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Research report

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

Claire V. Day [a,b,c,d], Justine M. Gatt [a,b,e,f], Amit Etkin [g,h], Charles DeBattista [g], Alan F. Schatzberg [g], Leanne M Williams [g,h,*,1]

[a] The Brain Dynamics Centre, Discipline of Psychiatry, Sydney Medical School, University of Sydney, Sydney 2006, NSW, Australia
[b] Westmead Millennium Institute, Westmead 2145, NSW, Australia
[c] Brain Resource Ltd., 235 Jones Street, Sydney, NSW, Australia
[d] Brain Resource Inc., 1000 Sansome Street, San Francisco, CA 94111, USA
[e] Neuroscience Research Australia, Randwick 2031, NSW, Australia
[f] School of Psychology, University of New South Wales, Sydney 2052, NSW, Australia
[g] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA
[h] Sierra-Pacific Mental Illness Research, Education and Clinical Center (MIRECC) Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, USA

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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,

* Corresponding author at: Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Rd, Mail Code 5717, Palo Alto, CA 94305, USA. Tel.: +1 650 723 3579.
E-mail address: leawilliams@stanford.edu (L. Williams).

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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

Inclusion Criteria

- Age 18-65
- Fluent and literate in English or Dutch
- Provide written informed consent
- Total $HRSD_{17}$ ≥16
- Meets DSM-IV* criteria for single or recurrent nonpsychotic MDD established by MINI Plus

Exclusion Criteria

- Suicidal ideation and/or tendencies, defined by a score ≥8 on Section C of the MINI Plus
- History of bipolar disorder (I, II, not otherwise specified) (lifetime)
- History of schizophrenia, schizoaffective disorder, or psychosis not otherwise specified (lifetime)
- Current primary diagnosis of anorexia or bulimia, obsessive-compulsive disorder, or primary post-traumatic stress disorder
- Known contra-indication for escitalopram, sertraline and/or venlafaxine-XR, or previous treatment failure at the highest recommended dose
- Taking any medication that is contraindicated with escitalopram, sertraline, or venlafaxine-XR
- Taking escitalopram, sertraline, or venlafaxine-XR in the current episode of MDD
- Use of any non-protocol antidepressant drug or CNS drug (antipsychotic, anticonvulsant anxiolytic, clonidine) that cannot be washed out prior to participation
- Has general medical condition that contraindicates protocol antidepressant treatments or interferes with protocol measurements (such as epileptic condition for EEG recording)
- Substance dependence (including alcohol intake equaling 29 standard alcoholic drinks per week for males; >15 for females) in the past six months
- History of brain injury or blow to the head that resulted in loss of consciousness for greater than five minutes
- Severe impediment to vision, hearing and/or hand movement that is likely to interfere with completion of assessments, or with comprehension of instructions or study requirements
- Participation in an investigational study within four months prior to baseline that could affect symptoms of MDD
- Is pregnant or breast-feeding

Fig. 1. Inclusion and exclusion criteria.

criteria used to recruit participants who would typically receive an ADM in clinical practice. An initial pre-screen for these criteria was made by telephone.

Study assessments included self-report items used to acquire information on demographic, medical history and social characteristics (Williams et al., 2011). DSM criteria according to the MINI-Plus and clinical interview were used to acquire clinical history, including MDD duration and psychiatric diagnoses and history according to the entry criteria (Fig. 1). Established self-report scales were used to assess depressive symptom severity: the 16-item Quick Inventory of Depressive Symptomatology-Self-Rated ($QIDS\text{-}SR_{16}$) (Rush et al., 2003; Trivedi et al., 2004) and the self-rated Depression Anxiety Stress Scale (DASS) (Lovibond, 1998; Lovibond and Lovibond, 1995) for a Depression severity sub-score. In addition, severity of anhedonia, stress and arousal-related anxiety were derived from DASS sub-scores. MDD duration was collected during the MINI-Plus assessment.

2.2. Definition of melancholic subtype

Some research, as suggested by their authors, may have been limited by their definition of melancholic depression. For example, Pier et al. (2004) used the DSM definition instead of a narrow definition with a combination of other scales such as a sign-based rating system of psychomotor disturbance (known as the "CORE" measure, Parker and Hadzi-Pavlovic, 1996). The CORE assesses 18 signs (observable features) which are rated by a trained observer or clinician at the end of a clinical interview. Each sign is rated on a four-point scale (0–3) and the summed total score can be used to assign patients to melancholic (total score >7) or non-melancholic subtypes (total score <7) (Parker et al., 1995). Austin et al. (1999) found that the DSM definition was less able to distinguish features in cognition than those defined by the CORE measure. In response, we decided on the following definition of melancholic depression: meeting the DSM-IV criteria for melancholic features (according to the MINI-Plus) and a CORE score of >7 based on the previously established cut-off score for a melancholi subtype (Parker et al., 1995). DSM-IV and CORE criteria were assessed by the trained observers at each site follo wing the in-person clinical interview. We used a definition of melancholia based on the combined DSM-IV and CORE criteria in order to minimize the possibility of overestimating the melancholic subsample.

