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Prevalence of Cognitive Impairment in Major Depression and Bipolar Disorder

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Abstract

Objectives: The current paper examines prevalence of cognitive impairment in four mood disorder samples, using four definitions of impairment. The impact of premorbid IQ on prevalence was examined, and the influence of treatment response.

Methods: Samples were: 1) 58 inpatients in a current severe depressive episode (unipolar or bipolar), 2) 69 unmedicated outpatients in a mild to moderate depressive episode (unipolar or bipolar), 3) 56 outpatients with bipolar disorder, in a depressive episode, and 4) 63 outpatients with bipolar disorder, currently euthymic. Cognitive assessment was conducted after treatment in Studies 1 (six weeks of antidepressant treatment commenced on admission) and 2 (16-week course of cognitive behaviour therapy or schema therapy), allowing the impact of treatment response to be assessed. All mood disorder samples were compared with healthy control groups.

Results: Prevalence of cognitive impairment was highest for the inpatient depression sample, and lowest for the outpatient depression sample. Substantial variability in rates were observed depending on the definition of impairment used. Correcting cognitive performance for premorbid IQ had a significant impact on the prevalence of cognitive impairment in the inpatient depression sample. There was minimal evidence that treatment response impacted on prevalence of cognitive impairment, except in the domain of Psychomotor Speed in inpatients.

Conclusions: As interventions aiming to improve cognitive outcomes in mood disorders receive increasing research focus, the issue of setting a cut-off level of cognitive impairment

for screening purposes becomes a priority. This analysis demonstrates important differences in samples likely to be recruited depending on the definition of cognitive impairment and begins to examine the importance of premorbid IQ in determining who is impaired.

Key words: Cognitive Impairment; Memory; Depression; Bipolar Disorder; Neuropsychology; Prevalence

Introduction

Cognitive impairment is a core feature of bipolar disorder and recurrent major depressive disorder (MDD) (1-4), is associated with difficulties in occupational and interpersonal functioning (5, 6), and thus has a major impact on depressed individuals' quality of life. First-line antidepressant and psychological treatments have limited beneficial impact on cognitive functioning and deficits persist into recovery (1, 3, 7-10). It is therefore crucial to focus not only on clinical outcomes in mood disorder intervention studies, but also cognitive and functional outcomes.

On the basis of a moderate to large effect size difference in group means between bipolar or MDD patients, and healthy controls, it has sometimes been assumed that those with mood disorders may all benefit from interventions specifically to improve cognition. However, studies have suggested that only a percentage of depressed patients (unipolar or bipolar), or euthymic bipolar disorder patients, show significant cognitive impairment, when judged by usual criteria of difference from a normative group mean by number of standard deviations (SD) (11-13). This has important implications for treatment and for screening for inclusion in studies which aim to improve cognitive function. Inclusion of a number of depressed individuals with unimpaired cognitive function may wash out any positive effect and result in failed trials (14, 15). Screening has recently been recommended by a task force of the International Society for Bipolar Disorders (16). If meaningful screening thresholds can be identified, this may prove beneficial in identifying those who could benefit from specific interventions.

Few studies have examined prevalence rates of cognitive impairment in mood disorder samples. Gualtieri and Morgan (13) examined rates in outpatient samples with bipolar disorder (I and II) and MDD. Using their conservative criteria of cognitive impairment (two or more cognitive domains impaired more than two SD below norms for healthy controls), they showed that 20 to 30% of those with bipolar disorder or MDD were impaired. Iverson and colleagues (12) studied prevalence rates of cognitive impairment in three different outpatient mood disorder samples (bipolar disorder, unmedicated MDD, and medicated MDD) who completed the same cognitive testing battery as in Gualtieri and Morgan (13) (CNS Vital Signs). Having two or more cognitive domain scores more than 1.5 SD below the control norm was suggested as a criterion for identifying significant cognitive impairment, based on low false positive rates (i.e., this classified a low percentage of the healthy control participants as impaired). Other approaches to defining cognitive impairment have been proposed outside mood disorder research, including examination of scores on individual cognitive test variables (e.g., greater than 1.5 or 2 SD below healthy controls on two or more cognitive test variables) or using a specified global cognitive composite (e.g., greater than 1.5 or 2 SD on a global cognitive composite). Overall, however, there is little consensus regarding how to define cognitive impairment in mood disorder research or what useful thresholds would be.

Premorbid IQ is an important and often neglected factor that should be taken into account when assessing degree of cognitive impairment. Individuals with a premorbid IQ of one or more SD below the population mean will, by definition, show results of at least one SD below the mean on several cognitive tests, and would therefore be defined as being ‘cognitively impaired’ if a threshold of one SD was set. Thus, while some individuals in studies of mood disorders may have illness-related cognitive impairment, others’ cognitive

impairment may simply be as a result of low premorbid cognitive function. In contrast, those with a premorbid IQ of one or more SD above the population mean are very unlikely to be detected as 'impaired' even if their performance is substantially lower than the level their premorbid IQ would predict. Variability in cognitive performance in mood disorder samples (4, 17) may be, in part, due to these individual differences in mechanisms underlying cognitive impairment. For the above reasons, it would therefore be of use to determine whether measures of premorbid IQ could be used to increase the accuracy of definition of cognitive impairment in mood disorder samples.

The current study aims to replicate and extend results of studies examining the prevalence of cognitive impairment in mood disorder samples (11-13). Findings will be presented from four well-defined mood disorder samples: inpatient depression, medication-free outpatient depression, bipolar depression, and euthymic bipolar disorder. Group comparisons with healthy controls for all four samples have been reported previously (18-21), but prevalence rates of cognitive impairment, as analysed here, have not been examined. Cognitive impairment will be defined according to:

1. deviation from controls on pre-defined domains of cognitive functioning by examining
    a. the *number* of domains impaired and
    b. the *type* of domains impaired,
2. deviation from controls on a number of individual test variables, and
3. deviation from controls on a global cognitive composite score.

Further analysis will correct the global cognitive composite scores for premorbid IQ. As far as we are aware, this is the first study in mood disorder samples which specifically determines the impact of premorbid IQ on prevalence of cognitive impairment at an individual level. Previous studies have tended to focus on the protective impact of premorbid IQ or cognitive reserve on cognitive functioning, for example, in bipolar disorder (22) and in depressed individuals receiving electroconvulsive therapy (23).

