Journal of Affective Disorders 260 (2020) 245–253

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Verbal memory predicts treatment outcome in syndromal anxious depression: An iSPOT-D report

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ARTICLE INFO

Keywords:
Anxiety
Depression
Anxious depression
Cognition
iSPOT-D
Antidepressant

ABSTRACT

Background: Major Depressive Disorder (MDD), anxiety disorders, and high levels of anxious symptoms are associated with impaired cognitive functioning. However, little is known of how cognitive functioning is impaired in people with anxious depression. Here, we compared cognitive functioning between people with anxious depression, non-anxious depression, and healthy controls. We also tested whether anxious depression moderated the relationship between cognitive functioning and treatment outcome.

Methods: 1008 adults with MDD and 336 healthy controls completed IntegNeuro: a computerized cognitive functioning test battery. Participants were then randomised to one of three antidepressants and reassessed at 8 weeks using the 17-item Hamilton Depression Rating Scale ($HRSD_{17}$) and the 16-Item Quick Inventory of Depressive Symptomatology-Self-Rated for remission and response. Syndromal anxious depression was defined as MDD with a comorbid anxiety disorder. HRSD anxious depression was defined as MDD with a comorbid $HRSD_{17}$ anxiety/somatisation factor score ≥ 7.

Results: Syndromal anxious depression was associated with better psychomotor functioning and poorer working memory, cognitive flexibility and information processing speed compared to their non-anxious counterparts. HRSD anxious depression was associated with better psychomotor functioning compared to their non-anxious counterparts. Syndromal anxious depression moderated the relationship between verbal memory and treatment outcome. In people with syndromal anxious depression, poorer baseline verbal memory predicted poorer treatment outcome.

Limitations: As DSM-IV criteria was used, the DSM-5 anxious distress specifier characterisation of anxious depression could not be assessed

Conclusions: Syndromal anxious depression is characterised by impaired executive functions and moderates the relationship between verbal memory functioning and treatment outcome.

1. Introduction

Anxiety disorders and clinically significant levels of anxiety symptoms co-occur in approximately half the Major Depressive Disorder (MDD) population (Gaspersz et al., 2018; Ionescu et al., 2013). These forms of anxious depression are commonly defined either syndromally (i.e., cooccurring MDD and anxiety disorder diagnoses) or using HRSD criteria (i.e., MDD diagnosis and an $HRSD_{17}$ anxiety/somatisation factor score of ≥ 7; Braund et al., 2019; Ionescu et al., 2013). Compared to the depressed only population, the anxious depressed population has been associated with more severe illness and poorer antidepressant treatment outcomes (Ionescu et al., 2013, 2014; Kessler et al., 2015). However, while much is known of their clinical and neurobiological functioning (Ionescu et al., 2013a,b) mixed results have been found regarding their cognitive functioning and whether it can predict antidepressant treatment outcome (Basso et al., 2007; Lyche et al., 2010).

MDD has been associated with a range of impairments in cognitive functioning spanning psychomotor speed, processing speed, executive functions (e.g., attention and working memory), and memory encoding and recall (Gotlib and Joormann, 2010; Hammar and Ardal, 2009; Snyder, 2013). Attentional Control Theory (ACT) suggests high anxiety is associated with impairments in the executive functions inhibition and shifting (Derakshan and Eysenck, 2009; Eysenck and Derakshan, 2011;

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https://doi.org/10.1016/j.jad.2019.09.028
Received 10 May 2019; Received in revised form 30 August 2019; Accepted 3 September 2019
Available online 04 September 2019
0165-0327/

Eysenck et al., 2007). Anxiety disorders have similarly been associated with impairments in executive and working memory functions (Castaneda et al., 2011; Ferreri et al., 2011).

