



## Research paper

# Gender differences in the association between physical activity and cognitive function in individuals with bipolar disorder



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## ABSTRACT

**Introduction:** Bipolar disorder (BD) is accompanied by a high number of comorbidities and associated with an overall increased mortality. Especially obesity, systemic inflammatory processes and cognitive deficits are highly prevalent and increase with the course of illness. Physical activity (PA) is associated with beneficial effects on somatic comorbidities such as obesity or cardiovascular disease in individuals without psychiatric disorder. Furthermore, PA might increase neurocognitive performance and reduce systemic inflammation.

**Objective:** The aim of the study was to investigate the association between PA and neurocognitive function in euthymic individuals suffering from BD.

**Methods and participants:** 120 individuals with BD, euthymic at test time, completed the self-reported International Physical Activity Questionnaire (IPAQ) assessing PA of the past seven days and were accordingly assigned to a specific activity category (low, moderate or vigorous). Furthermore, clinical parameters were gathered and cognitive tests analysing verbal-dependent intelligence, attention, executive functioning as well as memory were administered.

**Results:** Female individuals in the vigorous PA group performed significantly higher in most of the cognitive domains compared to females with moderate or low PA. In males, we only found a significant difference in one test for attention between moderate/vigorous and the low activity group.

**Conclusion:** Differences between PA groups in cognitive performance in female individuals with BD were obvious in almost all cognitive domains. As cognitive deficits are strongly associated with a worse course of disease and outcome, PA might offer a concomitant therapy targeting not only somatic comorbidities such as obesity and cardiovascular disease, but also neurocognition.

## 1. Introduction

Bipolar disorder (BD) is a severe psychiatric disease that has a high impact on patients' daily life, not only due to the mood symptoms but also due to the high number of somatic and psychiatric morbidities. It was shown that overweight and obesity are more prevalent in BD than in the general population (Elmslie et al., 2000; Reininghaus et al., 2014). A multitude of reasons may be responsible for these high prevalence rates. Beside others, individuals with BD tend to lead an unhealthy lifestyle, especially in acute affective episodes, which might be partly responsible for increased rates of somatic comorbidities (Swartz and Fagiolini, 2012). Furthermore, side effects of psychopharmacological medication might have a negative impact on weight and activity levels in a high proportion of patients (Geddes and Miklowitz, 2013; Gurpegui et al., 2012). However, there is data that overweight is

already more prevalent in drug naive BD individuals compared to healthy controls or other drug naive mentally ill populations (Maina et al., 2008). Overweight and obesity are not only associated with a more severe course of illness, higher relapse rates and non-recovery (Silveira et al., 2014), but are also risk factors for the development of cardiovascular disease and metabolic syndrome (Janney et al., 2014). The rates of somatic comorbidities tend to increase with the progression of the illness, deteriorate the prognosis of BD illness (Fries et al., 2012) and lead to elevated mortality compared to the general population (Kucyi et al., 2010).

Physical activity (PA) is defined as skeletal muscle movement leading to energy usage (McCormick et al., 2008). While physical inactivity (PIA) is a risk factor for several diseases, it has been shown that PA has a beneficial effect on various somatic diseases including obesity (Buoli et al., 2014). Moreover, it was shown that PA leads to a reduction

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of risk factors for cardiovascular disease by decreasing arterial pressure, reduced systemic inflammation, improved glucose levels and insulin sensitivity (Kucyi et al., 2010). More so, a decrease of the relative risk of death can be achieved by increasing one's level of activity, even when already suffering from risk factors for cardiovascular disease (Warburton et al., 2006). It has been assumed that regular exercise might also reduce the effect of mental stress on the circulatory system (Blumenthal et al., 1990).

There is growing evidence that BD is accompanied by cognitive impairment, which is present during mania and depression (Dixon et al., 2004) but is also detectable during euthymia (Buoli et al., 2014; Lackner et al., 2015). The main domains affected are executive functions, processing speed, attention, verbal learning and memory (Robinson et al., 2006). The number of previous episodes and the duration of illness seem to positively correlate with the extent of cognitive deficits (Martinez-Aran et al., 2004).

In addition, there is knowledge that overweight and obesity, in otherwise healthy individuals, are associated with neurocognitive impairment (Yim et al., 2012). In contrast, it was shown that PA might have a beneficial effect on cognition and even lower the risk for dementia (Nagandu et al., 2015; Kramer et al., 2006; Kishimoto et al., 2016).

To date, no large trial has analyzed the possible association between the level of PA and cognitive function in euthymic individuals with BD. The euthymia in BD is of special interest, as the confound of state effect is removed. Thus, the purpose of the present study was to find differences in cognitive test performance (e.g. measures of executive function, attention, verbal learning and memory) between different PA groups (low, moderate, vigorous) in euthymic individuals with BD. The analyses were conducted separately for men and women as gender differences were found to have an important impact on clinical parameters in bipolar disorder.

