utilisation): Results from the netherlands mental health survey and incidence study (nemesis). *Journal of Affective Disorders*, 68(2-3), 203-13.

Vaskinn, A., Sundet, K., Simonsen, C., Hellvin, T., Melle, I., & Andreassen, O. (2011). Sex differences in neuropsychological performance and social functioning in schizophrenia and bipolar disorder. *Neuropsychology*, *25*(4), 499-510. https://doi.org/10.1037/a0022677

Vonk, R., van der Schot, A. C., Kahn, R. S., Nolen, W. A., & Drexhage, H. A. (2007). Is autoimmune thyroiditis part of the genetic vulnerability (or an endophenotype) for bipolar disorder?. Biological psychiatry, 62(2), 135–140. https://doi.org/10.1016/j.biopsych.2006.08.041