Of the available models of anxiety and depression, the approach-withdrawal model (Davidson, 1992) and the valence-arousal model (Heller, 1990, 1993) offer insights into why cognitive functioning may be impaired in people with anxious depression. These models attempt to explain how motivation and emotion, as well as the neural circuits assumed to underlie these constructs, interact with depression and anxiety. For example, in the approach-withdrawal model, behavioural motivation towards reward (i.e., the "approach system") is suggested to be hypoactive in depression and associated with left frontal lobe regions, while behavioural inhibition (i.e., the "withdraw system") is hyperactive in anxiety and associated with right frontal lobe regions. Evidence from neurobiological studies suggests this frontal asymmetry may be most pronounced in people with cooccurring anxiety and depression (Gaspersz et al., 2018; Ionescu et al., 2013). The valence-arousal model further extends on the approach-withdraw model by splitting anxiety into anxious apprehension, which is associated with left frontal activity, and anxious arousal, associated with right frontal activity. Taken together, these models suggest cognitive functioning that relies on frontal functioning, such as executive functions, may be most impaired in people with anxious depression.

Studies investigating cognitive functioning in people with anxious depression have reported mixed results. For example, Basso et al. (2007) found people with syndromally defined anxious depression showed greater overall impairment compared to people with non-anxious depression. Furthermore, people with anxious depression, but not people with non-anxious depression, showed impairments in psychomotor speed and the executive functions attention and working memory when compared to healthy controls. Lyche et al. (2010) on the other hand found no differences in psychomotor speed, executive functions, or general cognition between people with syndromal anxious depression and people with non-anxious depression. Again however, only people with anxious depression showed impairments in the executive functions shifting and updating when compared to healthy controls. Finally, Nelson et al. (2012) found people with syndromal anxious depression showed poorer performance in a design fluency task, but not a verbal fluency, compared to people with non-anxious depression and controls.

Methodological and sample-related variability may explain some of the differences observed between these studies. For example, Basso et al. (2007) diagnosed participants retrospectively using available medical records, while Lyche et al. (2010) and Nelson et al. (2012) used structured clinical interviews for DSM-IV criteria. Basso et al. (2007) and Nelson et al. (2012) administered their cognitive assessments using a paper-and-pencil approach. Lyche et al. (2010) on the other hand used the Cambridge Neuropsychological Test Automated Battery (CANTAB) – a computerised cognitive test battery. In terms of sample composition, Basso et al. (2007) excluded participants with OCD due to suggestions it may not be purely an anxiety disorder, which is consistent with the removal of OCD from the anxiety disorder section in the DSM 5 (American Psychiatric Association, 2013). Comparatively, Lyche et al. (2010) and Nelson et al. (2012) included participants with OCD. Moreover, all studies used relatively small sample sizes and patients were not medication free at the time of their assessments.

Given cognitive functioning reflects underlying neurobiology, then poor cognitive functioning at baseline reflects impaired neurobiological functioning that may prevent individuals from benefitting as strongly from antidepressant treatments (Etkin et al., 2015; Gordon et al., 2015; Groves et al., 2018; Shilyansky et al., 2016). Moreover, if anxiety further impairs cognitive functioning in people with MDD, these effects of cognitive functioning on treatment outcome may be strongest for people with anxious depression. This is in line Kircanski et al. (2019), who recently found anxious depression to moderate the relationship between baseline measures of physiological functioning and antidepressant treatment outcome.

The aims of our study were two-fold. First, we aimed to identify whether people with anxious depression showed larger impairments in cognitive functioning compared to people with non-anxious depression and healthy controls. Second, we aimed to determine whether anxious depression moderated the relationship between cognitive functioning and antidepressant treatment outcome. These aims were investigated in a large patient sample from the International Study to Predict Optimize Treatment Outcomes for Depression (iSPOT-D; Williams et al., 2011). In line with the approach-withdrawal and valence-arousal models (Davidson, 1992; Heller, 1990, 1993), as well as previous research exploring differences in cognitive functioning between people with anxious and non-anxious depression (Basso et al., 2007; Lyche et al., 2010; Nelson et al., 2012), we expected people with anxious depression to show larger impairments in executive related functions compared to people with non-anxious depression. Furthermore, given poor cognitive functioning at baseline reflects impaired neurobiological functioning that may prevent individuals from benefitting as strongly from antidepressant treatments (Etkin et al., 2015; Gordon et al., 2015; Groves et al., 2018; Shilyansky et al., 2016), we also expected the effect of poorer cognitive functioning at baseline on treatment outcome would be stronger for patients with anxious depression than for patients with non-anxious depression (i.e., there would be a significant interaction between anxious depression and cognitive functioning).

