Neuropsychology of bipolar disorder

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Abstract

Bipolar disorder is associated with significant dysfunction in a broad range of neuropsychological domains and processes. Deficits have been reported to occur in symptomatic states (depression, [hypo]mania) as well as in remission (euthymia), having consequences for psychological well-being and social and occupational functioning. The profile and magnitude of neuropsychological deficits in bipolar disorder has been explored in a number of systematic reviews and meta-analyses. After discussing these briefly, this chapter will focus on examining the clinical and demographic factors that that influence and modify the pattern and magnitude of deficits, as well as reviewing methods of assessment and analysis approaches which may improve our understanding of these problems.

Keywords: Neuropsychology; bipolar disorder; depression; mania; memory; attention; processing speed; attention

Pattern and magnitude of impairment

Early studies of neuropsychological impairment in bipolar disorder were typically small and clinically heterogeneous samples (Henry et al. 1973; Johnson and Magaro 1987). Assessing the verbal memory and fluency of twelve participants with bipolar depression, Wolfe et al. (1987) reported significantly poorer performance compared to those with major depression, with memory dysfunction which was qualitatively similar to patients with early Huntingdon's disease. While in twenty bipolar patients in the manic state, Morice (1990) reported significant deficits in cognitive flexibility (Wisconsin Card Sorting Test performance) which were similar to those in schizophrenia. An initial narrative review of the literature highlighted the difficulties inherent in comparing neuropsychological profiles across groups that differ, in terms of symptoms and concomitant treatments (Murphy and Sahakian 2001).

Around this time, an increasing interest emerged in understating the 'trait' aspects of neuropsychological dysfunction in bipolar disorder[1]. One of the earliest systematic assessments by Ferrier et al. (1999) suggested that executive function/working memory dysfunction was evident in euthymic patients compared to matched, healthy controls, including when factors such as age, IQ and residual depressive symptoms were accounted for in the analysis. Subsequent work sought to minimise the potential confounding effects of residual symptoms in the study design, for example, through prospective verification of euthymia. Thompson et al. (2005) assessed 63 patients with bipolar disorder (where euthymia was confirmed through clinical

[1] Unlike many other clinical conditions in which neuropsychological problems have been characterised, the focus of a great many studies in bipolar disorder has been when individuals are asymptomatic or euthymic. This is most likely a consequence of challenging the Kraepelinian dichotomy, in which cognitive decline was believed to occur in dementia praecox (schizophrenia), but not in manic-depressive psychosis (bipolar disorder) Kraepelin E (1899) Psychiatrie. Ein Lehrbuch für Studierende und Ärzte, 6th edn. Barth, Leipzig, Germany.

ratings over the month prior to testing) and a matched control group with a wide-ranging neuropsychological test battery. While the patient group was found to have performed statistically worse than controls across multiple cognitive domains (executive function and attention, working memory, verbal and visuo-spatial memory, and psychomotor/processing speed), clinically significant deficits – defined as performance below the 5th percentile of controls on any outcome – were also noted in a high proportion of patients (for example, 36% in processing/psychomotor speed and 19-34% on a number of the attentional, executive and memory measures).

Following the increase in studies focussed on the neuropsychological profile of euthymia, Robinson et al. (2006) published the first systematic meta-analysis synthesising the results of 26 studies, involving a total of 689 patients with bipolar disorder and 721 controls. Statistically significant differences were found in every measure assessed. The largest effect sizes were observed in measures of executive function (category fluency, mental manipulation) and in verbal learning, while medium effect sizes ($0.5 \leq d < 0.8$) were observed for short-term and delayed verbal memory, other executive measures (abstraction and set-shifting), sustained attention, response inhibition, and psychomotor speed. Small effect sizes ($0.2 \leq d < 0.5$) were observed in verbal (letter) fluency and immediate memory. Subsequent meta-analyses supported this initial synthesis, reporting a similar pattern of results (Arts et al. 2008; Bora et al. 2009). In a recent systematic review of 250 studies of neuropsychological function across all illness phases (which included a summary of previous meta-analyses), Tsitsipa and Fountoulakis (2015) reported that across these studies there is evidence that almost every cognitive domain that has been assessed has found poorer performance in BD compared to controls, in the 'medium' range (Cohen 1988) in euthymia, but of greater magnitude in acute episodes. However, it has also been

