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Review article

A meta-analysis of cognitive performance in melancholic versus non-melancholic unipolar depression

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ABSTRACT

Background: Recently there is increasing recognition of cognitive dysfunction as a core feature of Major Depressive Disorder (MDD). The goal of the current meta-analysis was to review and examine in detail the specific features of cognitive dysfunction in Melancholic (MEL) versus Non-Melancholic (NMEL) MDD.

Methods: An electronic literature search was performed to find studies comparing cognitive performance in MEL versus NMEL. A meta-analysis of broad cognitive domains (*processing speed*, *reasoning/problem solving*, *verbal learning*, *visual learning*, *attention/working memory*) was conducted on all included studies (n=9). Sensitivity and meta-regression analyses were also conducted to detect possible effects of moderator variables (age, gender, education, symptom severity and presence of treatments).

Results: MEL patients were older and more severly depressed than NMEL subjects. The MEL group was characterized by a worse cognitive performance in *attention/working memory* (ES=−0.31), *visual learning* (ES=−0.35) and *reasoning/problem solving* (ES=−0.46). No difference was detected in drug-free patients by sensitivity analyses. No effect was found for any of our moderators on the cognitive performance in MEL *vs* NMEL.

Conclusion: Our findings seem to support a moderate but specific effect of melancholic features in affecting the cognitive performance of MDD, in particular as regards visual learning and executive functions.

Contents

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1. Introduction

Recently there is increasing recognition of cognitive dysfunction as a core feature of Major Depressive Disorder (MDD) (for a comprehensive overview see (Lee et al., 2012) and (Bora et al., 2013)). Nonetheless, MDD subjects seem to display a wide range of cognitive deficits – ranging from no impairment to extreme impairment – depending on the effect of different factors, such as age (Herrmann et al., 2007), gender (Richard-Devantoy et al., 2013), education level (Elgamal et al., 2007), recurrence of episodes (Gorwood et al., 2008), symptom severity (McClintock et al., 2010) and antidepressant treatment (Rosenblat et al., 2015). The study of cognitive performance in MDD is made even more complex by the fact that different depressive subtypes, such as psychotic, atypical and melancholic features, have shown specific effects on cognition (Exner et al., 2009; Fleming et al., 2004; Lin et al., 2014; Markela-Lerenc et al., 2006; Michopoulos et al., 2008; Pier et al., 2004; Quinn et al., 2012a; Quinn et al., 2012b; Roca et al., 2015; Rush et al., 1983; Withall et al., 2010; Zaninotto et al., 2015).

On the other hand, cognitive dysfunctions, together with other genetic and neurobiological markers, have been regarded as a key factor for the definition of clinical phenotypes of mood disorders (Bora et al., 2010b, 2013; Zaninotto et al., 2015). Among those, Melancholic depression (MEL) has been consistently defined on the basis of three main validators: a) characteristic ("*endogeneity*") clinical signs and symptoms, such as a distinct quality of mood and psychomotor disturbances (Carroll, 2012; Parker, 2007); b) pathophysiologic and neurobiologic correlates, including hypercortisolemia, abnormal sleep pattern, alterations of the dopamine transporter and dysregulation of inflammatory processes (Antonijevic, 2008; Armitage, 2007; Buyukdura et al., 2011; Camardese et al., 2014; Dinan and Scott, 2005; Dunjic-Kostic et al., 2013; Gold and Chrousos, 2002; Gold et al., 1988; Heim et al., 2004; Leventhal and Rehm, 2005; Parker et al., 2010a; Patas et al., 2014; Taylor and Fink, 2008); and c) a supposedly superior response to somatic treatments (Joyce et al., 2003; Perry, 1996) (for a comprehensive overview see (Kendall, 1976; Parker, 1996; Taylor et al., 2006)). On this basis, some authors have also argued that MEL may represent a distinct mood disorder (Parker et al., 2010a, 2010b).

