Journal of Psychiatric Research 57 (2014) 1–11

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Review

A meta-analysis of neuropsychological functioning in first-episode bipolar disorders

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ARTICLE INFO

Article history:
Received 10 February 2014
Received in revised form
25 May 2014
Accepted 23 June 2014

Keywords:
Neuropsychology
Cognitive deficits
Bipolar disorder
First-episode
Meta-analysis
Early intervention

ABSTRACT

Broad neuropsychological deficits have been consistently demonstrated in well-established bipolar disorder. The aim of the current study was to systematically review neuropsychological studies in first-episode bipolar disorders to determine the breadth, extent and predictors of cognitive dysfunction at this early stage of illness through meta-analytic procedures. Electronic databases were searched for studies published between January 1980 and December 2013. Twelve studies met eligibility criteria ($N = 341$, mean age = 28.2 years), and pooled effect sizes (ES) were calculated across eight cognitive domains. Moderator analyses were conducted to identify predictors of between-study heterogeneity. Controlling for known confounds, medium to large deficits (ES $\geq$ 0.5) in psychomotor speed, attention and working memory, and cognitive flexibility were identified, whereas smaller deficits (ES 0.20–0.49) were found in the domains of verbal learning and memory, attentional switching, and verbal fluency. A medium to large deficit in response inhibition was only detected in non-euthymic cases. Visual learning and memory functioning was not significantly worse in cases compared with controls. Overall, first-episode bipolar disorders are associated with widespread cognitive dysfunction. Since euthymia was not associated with superior cognitive performance in most domains, these results indicate that even in the earliest stages of disease, cognitive deficits are not mood-state dependent. The current findings have important implications for whether cognitive impairments represent neurodevelopmental or neurodegenerative processes. Future studies need to more clearly characterise the presence of psychotic features, and the nature and number of previous mood episodes.

1. Introduction

Numerous studies on bipolar disorders show that neuropsychological deficits are detectable in euthymia and contribute to poor outcome and impaired functioning independently of other symptoms and factors (Bourne et al., 2013; Depp et al., 2012; Murphy and Sahakian, 2001; Olley et al., 2005; Robinson and Ferrier, 2006). A spate of systematic reviews and meta-analyses in bipolar disorder (BD) indicate that these cognitive impairments are similar in range to those seen in schizophrenia, but that they are usually of lesser magnitude (Arts et al., 2008; Bora et al., 2009, 2010, 2011; Bourne et al., 2013; Kurtz and Gerraty, 2009; Mann-Wrobel et al., 2011; Murphy and Sahakian, 2001; Robinson and Ferrier, 2006; Torres et al., 2007). There are also suggestions that neuropsychological impairments may represent a putative 'endophenotype' for BD, or intermediate phenotype between genotype and the clinical syndrome (Daban et al., 2012; Glahn et al., 2010, 2006; Robbins et al., 2012). A recent review of cognitive dysfunction in BD and schizophrenia concluded that there were differences in the deficits observed prior to illness onset (partly associated with differences in pre-morbid intellectual functioning; IQ), but that post-illness onset, BD and schizophrenia were associated with common deficits across diagnostic boundaries (Lewandowski et al., 2011).

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http://dx.doi.org/10.1016/j.jpsychires.2014.06.019
0022-3956/

Currently, it remains unclear whether the neuropsychological deficits in BD can be viewed as supportive of underlying neurodevelopmental or neurodegenerative processes (Goodwin et al., 2008).

One approach to further clarify the time-course and aetiology of cognitive dysfunction in BD is to examine neuropsychological and/or neuroimaging studies in first-episode cases. Despite a sizable body of neuroimaging evidence demonstrating structural brain changes in first-episode bipolar disorders (Vita et al., 2009), and systematic reviews of neuropsychological functioning in first-episode major depressive disorder (Lee et al., 2012), and schizophrenia-spectrum psychoses (Mesholam-Gately et al., 2009), there are no meta-analyses to date that specifically examine cognitive functioning in those presenting with a first episode of BD. This represents a significant gap in the evidence-base that we seek to address in this systematic review and meta-analysis.

2. Methods

2.1. Data sources

Searches of peer-reviewed empirical studies between January 1980 and December 2013 were conducted in PubMed and PsycInfo databases (1980 was selected since this was the first year that the term 'bipolar disorder' was codified in the DSM). Various combinations of search terms were used, including: first, single, early, episode, bipolar, manic, mania, neuropsycho*, neurocognit*, cogniti*, impairment, deficit, and functioning. Citations were also reviewed for additional studies.