2. Method

2.1. Study overview

The International Study to Predict Optimized Treatment for Depression (iSPOT-D) is a phase-IV, multi-site, international, randomized, open-label trial designed to identify markers of treatment response to commonly prescribed medications in an adult depressed, outpatient population. All participants were either antidepressant medication naive or washed out. Assessments were collected at pre-treatment and post-treatment at 8 weeks. The iSPOT-D trial was designed with no placebo arm and participants were aware of the medication that they were taking to best match real-world practice. In this way, findings also reflect treatment regimens that exist in routine practice and promote the translatability of the findings. For more details on the study protocol design, rationale and methods, see Williams et al. (2011).

2.2. Participants

Participants (N = 1008) were adults (18–65 years old) with a current diagnosis of single-episode or recurrent, nonpsychotic, MDD as diagnosed on the Mini-International Neuropsychiatric Interview – Plus (MINI-Plus; Sheehan et al., 1998) according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria (American Psychiatric, 1994). All participants required a 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) score >16 at entry. Healthy controls (N = 336) were also recruited with a similar age and years of education, as well as an equivalent proportion of males and females compared to MDD participants. Participants provided written informed consent after receiving a complete description of the study. The study was approved by institutional or ethical review boards at each site, and its protocols followed International Conference on Harmonization and Good Clinical Practice principles, the U.S. Food and Drug Administration Code of Federal Regulations, and country-specific guidelines.

2.3. Anxious depression definitions

2.3.1. Syndromal anxious depression

Syndromal Anxious depression was defined as a DSM-IV MDD diagnosis and one concurrent MINI-Plus identified anxiety disorder

Table 1
Individual neurocognitive tests that make up the IntegNeuro battery.

Summary measure name	Test	Outcome measures	Test description	Tests assessing equivalent constructs
Psychomotor function	Motor tapping	Number and variability of taps	Tapping index finger as fast as possible for 30 s; assessing sensorimotor response speed	Finger tapping
Decision speed	Choice reaction time	Average RT, variability of RT	Respond to one of four circles as they light up; assesses decision related reaction time. Assessing sensorimotor coordination and speed.	Corsi blocks
Verbal memory	Memory recall	Accuracy (recall, intrusion errors), learning rate	Learn and then recall lists of 12 words; assesses learning, memory recall.	Rey auditory verbal learning test California verbal learning test
Working memory	Digit span	Accuracy (total recall, maximum recall span)	Repeat a series of digits in forward and backward order; assessing working memory	Digit span
Cognitive flexibility	Verbal interference	Accuracy (errors), RT	Respond to the name of colour word (ignore colour) and then colour word presented (ignore name); assessing suppression of automatic responses.	Stroop
Attention	Continuous performance test	Accuracy (total, false positive, false negative errors), RT, variability of RT	Sustained attention to series of letters (D, C, G, or T). Identify when same letter is 1-back. Requires working memory updating.	Conner's CPT, TOVA
Response inhibition	Go/No-Go	Accuracy (total, false positive, false negative errors), RT, variability of RT.	Press response pad as quickly as possible to 'Go' (green) trials, and withhold to 'No-Go' (red) trials. Assessing impulsivity vs inhibition.	
Information processing speed	Switching of attention	Accuracy (switching errors), completion time, connection time	Connect a sequence of alternating numbers and letters; assesses information processing efficiency	Trails A and B (paper and pencil)
Executive function	Executive maze	Accuracy (total, overrun errors), completion time	Discover (by trial and error) a maze path; reflecting planning, monitoring feedback, and error correction	Austin maze

Abbreviations: CPT, Continuous Performance Test; RT, Reaction Time; TOVA, Test Of Variables of Attention.

(23.8%, 239/1005), including generalised anxiety disorder, panic disorder, agoraphobia, social phobia and specific phobia (Ionescu et al., 2013).

2.3.2. HRSD anxious depression

HRSD anxious depression was defined as a DSM-IV MDD diagnosis and a $HRSD_{17}$ anxiety/somatization factor score of ≥ 7 (41.9%, 422/1008; Ionescu et al., 2013). The anxiety/somatisation factor was derived from a factor analyses of the HRSD by Cleary and Guy (1977) and includes six items; hypochondriasis, insight, general and gastrointestinal somatic symptoms, and psychic and somatic anxiety.

