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Review article

Executive functioning deficits among adults with Bipolar Disorder (types I and II): A systematic review and meta-analysis

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ABSTRACT

Background: Executive functioning (EF) deficits contribute to a significant proportion of the burden of disease associated with bipolar disorder (BD). Yet, there is still debate in the literature regarding the exact profile of executive functioning in BD. The purpose of the present project was to assess whether EF deficits exist among adults suffering BD, and whether these deficits (if apparent) differ by BD subtype.

Methods: A systematic search identified relevant literature. Randomised controlled trials that used neuropsychological assessment to investigate EF among adults 16–65 years) with a remitted DSM diagnosis of BD (type I or II) were included. Studies were published between 1994 and 2015. A systematic review and meta-analysis were undertaken. For individual studies, standardised mean differences (Cohen's *d*) and 95% confidence intervals were calculated and represented in forest plots to illustrate differences in executive performance between groups. Summary effects were produced and tests of heterogeneity employed to assess the dispersion and generalisability of results.

Results: Thirty-six studies met criteria for inclusion. Six domains of EF were identified: Set-shifting (SS), inhibition (INH), planning (PLA), verbal fluency (VF), working memory (WM), and attention (ATT). BD1s performed worse than HCs in all domains. BD2s demonstrated impairment in VF, WM, SS, and ATT. The results were mixed for comparisons between BD1s and BD2s, but revealed that BD2s can experience similar (or sometimes greater) EF impairment.

Limitations: Only a limited number of studies that included BD2 samples were available for inclusion in the current study. Subgroup analysis to elucidate potential moderators of within-study variance was not undertaken.

Conclusion: This is the first systematic review and meta-analysis to have compared the EF of remitted BD1s, BD2s, and HCs. The results provided useful insight into the EF profile of patients with BD, and offered commentary as to some of the contradictory results reported in the literature. A standardised methodological protocol for assessment of EF in BD was proposed. The information in this review could enhance our understanding of EF impairment inherent in BD, and the methods and efficacy with which clinicians assess and treat this population.

1. Introduction

Bipolar Disorder affects nearly 4.4% of the global population, and is ranked by the World Health Organisation as the seventh leading cause of years of life lost due to disability in males, and eighth in females (Sole et al., 2011a). The Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5) (APA, 2013) recognises two subtypes, BD1 and BD2: BD1 is characterised by the experience of a full manic episode, and often (but not always) accompanied by major depressive, or hypomanic episodes; and BD2 is defined by alternating periods of milder manic symptoms (hypomania) and depression. A significant body of evidence suggests that much of the difficulties in BD can be attributed to weaknesses in cognitive capacity, particularly those of the executive faculties (Goswami et al., 2006; Levy and Manove, 2012; Thompson et al., 2005; Torres et al., 2007).

Numerous definitions of EF have been rehearsed in the literature (see, Baddeley, 1996, 1998; Jurado and Rosselli, 2007; Lezak, 2004). Today, the term 'executive function(s)' is often used as an umbrella

Abbreviations: BD, bipolar disorder; BD1, bipolar disorder type-1; BD2, bipolar disorder type-2; EF, executive functioning; SS, set-shifting; PLA, planning; INH, inhibition; WM, working memory; ATT, attention; VF, verbal fluency

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term to encapsulate an array of complex cognitive processes and sub-processes (Elliot, 2003). As defined by Miyake and Friedman (2012), the EFs are 'a set of general-purpose control mechanisms, often linked to the pre-frontal cortex of the brain, that regulate the dynamics of human cognition and action'.

Numerous theoretical frameworks have been posited for understanding the executive system (Baddeley, 2002; Banich, 2009; Barkley, 1997; Fuster et al., 1985; Lezak, 2004; Miller and CohenCohen, 2001; Norman and Shallice, 1986; Zelazo et al., 1997), most of which can be distinguished by the degree of responsibility attributed to a 'central executive' for the control of executive and related processes. From these foundations, modern theorists conceptualise executive system as a 'macro-system', made up of executive 'sub-functions' that work together to achieve specific goals (Elliot, 2003; Jurado and Rosselli, 2007; Miyake et al., 2000; Miyake and Friedman, 2012). It is now generally accepted that the EFs operate across a vast network of neural circuitry, rather than within prefrontal areas alone (Elliot, 2003; Miyake et al., 2000). Due to such complexity, however, attempts to define EF often result in lists of cognitive abilities (e.g., SS, WM, PLA), reflecting the notion that EF is not a unitary, or straightforward concept (Elliot, 2003).

2. Executive functioning in Bipolar Disorder

Various executive impairments have been identified in the BD literature, impacting functioning in the domains of WM (Dias et al., 2008), SS (Trivedi et al., 2008a, 2008b), PLA (Xu et al., 2012), ATT (Pattanayak et al., 2012), VF (Erol et al., 2014), and updating (Miyake and Friedman, 2012), for example. Importantly, executive deficits have been shown to have broad and significant implications in 'real life', often demonstrated as severe problems in the control and regulation of behaviour (Mischel et al., 2011; Miyake and Friedman, 2012; Moffit et al., 2011). Despite a wealth of investigation undertaken to date, what we know of the executive abilities of individuals suffering BD is limited.