consistently noted that this conclusion lies very much 'at the group level' and there is notable heterogeneity of neuropsychological performance in BD (Bourne et al. 2013; Cullen et al. 2016; Douglas et al. 2018; Iverson et al. 2011; Krabbendam et al. 2005; Lima et al. 2019; Russo et al. 2017). When more stringent criteria are used to define 'impairment' (i.e. proportion of BD falling below a specific healthy control-derived cut off, such as <5th percentile or <1.5 standard deviations) the majority of many BD samples fall out of this range, with only a minority of individuals demonstrating global impairment (Douglas et al. 2018; Iverson et al. 2011; Iverson et al. 2009).

A number of diagnostic/clinical features and illness-related physical symptoms have been found to affect the pattern and particularly, severity of impairment.

What are the factors that affect cognition?

As previously outlined, there is a great deal of interest in neuropsychological heterogeneity and further, in determining whether cognitive deficits are a consequence or simply covary with clinical or illness-related features of bipolar disorder.

Diagnostic features

One area of focus has been in determining the profile of bipolar subtypes i.e. BD-I and BD-II. In general, neuropsychological performance of individuals with a history of full-manic episodes is worse than those with a history of hypomania (Bora 2018; Kessler et al. 2013; Schenkel et al. 2012; Torrent et al. 2006) although there are inconsistencies across specific domains (Harkavy-Friedman et al. 2006; Solé et al. 2012; Tsitsipa and Fountoulakis 2015). In a meta-analysis focussed on six executive function processes, Dickinson et al. (2017) found that while BD-II was associated with significant

impairment in 4 of 6 measures compared to controls, BD-I was associated with impairment in 6 of 6. However, direct comparison of subtypes revealed significant variability in effects across studies, with some processes (e.g. planning) being more impaired in BD-II. This heterogeneity has beset attempts to identify specific differences in the neuropsychological profile of BD-I and BD–II (Solé et al. 2011), although it has been suggested that there may be latent cognitive subgroups across the bipolar spectrum, especially in terms of impaired verbal memory (Aminoff et al. 2013).

More consistently, it has been demonstrated that psychotic symptoms are associated with worse neuropsychological function in bipolar disorder (Allen et al. 2010; Bora 2018; Glahn et al. 2006; Martinez-Aran et al. 2008; Tsitsipa and Fountoulakis 2015). This has been supported by meta-analysis, with performance in individuals with a history of psychosis being significantly worse than those without in 4 of 6 cognitive domains: planning and reasoning, working memory, verbal memory and processing speed (Bora et al. 2010). However, it should be noted that psychosis may not influence the neuropsychological profile of first-episode BD (Demmo et al. 2016).

Sleep

Sleep and circadian rhythm disturbance is a commonly reported clinical feature of bipolar disorder (Bradley et al. 2017; Eidelman et al. 2010; Geoffroy et al. 2015; Gruber et al. 2009; Harvey et al. 2005; Kelly et al. 2013; Millar et al. 2004). It is notable that the pattern and magnitude of neuropsychological dysfunction as a consequence of primary sleep disorder closely resembles that described in BD (Lim and Dinges 2010; Waters and Bucks 2011), with 'moderate' general deficits across a range of domains, but with larger effects in processing speed/attention – this closely resembles that seen in BD

depression (Boland and Alloy 2013; Gallagher et al. 2014; Gallagher et al. 2015b). Interestingly, recent work incorporating contiguous assessment of sleep and neuropsychological function in BD has found that, rather than exacerbating neuropsychological deficits, only individuals with sleep disturbance exhibited deficits (particularly processing speed and attentional deficits), while those with 'normal' sleep did not differ from controls (Bradley et al. 2020). This raises the possibility that sleep problems may be a primary driver of neuropsychological dysfunction, and therefore opens up novel treatment possibilities targeting sleep and circadian rhythm disturbance (Harvey et al. 2015; Jansson-Fröjmark and Norell-Clarke 2016).