2.4. Cognitive functioning

Participants completed IntegNeuro™, a computerized battery of tests designed to evaluate a range of cognitive capacities including attention, working memory, psychomotor response speed, cognitive flexibility, response inhibition, verbal memory, processing speed, and decision speed (Table 1; Mathersul et al., 2009; Paul et al., 2005; Williams et al., 2009). IntegNeuro™ is presented at a grade 5 reading level and was run locally at each study site on a computer equipped with dedicated software and a touch screen. Accuracy and reaction time were recorded for each assessment task. Summary performance measures for each of the 9 tests were created by normalizing measures (e.g., accuracy and reaction time) to the 336 healthy controls, correcting measures so that positive values meant better performance and negative values meant worse performance, then averaging across measures within each test. For correlations between cognitive functioning measures in people with MDD and healthy controls, see Supplementary Material Tables 1 and 2, respectively.

2.5. Protocol treatment

Participants were randomized to receive escitalopram, sertraline, or venlafaxine-extended release (venlafaxine-XR) with equal probability. All psychotropic medications (except sleep aids and anxiolytics) were discontinued and washed-out prior to baseline assessments. Antidepressants were prescribed and doses were adjusted by the participant's treating physician according to routine clinical practice. Additional medication for associated symptoms (e.g., insomnia) or medication-induced side effects (e.g., nausea) were allowed as they reflect common practice. Any treatment for concurrent general medical conditions, except medications contraindicated with the study-assigned antidepressants, were allowed and recorded.

2.6. Post-treatment measures

Outcome measures were remission and response. Remission was defined as a week 8 $HRSD_{17}$ score < 7 or a week 8 16-Item Quick Inventory of Depressive Symptomatology-Self-Rated ($QIDS\text{-}SR_{16}$) score < 5 (Rush et al., 2003; Trivedi et al., 2004). Response was defined as a > 50% decrease from baseline on the $HRSD_{17}$ or $QIDS\text{-}SR_{16}$. Study site personnel contacted participants by telephone at day 4 and weeks 2, 4 and 6 to monitor antidepressant dosage, compliance, concomitant medications and adverse events.

2.7. Statistical analysis

Missing baseline data were imputed using multivariate imputation by chained equations (MICE; where $m = 10$), a multiple imputation (MI) technique able to handle both continuous and categorical data (Azur et al., 2011; van Buuren and Groothuis-Oudshoorn, 2011). Data missing at random ranged from 0% to 21.9% (attention), with 6.2% of data missing in total. Missing data was in the acceptable range for multiple imputation (i.e. up to 60% missing data; Barzi and Woodward, 2004). Models were run on each imputed dataset, then combined

according to Rubin's rule (Rubin, 1987). However, to avoid predicting group membership, people with missing data on measures used to create definition groups were first excluded.

T-tests and chi-squared tests were used to compare demographic characteristics between people with anxious and non-anxious depression. ANOVA's were used to test whether there were differences in cognitive functioning between people with anxious depression, non-anxious depression, and healthy controls. Follow up t-tests were used to identify which groups cognitive functioning differed. Follow up ANCOVA's adjusted for age, sex, years of education, study site, depression severity (as measured by the $HRSD_{17}$ score with items from the anxiety/somatisation factor removed), were used to assess whether differences in cognitive functioning between groups occurred independent of these covariates. ANCOVA's comparing anxious and non-anxious depression were additionally controlled for MDD duration, recurrent MDD, and sleep aids/anxiolytics. Follow up *t*-tests and ANCOVA's *p*-values were corrected for using the Holm (1979) method. Bivariate logistic regressions were used to assess whether anxious depression moderated the relationship between baseline cognitive functioning and antidepressant treatment outcome. Bivariate logistic regression models were also adjusted for using the same covariates used in ANCOVA analyses. The false discovery rate for bivariate logistic regression models were corrected for using the Benjamini and Hochberg (1995) method.