2.3. Tests of general and emotional cognitive function

Following the clinical assessments, participants completed the standardized battery for behavioral assessment of general and emotional cognitive functions. Norms have been established for both the general cognitive (Clark et al., 2006) and emotional (Williams et al., 2009) function tasks. The battery was computerized and presented using a touchscreen; participants were provided with headphones and a microphone. Practice trials were included with instructions. A member of the research team monitored the participant by video surveillance and a mirrored copy of the touchscreen showing participant's progress. Video surveillance was not recorded for participant privacy.

The touchscreen battery included the following domains and individual tests.

2.4. General cognition

2.4.1. Motor coordination

Finger tapping: The participant was asked to tap a circle on the touch screen with their index finger as many times as possible in 30 s. This was repeated for both hands. It assesses basic motor function, hand eye coordination, fine movement speed and manual dexterity.

2.4.2. Response inhibition

Go–NoGo: The participant was required to tap in response to green "Go" stimuli (word "press" in green) and to inhibit responses when

the word was in red ("No Go" stimuli). This task assesses inhibition (i.e., the capacity for suppressing well-learned, automatic responses) and the ability to re-initiate response after response inhibition.

2.4.3. Sustained attention

Continuous performance test (N-Back CPT task): Participants were presented with letters, one by one, and asked to press when the same letter appeared twice in a row. This assesses the participant's ability to sustain attention over an extended period of time, as well as the ability to update information held in short-term stores of working memory.

2.4.4. Information processing

Information processing speed: Switching of attention task: The participant was asked to connect numbers and letters in an ascending, but alternating, sequence (i.e., 1-A-2-B-3-C, etc.). This assesses constructs of effort-based decision-making under cognitive load demands.

Decision speed: Choice reaction time task: The participant was asked to press the lit circle as quickly as possible (choice of four circles lighting up, in different positions on the touch-screen). This test assesses decisions under time demands.

2.4.5. Verbal memory

Memory recall and recognition: The participant was presented with a list of 12 words, which they were asked to recall immediately and again after 25 min. This task assesses constructs of immediate, short-delay and long-delay recall equivalent to the constructs assessed by the California Verbal Learning and Memory test.

2.4.6. Working memory

Digit span task: The participant was verbally presented a series of digits and was then immediately asked to enter the digits on a numeric keypad, either in forward or reverse order (series increasing from 3 to 9 digits).

2.4.7. Executive function

Maze task: The participant was required to find the hidden path through a grid of circles by trial and error. This task assesses planning, abstraction, foresight, error correction, and the ability to choose, try, reject and adapt alternative courses of thought and action. The maze task assesses constructs equivalent to those assessed by the Austin Maze.

2.4.8. Verbal interference

Cognitive flexibility: First, the participant was asked to indicate the color spelled out by a written word (and not the incongruent color in which the word is written). Next, the participant was asked to name the color in which a word was written (and ignore the word that was spelled out). The first part measures reading speed and accuracy for individual words. The second part measures the ability to inhibit inappropriate well-learned impulsive automatic responses. This task assesses constructs equivalent to those assessed by the Stroop test (Stroop, 1935).

2.5. Emotional cognition

2.5.1. Explicit identification of emotion

Forty-eight photographs of faces were presented one at a time in a pseudorandom order, each presented for 2 s. Faces consisted of 4 males and 4 females showing evoked basic facial expressions (happy, sad, fear, anger, disgust or neutral). The photographs were standardized by size, luminance and central alignment of the eyes, and norms for ages 6–92 years have been established (Williams et al., 2009; Mathersul et al., 2009). These emotions signal potential reward (happy), threat (fear, anger, disgust) and loss (sad). The participant was instructed to identify the emotion predicted on each face by selecting the corresponding emotion label from a six-option response format. Both accuracy and response time for each emotion were recorded. Emotion identification 'bias' was calculated from the response time for identifying neutral faces minus the response time for identifying each emotion.

2.5.2. Implicit face recognition priming

Twenty-four face stimuli (2 females and 2 males depicting each of the six expressions) were randomly selected from the 48 faces presented in the first task. These stimuli were presented along with a new set of 24 face stimuli (also comprising 2 females and 2 males depicting each of the six expressions) in a pseudorandom sequence. Participants selected the faces they recognized from the original 48 presented under the emotion identification condition. The 'priming' measure (with prior exposure to facial expressions of emotion in the explicit identification condition) was calculated using the difference in the reaction time for the implicit recognition minus the explicit identification condition for each emotion.

2.5.3. Statistical analyses

Independent *t*-tests and chi-squared analyses were used to compare groups regarding demographic and clinical characteristics to define group differences that may influence the general and emotional cognitive data, or deem it difficult to compare groups.

Clinical group differences were calculated in four ways:

(1) to test the interaction between the clinical groups and 13 general and emotional cognitive test summary scores, a general linear method with the 3 clinical groups as the between-participants factor was used to determine whether an interaction was present;
(2) to explore where the interaction existed, general (28 within-participants levels) and emotional cognitive individual scores (23 levels within-participants levels) were investigated using a repeated measures mixed-design ANOVA model to test whether the groups (3 between-participants factors) differed on task performance;
(3) *A priori* univariate contrasts were then undertaken to decompose the effects from these models for melancholic verses non-melancholic, melancholic verses healthy control and non-melancholic verses control group comparisons. In the clinical group contrasts (i.e., melancholic verses non-melancholic groups), we included HDRS17 as a covariate to control for variation that may be caused by the depression severity (confirmed to be significantly different in independent t-tests). The profile of correlations with behavioral performance between these clinical groups (Supplementary results, Table 2) and independent *t*-test group differences demonstrated that no further co-varying was required. Because all participants were unmedicated, medication status was not covaried in these analyses reasonable due to the case-to-variable ratio;
(4) A discriminant analysis to assess whether the significant individual scores that differentiated the melancholic and non-melancholic groups combined into a single (or into multiple) discriminant functions, and the associated classification rate.

