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Research report

Cognitive and emotional biomarkers of melancholic depression: An iSPOT-D report

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ABSTRACT

Background: Depressed patients with melancholic features have distinct impairments in cognition and anhedonia, but it remains unknown whether these impairments can be quantified on neurocognitive biomarker tests of behavioral performance. We compared melancholic major depressive disorder (MDD) patients to non-melancholic MDD patients and controls on a neurocognitive test battery that assesses eight general and emotional cognitive domains including the hypothesized decision-making and reward-threat perception.

Methods: MDD outpatients ($n=1008$) were assessed using a computerized battery of tests. MDD participants met DSM-IV criteria for MDD and had a score ≥ 16 on the 17-item Hamilton Rating Scale for Depression. Melancholic MDD was defined using the Mini-International Neuropsychiatric Interview and a psychomotor disturbance observer-rated CORE measure score >7. Controls were age- and gender-matched with no previous DSM-IV or significant medical history.

Results: Melancholic participants (33.7% of the MDD sample) exhibited significantly poorer performance than controls across each domain of cognitive function and for speed of emotion identification and implicit emotion priming. Compared to the non-melancholic group, specific disturbances were seen on tests of information speed, decision speed, and reward-relevant emotional processing of happy expressions, even after co-varying for symptom severity.

Limitations: Assessments were taken at only one medication-free time point. Reward was investigated using an emotional faces task.

Conclusions: Melancholic MDD is distinguished by a specific neurocognitive marker profile consistent with reduced decision-making capacity under time demands and loss of reward sensitivity. This profile suggests an underlying deficit in mesolimbic-cortical circuitry for motivationally-directed behavior.

1. Introduction

The mechanisms that differentiate depressed patients with and without melancholic features are not yet understood. This limits our ability to define objective markers of the disorder and potentially treat the subtype. Along with psychomotor disturbances, cognitive impairments are considered cardinal features of melancholic depression (Austin et al., 1999; Pier et al., 2004; Rogers et al., 2010, 2002, 2004, 2000a; American Psychiatric Association, 2000; Parker and Hadzi-Pavlovic, 1996). However, there has not been a comprehensive study of multiple domains of general and emotional cognition aimed at characterizing what specific profile of cognitive disturbance defines melancholic depression.

To date, the research into the general and emotional cognitive biomarkers of melancholic depression can be summarized into eight domains: motor coordination, response inhibition (impulsivity), attention and concentration, information processing, verbal memory,

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working memory, executive function, verbal interference and emotional function. Supplementary Table 1 presents a summary of this literature. We suggest that the interpretation of research findings could be guided by one of the cardinal criteria for melancholia: anhedonia. Anhedonia is associated with negative affect and a loss of motivated behavior. It has previously been hypothesized that anhedonia, is a particularly prominent feature of melancholic depression (Austin and Mitchell, 1995; Bracht et al., 2014; Wacker et al., 2009). Features of anhedonia implicate the dopaminergic mesolimbic and mesostriatal cortical circuits which mediate cognition and modulation of behaviors linked with motivation and reward (Treadway and Zald, 2011; Haber and Knutson, 2010; Wacker et al., 2009). Both functional and structural neuroimaging studies point to specific brain changes in melancholic MDD, ones which involve regions of reward-related circuits (Korgaonkar et al., 2011; Pizzagalli et al., 2004). In MDD, earlier definitions of anhedonia emphasized the loss of positive feelings, while more recent definitions emphasize the loss of effort-based decision-making, referred to as "motivational anhedonia" (Treadway et al., 2012; Treadway and Zald, 2011).

In regard to general cognitive disturbances, the evidence to date suggests that melancholia is distinguished by disturbances that reflect a loss of motivated behavior or a lack of effort-based decision-making under time or cognitive load demands. For example, Rogers et al. (2004) found that the melancholic verses non-melancholic distinction is only significant in cases of increased cognitive load. For example, the difference is significant when the Stroop and spatial stimulus-response (SRC) compatibility tasks are combined, but not when simpler tasks of choice reaction time, spatial Stroop or SRC tasks are performed separately. Other studies that show a differentiation between melancholic and non-melancholic groups involve increased task difficulty, such as increased symbol rotation (Rogers et al., 2002) or the removal of external cues (Rogers et al., 2000a, 2000b). Generally, the research to date suggests that the cognitive profile between melancholic and non-melancholic patients cannot be explained by severity alone (Quinn et al., 2012c; Exner et al., 2009), attentional difficulties (Austin et al., 1992), concept formation or planning (Michopoulos et al., 2008; Austin et al., 1992), or learning or memory (Michopoulos et al., 2008; Exner et al., 2009), but instead by tasks that require set-shifting (Michopoulos et al., 2008), cognitive flexibility (Withall et al., 2010) or interference (Withall et al., 2010) that involve action under time demands. Differences between melancholic patients and controls on cognitive tasks appear to be widespread across all domains. In summary, while melancholic subtype patients and controls tend to be able to be differentiated across cognitive domains, tasks that differentiate melancholic and non-melancholic MDD appear to require decision-making with increased cognitive load under time demands in the areas of set-shifting and multi-tasking.

