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The effect of erythropoietin on cognition in affective disorders – Associations with baseline deficits and change in subjective cognitive complaints

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Abstract
This is a secondary data analysis from our erythropoietin (EPO) trials. We examine (I) whether EPO improves speed of complex cognitive processing *across* bipolar and unipolar disorder, (II) if objective and subjective baseline cognitive impairment increases patients' chances of treatment-efficacy and (III) if cognitive improvement correlates with better subjective cognitive function, quality of life and socio-occupational capacity. Patients with unipolar or bipolar disorder were randomized to eight weekly EPO ($N=40$) or saline ($N=39$) infusions. Cognition, mood, quality of life and socio-occupational capacity were assessed at baseline (week 1), after treatment completion (week 9) and at follow-up (week 14). We used repeated measures analysis of covariance to investigate the effect of EPO on speed of complex cognitive processing. With logistic regression, we examined whether baseline cognitive impairment predicted treatment-efficacy. Pearson correlations were used to assess associations between objective and subjective cognition, quality of life and socio-occupational capacity. EPO improved speed of complex cognitive processing across affective disorders at weeks 9 and 14 ($p \leq 0.05$). In EPO-treated patients, baseline cognitive impairment increased the odds of treatment-efficacy on cognition at weeks 9 and 14 by a factor 9.7 (95% CI:1.2-81.1) and 9.9 (95% CI:1.1-88.4), respectively ($p \leq 0.04$). Subjective cognitive complaints did not affect chances of treatment-efficacy ($p \geq 0.45$). EPO-associated cognitive improvement correlated with reduced cognitive complaints but not with quality of life or socio-occupational function. As the analyses were performed post-hoc, findings are only hypothesis-generating. In conclusion, pro-cognitive effects of EPO occurred across affective disorders. Neuropsychological screening for cognitive dysfunction may be warranted in future cognition trials.

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1. Introduction

Cognitive deficits are common across unipolar and bipolar disorder and often persist after clinical remission from acute mood episodes (Arts et al., 2008; Bortolato et al., 2016). There are currently no available treatments to directly target cognitive dysfunction in affective disorders although some candidate compounds seem promising (for reviews see Bortolato et al. (2016) and Miskowiak et al. under review). A particularly interesting candidate treatment is recombinant human erythropoietin (EPO), which has neuroprotective effects, stimulates neuroplasticity and improves cognition in preclinical models and across several neuropsychiatric patient groups (for reviews see Miskowiak et al. (2012), Sargin et al. (2010), and Sirén et al. (2009)). We previously demonstrated in a randomized placebo-controlled trial that (EPO) improves speed of complex cognitive processing across attention, memory and executive function in partially remitted patients with bipolar disorder (BD) (Miskowiak et al., 2014a). In a parallel trial we investigated the effects of EPO on mood symptoms in moderately depressed patients with treatment-resistant unipolar disorder (UD), and observed a mood-independent improvement of verbal memory in EPO versus saline treated patients (tertiary outcome) (Miskowiak et al., 2014b). Pooling verbal memory data from these two studies showed that the effect of EPO on verbal memory was comparable across UD and BD (Miskowiak et al., in press). However, it remains to be investigated whether the observed effects of EPO on "speed of complex cognitive processing" across several cognitive domains in BD (Miskowiak et al., 2014a), also occur *across* unipolar and bipolar disorder. Indeed, it cannot be assumed that a pro-cognitive effect of an intervention in one patient group necessarily applies to other groups, as illustrated by the discrepancy between meta-analytic evidence for beneficial effects of cognitive remediation (CR) on cognition in schizophrenia, but lack of cognitive benefits of CR in BD patients (Demant et al., 2015b). Interestingly, we recently demonstrated that baseline cognitive dysfunction substantially increased patients' chances of achieving EPO treatment efficacy on verbal memory in a pooled sample of UD and BD patients (Miskowiak et al., in press). Subjective cognitive complaints at baseline and longer illness duration were also associated with a small but significant increase in the odds for EPO treatment efficacy on cognition. These preliminary findings suggest that treatments targeting memory dysfunction may be particularly efficacious in patients with baseline cognitive deficits and greater illness progression, in line with the staging and allostatic load models of affective disorders (Berk et al., 2011; Grande et al., 2015; Kapczinski et al., 2008; Vieta et al., 2013).