In two studies (inpatient and outpatient depression samples), depressed and healthy control groups underwent treatment and completed follow-up cognitive testing. Thus, the first three analyses above were repeated on follow-up data and assessed in relation to treatment response.

Methods

The first two samples presented in this paper completed cognitive assessment at two time-points. To ensure accurate comparison of prevalence rates across time-points, only participants who completed baseline and follow-up cognitive assessment are included in this paper.

All studies used the Structured Clinical Interview for DSM–IV Axis I Disorders (SCID–I) (24) to confirm mood disorder diagnosis. At least one widely-used mood rating scale (Montgomery-Asberg Depression Rating Scale, MADRS (25); 17-item Hamilton Depression Rating Scale, HDRS-17 (26); and Young Mania Rating Scale, YMRS (27)) was administered in all studies to assess severity of mood symptoms. Exclusion criteria for depressed and healthy control groups for Studies 1, 2 and 4 were: schizophrenia, current serious alcohol or

drug misuse or dependence, comorbid endocrinological, neurological or chronic medical conditions, pregnancy, previous serious head injury, electroconvulsive therapy (ECT) in the past 12 months, or taking medications likely to interfere with cognitive functioning. For Study 3, current serious alcohol or drug misuse or dependence was the only exclusion criterion. Healthy control groups for all studies consisted of age- and gender-matched psychologically healthy individuals without a personal history, or a history in a first-degree relative, of major mental illness.

Study 1: Inpatient Depression Sample

Study Design

Cognitive functioning in depressed participants was assessed within two days of admission (baseline) to an acute psychiatric inpatient ward in Christchurch, New Zealand, and six weeks after baseline. Treatment was naturalistic, with inpatients receiving standard care. Healthy control participants completed cognitive assessment at the same time-points.

Participants

Fifty-eight inpatients aged between 18 and 60 years, with a primary DSM-IV (28) diagnosis of major depressive episode (MDE; unipolar, $n = 50$ or bipolar, $n = 8$), completed both clinical and cognitive assessments. At baseline, 19 participants were unmedicated and subsequently commenced on an antidepressant medication. Of the remaining participants ($n = 39$), the dose of their existing antidepressant was increased or they were changed to another antidepressant medication (see Douglas et al., 2011, for a detailed report of antidepressant use in the depressed group). No significant differences between medicated and unmedicated patients were observed on any cognitive variables at baseline**.** At follow-up, all were medicated with an antidepressant, the vast majority with a selective-serotonin reuptake

inhibitor (SSRI) or serotonin-noradrenaline reuptake inhibitor (SNRI). Participants were classified according to treatment response at the six-week follow-up (treatment response ≥ 50% reduction in MADRS score from baseline to follow-up). The healthy control group consisted of 50 individuals, who were screened for current and past psychiatric conditions using the Mini International Neuropsychiatric Interview (MINI) (29). See Douglas et al. (18) for main cognitive outcome data and additional study information.

Study 2: Outpatient Depression Sample

Study Design

Participants were enrolled in a randomised controlled trial (RCT) comparing the effectiveness of Cognitive Behaviour Therapy (CBT) with Schema Therapy (ST) for major depression (see Carter et al. (30) for main clinical outcomes). Cognitive functioning was assessed prior to randomisation (baseline) and after the first 16 weeks of psychological therapy.

Participants

Sixty-nine depressed outpatients, aged between 18 and 65 years, with a DSM-IV defined MDE without psychotic features (single or recurrent major depressive disorder, $n = 64$ or bipolar II depression, $n = 5$) completed both cognitive assessments. The depressed sample was psychotropic-medication-free for at least six weeks prior to recruitment and remained medication-free at follow-up. The definition of treatment response was the same as Study 1. Fifty-eight healthy control participants (screened using the MINI), completed both cognitive assessments. Cognitive data from this sample has been published previously for baseline (19) and longitudinal findings (9).

Study 3: Bipolar Depression Sample

Study Design

Depressed participants were part of an RCT investigating the long-term efficacy of mifepristone as an adjunctive treatment for bipolar depression. Patients were randomised to receive mifepristone or placebo for one week and were followed up for seven weeks following treatment cessation. Cognitive assessment occurred prior to randomisation (baseline), and 8 weeks after baseline.

Participants

Fifty-six depressed individuals with a DSM-IV diagnosis of bipolar disorder I or II, current episode depressed, completed cognitive assessment. Patient medication was unchanged for four weeks prior to participation. Fifty-three healthy controls completed a single cognitive assessment. Cognitive outcome data from this study are published in Watson et al. (20).

Study 4: Euthymic Bipolar Disorder Sample

Study Design

This was a cross-sectional study of cognitive functioning in prospectively-verified euthymic individuals with bipolar disorder. One cognitive assessment was conducted for both euthymic bipolar disorder and healthy control participants.

Participants

Sixty-three outpatients with a DSM-IV diagnosis of bipolar disorder (I and II) completed cognitive assessment. Euthymia was confirmed prospectively, with scores below seven on the HDRS-17 and YMRS over a period of one month required prior to study entry. With the exception of three participants with bipolar disorder who were taking no medication, all were

stabilised on prophylactic medication. There were 63 individuals in the healthy control group. Cognitive outcome data from this sample have been published in Thompson et al. (21).

Cognitive Testing

Cognitive tasks used and variables reported across the four samples are displayed in Table 1. For an explanation of the cognitive tests and testing conditions (e.g. time of day, computer software), see original cognitive outcome papers from these studies (9, 18-21).

INSERT TABLE 1 ABOUT HERE

Statistical Analysis

Statistical analyses were conducted using SPSS, version 22-x for Windows (31). All cognitive variables and IQ scores were normally distributed. For demographic and clinical characteristics, categorical variables were analysed with χ^2 tests and continuous variables with independent sample *t*-tests.

For each of the four studies, mean scores and SD from cognitive and IQ variables in the healthy control group at baseline were calculated. *Z*-scores for depressed and control samples for each of these variables were then calculated using the following equation: (raw score – $\text{mean}_{\text{control group}}$)/$\text{SD}_{\text{control group}}$. For Studies 1 and 2, both of which had follow-up cognitive data in depressed and control groups, this procedure for calculating *Z*-scores was repeated using mean scores of the control participants at follow-up. *Z*-scores were calculated so that a positive *Z*-score always represented an individual performing more poorly than the mean of the healthy control group, regardless of whether the cognitive variable produced outcomes of accuracy, number of errors or reaction time.