All analyses were conducted using R 3.4.0 (Team, 2017). MI was performed using the "mice" package in R (van Buuren and Groothuis-Oudshoorn, 2011). Chi-squared, ANOVA and ANCOVA tests were performed using the "miceadds" package in R (Robitzsch et al., 2018). T-tests were performed using the "MKmisc" package in R (Kohl, 2018). Interaction plots were made using the "jtools" package in R (Long, 2018).

3. Results

3.1. Demographics

Table 2 provides the demographic information for people with anxious depression, non-anxious depression, and healthy controls. Ages ranged from 18.02 to 65.82 (*SD* = 12.70). People with syndromal anxious depression were less educated ($p < 0.001$), had longer MDD durations ($p = 0.049$) and less cases of recurrent MDD ($p < 0.001$), and used more sleep aids/anxiolytics ($p = 0.002$) compared to their non-anxious counterparts. People with HRSD anxious depression were significantly more depressed than their non-anxious counterparts ($p < 0.001$). There was low agreement between anxious depression definitions ($\kappa = 0.15$, 95% confidence interval [CI = 0.09, 0.20], $p < 0.001$), with 23.8% (239/1008) meeting the criteria for syndromal anxious depression, 41.9% (422/1008) meeting criteria for HRSD anxious depression, and 13.2% (133/1008) of participants meeting criteria for both definitions of anxious depression (for further details, see Braund et al., 2019).

3.1.1. Differences in cognitive functioning between people with anxious depression, non-anxious depression, and healthy controls

People with syndromal anxious depression, non-anxious depression, and healthy controls differed significantly across every measure of cognitive functioning, except for decision speed ($p = 0.447$; for all results, see Supplementary Material Table 3). Similarly, people with HRSD anxious depression, non-anxious depression, and healthy controls differed significantly across most measures of cognitive functioning, except for decision speed ($p = 0.610$). Follow up *t*-tests and ANCOVA's corrected for using the Holm (1979) method were used to identify which groups differed significantly, and whether groups differed significantly after controlling for covariates.

3.1.2. Anxious depression vs non-anxious depression

Fig. 1 shows the differences in cognitive functioning between people with anxious depression, non-anxious depression, and healthy controls. People with syndromal anxious depression had better psychomotor functioning ($p = 0.008$, $d = 0.21$), and poorer working memory ($p = 0.018$, $d = 0.19$), cognitive flexibility ($p = 0.033$, $d = 0.16$), and information processing speed ($p = 0.027$, $d = 0.14$) compared to people with non-anxious depression. All results remained significant after adjusting for covariates (for all results, see Supplementary Material Table 4).

People with HRSD anxious depression had better psychomotor functioning ($p = 0.010$, $d = 0.18$) compared to people with non-anxious depression, which remained significant after adjusting for covariates ($p = 0.008$, $\eta_p^2 = 0.008$).

3.1.3. Anxious depression vs healthy controls

People with syndromal anxious depression had poorer verbal memory ($p = <0.001$, $d = 0.39$), working memory ($p = <0.001$, $d = 0.39$), cognitive flexibility ($p = 0.006$, $d = 0.36$), attention ($p < 0.001$, $d = 0.57$), response inhibition ($p = 0.046$, $d = 0.23$), and information processing ($p = <0.001$, $d = 0.48$) compared to healthy controls. After adjusting for covariates, all results remained significant, except for response inhibition ($p = 0.273$, $\eta_p^2 = 0.018$; for all results, see Supplementary Material Table 5).

People with HRSD anxious depression had poorer psychomotor functioning ($p = 0.024$, $d = 0.17$), verbal memory ($p = <0.001$, $d = 0.31$), working memory ($p = 0.021$, $d = 0.21$), cognitive flexibility ($p = 0.006$, $d = 0.23$), attention ($p < 0.001$, $d = 0.51$), and information processing ($p = <0.001$, $d = 0.34$) compared to healthy controls.