To date, there is inconsistency across the literature as to the presence and extent of executive deficits for BD patients compared to HCs, as highlighted by previous reviews on the topic (Bora et al., 2009; Bora et al., 2011; Daglas et al., 2015; Sole et al., 2011a, 2011b). The incongruous results may be attributed to the absence of a methodological standard for assessing executive performance. For example, some research failed to appropriately subtype BD, increasing risk of type 1/type 2 error through mistakenly attributing executive deficit to BD 'in general', without distinguishing between the two different forms (Linke et al., 2013; Mur et al., 2007). In other research, some authors differed in their definition of EF and subsequent selection of assessment measures (Dittmann et al., 2008; Larson et al., 2005; Osher et al., 2011). Others did not control for confounds, such as medication use (Altshuler et al., 2004; Antila et al., 2007; Brissos et al., 2008; Dias et al., 20082008), comorbid psychiatric conditions (Savitz et al., 2008), or the impact of residual mood symptoms (Kaya et al., 2007). Along this line, many studies did not adequately control for the impact of mood on cognition, testing during acute phases rather than in remission (Jamrozinski et al., 2009; Oliveira et al., 2011; Palsson et al., 2013). Furthermore, remission criteria applied across the literature varied widely, or was not specified (Juselius et al., 2009; Larson et al., 2005; Lopera-Vasquez et al., 2014). Whereas, some studies did not report their results statistically, disallowing interpretation, comparison, or further analysis (Rubinsztein et al., 2006; Ryan et al., 2012). Other studies assessed only a single dimension of EF, but extrapolated their results to EF in general. Such an approach undermines the complexity and influence of the executive system as a whole (Hsiao et al., 2009). Without the guidance of a set of standardised assessment procedures, researchers have taken a range of approaches, making it difficult to interpret and consolidate findings. Twenty-four systematic reviews have been published between 1994 and 2015, with a focus on BD and some mention of EF; of these:

(a) Only three specified which bipolar subtype was the focus of investigation;
(b) Most included studies that pre-dated bipolar subtyping (1994), indicating a bias toward ICD-10 nosology, and potential misrepresentation of executive performance in BD;
(c) Many reviews included studies of various date ranges post-1994, without appropriate rationale for doing so, potentially omitting important studies (and thus contribution) to their findings.
(d) Not one systematic review was limited to studies post-bipolar subtyping in 1994.

Of all of the systematic reviews mentioned above, none focused specifically on EF deficits among individuals with BD.

Despite numerous empirical studies and reviews on the topic, due to methodological variation across existing literature, it remains unclear as to whether EF is significantly impaired among individuals suffering BD compared to HCs, and if it is, whether significant performance differences exist between subtypes. Therefore, the primary objective of the present review was to assess the presence of EF deficits among adults suffering BD, and whether these deficits (if apparent) differed by subtype. Secondary objectives included: 1) To provide an account for the contradictory findings across the literature, and 2) to define a set of standardised procedures for the assessment of EF deficits among individuals with BD, including appropriate assessment tools, remission criteria, and a standardised definition of EF.

3. Method

3.1. Study design and inclusion criteria

A systematic review and meta-analysis of studies were undertaken. Studies included were randomised controlled trials (RCTs) conducted between 1994 and 2015 that included an experimental group with BD, and a healthy control group. All included studies assessed EF using neuropsychological assessment measures appropriate for that purpose. Studies based on subjective (self) report were excluded. Studies were published in full-text, in English, and included the results of the study as descriptive statistics. Dissertations were not included.

3.1.1. Types of participants

Participants included in the reviewed studies were adults (both male and female) between the ages of 16 and 65 years. Such population delimiters ensured appropriate maturation of the brain and decreased the likelihood of cognitive decline due to aging (Ylikoshki et al., 1999). Experimental group participants held a diagnosis of BD (in remission), subtyped according to DSM-IV criteria. Studies were excluded if participants reported a concurrent mental health condition, neurological injury/disorder, or illness of any type that may have confounded results.

3.2. Search methods

The search strategy involved databases and internet search engines including CINAHL Plus, ERIC, MEDLINE, PsychInfo, and Google Scholar, as well as hand-searching. In addition to the use of traditional search engines, Google Scholar was included to ensure no relevant paper was excluded. Hand-searching involved manually scanning the references lists of relevant journal articles for additional of interest. The search was limited to articles published between 1994 and 2005, in accordance with the date BD (APA, 1994) was officially subtyped.

3.2.1. Electronic searches

Prior to undertaking an online search, the review question was converted into key search terms. Synonyms were identified for all components of the question, and combined using Boolean operators, such as Or, And, and Not. Key words included: a) For BD: bipolar,