For each study, cognitive variables were grouped to fit into one of four cognitive domains: 1) verbal learning and memory, 2) visuospatial learning and memory, 3) executive function/attention, and 4) psychomotor speed. Domain scores were calculated by averaging the *Z*-scores of tests within each domain. A Global Cognitive Composite was created by averaging *Z*-scores across the four domain scores from the cognitive testing battery for each study.

Four approaches to defining cognitive impairment were used.

1. Number of cognitive domains impaired: for ease of comparison with previous studies in this area (12, 13), performance was evaluated as the number of cognitive domains in which participants scored below healthy controls by 1, 1.5 and 2 SD. Three SD cut-offs were included because there is no consensus regarding an ideal cut-off, with some studies in mood disorder samples suggesting a conservative cut-off of 2 SD below 'normal' (13) as reflecting meaningful cognitive impairment, and other studies suggesting less-conservative cut-offs of 1 or 1.5 SD (12, 32, 33).
2. Percentage of depressed participants impaired in each cognitive domain: in order to examine whether specific cognitive domains had higher prevalence rates of impairment, the percentage of participants impaired at 1, 1.5 and 2 SD cut-offs on each cognitive domain was calculated for depressed participants and healthy controls.
3. Global Cognitive Composite: the prevalence of cognitive impairment when using the Global Cognitive Composite was assessed in depressed and healthy control groups, at 1, 1.5 and 2 SD cut-offs.
4. Number of test variables impaired: a commonly cited approach to categorising cognitive impairment involves determining the percentage of depressed participants

impaired on a certain number of individual test variables. In the present study, the percentage of participants impaired (1, 1.5 and 2 SD cut-offs) on at least two individual cognitive variables from different tasks (for example, impairment on RAVLT total learning and RAVLT delayed recall did not constitute two cognitive variables because of the close relationship between these measures) was examined.

The above four approaches were repeated with follow-up data for Studies 1 and 2 for treatment responders, non-responders and healthy controls. Statistical comparisons between responders and non-responders were conducted using Mann-Whitney U tests (for approaches 1 and 2 above) or χ^2 tests (for approaches 3 and 4 above). Change in prevalence rates (comparison of single values or spread of rates, depending on the approach) of cognitive impairment in healthy control groups from baseline to follow-up was assessed using McNemar tests or paired *t*-tests (Wilcoxon Signed Rank Test).

The influence of premorbid IQ (from National Adult Reading Test (NART) (34) scores) on cognitive performance was taken into account by re-analysing the Global Cognitive Composite scores from each study. For each individual, the *Z*-score for premorbid IQ was subtracted from the *Z*-score for the Global Cognitive Composite. For example, if an individual was 1 SD worse than healthy controls on both their premorbid IQ and overall cognitive performance, their corrected score of 0 would reflect this balance. However, if an individual performed 1 SD worse than healthy controls on overall cognitive performance but had an IQ of 0.5 SD better than healthy controls, the cognitive score was corrected by reducing it to 1.5 SD worse than controls (corrected *z*-score = - 1.5) to reflect this discrepancy. Percentage of depressed individuals who were impaired at 1, 1.5 and 2 SD cut-offs on the IQ-corrected Global Cognitive Composite was then calculated for each study.

Results

Demographic details are presented in Table 2. No significant differences between depressed and healthy control groups were found for gender, age, number of years of formal education, or premorbid IQ (NART).

** INSERT TABLE 2 ABOUT HERE **

Table 3 presents clinical data from the four samples. Missing scores on measures in Table 3 is due to differences in clinical data collected between studies. The inpatient depression sample was severely depressed at baseline assessment, with an average MADRS score of 35.7. Scores from the MADRS and HDRS-17 in outpatient depressed and bipolar depressed samples indicated moderate depression severity, and the euthymic bipolar sample (who were excluded if they were depressed) scored in the normal range on the HDRS-17.

** INSERT TABLE 3 ABOUT HERE **

Baseline Prevalence of Cognitive Impairment

Prevalence rates of cognitive impairment using four approaches to define impairment, are presented in Table 4. Regarding the number of cognitive domains impaired (first approach), most healthy control participants were not impaired on any cognitive domains at 1.5 SD (82-94%) and 2 SD (92-97%) cut-offs. Participants with mood disorders, particularly the inpatient depressed sample, were generally impaired on a greater number of cognitive domains than

healthy controls. For example, at the 1.5 SD cut-off, 37.5% of the inpatient depression sample (Study 1) were impaired in two or more cognitive domains, while in Studies 2 to 4, 9-21% of patients were impaired.

The percentage of patients categorised as cognitively impaired on each cognitive domain (second approach) varied widely between studies, and within cognitive domains. For healthy control groups across studies, prevalence rates of cognitive impairment at the 1.5 SD cut-off were all less than 8%, and less than 5% for the 2 SD cut-off. The domain of Verbal Learning and Memory had the highest prevalence of impairment in the three samples of participants who were currently depressed (17.4 to 36.2% at the 1.5 SD cut-off; Study 1-3). A clear profile of impairment when examining patterns across all cognitive domains, using this method, was not evident.

Prevalence of impairment on a Global Cognitive Composite (third approach) was low in healthy control groups from all studies (e.g., impaired by > 1.5 SD = 0-1.9%; impaired by > 2 SD, all = 0%). For patient groups, prevalence rates at the 2 SD cut-off were also low (0-7.5%). 18.9% of the inpatient depression sample were impaired at the 1.5 SD cut-off, compared with only 2.9% of the outpatient depression sample. Both bipolar samples had similar rates of cognitive impairment at the 1.5 SD cut-off (12.5-14.3%).

Prevalence rates from the final method of defining cognitive impairment, which calculated the percentage of participants impaired on at least two individual test variables, are shown in Table 4, and discussed further below.

