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Research report

Identifying a cognitive impairment subgroup in adults with mood disorders

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ABSTRACT

Background: We hypothesized that only a minority of patients with mood disorders have measurable cognitive impairment, and this minority drives the small-to-medium effect sizes detected in group studies. Removal of this minority from group statistical analyses will illustrate that the majority appear to have broadly normal cognitive functioning.

Methods: Participants were adults between the ages of 20 and 54, including 659 healthy control subjects, 84 unmedicated outpatients diagnosed with depression, 59 outpatients diagnosed with depression who were on medications at the time of the evaluation, and 43 outpatients with bipolar disorder. All completed the CNS Vital Signs computerized cognitive screening battery.

Results: The prevalence rates of low cognitive test scores were calculated for the healthy control subjects and the patients with mood disorders. Having two scores at or below the 5th percentile occurred in 31.2% of the patients and only 8.2% of the control subjects [$\chi^2(1) = 66.67$, $p < .0001$; Odds Ratio = 5.1, 95% CI = 3.4–7.7]. For the control subjects, this low false positive rate for cognitive impairment was maintained across age groups, sexes, and education levels. A larger proportion of patients with bipolar disorder (41.9%) than patients with depression (27.1–28.6%) met this criterion for cognitive impairment.

Conclusions: This study suggests that cognitive impairment associated with mood disorders is limited to a minority of patients with the majority being broadly cognitively normal. Future research should determine if this identified subgroup has neuroanatomical, neurophysiological, or neuroendocrine abnormalities. Cognitive screening tools of this type might be useful in selecting participants for studies.

1. Introduction

It is well established that mood disorders are associated with cognitive impairment (Robinson et al., 2006; Zakzanis et al., 1998). The nature and extent to which depression causes objective cognitive impairment, however, is not fully understood. Some studies suggest that cognitive impairment associated with depression is quite limited (Grant et al., 2001; Rohling et al., 2002), difficult to detect, and is more likely to occur in those who are more seriously ill (Fossati et al., 2002; MacQueen et al., 2003; McDermott and Ebmeier, 2009; Tarbuck and Paykel, 1995). There is evidence that neurocognitive functioning improves following treatment (e.g., Bayless et al., 2010; Deuschle et al., 2004; Doraiswamy et al., 2003; Hviid et al., 2010; Neu et al., 2005; O'Connor et al., 2005; Rocca et al., 2005; Vythilingam et al., 2004; Wroolie et al., 2006), although this is not always the case (Frasch et al., 2009; Paelecke-Habermann et al., 2005; Reppermund et al., 2009; Weiland-Fiedler et al., 2004) — especially in older adults

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(Bhalla et al., 2009; Culang et al., 2009). Indeed, there is some suggestion that cognitive or executive functioning deficits may be a trait risk factor for depression (Douglas and Porter, 2009; Frasch et al., 2009; Micco et al., 2009; Reppermund et al., 2009). Furthermore, worse neuropsychological test performance at baseline is associated with poorer response to treatment (Dunkin et al., 2000; Kampf-Sherf et al., 2004; Mohlman and Gorman, 2005), and cognitive deficits are more pronounced in patients who are unemployed (Baune et al., 2010). It is possible that treatment refractory depression is a subtype characterized in part by cognitive impairment. Likewise, cognitive impairment is pronounced in patients with bipolar disorder and it persists when the patients are euthymic (Langenecker et al., 2007, 2010; Robinson et al., 2006; Torres et al., 2007), with lesser extent and severity of cognitive difficulties relative to schizophrenia (Schretlen et al., 2007). Cognitive impairment is associated with poor treatment adherence in bipolar disorder, but the direction of the relationship is unknown (Martinez-Aran et al., 2009). Mood disorders with psychosis are associated with a large adverse effect on neurocognitive functioning (Bora et al., 2009).