3. Results

3.1. Demographic variables and clinical measures

Outpatients with MDD ($n=1008$) and matched healthy controls ($n=336$) were enrolled and assessed at 17 sites across five countries. Two MDD participants had missing information that prevented

defining the presence or absence of melancholia, reducing the MDD total to 1006. The melancholic MDD group ($n=339$), non-melancholic MDD group ($n=667$) and healthy controls were matched within 1 year on age and years of education, and had an equivalent distribution of males and females. For clinical characteristics, the melancholic group had a significantly higher depression severity score than the non-melancholic group according to the $HRSD_{17}$ ($p<0.01$), QIDS-SR_{16} ($p<0.01$) and DASS depression ($p<0.01$). Thus, we covaried for these severity scores in our subsequent *a priori* contrasts of the melancholic and non-melancholic groups. MDD duration, anxiety (according to the DASS), age and gender did not significantly differ between these groups (Table 1).

3.2. Summary scores

3.2.1. Interaction between clinical group and cognitive-emotional domain

There was a significant interaction between the three clinical groups and the 13 summary scores across the general and emotional cognitive test domains ($F=4.693$, df=24, 18.251, $p<0.001$, greenhouse-geisser corrected). There was also a significant group main effect of the clinical group ($F=32.073$, df=2.1339, $p<0.001$) whereby the melancholic group showed poorer performance compared to non-melancholic and healthy controls across all cognitive test domains (except motor coordination and emotion bias summary scores). The z-score means for each group for each cognitive domain are shown in Fig. 2. For repeated measures mixed-design ANOVA and contrasts for summary scores, see Supplementary Table 2.

3.3. Individual general cognition test scores

3.3.1. A priori contrasts between clinical groups and cognitive domain individual scores

Contrasts showed that the melancholic group was impaired relative to the non-melancholic group on specific aspects of speeded responses within the information processing speed, decision speed and cognitive flexibility domains ($p<0.01$; Table 2; Fig. 3). Specifically, melancholic participants showed a slowing of average response time (but not more total errors) within the information processing speed domain, slowed decision speed and slowed responses to name the word in the verbal interference task (but not on naming the color or the interference score) within the cognitive flexibility domain ($p<0.01$, Cohen's d range; 0.168–0.263). These specific differences were further pronounced when compared with controls ($p<0.0001$, Cohen's d range; 0.263–0.387). When the non-melancholic sample were compared to the controls on these items, the effect size was smaller than those for melancholic participants ($p<0.05$, Cohen's d range; 0.142–0.220) with decision speed not significantly different. This pattern suggests that melancholic depressed patients are distinguished from both controls and non-melancholic patients by their particularly pronounced impairments in response time for task processing under time demands.

Across all general cognitive items, compared to controls, melancholic participants showed the greater differences in speed related tasks within the response inhibition, sustained attention and executive function domains, with moderate effect sizes of 0.439 to 0.478. Non-melancholic MDD participants were impaired on corresponding domains, but again with smaller effect sizes of 0.271 to 0.429 (Table 2).

Table 1
Sample characteristics.

Characteristic	Melancholic ($n=339$)		Non-mel MDD ($n=669$)		Controls $n=336$	
Gender (M:F)	***N* (%) 156 (46%) Mean**	***N* (%) 183 (54%) SD**	***N* (%) 281 (42%) Mean**	***N* (%) 388 (58%) SD**	***N* (%) 145 (43%) Mean**	***N* (%) 243 (57%) SD**
Demographics						
Age in years	37.68	12.61	37.91	12.57	36.99	13.08
Yrs. of education[a]	14.14	2.93	14.75	2.72	14.94	2.5
Clinical characteristics						
$HRSD_{17}$	23.69	4.40	20.98	3.65	1.15	1.63
QIDS-RS_{16}	15.15	3.76	14.13	3.80	2.13	2.13
DASS depression[42-14]	23.54	9.74	21.57	9.42	1.07	2.27
DASS anhedonia[42-4]	6.76	2.93	6.16	3.01	0.22	0.65
DASS anxiety[42-14]	9.36	6.88	8.47	6.60	0.75	1.75
DASS stress[42-14]	18.41	8.74	18.08	8.22	2.90	3.36
MDD duration in years	14.82	12.13	14.16	12.20	–	–

Abbreviations: DASS—depression anxiety stress scale; F—female; $HRSD_{17}$—17-item Hamilton Rating Scale for Depression; M—male; MDD—Major depressive disorder; QIDS-SR_{16}—16-item Quick Inventory of Depressive Symptomatology.

[a] Years of education was statistically lower for melancholic than non-melancholic groups, however due to a highly educated sample and the small education range this significant difference is not considered clinically significant. The difference in means is just over 7 months.