Table 2
Demographic information for people with anxious depression, non-anxious depression, and healthy controls.

	iSPOT-D (*N* = 1008)	Healthy Controls (*N* = 336)		Syndromal Anxious Depression (*N* = 239)	Syndromal Non-Anxious Depression (*N* = 766)		HRSD Anxious Depression (*N* = 422)	HRSD Non-Anxious Depression (*N* = 586)	
	Mean (SD)	Mean (SD)	*p*-value	Mean (SD)	Mean (SD)	*p*-value	Mean (SD)	Mean (SD)	*p*-value
Age	37.85 (12.57)	36.99 (13.08)	0.287	38.19 (13.41)	37.73 (12.31)	0.622	37.02 (13.16)	38.44 (12.11)	0.171
Years of Education	14.54 (2.80)	14.94 (2.50)	0.021	13.98 (3.01)	14.71 (2.71)	<0.001	14.71 (2.86)	14.42 (2.75)	0.219
HRSD (Minus anxiety items)	15.72 (3.32)	0.57 (0.97)	<0.001	15.39 (3.54)	15.81 (3.25)	0.087	16.23 (3.90)	15.35 (2.77)	<0.001
MDD Duration	14.86 (12.17)	–	–	16.30 (13.18)	14.41 (11.82)	0.037	14.98 (12.37)	14.78 (12.04)	0.798
	N (%)	**N (%)**	**p-value**	**N (%)**	**N (%)**	**p-value**	**N (%)**	**N (%)**	**p-value**
Sex (Female)	571 (56.6)	191 (56.8)	1	131 (54.8)	439 (57.3)	0.496	248 (58.8)	323 (55.1)	0.434
Recurrent MDD (Yes)	884 (87.7)	–	–	193 (82.8)	688 (91.4)	0.001	367 (89.1)	517 (89.6)	0.723
Sleep aids/ Anxiolytics (Yes)	58 (5.8)	–	–	23 (9.6)	34 (4.4)	0.003	25 (5.9)	33 (5.6)	0.955

Abbreviations: iSPOT-D, international Study to Predict Optimised Treatment for Depression; MDD, Major Depressive Disorder; HRDS, Hamilton Rating Scale for Depression.