2.2. Study selection

Inclusion criteria were: 1/ an adult sample was recruited (age $\geq$ 18 years) given evidence that paediatric BD may be phenomenologically different from adult BD (Pavuluri et al., 2005); 2/ diagnoses of BD were made according to DSM (i.e. Bipolar I Disorder, Bipolar II Disorder) or ICD (i.e. Mania, or Bipolar Affective Disorder) criteria; 3/ findings for BD cases were compared with controls; 4/ the assessment of traditional neuropsychological functions using valid and reliable tests (Strauss et al., 2006) used routinely in clinical practice (i.e. excluding measures of cognitive biases, or experimental paradigms with wide-ranging design parameters and administration procedures, such as N-back tasks); 5/ sufficient statistical data were reported for transformation into effect sizes (ES), or the relevant data were available from the original researchers; and 6/ studies were published in the English language. We did not impose a strict criteria regarding whether the 'first episode' constituted a manic, hypomanic, mixed, depressive or psychotic episode (according to the DSM or ICD), or first hospitalisation, since very few studies recruited a homogenous clinical group based on current mood state.

Studies were excluded if they included cases who: i/ were diagnosed with a schizophrenia-spectrum psychosis (e.g. schizophrenia, schizoaffective disorder) according to DSM or ICD criteria; ii/ had electroconvulsive therapy in the preceding 12 months; or iii/ included cases potentially confounded by neurodegenerative disease (i.e. age >64). Fulfilment of eligibility criteria was confirmed by two authors (RSCL, KRG), who independently rated the studies; any discordance was then resolved by consensus. Only studies with the largest sample were included in the instance of overlapping samples.

As shown in Fig. 1, 309 titles and abstracts were initially identified, with the final inclusion of 12 studies that met eligibility criteria in full.

2.3. Meta-analytic procedure

Pooling of ES, tests of homogeneity, assessment of publication bias, and moderator analyses, were all conducted using random effects modelling in Comprehensive Meta-Analysis Version 2.0 software (Borenstein et al., 2005). Random effects modelling for pooling ES was used because the population varied across studies (Hedges and Olkin, 1985). Random effects modelling was implemented for meta-regression (unrestricted-maximum likelihood) and subgroup analyses (method of moments) since this carried the least restrictive set of statistical assumptions.

All ES was represented by the standardised mean differences (SMD) in neuropsychological performance between BD cases and controls, and was calculated using Hedges' correction for bias in small samples (Hedges' *g*; Hedges and Olkin, 1985). A positive SMD indicated poorer performance in BD cases compared with controls; the size of the ES was interpreted according to Cohen's *d* (0.2 = small; 0.5 = medium; 0.8 = large; Cohen, 1988; Lee et al., 2012). As described in Table 1, cognitive domains included were psychomotor speed, attention and working memory, verbal learning and memory, visual learning and memory, attentional switching, verbal fluency, cognitive flexibility, and response inhibition. These were grouped according to empirical models of neuropsychological functioning (Table 1; see Lezak et al., 2012, for a detailed overview). In longitudinal studies, only baseline neuropsychological results were used to circumvent practice effects. If a study used more than one test for the same domain, the averaged ES was calculated.

Homogeneity was tested using the *Q*-statistic (χ^2). The I^2 statistic was used to quantify the proportion of between-study variability that reflected differences in real effects rather than random error. In keeping with the literature, I^2 values of 25%, 50% and 75% were interpreted as indicating small, moderate and high proportions of heterogeneity, respectively (Higgins et al., 2003). Tau^2 was used to quantify the absolute degree of heterogeneity. Eggers' test (Egger et al., 1997) was conducted to determine the presence of publication bias, and Rosenthal's Fail-Safe N (Rosenthal, 1979) was subsequently conducted to determine the number of studies that would be theoretically required to render the pooled ES non-significant. Duval and Tweedie's Trim and Fill method (Duval and Tweedie, 2000a, 2000b) was applied to hypothetically incorporate studies that may have been unpublished due to publication bias, yielding an adjusted pooled ES.

Sensitivity analyses were conducted for each cognitive domain to determine the robustness of the current findings. That is, the resiliency of every pooled ES to individual studies was tested to control for the potential peculiarity of each single study.

2.4. Moderator analyses

Variability in ES was examined using meta-regression (for continuous predictors) and subgroup analyses (Q_{bet}, or between subgroup homogeneity, for dichotomous/categorical predictors). The predictors of heterogeneity were selected on the basis of previous reviews and meta-analyses, and were included if a sufficient number of studies had reported these variables (i.e. no more than one study missing per cognitive domain). These were grouped as either:

1) *Demographic predictors* included 'age', 'sex', and 'IQ'. IQ was not separated into premorbid and current IQ since, contrary to schizophrenia-spectrum psychoses, BD is not associated with premorbid intellectual decline, and as such, premorbid and current IQ should be equivalent (Lewandowski et al., 2011;