** INSERT TABLE 4 ABOUT HERE **

Prevalence of Cognitive Impairment Corrected for Premorbid IQ

Global Cognitive Composite scores, corrected for premorbid IQ, for each mood disorder sample are presented in Figure 1. Prevalence rates of cognitive impairment for the 1.5 SD cut-off increased for Study 1 and 2 when premorbid IQ was taken into account. The increase was significant for the inpatient depression sample (Study 1; increased from 18.9 to 41.5%; χ^2 = 4.1, p = 0.04). Five percent of inpatients (3 of 58 participants) moved from being defined as cognitively impaired to unimpaired after correction for premorbid IQ, while 28% (16 of 58 participants) moved from being unimpaired to impaired. Of the 16 individuals who were identified as impaired following correction for premorbid IQ, 15 had above average (> 100) premorbid IQ scores. Prevalence rates remained similar after adjusting for premorbid IQ in the bipolar samples (Study 3 and 4).

** ADD FIGURE 1 ABOUT HERE **

Prevalence of Cognitive Impairment in Relation to Treatment Response

Table 5 presents the same four approaches to determining prevalence rates of cognitive impairment using follow-up data. In Study 1, prevalence of cognitive impairment in the domain of Psychomotor Speed was significantly greater in treatment non-responders compared with treatment responders at follow-up (e.g., 1.5 SD = 0.0% vs 18.2%; 2 SD = 0.0% vs 3.0%: p=0.01). No significant differences between treatment responders and non-responders were found for any other comparisons from the four approaches to classifying

cognitive impairment (all $p \geq 0.05$) in either inpatient or outpatient depression samples. Prevalence of cognitive impairment in the healthy control samples between baseline and follow-up did not differ significantly using any approach (all $p \geq 0.1$).

** ADD TABLE 5 ABOUT HERE **

Discussion

Prevalence of Cognitive Impairment in Mood Disorders

Due to differences in cognitive testing batteries and demographic characteristics, the current study cannot accurately compare prevalence rates between the four samples. However, it does give an indication of the percentage of participants in each sample who would be classified as impaired and who might therefore be eligible for treatment studies of cognitive impairment depending on the method of enrichment used and the sample being recruited.

The four approaches used to define cognitive impairment resulted in very different prevalence rates. The method of categorising cognitive impairment based on the percentage of participants impaired on a certain number of individual test variables proved problematic. Part of the definition of mild cognitive impairment in Alzheimer's Disease research is that scores on one or more individual test variables should be at least 1 SD below the mean for their age (35). Of course, 16% of healthy individuals will score more than 1 SD below the norm on a single cognitive test (12), and thus, it was decided that scores on at least *two* different cognitive tests should be impaired for the classification used here. This definition has been used recently in a clinical trial of a cognitive remediation intervention in bipolar disorder, screened for objective cognitive impairment (36). However, this definition of

impairment appeared to be influenced by the number of tests in the cognitive testing battery. That is, in the study that included the most cognitive tests (Study 4), a high prevalence of patients (78%), and more unusually, healthy controls (49%), were categorised as impaired. In comparison, rates of impairment in other healthy control samples ranged from 13 to 26% at the same cut-off. This approach may be of more use across studies in similar clinical populations using identical cognitive testing batteries.

The method of determining the number of cognitive domains impaired (with no focus on the type of cognitive domain), has been examined previously in depressed samples. Cut-offs of 1.67 SD and 2 SD, on two or more cognitive domains, have been suggested since this gives low false positive rates (i.e., low rates for healthy control groups). Using the 2 SD cut-off, Gualtieri and Morgan (13) found that 21% of their MDD sample and 30% of their bipolar disorder sample were impaired on at least two domains, compared with 3.6% of healthy controls. In the current sample, using the same criteria, a lower rate of impairment was found; ranging from 4.4% (outpatient depression sample) to 14.3% (inpatient depression sample). These lower rates are of note since the inpatient sample in the current study was likely to be much more severely depressed than the outpatient samples from Gualtieri and Morgan's study (although mood rating scales were not used in that study). The cognitive testing battery completed by the inpatient depressed sample in the current study was brief because of the severity of depression. This briefness may have come at the expense of being sensitive to cognitive impairment and also of having a reliable representation of the specified cognitive domain. Lower prevalence of cognitive impairment in comparison with Gualtieri and Morgan's study in our three outpatient samples (Studies 2-4) may be explained by our samples being less severely depressed.

This paper does not directly compare matched samples of patients with bipolar disorder and unipolar MDD. For example, the samples consisting of patients who were in mood episode (Studies 1-3) were not matched for severity or treatment. Therefore, rates of impairment in bipolar depression cannot be compared usefully with those in unipolar depression. We also note that in Studies 1 and 2, the small percentage of patients with bipolar depression (Study 1 = 13.8% bipolar depression, Study 2 = 7.2%) meant that a separate analysis to compare rates of impairment in bipolar and unipolar depressed patients was not warranted. In these two studies, we have previously reported results of re-analyses of main cognitive measures that omitted bipolar patients, with these re-analyses not changing results significantly in terms of p-values or effect size differences (18, 19).

A less commonly used approach for defining cognitive impairment is to examine rates of impairment for each cognitive domain. In the current study, large variability in rates of impairment was seen between cognitive domains. The domain of Verbal Learning and Memory produced the highest rates of impairment in three of the samples (17-36% impairment at 1.5 SD cut-off), however, variability between rates of impairment in other cognitive domains made it difficult to determine meaningful patterns. Cullen et al. (11), in their review of euthymic bipolar samples, found substantial variability in rates of impairment within cognitive domains, which they attributed to small sample sizes and mixed study designs. Regardless of these mixed findings, the profile of impairment across cognitive domains is important to consider. Significant impairment on a single cognitive domain may still impact on general functioning in tasks related to this domain, and if looking only at

global cognitive functioning, marked impairment on one domain may be diluted to the extent that impairment is no longer evident.

This dilution of any marked impairment on a single domain was indeed observed when using a Global Cognitive Composite score from each cognitive testing battery to define impairment. This approach resulted in generally lower rates of cognitive impairment (range over the four samples at the 1.5 SD cut-off = 1.6 to 18.9%) compared with other approaches, which, as suggested previously, was likely due to a flattening out of variability in areas of strengths and weaknesses in cognitive domains for each individual. An advantage of this approach, however, was that it was simplest to calculate and interpret prevalence rates of impairment.