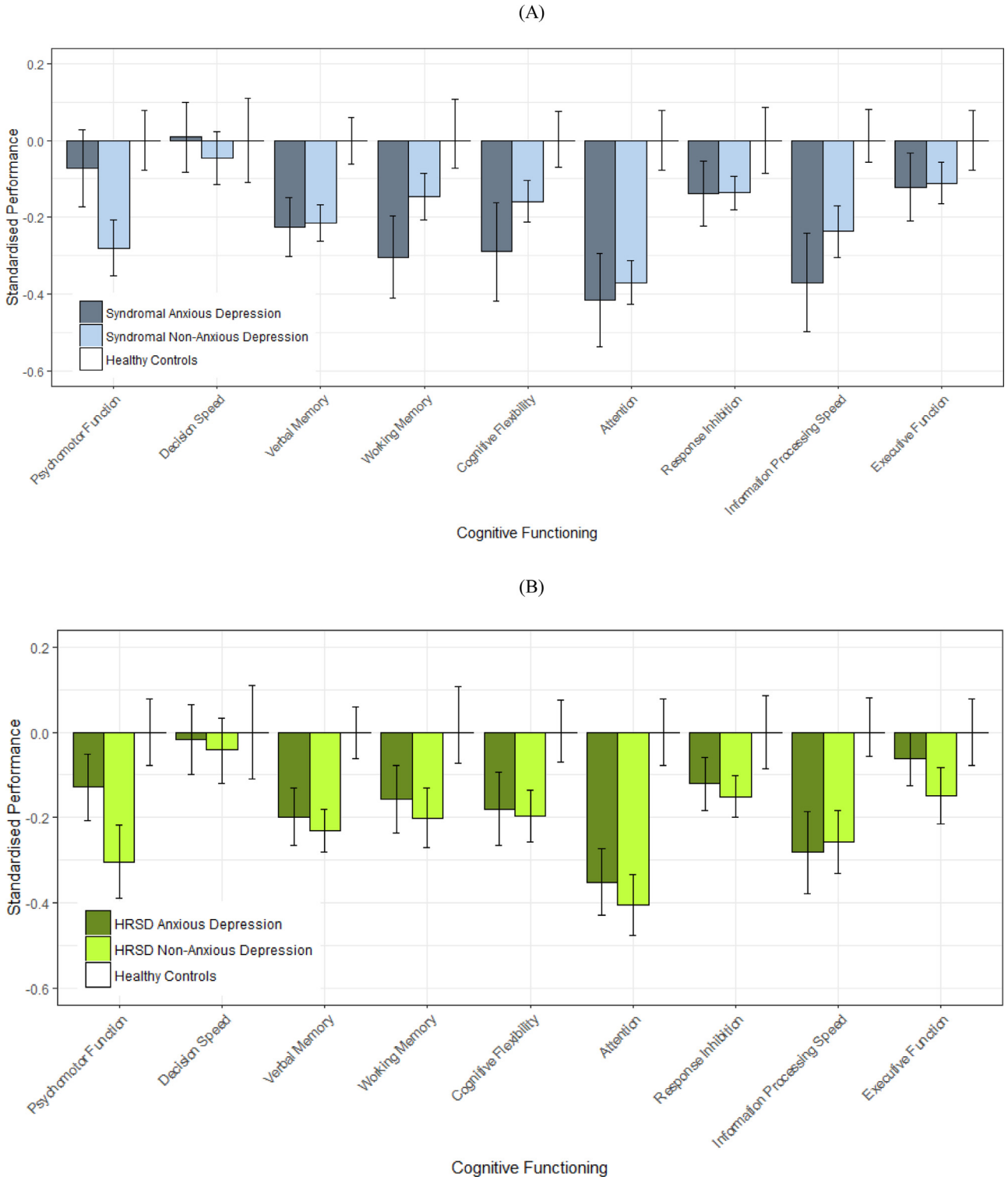

Fig. 1. Differences in cognitive functioning between people with syndromal anxious depression, non-anxious depression, and healthy controls (A), and HRSD anxious depression, non-anxious depression, and healthy controls (B).
Note. 95% confidence intervals shown.
Abbreviations: HRDS, Hamilton Rating Scale for Depression.

After adjusting for covariates, all results remained significant, except for attention ($p = 0.274$, $\eta_p^2 = 0.061$).

3.1.4. Non-anxious depression vs healthy controls

People with syndromal non-anxious depression had poorer psychomotor functioning ($p = <0.001$, $d = 0.30$), verbal memory ($p = <0.001$, $d = 0.35$), working memory ($p = 0.037$, $d = 0.20$), cognitive flexibility ($p = 0.006$, $d = 0.22$), attention ($p = <0.001$, $d = 0.52$), response inhibition ($p < 0.001$, $d = 0.23$), information processing ($p = 0.006$, $d = 0.29$), and executive maze function ($p = 0.012$, $d = 0.16$) compared to healthy controls. After adjusting for covariates, people with syndromal non-anxious depression only had

Table 3
Results from models where anxious depression significantly interacted with cognitive functioning when predicting antidepressant treatment outcome.

	$HRSD_{17}$ Remission			$HRSD_{17}$ Response			QIDS-SR_{16} Remission			QIDS-SR_{16} Response		
	Odds Ratio	CI 95% (Lower, Upper)	p	Odds Ratio	CI 95% (Lower, Upper)	p	Odds Ratio	CI 95% (Lower, Upper)	p	Odds Ratio	CI 95% (Lower, Upper)	p
Verbal Memory	0.99	0.74, 1.34	0.972	0.98	0.77, 1.25	0.892	1.09	0.81, 1.46	0.578	1.16	0.88, 1.52	0.283
Anxious Depression	1.09	0.76, 1.56	0.654	1.04	0.73, 1.49	0.817	0.98	0.66, 1.44	0.913	1.67	1.16, 2.40	0.006
Interaction Term	2.29	1.29, 4.06	0.005	1.85	1.05, 3.24	0.032	1.99	1.02, 4.06	0.050	2.03	1.04, 3.93	0.035
			q			q			q			q
Verbal Memory			0.972	0.972	0.892	0.892	1.09	0.650	1.16	0.340		
Anxious Depression			0.654	0.995	1.04	0.817	0.938	0.98	0.913	1.67	0.034	
Interaction Term			0.005	0.045	1.85	0.032	0.288	1.99	0.050	0.377	2.03	0.198

Abbreviations: $HRDS_{17}$, 17-item Hamilton Rating Scale for Depression; QIDS-SR_{16}, 16-Item Quick Inventory of Depressive Symptomatology-Self-Rated.

poorer psychomotor functioning ($p = <0.001$, $\eta_p^2 = 0.018$) and working memory ($p = 0.031$, $\eta_p^2 = 0.009$; for all results, see Supplementary Material Table 6).