3.4. Individual emotional cognition test scores

3.4.1. A priori contrasts between clinical groups and emotion domain individual scores

The melancholic group was distinguished from the non-melancholic group by a corresponding pattern of slowed responses to happy emotion. The melancholic group demonstrated significantly slower explicit identification of happy emotions than the non-melancholic group ($p<0.05$, Cohen's $d=0.155$) and slowed recognition of faces when primed implicitly by happy ($p<0.01$, Cohen's $d=0.191$) (Table 3, Fig. 4). Melancholic participants were also slowed compared to controls for the explicit identification of happy $p<0.0001$, Cohen's $d=3.33$), but not significantly slower on recognition of faces when primed implicitly by happy (Table 3; Fig. 4). This pattern suggests that melancholic depressed patients are distinguished

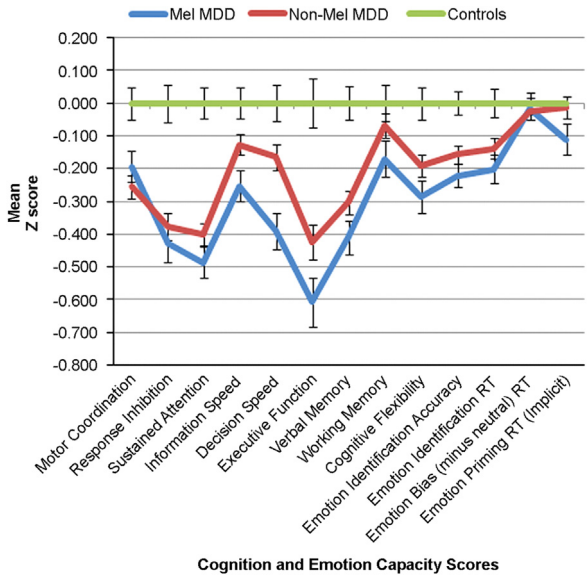

Fig. 2. *z* Score means for each group for summary scores for each general and emotional cognitive domain. *Abbreviations:* MDD—major depressive disorder; mel—melancholic; RT—reaction time.

Table 2
Means and between-group contrasts for summary scores across individual cognition test scores.

Domain	Individual test	Test variable	Mean individual test score			Contrasts; *p* and *d* (effect size) values		
			M (n=279)	**NM** (n=544)	**HC** (n=247)	**M vs. NM**	**M vs. HC**	**NM vs. HC**
Motor coordination	Finger tapping dominant hand	Number of taps	148.477 (1.686)	148.551 (1.200)	158.401 (1.758)	–	**M < HC**; $p < 0.0001$, $d = 0.286$	**NM < HC**; $p < 0.001$, $d = 0.247$
		Variability of taps	86.585 (8.588)	88.627 (6.113)	68.740 (8.952)	–	–	–
	Finger tapping non-dominant hand	Number of taps	142.125 (1.800)	139.179 (1.216)	145.886 (1.467)	–	**M < HC**; $p < 0.01$, $d = 0.230$	**NM < HC**; $p < 0.001$, $d = 0.255$
		Variability of taps	66.023 (8.651)	79.180 (5.846)	68.954 (6.747)	–	–	–
Response inhibition	Go–NoGo	RT	322.305 (3.661)	312.750 (2.606)	300.752 (3.798)	–	**M > HC**; $p < 0.0001$, $d = 0.286$	**NM > HC**; $p < 0.01$, $d = 0.201$
		Variability of RT	112.884 (3.469)	105.040 (2.470)	81.308 (3.599)	–	**M > HC**; $p < 0.0001$, $d = 0.478$	**NM > HC**; < 0.0001, $d = 0.424$
		False positive errors	2.533 (0.112)	2.502 (0.079)	2.063 (0.116)	–	**M > HC**; $p < 0.01$, $d = 0.247$	**NM > HC**; $p < 0.01$, $d = 0.211$
		False negative errors	3.829 (0.630)	3.681 (0.449)	1.632 (0.654)	–	**M > HC**; $p < 0.01$, $d = 0.180$	**NM > HC**; $p < 0.01$, $d = 0.211$
		Total errors	6.319 (0.646)	6.134 (0.460)	3.695 (0.670)	–	**M > HC**; $p < 0.01$, $d = 0.220$	**NM > HC**; $p < 0.001$, $d = 0.247$
Sustained attention	N-Back CRT	Reaction time (RT)	585.924 (7.483)	584.661 (5.327)	542.308 (5.327)	–	**M > HC**; $p < 0.001$, $d = 0.271$	**NM > HC**; $p < 0.001$, $d = 0.333$
		Variability of RT	187.795 (4.933)	180.481 (3.511)	143.956 (5.093)	–	**M > HC**; $p < 0.0001$, $d = 0.478$	**NM > HC**; $p < 0.0001$, $d = 0.429$
		False positive errors	1.748 (0.196)	1.539 (0.140)	1.091 (0.203)	–	**M > HC**; $p < 0.05$, $d = 0.178$	–
		False negative errors	2.907 (0.165)	2.564 (0.117)	1.509 (0.170)	–	**M > HC**; $p < 0.0001$, $d = 0.408$	**NM > HC**; $p < 0.0001$, $d = 0.387$
		Total errors	4.687 (0.271)	4.132 (0.193)	2.601 (0.280)	–	**M > HC**; $p < 0.0001$, $d = 0.387$	**NM > HC**; $p < 0.0001$, $d = 0.320$
Information processing	Switching of attention	Completion time	49,318.330 (592.834)	47,187.487 (422.007)	45,012.107 (11,294.305)	**M > NM**; $p < 0.01$, $d = 0.168$	**M > HC**; $p < 0.0001$, $d = 0.387$	**NM > HC**; $p < 0.01$, $d = 0.220$
		Total errors	2,049.369 (40.591)	1,917.061 (28.894)	1,767.304 (715.885)	–	–	–
Decision speed	Choice reaction time	Reaction time	843.164 (15.469)	787.292 (11.011)	771.160 (16.389)	**M > NM**; $p < 0.01$, $d = 0.211$	**M > HC**; $p < 0.0001$, $d = 0.327$	–
Verbal memory	Verbal learning and recall	Immediate recall	29.454 (0.335)	29.955 (0.239)	31.875 (0.341)	–	**M < HC**; $p < 0.0001$, $d = 0.381$	**NM < HC**; $p < 0.0001$, $d = 0.278$
		Delayed recall	6.475 (0.129)	6.811 (0.092)	7.482 (0.131)	–	**M < HC**; $p < 0.0001$, $d = 0.398$	**NM < HC**; $p < 0.01$, $d = 0.230$
Working memory	Digit span	Maximum span	6.387 (0.080)	6.530 (0.057)	6.576 (0.081)	–	–	–
		Total score	7.562 (0.138)	7.831 (0.098)	8.040 (0.141)	–	**M < HC**; $p < 0.05$, $d = 0.191$	–
Executive function	Maze	Number of errors	102.586 (7.099)	87.647 (5.054)	66.133 (8.998)	–	**M > HC**; $p < 0.0001$, $d = 0.320$	**NM > HC**; $p < 0.01$, $d = 0.230$
		Overrun errors	49.781 (3.975)	41.508 (2.830)	28.995 (5.039)	–	**M > HC**; $p < 0.0001$, $d = 0.320$	**NM > HC**; $p < 0.01$, $d = 0.201$
		Completion time	336,804.187 (11,005.214)	300,172.508 (7,834.031)	285,193.491 (13,949.451)	–	**M > HC**; $p < 0.0001$, $d = 0.439$	**NM > HC**; $p < 0.0001$, $d = 0.271$
		Number of trials	12.440 (0.366)	11.540 (0.261)	10.943 (0.464)	–	**M > HC**; $p < 0.0001$, $d = 0.340$	**NM > HC**; $p < 0.001$, $d = 0.247$
Cognitive flexibility	Verbal interference	RT name word	1,151.530 (12.476)	1,104.455 (8.881)	1,056.896 (13.089)	**M > NM**; $p < 0.01$, $d = 0.168$	**M > HC**; $p < 0.001$, $d = 0.263$	**NM > HC**; $p < 0.05$, $d = 0.142$
		RT name color	1,568.742 (27.504)	1,542.888 (19.579)	1,457.698 (28.855)	–	**M > HC**; $p < 0.01$, $d = 0.247$	**NM > HC**; $p < 0.05$, $d = 0.168$
		RT interference	438.066 (24.575)	453.087 (17.494)	400.802 (25.782)	–	–	–