The accurate identification and quantification of neurocognitive impairment are important for research relating to neurobiological underpinnings, treatment, and functional outcome in patients with mood disorders. It is essential, methodologically, that we have accurate methods for identifying those patients who are objectively cognitively impaired and separate them from patients who have the subjective experience of poor thinking skills or thinking that is easily perturbed by negative affect, but perform normally on cognitive testing in controlled conditions. The treatments and outcomes for these two groups may differ markedly, as well as the prognosis. Based on group statistics, in individual studies or in meta-analyses, mood disorders are associated with a small-to-medium adverse effect on cognitive functioning (Robinson et al., 2006; Torres et al., 2007; Zakzanis et al., 1998). However, group statistics can obscure individual and subgroup differences. If present, these individual or subgroup differences in cognition might have important implications for research and clinical practice.

The purpose of this study was to examine cognitive functioning in mood disorders at the level of the individual. We hypothesized, based on our preliminary research, that (a) only a minority of patients with mood disorders have measurable cognitive impairment, (b) this minority is driving the small-to-medium effect sizes detected in group statistics (see also Bora et al., 2009; Burt et al., 1995), and (c) if you remove this minority from the group statistical analyses, the significant effect sizes will virtually disappear. The alternative hypothesis would be that the entire distribution of performance in depressed subjects is shifted about one half standard deviation lower relative to the control group without a bimodal distribution. If our hypotheses are true, the effect sizes reported in the literature seriously under-estimate the degree to which cognitive impairment is associated with mood disorders in a subset of patients. They are diluted by the majority of patients who have no measurable cognitive impairment. Using a large healthy normative sample and archival clinical groups, we will (a) develop and evaluate psychometric criteria for identifying cognitive impairment in adults with mood disorders, and (b) evaluate the above-mentioned hypotheses.

2. Methods

2.1. Participants

A healthy normative sample and three clinical groups were used for this study. Ethical approval for the use of this large, de-identified, archival database was granted by the University of British Columbia. Older adults were excluded. Participants were adults between the ages of 20 and 54, including 659 healthy control subjects, 84 unmedicated outpatients diagnosed with depression, 59 outpatients diagnosed with depression who were on medications at the time of the evaluation, and 43 outpatients with bipolar disorder. Clinicians at the North Carolina Neuropsychiatry Clinics gave a primary diagnosis of depression or bipolar disorder to all patients.

This is a sample of convenience; no formal diagnostic interviewing or symptom rating scales were collected. The clinical characteristics of the patient samples (e.g., age of onset, number of prior episodes, and severity/phase of illness) were not recorded in the database. The authors of this study utilized an archival database; we had no role in data collection or the clinical evaluations of the subjects. The unmedicated outpatients with depression (Iverson et al., 2009a) and the patients with bipolar disorder (Iverson et al., 2009b) were selected from previously published studies. This study is primarily methodological in nature. It was not our intent to characterize or differentiate the nature or pattern of cognitive deficits in depression or bipolar disorder. Heterogeneous samples of outpatients with mood disorders were sufficient to examine the methodological hypotheses and subsequent studies can use carefully characterized clinical information to better understand the causes and mechanisms of cognitive impairment in major depressive disorder and bipolar disorder.

The demographic characteristics of the four samples are described in Table 1. The majority of each sample was women, and the vast majority was Caucasian. Each participant self-reported their total number of years of education. Our experience, when conducting follow-up interviews with research subjects, is that some over-estimate their years of

Table 1
Demographic characteristics of the samples.

	Healthy normative sample	Depression unmedicated	Depression medicated	Bipolar disorder
Sample size	659	84	59	43
Mean age (SD)	38.1(10.2)	37.7 (9.9)	40.1 (8.9)	36.6 (9.9)
Age range	20–54	20–54	20–54	21–54
Mean education (SD)	15.8 (2.2)	15.1 (2.2)	14.8 (2.5)	15.1 (2.3)
Education range	7–20	8–20	8–18	8–19
Male/female (%)	36/64	26.2/73.8	27.1/72.9	32.6/67.4
Caucasian/African American/ Hispanic (%)	86.5/7.4/ 2.4	94.9/5.1/ 0	88.1/10.7/ 1.2	95.3/2.3/ 2.3
Computer use sample size	378	80	39	43
Computer use: none/some/ frequent (%)	2.1/19.3/ 78.6	1.3/16.3/ 82.5	12.8/25.6/ 61.5	4.7/27.9/ 67.4

Note: SD = standard deviation. Years of education is based on self-report.