Physical health

There are a number of concomitant physical health-related illness features which may contribute to or exacerbate neuropsychological dysfunction in bipolar disorder. Obesity, metabolic syndrome and cardiovascular risk have all been found to be increased in bipolar disorder (Czepielewski et al. 2013; Silarova et al. 2015), which in turn may negatively affect neuropsychological function (McIntyre et al. 2017; Mora et al. 2017). Although the mechanism is complex, hyperactivity of the hypothalamic-pituitary-adrenal axis may be implicated (Gallagher et al. 2009). There is a wealth of evidence that these problems are linked to neuropsychological impairment independently of mood disorder, and possibly that they are worsened by some medications (Mackin et al. 2007), therefore more work is needed to understand the temporal relationship between these observations.

Medication

A long-standing question is the degree to which treatment with psychotropic medication contributes to neuropsychological dysfunction in bipolar disorder. Some systematic reviews have suggested that there may be some evidence of poorer performance in those treated with antipsychotics (Cullen et al. 2016), although others have suggested that the effects are limited and may be confounded by the clinical symptoms leading to their use (Tsitsipa and Fountoulakis 2015). A recent analysis of data from UK Biobank analysed a sample of n=2709 individuals characterised as having bipolar disorder revealed small neuropsychological effects restricted to visuospatial memory with around a quarter of this effect attributable to psychotropic medication (Cullen et al. 2019), however the method of ascertaining diagnosis and the restricted cognitive testing protocol may have limited these findings. It should also be noted that several primary data studies have reported evidence of widespread neuropsychological impairment in medication-free samples (Goswami et al. 2009; Goswami et al. 2006; Pavuluri et al. 2006). And in a pooled analysis of data from n=1267 BD patients, regression analysis of specific medication classes revealed few effects on performance other than subtle effects on verbal learning, with the majority of contrasts suggesting no relationship (Bourne et al. 2013). Thus, it appears that broadly, the neuropsychological deficits seen in bipolar disorder are not iatrogenic.

Summary

It is clear that individuals with a diagnosis of bipolar disorder, when symptomatic and when euthymic, exhibit neuropsychological dysfunction. However, it is also clear that this conclusion relates specifically to the 'cohort level' – there is considerable heterogeneity in the actual profile of deficits, with numerous diagnostic and clinical features that are deleterious to performance. In the next section, the focus will be on

exploring a range of methods of assessment (both in terms of design and analysis) that may provide a better understanding the neuropsychology of bipolar disorder.

Methods of assessment

One of the most pressing questions for this field of research is whether there are specific methods or approaches at our disposal that may take us closer to establishing a cognitive profile of bipolar disorder - or even, to understand to what extent this is possible?

Longitudinal changes

The majority of studies conducted examined neuropsychological function in bipolar disorder are cross-sectional and therefore cannot further our understanding the stability and temporal trajectory of cognitive deficits (Ryan et al. 2016). Findings from a recent meta-analysis suggest that there is no relative cognitive decline between bipolar disorder and controls in either short-term (~1.5 years) or longer-term (~5.5 years) follow-up studies (Bora and Özerdem 2017). In terms of short-term changes in response to treatment, the extent to which neuropsychological processes improve is domain specific. Xu et al. (2012) found that in the depressed phase, while the predicted processing speed, memory and executive deficits were observed, after treatment for 6 weeks, those who remitted continued to exhibit impairments in processing speed and memory. Diagnostic subtype has also been observed to affect changes during early remission, with psychotic symptoms leading to higher rates of residual symptoms, neuropsychological dysfunction and poorer functional recovery (Levy et al. 2013). Examination of longer timeframes has demonstrated an association between

neuropsychological performance and 1-year functional outcome in bipolar disorder (Tabarés-Seisdedos et al. 2008). However, it is important to understand the temporal trajectories as recent work utilizing a cross-lagged panel model approach suggested that while neuropsychological function was causally primary and moderately predictive of subsequent functional outcome (1 year later), the converse did not hold – psychosocial functioning did not predict subsequent neuropsychological performance (Ehrminger et al. 2019).