Note. Melancholic verses non-melancholic comparisons are co-varied for baseline symptom severity as measured by the 17-item Hamilton Rating Scale for Depression.
Abbreviations: M—melancholic patients; NM—non-melancholic patients; HC—healthy controls; CRT—choice reaction time task; RT—reaction time; *d*—Cohen's *d* effect size.

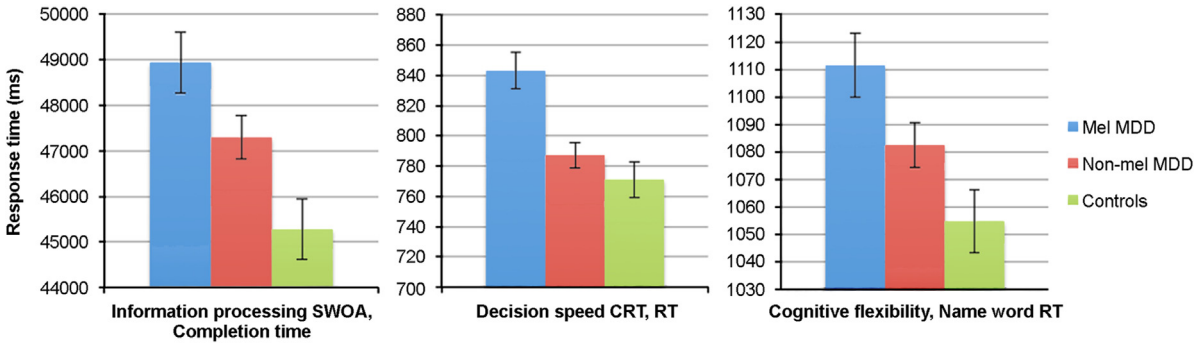

Fig. 3. The melancholic group performed significantly poorer on information processing completion time individual score and decision speed's individual score. Information processing's individual score of total errors was not significantly different. *Abbreviations:* CRT—choice reaction time; MDD—major depressive disorder; mel—melancholic; RT—reaction time; SWOA—switching of attention task.

specifically from non-melancholic patients by their slowed recognition of happy faces.

Compared to controls, melancholic participants showed poorer accuracy for identifying all emotions, except sadness (i.e. happy, fear, anger, disgust and neutral). Melancholic participants also had comparatively slowed identification of happy, fear and neutral. The non-melancholic group showed more focal impairments: poorer accuracy than controls for identifying disgust and fear and slower identification of fear (Table 3).