Psychomotor disturbances involving slowed or disrupted functions have commonly been described as a central feature of melancholic MDD (Rush and Weissenburger, 1994; Winograd-Gurvich et al., 2006). It has been argued that psychomotor slowing is the "core" behavioral pattern that defines melancholic MDD (Parker, 2007; Sachdev and Aniss, 1994). When the CORE measure is used to define melancholic status, psychomotor disturbances and their biological correlates have been found to distinguish the melancholic subtype of MDD (Parker et al., 1990; Spanemberg et al., 2014).

Relatively fewer studies have used neurobehavioral measures to examine emotional disturbances and loss of positive affect in melancholic MDD. Based on the concept of "motivational anhedonia", we expect melancholic MDD to be characterized by a loss of sensitivity to signals of reward and a corresponding supersensitivity to signals of potential threat/punishment and loss. Basic facial expressions of emotion are biologically salient signals of potential reward (e.g., the intrinsic reward value of a smiling face looking directly at an individual) and potential threat (anger, fear) and loss (sad) (Shechner et al., 2012). MDD and melancholia in particular have been associated with a supersensitivity to sad, reflected in a greater tendency to recall or identify these sad expressions (e.g., Linden et al., 2011; Surguladze et al., 2004). In the Linden et al., 2011 study, sensitivity to sad was not a consequence of symptomatic mood but instead a primary neurocognitive feature of melancholic depression. From the motivational anhedonia framework, higher anhedonia might slow responses to happy faces (insensitivity) and speed up responses to expressions of threat or loss (hypersensitivity). These emotions need to be studied in the same melancholic patients to test the specificity of impairments to happy versus other emotions, and to ensure that emotion processing impairments do not simply reflect a global flattening of emotion processing.

In this study, we investigated a broad set of general and emotional cognitive domains of function in a large cohort of melancholic and non-melancholic patients, and matched healthy peers, from the International Study to Predict Optimized Treatment—in depression (iSPOT-D). Our working hypotheses were that melancholic MDD is distinguished by (1) a general cognitive profile that shows deficits in effort-based decision-making under time or cognitive load demands for tasks such as processing speed and set-shifting, as opposed to other tasks that target other core functions such as memory (verbal memory, N-back working memory and executive maze memory) or response inhibition (Go–NoGo task), (2) emotion processing impairments reflecting a reduced sensitivity to reward (specifically, slower reaction time for the identification of happy faces and priming of face recognition by happy valence) and hypersensitivity to threat and loss (and opposing profile of faster reaction time to fear, anger and sad).

2. Methods

The following data were collected as part of a larger Phase IV iSPOT-D trial. A complete description of the iSPOT-D study protocol, clinical assessments, inclusion/exclusion criteria, and diagnosis procedures is provided in Williams et al. (2011). This study complies with the "Good Clinical Practice" (GCP) principles in the US FDA Code of Federal Regulation as well as the laws and regulations of each country in which the study was conducted. The study was approved by each site's governing Institutional Review Board and was conducted according to the principles of the Declaration of Helsinki 2008, the International Conference on Harmonization (ICH) guidelines. All participants provided written informed consent, according to ICH and GCP standards prior to being involved in this study. Study procedures were fully explained, participants had the opportunity to ask questions and the voluntary nature of their participation was confirmed.

2.1. Participants

Participants were recruited through the study management sites or from a total of 17 community general practice clinics and university general health centers across 5 countries (USA, Australia, The Netherlands, New Zealand and South Africa). Study management sites oversaw local study recruitment and participation. There were no differences in participant characteristics as a function of recruitment site, adding weight to the point that MDD patients in primary care requiring treatment are not less depressed than those in speciality settings (for details, Saveanu et al., 2015).

Inclusion was based on the Mini-International Neuropsychiatric Interview (MINI-Plus) (Sheehan et al., 1998) to establish a diagnosis on current, nonpsychotic MDD, the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) (Hamilton, 1960) to confirm fully symptomatic status (score of ≥ 16 as outlined by Keller, 2003), urine toxicology (to provide data on illicit or prescribed drug use) and a pregnancy screen. Fig. 1 outlines the inclusion and exclusion