Global Cognitive Composite data illustrated a potential methodological weakness of all four studies reported in the current paper. While the distributions of cognitive scores in control participants did not depart significantly from normal, in a perfectly normal distribution, the rate of impairment in the healthy control groups should have been 6.7%. The actual result in the combined control group was 1%. This skew may arise from the fact that people with a perception that they have cognitive impairment are unlikely to volunteer to take part in a study involving cognitive testing, thereby giving rise to an attenuated tail in the distribution.

The current paper reported prevalence of cognitive impairment based on pre-selected, mathematical cut-off points that have been used previously in mood and neurological disorder research. True cognitive impairment, however, would involve an obvious functional impact that is reasonably attributable to the problem. While functional impairment is likely to

have been present in individuals defined as cognitively impaired in the current paper, data on functional impairment was not collected. Further, this paper did not seek to determine the most clinically and functionally meaningful definition of cognitive impairment, but rather, to illustrate that groups categorised as 'cognitively impaired' can be vastly different depending on the approach used to define impairment. Certainly, future research to determine definitions that relate strongly to functional impairment will be integral to clinical trials that aim to improve cognitive and functional outcomes in mood disorder patients. In the area of psychotherapy research, Jacobson et al. (37) have suggested that clinically significant change may be the extent to which therapy moves an individual outside of the range of the 'dysfunctional' population, or within the range of the 'functional' population. Definitions such as these may be useful to incorporate into discussion of approaches to categorising cognitive impairment in the future.

Changes in Rates of Cognitive Impairment with Treatment

In the inpatient depression sample, there was a difference in rates of impairment between responders and non-responders only when examining the domain of Psychomotor Speed. No treatment responders were impaired in this domain at 1.5 and 2 SD cut-offs at follow-up testing, while 18.2% and 3% of non-responders were impaired at these cut-offs, respectively. In the outpatient depression sample, after 16 weeks of weekly psychological therapy, there was no evidence of rates of cognitive impairment reducing in treatment responders compared with non-responders, in keeping with an analysis based on group means (9).

These findings generally support studies suggesting limited effects of treatment, even when otherwise successful, on cognitive function (1, 7-10). Reduced rates of impairment in

psychomotor speed in the inpatient depression sample should be interpreted with caution since it was an isolated finding in this analysis. However, it is in accord with a previous study in an inpatient sample (38) and previous reviews have suggested that psychomotor speed may be the domain most likely to improve with successful treatment (1).

Influence of Premorbid IQ on Rates of Cognitive Impairment

In the current study, the Global Cognitive Composite was corrected to take into account the premorbid IQ of each participant. This then allowed determination of whether each participant was performing above or below their expected level of functioning on cognitive tests. Correction for premorbid IQ increased the number of participants categorised as cognitively impaired in the inpatient and outpatient depression samples (Study 1 and 2), significantly so for the inpatient sample. The higher prevalence in the inpatient sample was due to a substantial portion of participants with above average premorbid IQ (> 100) being re-categorised as impaired after correction for IQ. Objectively, these individuals did not show significant cognitive impairment in relation to healthy control norms, however, they were performing much more poorly than their premorbid IQ would have suggested. In line with this finding, research in late-life depression has found that individuals with high cognitive reserve show greater cognitive impairment as depressive symptoms increase, perhaps because they have 'more to lose' (39, 40). It is likely that these individuals have occupations that match their premorbid IQ level, and require strong cognitive skills. It is possible that patients who function at a relatively high level, and who develop severe depression, are more likely to become inpatients because of the social and occupational effects of being unable to cope with a reduction in cognitive capacity. This analysis emphasises the importance of taking

premorbid IQ into account, particularly when screening for cognitive impairment prior to commencing cognitive remediation interventions.

Limitations

First, because cognitive batteries differed, comparison of prevalence rates across groups has limited value. Of greater interest, however, was how prevalence rates varied within samples based on different definitions of impairment. Second, cut-offs for degree of impairment in the current paper used comparison with performance of matched healthy control groups rather than standardised norms. Healthy control group scores are likely to be more variable than standardised norms. On the other hand, using healthy control group norms may be a more accurate way of determining scores in a population of a particular age, gender and premorbid IQ, particularly because some less traditional tests used in the cognitive testing batteries in the current study had limited norm data available (e.g., the Simple Reaction Time Test in Studies 1 and 2, and the Consonant Vowel Consonant Verbal Learning Test in Study 2). It is worth noting, however, that norms from healthy control groups would not usually be used to inform screening in clinical trials of cognitive treatments. As discussed in Cullen et al.'s (11) review of prevalence of cognitive impairment in euthymic bipolar disorder, there is no clear association between choice of reference (e.g., standardised norms or healthy control groups) and prevalence rates of impairment. Some studies in Cullen's review showed low prevalence rates using standardised norms compared with studies using comparison groups, while other studies showed some of the highest prevalence rates in bipolar disorder across cognitive domains when using standardised norms. Overall, it appears that choice of reference can impact on prevalence rates observed, and thus, this should be considered when comparing rates across studies. Third, there was substantial variability in the type of antidepressant

medication patients were treated with in the depressed inpatient sample (Study 1). This study was not a regimented treatment trial, but rather, a naturalistic study of treatment as usual in an inpatient setting. There is the suggestion that different classes of antidepressants may have differential impacts on cognitive function (41), and if so, cognitive findings in Study 1 may be limited by variability in treatment regimes. Such wide range in types of antidepressant medications prescribed meant that sub-analyses to examine differential effects of medications on cognitive function was not warranted. Of note, however, is that baseline analysis comparing cognitive performance of medicated and non-medicated patients did not produce any significant differences. In addition, a recent large-scale RCT (n = 1008) found no evidence that three types of antidepressant medication (escitalopram, venlafaxine or sertraline) differentially improved cognitive impairment over time (10).