The five individual variables that distinguished the melancholia and non-melancholia groups formed a single significant discriminant function ($X=22.081$, $p<0.001$). A leave-out method was utilized to cross-validate the discriminant function. Accuracy was 66.7% to correctly classify the melancholic versus non-melancholic clinical groups.

4. Discussion

Findings support the concept that a melancholic MDD subtype can be distinguished from both healthy controls and from non-melancholic MDD by a distinct profile of neurocognitive performance. The melancholic subtype was distinguished by specific and pronounced deficits in processing during tasks of motivated behavior and explicit and implicit positive emotion processing. This profile is consistent with a loss of reward sensitivity and reduced decision-making under time demands.

Given the robust size of the present cohort, the findings may be interpreted with some confidence, even when representing small effect sizes. The findings are also relevant to a representative sample of outpatients with MDD seeking treatment in primary care settings.

4.1. The melancholic subtype is distinguished by slowed performance on tasks requiring processing speed and set-shifting

Consistent with predictions, the cognitive profile of the melancholic compared to the non-melancholic MDD group showed specific deficits in tasks that require effort-based decision-making, as well as a poorer general performance relative to controls. These tasks (switching of attention completion time, decision speed and naming the word during verbal interference) require speed of decision-making and shifting between modes of thought under time demands. Impairments that distinguished melancholic participants were observed independent of symptom severity. In addition to these specific impairments, the melancholic group showed a profile of widespread impairments relative to healthy controls. These impairments were more pronounced (and of larger effect sizes) than those observed for non-melancholic participants compared to controls. Together, this pattern of results suggests that a melancholic subtype may be distinguished by widespread and substantive deficits in neurocognition, which are particularly exacerbated when effort-based decision-making and set-shifting is required.

Our results suggest that melancholic depression (defined by a combination of DSM-IV and CORE criteria) is not distinguished by specific deficits in more basic motor coordination and tapping speed. Although melancholia has been considered a subtype characterized by psychomotor disturbances (Parker, 2007; Sachdev and Aniss, 1994) some studies have also reported null results for simple reaction time and motor performance in melancholia (Austin et al., 2000; 1999). Our results suggest that more fundamental alterations in psychomotor function might be secondary to deficits in attention, arousal and motivation (Lemke et al., 1999). This possibility requires further investigation using additional objective measures of psychomotor slowing.

Our observation that melancholic patients have widespread neurocognitive deficits compared to healthy controls is consistent with past studies of smaller cohorts (Pier et al., 2004; Austin et al. 1992; Exner et al., 2009; Quinn et al., 2012a, 2012b; Rogers et al., 2000a, 2002, 2004; Michopoulos et al., 2008). For studies in which a difference for melancholia compared to controls was not observed (Austin et al., 1999, 2000), it is possible that the smaller sample size was not sufficiently powered to reveal differences of small-to-moderate effect size.

4.2. The melancholic subtype is also distinguished by loss of reward sensitivity

Compared to non-melancholic MDD participants, melancholic participants were significantly slower at explicitly identifying happy faces and for recognition memory of faces when primed implicitly by the same happy faces. Notably, implicit priming was slowed compared to controls, while recognition memory was speeded in non-melancholic participants when primed by happy. This is consistent with a lack of reward sensitivity in the melancholia subtype, and may reflect motivation anhedonia. It is notable that melancholic participants were distinguished specifically by impairments related to processing happy (positive emotion), and did not show a global slowing or flattening of emotion processing, even in comparison to healthy controls. This profile of emotion processing was independent of symptom severity, in contrast to a previous report of a negative association between overall facial emotion identification and symptom severity in MDD (Csukly et al., 2009). Our results suggest that emotion impairments are robust and specific, but of small effect size, and it may require a highly powered sample to detect them.

Table 3
Means and between-group contrasts for summary scores across individual emotion test scores.