Identifying neuropsychological phenotypic clusters

Several different approaches have been utilized to better understand the specific neuropsychological profile of bipolar disorder. Burdick et al. (2014) applied hierarchical cluster analysis to data from the MATRICS test battery in n=136 participants proposing three specific clusters – globally impaired, globally intact and an intermediate group with selective deficits in processing speed, attention, verbal learning and social cognition. This pattern has also been observed in other studies (Russo et al. 2017) where it has been suggested that such clusters are actually representative of sub-sections of a continuum (Lima et al. 2019; Van Rheenen et al. 2017). Similar approaches have been applied to executive processes and imaging data, also producing three clusters (Kollmann et al. 2019) and to reward processing (Jimenez et al. 2018). In a larger dataset of general neuropsychological measures from n=258 euthymic patients, Roux et al. (2017) proposed a four-cluster pattern, with a globally impaired cluster, a globally intact (above average performance) cluster and two further clusters that were normal with the exception of impaired or superior verbal performance. This pattern is very similar to that found in an earlier study in individuals with psychosis, including

n=73 with bipolar disorder (Lewandowski et al. 2014) which was later replicated (Lewandowski et al. 2018). Interestingly, in a cross-diagnostic cluster analysis, Lee et al. (2017) found only two clusters – impaired and intact/superior – but this did not map onto clinical diagnosis (although poorer social functioning appeared to differentiate those with a diagnosis of schizophrenia from bipolar disorder in the 'impaired' cluster). Collectively, this approach appears to confirm the heterogeneity described previously, when examining the proportions of bipolar samples falling below percentile cut-offs. However, it is also uncertain whether these clusters represent clear, clinically-independent subgroups or are simply categories of severity along a continuum.

A related approach has focussed on attempts to elaborate the factor structure of cognition within bipolar disorder and other related groups, and to explore their differences from healthy controls. In a large dataset from up to n=5,414 individuals with a diagnosis of bipolar disorder BPI and n=3,942 schizophrenia, Harvey et al. (2016) used principal components (PCA) and factor analysis to determine that neuropsychological performance and functional capacity measures combined (as well as the neuropsychological measures, or the diagnoses independently), could be reduced to a single principal component that explained most of the variation in the original variables. This is of note as the authors point to earlier studies that have identified as many as 6 components, consistent between bipolar and schizophrenia samples (Czobor et al. 2007; Schretlen et al. 2013).

Other studies have used PCA as a data-reduction technique (acknowledging that resultant component solutions are frequently data-set specific) to explore the cognitive process loadings within each component between bipolar disorder and healthy controls (Gallagher et al. 2014). In controls, there was a clear delineation between components along theoretically-derived lines (e.g. visuo-spatial, verbal memory). However, there

were fewer extracted components in the bipolar sample suggesting greater functional homogeneity, particularly of visuospatial processes. It is also of note that the individual variables that loaded into these components were less specific in terms of modality, with every one containing combinations of both verbal and visuospatial measures. In bipolar disorder, there were also some measures that loaded heavily across all components, such as processing speed. This pattern was interpreted as being similar to that seen in cognitive ageing, where *dedifferentiation* also leads to a loss of process specificity; notably, previously functionally discrete processes become more amorphous and less differentiated through decline in neural connectivity (Dolcos et al. 2002). Another parallel was highlighted – that of *cognitive scaffolding*, whereby interindividual adaptive changes may occur in underlying neural circuitry engaged in the 'normal' performance of cognitive tasks, resulting in the recruitment of alternative circuits or supportive processes than those typically used (Park and Reuter-Lorenz 2009). There is some suggestion that this may occur in bipolar depression, where it has been shown that deficits in facets of visuo-spatial memory may be compensated through verbal memory scaffolding (Gallagher et al. 2015a).

Therefore, any attempt to capture the specific neuropsychological profile of bipolar disorder needs to consider this heterogeneity – that while subgrouping by cognitive phenotype (and with a better understanding of the clinical and illness correlates of these) we may come closer to a 'profile', further heterogeneity may be introduced from other adaptive cognitive changes that might occur, closer to the individual level.