Limitations of using a word-reading test, such as the NART, as a measure of premorbid cognitive functioning should be noted. Evidence suggests the NART to be a reliable and valid proxy measure of general IQ, as well as being relatively resistant to the effects of psychiatric disorders (42). However, at a more conceptual level, using NART performance as an estimate of premorbid IQ, and then generalising this to performance on a broad range of cognitive tests (e.g., memory and executive function) may be overly simplistic. Incorporation of demographic variables (e.g., age, education level, SES) into a formula to estimate premorbid cognitive functioning may be more comprehensive, but to date, research has typically focused on such formulae to predict general IQ, rather than premorbid cognitive ability. Finally, it is possible that scores on the NART are affected by a phenomenon of lower cognitive performance in those susceptible to mood disorder. This could be related either to a trait biological effect (43) or to adversity associated with parental mood disorder.

Implications and Conclusions

The traditional presentation of cognitive data as group means of depressed versus control groups (or treatment responders versus non-responders) does not give a good indication of the numbers of participants in the sample with clinically significant cognitive impairment. Determining which individuals suffer from significant cognitive impairment is particularly important in treatment trials which will involve screening to improve cognitive outcomes (16). The specific definition of impairment used for screening depends to some degree on the type of cognitive remediation intervention used. For example, if a cognitive remediation intervention is to be tailored to an individual's cognitive profile, then a definition that incorporates performance on each cognitive domain would be required. If a drug treatment known to have a side-effect burden was being trialed, then a particularly stringent definition of cognitive impairment would be most appropriate since this would only be used in individuals likely to gain very significant cognitive benefit. Thus, this current paper cannot provide a single recommendation for a method of screening for cognitive impairment. It has, however, highlighted the substantial variability in rates of cognitive impairment based on the definitions used and gives an indication of the percentages of different clinical groups who are likely to be classified as having impairment using these different definitions. This paper has also identified definitions of cognitive impairment that are less useful in mood disorder studies; the use of a definition based on a number of individual test results is less useful unless a set battery is used consistently. Furthermore, the study has highlighted the importance of taking into account premorbid IQ, particularly in individuals with severe depression.

Alongside the direct implications of findings from this paper is the question of *who* should be remediated in mood disorder samples. Typically, treatment decisions for mood symptoms are individualised to the patient. For example, if patients have a history of trauma, they are more likely to respond to therapy rather than medication (44). The same may be true for cognitive remediation, in that if patients have cognitive impairment, they are more likely to respond than those who are functioning well. Certainly, research indicates that individuals with the most severe cognitive impairment receive the greatest benefit from interventions aimed at improving cognitive outcomes (45). As in all clinical trials, there is a difficult balance between the imperative of the clinical trial – to produce a positive result, often achieved by selecting the most impaired patients, and the ability to develop treatments which may be effective across a range of impairment and are generaliseable. Impairments of 0.5 to 1 SD in key cognitive functions may still be disabling but statistically less likely to show differences between an investigational treatment and placebo.

A related issue is that in MDD, psychological treatments based on cognitive activation may have positive effects on mood and cognition and therefore be potentially beneficial in individuals with milder cognitive impairment (46, 47). Allowing only those with serious cognitive impairment to partake in cognitive remediation interventions, thus, means that the majority of individuals with mood disorders will not have the opportunity to experience the activating effects on mood of repetitive cognitive training. The purpose of any proposed cognitive intervention, whether to activate or remediate, is important to consider prior to conducting screening procedures.

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Table 1. Cognitive Tests Administered to the Four Mood Disorder Samples

	Study 1 – inpatient depression	**Study 2 – outpatient depression**	**Study 3 – bipolar depression**	**Study 4 – euthymic bipolar**
Verbal Learning and Memory	Rey Auditory-Verbal Learning Test	Rey Auditory-Verbal Learning Test Consonant Vowel Consonant Verbal Learning Test	Rey Auditory-Verbal Learning Test	Rey Auditory-Verbal Learning Test
Visuospatial Learning and Memory	Groton Maze Learning Test (CogState©)	Pattern Recognition Memory (CANTAB®) Spatial Recognition Memory (CANTAB®)	Pattern Recognition Memory (CANTAB®) Spatial Recognition Memory (CANTAB®)	Pattern Recognition Memory (CANTAB®) Spatial Recognition Memory (CANTAB®) Simultaneous and Delayed Match to Sample (CANTAB®) Paired Associates Learning (CANTAB®)
Executive Function / Attention	Stroop Test	Controlled Oral Word Association Test Digit Span Forwards and Backwards Spatial Span (CANTAB®) Spatial Working Memory (CANTAB®)	Controlled Oral Word Association Test Digit Span Forwards and Backwards Spatial Span (CANTAB®) Spatial Working Memory (CANTAB®)	Controlled Oral Word Association Test Digit Span Forwards and Backwards Spatial Span (CANTAB®) Spatial Working Memory (CANTAB®) Stroop Test Trail Making Test Part B Vigil Test (errors) Tower of London (min. move solutions)
Psychomotor Speed	Simple Reaction Time Task Timed Chase Test (CogState©)	Simple Reaction Time Task Motor Screening (CANTAB®)	Digit Symbol Substitution Test	Trail Making Test Part A Digit Symbol Substitution Test Vigil Test (response latency)

Table 2. Demographic Characteristics of Mood Disorder and Healthy Control Samples

	Study 1 Inpatient Depression				**Study 2** Outpatient Depression				**Study 3** Bipolar Depression				**Study 4** Euthymic Bipolar Disorder			
	Patient (n=58)		**Control (n=50)**		**Patient (n=69)**		**Control (n=58)**		**Patient (n=56)**		**Control (n=53)**		**Patient (n=63)**		**Control (n=63)**	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age	39.0	10.7	38.5	11.6	39.7	11.9	38.0	12.8	48.1	9.2	45.5	13.1	44.4	8.6	45.4	9.1
Gender (male:female)	22:36	-	18:32	-	23:46	-	19:39	-	30:26	-	28:25	-	37:26	-	37:26	-
Predicted verbal IQ	106.8	8.5	107.4	6.6	108.4	8.7	108.6	7.7	110.2	10.5	113.2	11.0	109.6	10.2	110.0	9.2
Formal education (total years)	13.1	2.5	13.1	1.9	13.9	2.4	13.8	2.5	14.5	3.3	14.8	4.3	14.2	3.0	14.2	3.1

Note: no significant differences between clinical and corresponding healthy control samples were found for any variables