The present study builds on these findings by investigating (I) whether the observed effects of EPO on speed of complex cognitive processing are specific to BD, or if they occur *across* diagnostic groups of affective disorders, (II) whether objective cognitive dysfunction and/or subjective cognitive complaints at baseline will increase EPO-treated patients' chances of achieving a clinically relevant improvement in cognition, and (III) whether treatment-related improvement in objective cognition is accompanied by increase in subjective cognitive function, quality of life and socio-occupational capacity. Insight into these questions has implications for future clinical trials of EPO by elucidating who is likely to show cognitive benefits of EPO treatment, and may also inform the design of other trials targeting cognition.

2. Experimental procedures

2.1. Participants

Participants were recruited through the Clinic for Affective Disorders, Psychiatric Centre Copenhagen, and through relevant websites. Schedules for Clinical Assessment in Neuropsychiatry (SCAN) was used to confirm the ICD-10 diagnosis. More extensive details about the recruitment procedure can be found in Miskowiak et al. (2014a, 2014b).

The study included 79 patients consisting of BD patients in partial remission ($N=43$), defined as Hamilton Depression Rating Scale 17-items (HDRS-17; Hamilton, 1960) and Young Mania Rating Scale (YMRS; Young et al. 1978) scores ≤ 14, and moderately depressed UD patients ($N=36$) (HDRS-17 ≥ 17), fulfilling the criteria for treatment resistance according to the Treatment Response to Antidepressant Outcome (TRAQ: Posternak et al., 2004). Patients were required to remain on a stable dose of mood-stabilising treatment for a minimum of two weeks before enrolment in the EPO trials.

2.2. Procedure

A more detailed description of the screening procedure of inclusion and exclusion criteria and safety precautions concerning EPO treatment can be found in Miskowiak et al. (2014a, 2014b). Patients were randomized to eight weekly infusions of EPO (40,000 IU/ml; Eprex, epoetin-alpha) ($N=40$) or saline infusions (NaCl 0.9%) ($N=39$). Cognitive assessment was performed at baseline, one week after treatment completion (week 9) and at a six-week follow-up (week 14). These assessments involved examination of objective cognitive function with neuropsychological tests, ratings of mood symptoms and completion of self-report questionnaires regarding subjective cognitive complaints, quality of life, and socio-occupational capacity.

The study was carried out in accordance with the latest version of the Declaration of Helsinki, was approved by the local ethics committee, Danish Medicines Agency, and Danish Data Agency, and was registered at clinicaltrials.gov (no. NCT00916552).

2.2.1. Objective and subjective measures of cognitive function

The included neuropsychological tests comprising the measure of 'speed of complex cognitive processing' were improved by EPO vs. saline in BD in Miskowiak et al. (2014a). They covered the domains of attention, memory and executive function, encompassing Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 2004) total recall across trials I-V, the total score on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Coding (Randolph, 1998), verbal fluency test with the letter D (Borkowski et al., 1967), WAIS-III Letter-Number Sequencing (Wechsler, 1997), Trail Making Test B (TMT B; Army Individual Test Battery, 1944) and the time to correct responses on the Rapid Visual Information Processing (RVP) from Cambridge Cognition (CANTAB). Subjective cognitive complaints were assessed using the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ; Fava et al., 2009).

2.2.2. Measures of mood symptoms, quality of life and socio-occupational function

Mood symptoms were rated with the HDRS-17 and the YMRS. Socio-occupational function was assessed with the Work and Social