Many studies have investigated and clearly shown a cognitive dysfunction in MEL, suggesting the presence of a specific neurocognitive marker profile for this depressive subtype (Day et al., 2015; Exner et al., 2009; Markela-Lerenc et al., 2006; Michopoulos et al., 2008; Pier et al., 2004; Quinn et al., 2012a, 2012b; Roca et al., 2015; Rush et al., 1983; Withall et al., 2010). However, most of them are limited either by a small sample size, or by the lack of control for possible confounders, such as symptom severity, age, gender, education level or presence of treatment.

To fill this gap, the current meta-analysis aimed to review and examine in detail the features of cognitive performance in MEL versus Non-Melancholic (NMEL) MDD. An additional aim was to determine the effect of potential moderators, including demographic (i.e. age) and clinical (i.e. depressive severity) variables, on the cognitive performance of MEL patients by the use of meta-regression procedures.

2. Methodology

2.1. Search strategy and selection of studies

PubMed, Scopus, Psychinfo, and EMBASE databases were scanned for articles written in English and published in peer-reviewed journals between January 1980 and June 2015. The following search key was used: ("*neuropsychology*" OR "*cognitive*" OR "*neurocognitive*") AND ("*melancholic*" OR "*melancholia*" OR "*endogenous*" OR "*endogenomorphic*") AND ("*major depressive disorder*" OR "*depressive disorder*" OR "*unipolar depression*" OR "*unipolar depressive disorder*" OR "*mood disorder*" OR "*affective disorder*"). The first search string was also replaced with keywords describing the cognitive domains ("*memory*" , "*processing speed*" , "*attention*" , "*problem solving*" , "*executive*"). Finally, "*depression*" was used as an inclusive term to capture as many relevant citations as possible. References from retrieved papers and from reviews and meta-analyses in relevant topics were also screened to identify any additional study (the list of the evaluated studies is available upon request).

Both cross-sectional and longitudinal studies comparing the cognitive performance of MEL *vs* NMEL subjects were included. Additional inclusion criteria were: 1) age over 17 years; 2) the use of Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria to diagnose MEL; 3) the presence of cognitive test scores (means and standard deviations) or other data to calculate effect sizes for group comparisons.

When neuropsychological assessment was repeated as the outcome measure (i.e. before and after treatment), only baseline scores were considered for the meta-analysis, since, due to attrition, the sample size was generally greater and the population more representative at baseline. Whenever no data were available on cognitive tests (i.e. no raw scores), an attempt was made to obtain supplementary information by contacting the authors. Studies examining depressed patients with co-morbid physical illness or relevant axis I or axis II disorders potentially affecting the cognitive performance (i.e. substance abuse or dementia) were excluded. In case of overlapping samples, only the study with the larger sample was included, unless the two studies used different tests (or examined different cognitive domains); in this case they were included both (i.e. – (Quinn et al., 2012a, 2012b)).

Some studies only used the generic term "*major depression*", without addressing the issue of longitudinal diagnosis: in these cases, when no supplementary information could be gathered (also, by contacting the authors), in absence of any explicit statement of bipolarity, the sample was considered unipolar.

Two independent investigators (LI and RG) screened the literature and checked the case-by-case inclusion criteria. Any disagreement was resolved upon consensus. The flow chart in Fig. 1 summarizes the study inclusion process (see Table 1 for included studies' details).

2.2. Outcome and quality assessment

The papers screened for inclusion were widely heterogeneous in terms of sample sizes, outcome measures, diagnostic and neuropsychological inventories and definitions of MEL. Thirty-one individual neuropsychological variables were considered for our analysis (Table 2). Task-specific meta-analyses were conducted when at least three independent studies reported on a given task (e.g. Trail Making Test).

Following previous studies on bipolar disorder and psychotic MDD (Bora et al., 2010c; Zaninotto et al., 2015), individual tasks were grouped under six cognitive domains (Table 2) inspired by the