European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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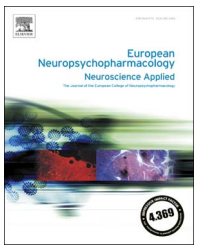

Glycogen synthase kinase-3β activity and cognitive functioning in patients with bipolar I disorder

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Received 14 November 2017; received in revised form 8 January 2018; accepted 26 January 2018

KEYWORDS
Cognition;
Bipolar disorder;
PBMC;
Glycogen synthase kinase-3;
Lithium

Abstract
Cognitive deficits are common in patients with bipolar disorder (BD) in remission and may be associated with glycogen synthase kinase-3 (GSK-3) activity, which is inhibited by lithium. GSK-3 may be a relevant treatment target for interventions tailored at cognitive disturbances in BD but the relation between GSK-3 activity, cognition and lithium treatment is unknown. We therefore investigated the possible association between GSK-3 activity and cognition and whether lithium treatment moderates this association in patients with BD. In a prospective 6–12 month follow-up study, GSK- 3β activity in peripheral blood mononuclear cells was measured concurrently with cognitive performance assessed using a comprehensive test battery in 27 patients with BD-I in early and late remission following a manic or mixed episode. The GSK-3β activity, measured as serine-9 phosphorylated GSK-3β (pGSK-3β) and the GSK-3β ratio (serine-9-pGSK-3β /total GSK-3β), was negatively associated with sustained attention ($p = 0.009$ and $p = 0.042$, respectively), but not with other cognitive domains or global cognition. A crossover interaction between lithium treatment and the GSK activity was observed, indicating that lower pGSK-3β levels ($p = 0.015$) and GSK ratio ($p = 0.010$) were associated with better global cognition in lithium users whereas the opposite association was observed in non-lithium treated patients. Findings were not statistically significant after Bonferroni correction. In conclusion, cognitive functioning may be associated with GSK-3 activity in patients with BD-I and lithium treatment may modulate

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https://doi.org/10.1016/j.euroneuro.2018.01.008

Please cite this article as: Munkholm, K., et al., Glycogen synthase kinase-3β activity and cognitive functioning in patients with bipolar I disorder. European Neuropsychopharmacology (2018), https://doi.org/10.1016/j.euroneuro.2018.01.008

this relationship. Future studies in larger sample sizes are warranted to confirm these associations.

1. Introduction

Cognitive deficits are common in patients with bipolar disorder (BD) in remission across several domains including verbal memory, attention and executive function (Cullen et al., 2016). They contribute to reduced socio-occupational capacity (Baune and Malhi, 2015) but there is no available efficacious cognition treatment (Miskowiak et al., 2016), partially due to the limited understanding of the nature and pattern of cognitive impairment in BD (Miskowiak et al., 2016) and methodological challenges (Miskowiak et al., 2017).

Preclinical evidence indicates a role for glycogen synthase kinase-3 (GSK-3) in cognitive function (O'Leary and Nolan, 2015). GSK-3, a serine/threonine kinase, which is present in most cells and tissues (Woodgett, 1990). GSK-3 is regulated in an inhibitory manner, primarily through phosphorylation of its two isoforms GSK-3α and GSK-3β at serine-9 and serine-21, respectively (Woodgett, 2003). Animal studies suggest that increased GSK-3 activity inhibits hippocampal neurogenesis and processes involved in learning and memory and may thus play a role in cognitive functioning (Giese, 2009).

Lithium, a cornerstone of BD pharmacological management owing to its mood stabilizing effects, inhibits GSK-3 by phosphorylation (Li et al., 2007). Animal models of Alzheimer's Disease (AD) suggest that inhibition of GSK-3 by lithium can improve cognitive impairment, although evidence is not conclusive (O'Leary and Nolan, 2015). Genetic variability in the GSK-3β gene encoding the β isoform of GSK has been found associated with response to lithium in patients with BD (Serretti and Drago, 2010; Serretti et al., 2009) and also with increased risk of suicidal behavior (Jimenez et al., 2013) and impulsivity (Jimenez et al., 2014), both of which are relevant targets of lithium treatment. In clinical populations evidence is conflicting and does not allow for definitive conclusions regarding the association between lithium treatment and cognitive function (Malhi et al., 2013; O'Leary and Nolan, 2015).

In contrast to the evidence from animal studies, clinical studies on GSK and cognition are scarce with no studies in patients with BD. Surprisingly, the potential relationship between peripheral blood GSK-3 activity, cognitive functioning and lithium treatment, has never been studied in humans.

This study was therefore conducted to investigate a) whether cognitive function is associated with GSK activity in patients with bipolar I disorder (BD-I) and b) whether lithium treatment modulates this association. To this end, we evaluated GSK-3β levels in peripheral blood mononuclear cells (PBMCs) and cognitive performance using a standardized test battery in patients with BD-I in remission after hospital admission for a manic or mixed episode. We hypothesized that impaired cognitive function is associated with increased GSK-3β activity and that the association is modulated by lithium treatment.

2. Experimental procedures

2.1. Study design

The present report concerns a cohort of patients with BD undergoing full cognitive testing as part of a multicenter, longitudinal study investigating peripheral blood GSK-3β levels and cognition in patients with BD I in remission following a manic or mixed episode (Jacoby et al., 2016). Study recruitment took place from December 2012 to December 2014.

Patients were followed prospectively during 6–12-months after the index episode with repeated assessment when patients experienced new affective episodes and/or after return to euthymia and in remission. The study being naturalistic, patients received treatment as usual with no influence from study investigators.

2.2. Participants

Patients with a potential diagnosis of BD I were consecutively recruited while hospitalised with a manic or mixed episode at six psychiatric centres, in the Mental Health Services - Capital Region of Denmark. Inclusion criteria were: adults aged 18–60 years and ICD-10 (WHO, 1992) diagnosis of BD. Exclusion criteria were: severe medical disorder, a present diagnosis of substance-related disorder, pregnancy and insufficient Danish language skills.

Our initial study sample included 60 patients with BD-I, of which complete cognitive test data were available for 27 patients, included in the current report. Among these, cognitive test data were available in early remission for 26 patients and for 6 patients in late remission.

The study was approved by the Committee on Health Research Ethics of the Capital Region of Denmark (protocol no.: H-4-2012-114). Participants provided written informed consent and the study complied with the Declaration of Helsinki.

2.3. Study procedure

2.3.1. Clinical assessments

The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (Wing et al., 1990) was used to confirm the diagnosis of BD I. At each study visit the present clinical state was established according to ICD-10 and severity of depressive and manic symptoms assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1967) and the Young Mania Rating Scale (YMRS) (Young et al., 1978), respectively. Remission was defined according to ICD-10 criteria, with early remission duration criteria of approximately 8 weeks for pragmatic reasons.

2.3.2. Cognitive testing

Cognitive testing using a comprehensive test battery was performed when patients with BD were in early remission and, if possible, repeated approximately three months later during sustained

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