Table 3. Clinical Characteristics of the Four Mood Disorder Samples

	Study 1 Inpatient Depression (n=58)		**Study 2** Outpatient Depression (n=69)		**Study 3** Bipolar Depression (n=56)		**Study 4** Euthymic Bipolar Disorder (n=63)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Baseline MADRS	35.7	8.8	23.4	6.3	27.2	7.3	-	-
Baseline $HDRS_{17}$	-	-	16.1	5.3	19.6	4.7	2.1	1.7
Baseline YMRS	-	-	-	-	1.9	2.8	1.4	2.0
Age at illness onset (years)	30.0	10.8	22.5	11.8	26.3	13.0	25.3	7.2
Unipolar MDD:Bipolar Disorder	50:8	-	64:5	-	0:56	-	0:63	-
No. depressive episodes	-	-	3.9	4.4	-	-	12.0	16.4
No. previous hospitalisations	0.8	1.5	-	-	3.1	4.2	5.0	6.1

MADRS = Montgomery-Asberg Depression Rating Scale; **$HDRS_{17}$** = Hamilton Depression Rating Scale (17-item version); **YMRS** = Young Mania Rating Scale

Note: a dash (-) refers to data not being available due to the item not being included in the study

Table 4. Prevalence (%) of Impairment using Four Approaches to Classify Cognitive Impairment

	Study 1 Inpatient Depression		**Study 2** Outpatient Depression		**Study 3** Bipolar Depression		**Study 4** Euthymic Bipolar	
	Patient	Control	Patient	Control	Patient	Control	Patient	Control
Cognitive domains: number of domains impaired								
1 SD								
No domains impaired	12.6	70.0	47.1	79.4	35.6	71.7	42.9	77.7
≥ 1 domains impaired	87.4	30.0	52.9	20.6	64.4	28.3	57.1	22.3
≥ 2 domains impaired	55.3	12.0	17.6	5.1	34.0	11.3	33.3	4.8
≥ 3 domains impaired	26.7	4.0	4.4	3.4	19.7	3.8	17.4	1.6
4 domains impaired	7.1	0.0	2.9	0.0	1.8	0.0	7.9	0.0
1.5 SD								
No domains impaired	41.1	82.0	76.7	86.3	53.5	86.8	61.9	93.6
≥ 1 domains impaired	58.9	18.0	23.3	13.7	46.5	13.2	38.1	6.4
≥ 2 domains impaired	37.5	4.0	8.9	3.4	17.9	1.9	20.6	1.6
≥ 3 domains impaired	7.1	0.0	1.5	1.7	5.4	0.0	11.1	0.0
4 domains impaired	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2 SD								
No domains impaired	62.5	92.0	85.3	93.1	67.8	94.3	76.2	96.8
≥ 1 domains impaired	37.5	8.0	14.7	6.9	32.2	5.7	23.8	3.2
≥ 2 domains impaired	14.3	0.0	4.4	0.0	7.2	1.9	11.1	0.0
≥ 3 domains impaired	0.0	0.0	0.0	0.0	1.8	0.0	3.2	0.0
4 domains impaired	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cognitive domains: percentage impaired on each domain								
Verbal learning and memory								
≥ 1.0 SD	51.7	10.0	36.2	8.6	39.3	9.4	19.4	11.1
≥ 1.5 SD	36.2	4.0	17.4	5.2	23.2	3.8	12.7	3.2
≥ 2.0 SD	15.5	2.0	8.7	1.7	12.5	1.9	4.8	1.6
Visual spatial learning and memory								
≥ 1.0 SD	45.6	10.0	17.6	8.6	26.8	15.1	28.6	6.3
≥ 1.5 SD	26.3	6.0	11.8	6.9	17.9	3.8	15.9	3.2
≥ 2.0 SD	19.3	0.0	4.4	3.4	14.3	3.8	9.5	1.6
Executive function / attention								
≥ 1.0 SD	50.9	14.2	8.8	1.7	16.1	3.8	30.2	1.6
≥ 1.5 SD	34.0	4.1	1.5	0.0	5.4	0.0	14.3	1.6
≥ 2.0 SD	15.1	4.1	0.0	0.0	0.0	0.0	9.3	0.0
Psychomotor speed								
≥ 1.0 SD	33.9	12.0	14.7	10.3	37.5	15.1	38.7	9.5
≥ 1.5 SD	14.3	8.0	7.4	6.9	23.2	7.5	29.0	1.6
≥ 2.0 SD	3.6	2.0	4.4	1.7	14.3	1.9	14.5	0.0
Global cognitive composite								
≥ 1.0 SD	45.3	4.1	11.8	3.4	28.6	7.5	30.2	3.2
≥ 1.5 SD	18.9	0.0	2.9	0.0	12.5	1.9	14.3	1.6
≥ 2.0 SD	7.5	0.0	1.5	0.0	0.0	0.0	3.2	0.0
Individual cognitive variables								
≥ 1 SD on ≥ 2 test variables	91.4	22.0	78.6	55.2	71.4	35.8	93.7	79.4
≥ 1.5 SD on ≥ 2 test variables	60.3	14.0	47.1	25.8	46.4	13.2	77.8	49.2
≥ 2.0 SD on ≥ 2 test variables	32.8	6.0	14.3	10.3	23.2	5.7	52.4	19.0

Table 5. Prevalence (%) of Impairment using Four Approaches to Define Cognitive Impairment in Relation to Treatment Response