## 2. Methods

### 2.1. Participants and procedure

All of the 120 individuals with BD (56 of them females) included in the study were former in- or outpatients of the Department of Psychiatry and Psychotherapeutic Medicine at the Medical University of Graz and were diagnosed with BD by a Structured Clinical Interview according to DSM-IV (SCID I; APA, 1996). Inclusion criteria for study participation was an euthymic state or subsyndromal symptomatology at test time, which was defined by a Hamilton-Depression scale (HAM-D; Hamilton, 1960) score  $\leq 14$  and a Young Mania Rating Scale (YMRS; Young et al., 1978) score  $\leq 8$ . Participants were of full age and had given written informed consent prior to participating in the study. Exclusion criteria were the presence of chronic severe somatic diseases, neurodegenerative and neuroinflammatory disorders (i.e. dementia, Huntington's and Parkinson's disorder, multiple sclerosis), and interferon- $\alpha$ -based immunotherapy. All patients were participants in the BIPFAT study, which included a complete psychiatric examination and history, blood samples, cognitive testing, magnetic resonance imaging, electroencephalography as well as various lifestyle and personality questionnaires. Detailed description of the BIPFAT study, as well as former results can be obtained from recent publications of our study (Bengesser et al., 2014; Birner et al., 2015; Lackner et al., 2015; Reininghaus et al., 2014). The study has been approved by the local ethics committee (Medical University of Graz) in compliance with the current revision of the Declaration of Helsinki, ICG guideline for Good Clinical Practice and current regulations (EK-number: 24–123 ex 11/12).

For the current study, in order to assess PA behaviour, all participants were asked to complete the long version of the self-administered International Physical Activity Questionnaire (IPAQ). The IPAQ-Long contains 27 questions pertaining to the duration and frequency of PA in

the last seven days. Vigorous, moderate and low intensity activities are recorded in the four following domains: work, transportation, household and leisure activities. Special algorithms differentiating between the intensities of activity performed allow the separation of participants into three categories: low, moderate and vigorous intensity.

A cognitive test battery evaluated the cognitive function. The Multiple-choice Word Test (MWTB; Lehl, 2015) was used to investigate the premorbid intelligence quotient (IQ). For testing the attention and the psychomotor processing speed the Trail Making Test-A (TMT-A; Reitan, 1992), the d2-test (Brickenkamp, 2002) and the Stroop Test (Baumler and Stroop, 1985) were conducted. Memory was investigated by the California Verbal Learning Test (CVLT; Niemann et al., 2008) and executive function by the Stroop Test as well as the Trail Making Test B (TMT-B). As the TMT-A/B and the Stroop Test are psychomotor tasks determining reaction time, higher values indicate poorer test performance. All tests were given in German.

### 2.2. Statistical analyses

For identifying covariates, *t*-tests, and correlations were conducted. Differences in cognitive test performance between individuals with low, moderate and vigorous PA were computed using MANCOVAs. All analyses were calculated separately for men and women. Error probabilities below .05 were accepted to denote statistical significance.

## 3. Results

### 3.1. Sample characteristics

The description of the cohort of this study can be obtained from Table 1. There were no significant differences in the PA categories between men and women as well as between in- and outpatients in our cohort. Furthermore, the PA groups did not significantly differ in the HAM-D or the YMRS score (see Table 2). However, we found differences between men and women in some cognitive parameters. Women performed significantly better than men in the d2 test, colour naming, colour reading as well as all CVLT domains.

Age, school education and BMI were inserted as covariates in all analyses because of their known influence on cognitive function (also

**Table 1**  
Descriptive statistics.

	Male			Female		
	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>
Age (years)	46.65	14.10	64	44.16	13.47	56
BMI (kg/m <sup>2</sup> )	29.07	6.72	62	27.19	5.77	55
Illness duration (years)	17.76	11.40	62	19.78	13.47	55
Inpatient			20 (31.3%)			14 (25.0%)
Smoker			29 (45.3%)			26 (47.3%)
Physical activity						
Low			11 (17.2%)			15 (26.8%)
Moderate			24 (37.5%)			14 (25.0%)
Vigorous			29 (45.3%)			27 (48.2%)
School education						
$\leq 8$ school years			19 (30.2%)			20 (36.3%)
9–11 school years with graduation			14 (22.2%)			13 (23.7%)
High school graduation			30 (47.6%)			22 (40.0%)
Medication						
Lithium			24 (37.5%)			15 (26.8%)
Atypical antipsychotics			41 (64.1%)			39 (69.6%)
Anticonvulsives			19 (29.7%)			19 (33.9%)
Antidepressants			43 (67.2%)			41 (73.2%)

Note. BMI = Body Mass Index.

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