Domain	Individual test	Test variable	Mean individual test score			Contrasts; *p* and *d* (effect size) values		
			M (n=279)/335	**NM** (n=544)/646	**HC** (n=247)	**M vs. NM**	**M vs. HC**	**NM vs. HC**
Explicit emotion identification	Identification accuracy	Happy % correct	96.71% (8.18)	97.01% (7.24)	97.52% (5.94)	–	**M < HC;** $p<0.01$, $d=0.220$	–
		Sad % correct	71.71% (23.64)	72.03% (22.22)	70.06% (23.01)	–	–	–
		Fear % correct	70.73% (22.42)	72.12% (21.32)	73.92% (20.60)	–	**M < HC**; $p<0.01$, $d=0.201$	–
		Angry % correct	60.44% (19.81)	60.63% (17.70)	62.19% (16.45)	–	**M < HC**; $p<0.05$ $d=0.191$	–
		Disgust % correct	45.57% (17.96)	46.19% (17.93)	49.05% (18.07)	–	**M < HC**; $p<0.0001$, $d=0.286$	**NM < HC**; $p<0.05$, $d=0.155$
		Neutral % correct	89.71% (14.27)	89.72% (13.43)	91.60% (11.13)–	–	**M < HC**; $p<0.01$, $d=0.211$	**NM < HC**; $p<0.05$, $d=0.142$
	Identification RT	Happy RT	1505.83 (375.00)	1446.72 (368.15)	1402.10 (336.19)	**M > NM**; $p<0.05$, $d=0.155$	**M > HC**; $p<0.0001$, $d=0.333$	–
		Sad RT	2463.74 (920.00)	2540.58 (1145.58)	2464.71 (930.71)	–	–	–
		Fear RT	3065.98 (1297.37)	3027.54 (1427.57)	2818.01 (1157.13)	–	**M > HC**; $p<0.01$, $d=0.220$	**NM > HC**; $p<0.05$, $d=0.142$
		Angry RT	2421.32 (935.35)	2421.88 (898.93)	2370.88 (906.46)	–	–	–
		Disgust RT	2673.35 (1328.50)	2577.31 (1178.31)	2504.57 (1059.95)	–	–	–
		Neutral RT	1652.23 (577.38)	1651.27 (602.42)	1575.34 (628.68)	–	**M > HC**; $p<0.05$, $d=0.180$	–
	Emotion-neutral RT (Bias)	Happy RT	−146.41 (499.22)	−204.54 (587.85)	−173.25 (574.08)	–	–	–
		Sad RT	811.51 (895.47)	889.32 (1030.03)	889.37 (776.51)	–	–	–
		Fear RT	1413.75 (1268.84)	1376.27 (1321.43)	1242.67 (1057.36)	–	–	–
		Angry RT	769.09 (866.42)	770.61 (840.87)	795.54 (799.43)	–	–	–
		Disgust RT	1021.12 (1294.34)	926.04 (1113.92)	929.23 (887.52)	–	–	–
Implicit emotion identification	Priming RT	By Happy RT	1112.46 (480.74)	1018.42 (376.02)	1051.26 (409.62)	**M > NM**; $p<0.01$, $d=0.191$	–	–
		By Sad RT	1053.46 (310.31)	1041.61 (297.36)	1035.79 (268.97)	–	–	–
		By Fear RT	1093.76 (407.30)	1059.15 (387.19)	1053.93 (342.89)	–	–	–
		Angry RT	1069.19 (410.05)	1046.26 (401.30)	1044.89 (328.14)	–	–	–
		Disgust RT	1068.35 (398.79)	1043.59 (350.12)	1055.31 (352.65)	–	–	–
		Neutral RT	1106.74 (406.37)	1076.96 (360.70)	1079.67 (343.55)	–	–	–

Note. Melancholic verses non-melancholic comparisons are co-varied for baseline symptom severity as measured by the $HRSD_{17}$.
Abbreviations: M—melancholic patients; NM—non-melancholic patients; HC—healthy controls; RT—reaction time; *d*—Cohen's *d* effect size.

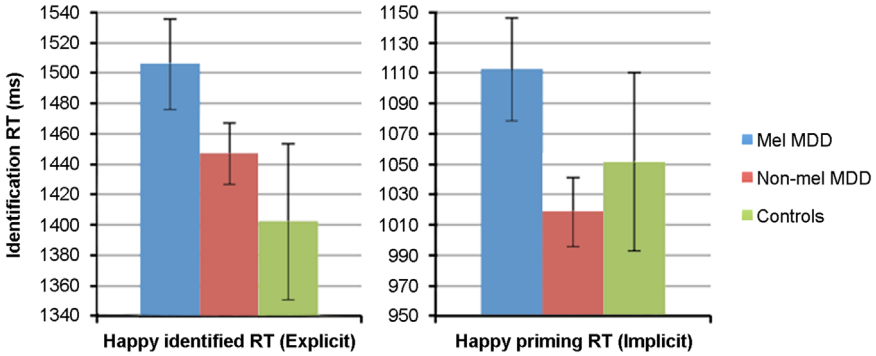

Fig. 4. On individual emotional cognitive test performance, Melancholic MDD patients were slowed for identification of happy emotion in the first/explicit task (A) and for priming of recognition memory by happy emotion in the second/implicit task (B). *Abbreviations:* MDD—Major depressive disorder; mel—melancholic; RT—reaction time.

4.3. The melancholic subtype was distinguished by an impairment for threat and loss relative to healthy controls

Contrary to predictions, the melancholic group was not characterized by a specific deficit on any measure of threat (fear, angry, disgust) or "loss" (sad) relative to the non-melancholic group. However, only melancholic participants showed a deficit on these emotions compared to healthy controls. Melancholic participants were poor at identifying expressions of fear, anger, disgust and neutral, and slower at identifying expressions of fear and neutral. In contrast to previous reports (Linden et al., 2011), we did not observe a bias toward identifying sadness in MDD participants. While the melancholic group was better at accurately identifying 'sad' faces compared to controls and quicker to respond to sad than neutral compared to both the non-melancholic group and controls, these differences were not significant.

4.4. Theoretical and clinical significance

Our findings provide new knowledge from a large cohort that suggests that melancholic depression is a subtype distinguished by a specific profile of slowed decision speed and reduced reward sensitivity, beyond the influence of symptom severity. Our findings suggest that neurocognitive impairments in melancholic MDD are not simply due to greater symptom severity, as might be presumed from a homogenous view of this melancholia (see Judd et al., 2002). Melancholic patients were characterized by both generalized and specific impairments. Both melancholic and non-melancholic participants were impaired overall compared to healthy controls, but the degree of impairment was greatest in melancholic participants. In addition, these melancholic participants were distinguished by specific impairments in decision speed and positive emotion processing.