	Study 1 Inpatient Depression					**Study 2** Outpatient Depression				
	Response *(n = 25)*	Non-Response *(n = 33)*	Control *(n = 50)*	χ^2/U	*P*-value	Response *(n = 37)*	Non-Response *(n = 32)*	Control *(n = 58)*	χ^2/U	*P*-value
Cognitive domains: number of domains impaired										
1 SD										
No domains impaired	8.0	12.1	58.0	344.5	0.2[a]	56.8	53.1	67.3	573.5	0.8[a]
≥ 1 domains impaired	92.0	87.9	42.0			43.2	46.9	32.7		
≥ 2 domains impaired	32.0	51.5	14.0			13.5	12.5	5.1		
≥ 3 domains impaired	16.0	27.3	6.0			0.0	3.1	1.7		
4 domains impaired	4.0	12.1	2.0			0.0	0.0	0.0		
1.5 SD										
No domains impaired	44.0	42.4	84.0	379.0	0.6[a]	78.4	65.6	94.9	508.5	0.2[a]
≥ 1 domains impaired	40.0	57.6	16.0			21.6	34.4	5.1		
≥ 2 domains impaired	12.0	27.3	6.0			0.0	6.3	1.7		
≥ 3 domains impaired	4.0	9.1	2.0			0.0	0.0	0.0		
4 domains impaired	0.0	3.0	0.0			0.0	0.0	0.0		
2 SD										
No domains impaired	64.0	57.5	92.0	391.0	0.7[a]	86.5	84.4	94.9	577.0	0.8[a]
≥ 1 domains impaired	28.0	42.5	8.0			13.5	15.6	5.1		
≥ 2 domains impaired	8.0	6.1	2.0			0.0	3.1	1.7		
≥ 3 domains impaired	0.0	0.0	0.0			0.0	0.0	0.0		
4 domains impaired	0.0	0.0	0.0			0.0	0.0	0.0		
Cognitive domains: percentage impaired on each domain										
Verbal learning and memory										
≥ 1.0 SD	40.0	48.5	18.0	405.5	0.9[a]	35.1	40.6	12.1	540.5	0.5[a]
≥ 1.5 SD	24.0	24.2	8.0			13.5	25.0	1.7		
≥ 2.0 SD	20.0	21.2	2.0			5.4	9.4	1.7		
Visual spatial learning and memory										
≥ 1.0 SD	58.3	42.4	16.0	329.0	0.2[a]	8.1	15.6	10.3	546.0	0.3[a]
≥ 1.5 SD	37.5	21.2	2.0			2.7	9.4	1.7		
≥ 2.0 SD	4.2	9.1	2.0			2.7	6.3	1.7		
Executive function / attention										
≥ 1.0 SD	30.4	41.9	12.0	305.5	0.3[a]	0.0	0.0	6.9	592.0	1.0[a]
≥ 1.5 SD	13.0	35.5	8.0			0.0	0.0	0.0		
≥ 2.0 SD	13.0	16.1	6.0			0.0	0.0	0.0		
Psychomotor speed										
≥ 1.0 SD	17.4	48.4	18.0	**249.5**	**0.01[a]**	13.9	6.3	12.1	534.0	0.3[a]
≥ 1.5 SD	0.0	18.2	6.0			5.6	6.3	5.2		
≥ 2.0 SD	0.0	3.0	2.0			5.6	3.1	5.2		
Global Cognitive Composite										
Impaired by ≥ 1.0 SD	27.3	45.2	10.0	1.8	0.2[b]	5.6	9.4	1.7	0.4	0.5[b]
Impaired by ≥ 1.5 SD	9.1	16.1	2.0	0.6	0.5[b]	2.8	3.1	1.7	-	0.5[c]
Impaired by ≥ 2.0 SD	4.5	3.2	2.0	-	1.0[c]	2.8	0.0	1.7	-	-
Individual Cognitive Variables										
Impaired ≥ 1 SD on ≥ 2 test variables	51.8	78.8	24.0	0.4	0.6[b]	75.7	71.9	55.2	0.1	0.7[b]
Impaired ≥ 1.5 SD on ≥ 2 test variables	32.0	57.6	12.0	**3.7**	**0.05[b]**	27.0	40.6	19.0	1.4	0.2[b]
Impaired ≥ 2.0 SD on ≥ 2 test variables	16.0	39.4	8.0	**3.8**	**0.05[b]**	14.3	20.7	5.2	0.5	0.5[b]

Statistical comparisons were conducted between responders and non-responders for each sample

[a] Mann-Whitney U test (testing the difference in distribution in number of domains impaired)

[b] Pearson chi-square test

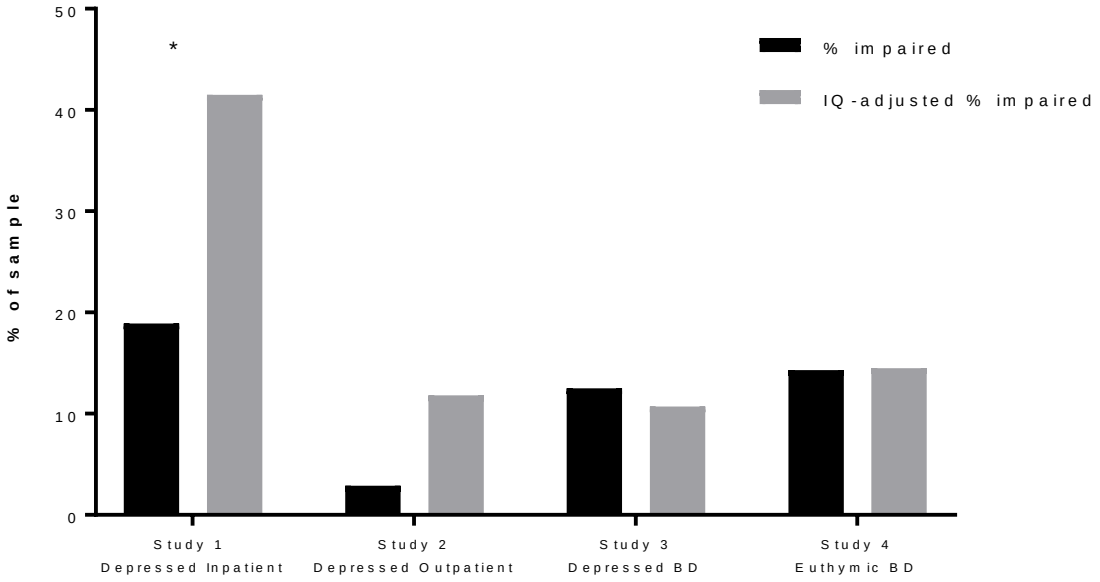
[c] Fisher's exact test (no statistical value available)

Figure Legend

Figure 1. Percentage of mood disorder samples impaired at 1.5 SD cut-off on Global Cognitive Composite after correction for premorbid IQ (BD = bipolar disorder)

* chi-square test, $\chi^2 = 4.1$, $p = 0.04$

Figure 1


50
40
30
20
10
0
% of sample
*
% impaired
IQ-adjusted % impaired
Study 1
Depressed Inpatient
Study 2
Depressed Outpatient
Study 3
Depressed BD
Study 4
Euthymic BD