Hierarchical organization of cognition

As already discussed, it is commonly reported that neurocognitive deficits in BD at the group level are relatively 'broad' and of moderate effect size. However, this does not account for both the hierarchical organisation of human cognitive functions and the complex interplay between different cognitive processes. The conceptualisation of any observed profile of deficits is changed fundamentally if we consider that neuropsychological functions do not operate independently and further, that some may be subordinate to impairments in more circumscribed but functionally primary processes. This approach has been applied to the neuropsychology of major depression in older adults, where hierarchical regression modelling of cognitive processes has revealed that broader deficits in episodic memory and visuospatial processes may be mediated by decreased fundamental processing resources (Nebes et al. 2000). Similar approaches applied in younger depressed patients have found that primary attentional deficits may similarly account for deficits in some executive processes (Nilsson et al. 2016). Such methods have been used extensively to develop a better understanding of the neuropsychology of typical and pathological ageing (Clarys et al. 2009), especially on the role of information processing speed and efficiency (Joy et al. 2000; Joy et al. 2004; Salthouse 1996; Salthouse 2000; Salthouse 2017). Here, it is also important to note the potential of applying approaches used in experimental neuropsychology studies to better understand the role of specific (primary) cognitive processes in common task performance (e.g. Cepeda et al. 2013; Davis and Pierson 2012; Tam and Schmitter-Edgecombe 2013) and complimentary task design aimed at manipulating specific processes or cognitive load during active task performance. Collectively this may lead to greater insights into the organisation of cognition in bipolar disorder, if applied to narrower well-defined clinical phenotypes.

One approach that may also facilitate a better understanding of individual profiles is the application of finite *partially ordered sets (posets)* as classification models (Tatsuoka 2002; Tatsuoka and Ferguson 2003). The approach involves the statistical modelling of cognitive processes in a manner which closely resembles that done during single-case clinical neuropsychological assessment. This has been applied to neuropsychological data for individuals with a diagnosis of schizophrenia (Jaeger et al. 2006a; Jaeger et al. 2006b) and would be of great interest to apply to bipolar disorder. Given the group-level heterogeneity described in the neuropsychological literature of bipolar disorder, it would similarly be of interest to explore a variety of available methods to assess patterns of performance at an individual level (Crawford and Garthwaite 2002; Crawford et al. 2009a; Crawford et al. 2009b). Some of these methods could overcome methodological issues that have not received a great deal of attention, such as comparisons against small sample control norms (Crawford and Garthwaite 2002; Crawford et al. 2009b), quantifying deficits when the psychometric properties of tests differ (Chapman and Chapman 1973) and assessing whether deficits qualify as differential deficits (Crawford et al. 2000), the latter having revealed hierarchical organisation of the cognitive profile of euthymic bipolar disorder (Thompson et al. 2006; Thompson et al. 2009).

Experimental analysis methods

There are a growing number of examples of the utility of applying novel analysis methods to refine the measurement of selective cognitive processes in bipolar disorder. One specific example is the assessment of attentional processes. By fitting reaction time (RT) data from sustained attention tests to non-Gaussian distributions (e.g. a mathematically convolved Gaussian and exponential; the ex-Gaussian), differential RT

profiles were observed between major depression and bipolar disorder, resulting in larger, statistically significant effect size differences which typical measures of central tendency failed to detect (Gallagher et al. 2015b; Moss et al. 2016). Given the potential importance of attention and processing speed within the cognitive hierarchy, and the relationship with structural and functional connectivity (Pavuluri et al. 2009; Poletti et al. 2015), such methods may offer unique insights into the cognitive profile of bipolar disorder. Similar approaches, coupled with assessment of intra-individual RT using Fast Fourier transform, have been applied successfully to explore candidate cognitive endophenotypes in ADHD (Vaurio et al. 2009), while drift-diffusion modelling and Bayesian approaches have revealed differences in information-processing efficiency and reward learning parameters in psychosis (Mathias et al. 2017; Moustafa et al. 2015).

Conclusions

Overall, we see clear evidence for neuropsychological impairment in bipolar disorder. Much of the evidence is at the group-level and from numerous sources it is apparent that specific demographic, diagnostic and illness-related features can influence the profile and/or severity of the observed deficits. To further our understanding of neuropsychological processes within bipolar disorder it is suggested that studies should be more cognizant of the hierarchical organisation of cognition and the existing methods of analysis and task design which might provide unique insights in future work. Such approaches hold promise in deriving a more refined conceptualisation of specific phenotypic presentations – beyond the 'group level' – which could ultimately aid illness stratification.

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