While replication studies are required, these findings support the concept of the melancholic subtype as a distinct entity that can be differentiated on the basis of a distinct profile of neurocognitive and emotional performance. The findings also open up the idea that objectively measured biomarkers other than psychomotor retardation may have value in screening for melancholia.

A concept of motivational and decisional anhedonia offers one model for conceptualizing the profile of disturbances that characterized melancholia in this study. That is, this profile may reflect impairments in motivationally directed behavior. The circuits implicated in such behavior involve the meso-limbic and meso-cortical system and dopamine pathways (Treadway and Zald, 2011; Nestler and Carlezon, 2006). Neuroimaging investigations are warranted to further probe the neural basis of slowed decision speed under time demands and slowed processing of happy in melancholic patients.

Impairments in motivated behavior might account for the severe disruption to daily function experienced by most patients with melancholic MDD. In a recent study, Radke et al. (2013) investigated cognitive biases and aberrant processing of facial emotions in an MDD sample compared to controls. We have previously observed a pattern of social avoidance and a lower capacity for social skills in the same patients with melancholic MDD (Day et al., 2015). Research has also linked reduced reward sensitivity (reflected in a deficit to happy emotions) to a loss of social decision-making capacity in MDD (Radke et al., 2013).

4.5. Limitations and future directions

This study has three important limitations that should be considered when interpreting the results. The first is that the cognitive assessment was only taken at one symptomatic, medication-free time point. Therefore, this study does not provide any insight into whether the melancholic profile of general and emotional cognitive impairment is state- or trait-dependent. Austin et al. (1999) observed cognitive impairment in symptom-free melancholic participants suggest that (at least some of) these impairments may be trait-like and not dependent on overt symptoms. The degree of general and emotional cognitive impairment might also vary with the functional status of the overall sample as reflected in the recruitment source. Pier et al. (2004) has suggested that MDD inpatients might show more pronounced cognitive impairments. Our findings suggest that substantive impairments are also present in MDD outpatient treatment seekers drawn from community clinical settings. Future studies might explicitly compare profiles of cognitive and emotional impairment in MDD across the different settings and time-points in which treatment is sought.

The second limitation is that we relied on positive emotional faces as a stimulus that signals reward. Facial emotion stimuli have been well established for studying reward-related functions in MDD (for meta-analysis; Zhang et al., 2013), including behavioral biases that reflect a loss of reward sensitivity (Shechner et al., 2012; Radke et al., 2013). However, we did not include other tasks designed to elicit reward processing, and had to infer a connection between our behavioral results and their relevance to anhedonic features of melancholia. It would be important to expand upon our approach using additional reward tasks and measures of anhedonia.

Third, our findings for melancholic MDD are relevant to a definition of melancholia based on the combined DSM-IV and CORE criteria. This rigorous definition may exclude a minority of participants who met melancholia criteria by one system or by the other and therefore influence the outcomes. Future investigations might explore the generalizability of the findings to other definitions of melancholia. A systematic study of the relationship between specific symptoms assessed by the CORE and its subscales – cognitive process, agitation and psychomotor retardation – is also warranted. Future studies might also test whether the profile of cognitive-emotional impairment we observed in the current study generalized to independent samples and accurately classifies new participants with melancholic MDD.

In conclusion, our findings suggest that on objective tests of neurocognitive and emotional function, MDD patients with melancholic features are quantitatively and qualitatively distinct from both MDD patients without melancholic features and healthy controls.

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iSPOT-D is sponsored by Brain Resource Company Operations Pty Ltd. Brain Resource personnel coordinated the research sites and data quality control, but did not participant in the collection of any data.

Conflict of interest

The authors disclose the following financial relationships within the past 3 years: The iSPOT-D study is sponsored by Brain Resource Company Operations Pty Ltd.

Research Support:

CVAD has received income and stock options with her current role as iSPOT Global Trial Manager.

JMG is currently supported by a NHMRC Career Development Fellowship (APP1062495), is a stock holder in Freedomsway Corp. Pte. Ltd., and has previously received consultancy fees from Brain Resource Ltd. for unrelated work.

AE has received research support from Brain Resource Ltd.

CD has received research support from Astra Zeneca, Takeda, CNS Response, Neuronetics, St. Jude, and Brain Resource Ltd. CD has also received consultancy fees from Mylan, Pfizer and Genentech. CD is a stock holder in Corcept Therapeutics.

AFS has received fees as a consultant from Brain Cells, CeNeRxm, CNS Response, Corcept, Eli Lilly, Forest Labs, Glaxo-Smith Kline, Jazz, Lundbeck, Merck and Company, Neuronectics, Novadel, Novartis, Pathway Diagnostics, Pfizer, PharmaNeuroBoost, Quintiles, Sanofi-Aventis and Takeda. He is a stockholder in Amnestix, Brain Cells, CeNeRx, Corpect, Forest, Merck and Company, Neurocrine, Pfizer, PharmaNeuroBoost, Somaxon and Synosis. AFS is a cofounder of Corcept.

LMW has received consulting fees and stock options in Brain Resource Ltd., and was a stock holder in Brain Resource Ltd.

The authors have no other relevant affiliations or financial involvement with any organization or entity that has a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2015.01.061.

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