People with HRSD non-anxious depression had poorer psychomotor functioning ($p = <0.001$, $d = 0.32$), verbal memory ($p = <0.001$, $d = 0.40$), working memory ($p = 0.021$, $d = 0.26$), cognitive flexibility ($p = <0.001$, $d = 0.28$), attention ($p = <0.001$, $d = 0.55$), information processing ($p = <0.001$, $d = 0.34$), and executive maze function ($p = <0.001$, $d = 0.21$) compared to healthy controls. After adjusting for covariates, all results remained significant, with HRSD non-anxiosu depression additionally having poorer response inhibition ($p = 0.030$, $\eta_p^2 = 0.014$) compared to healthy controls.

3.1.5. Anxious depression interacting with cognitive functioning in predicting antidepressant treatment outcome

Treatment type did not significantly interact with either syndromal or HRSD anxious depression and cognitive functioning in predicting antidepressant treatment outcome (for all results, see Supplementary Material Tables 7 and 8), so treatments were pooled for analyses. Table 3 shows the models with significant interactions between syndromal anxious depression and cognitive functioning in predicting antidepressant treatment outcome (for all results, see Supplementary Material Table 9). Syndromal anxious depression interacted with verbal memory in predicting $HRSD_{17}$ remission ($OR = 2.29$, 95% CI [1.29, 4.06], $p = 0.005$) and response ($OR = 1.85$, 95% CI [1.05, 3.24], $p = 0.032$), as well as QIDS-SR_{16} remission ($OR = 1.99$, 95% CI [1.02, 4.06], $p = 0.050$) and response ($OR = 2.03$, 95% CI [1.04, 3.93], $p = 0.035$). After adjusting for multiple comparisons, syndromal anxious depression interacted with verbal memory in predicting $HRSD_{17}$ remission ($OR = 2.29$, 95% CI [1.29, 4.06], $q = 0.045$).

Fig. 2 shows the predicted probabilities of remission/response as a function of verbal memory and syndromal anxious depression. Simple slopes analysis revealed that for people with syndromal anxious depression, better verbal memory was associated with better $HRSD_{17}$ remission ($OR = 2.64$, 95% CI [1.43, 4.87], $p = 0.002$) and response ($OR = 2.04$, 95% CI [1.16, 3.60], $p = 0.013$), as well as better QIDS-SR_{16} remission ($OR = 2.17$, 95% CI [1.16, 4.06], $p = 0.016$) and response ($OR = 2.98$, 95% CI [1.58, 5.64], $p < 0.001$). After adjusting for covariates, better verbal memory performance was still associated with better $HRSD_{17}$ remission ($OR = 2.27$, 95% CI [1.13, 4.53], $p = 0.021$), as well as QIDS-SR_{16} remission ($OR = 2.04$, 95% CI [1.01, 4.09], $p = 0.045$) and response ($OR = 2.97$, 95% CI [1.47, 6.02], $p = 0.002$). Verbal memory performance was not associated with better $HRSD_{17}$ response after adjusting for covariates. Verbal memory was not associated with treatment outcome for people with non-anxious depression. No other measure of cognitive functioning interacted with syndromal anxious depression in predicting treatment outcome. Furthermore, no measure of cognitive functioning interacted with HRSD anxious depression in predicting treatment outcome (for all results, see Supplementary Material Table 10).

4. Discussion

We aimed to identify whether people with anxious depression showed larger impairments in cognitive functioning compared to people with non-anxious depression and healthy controls. Our study found that people with syndromal anxious depression were associated with better psychomotor functioning and poorer working memory, cognitive flexibility and information processing compared to people with non-anxious depression. People with HRSD anxious depression were only associated with better psychomotor functioning compared to people with non-anxious depression. We also aimed to determine whether anxious depression moderated the relationship between cognitive functioning and antidepressant treatment outcome. We found that poorer baseline verbal memory performance in people with syndromal anxious depression predicted poorer antidepressant treatment

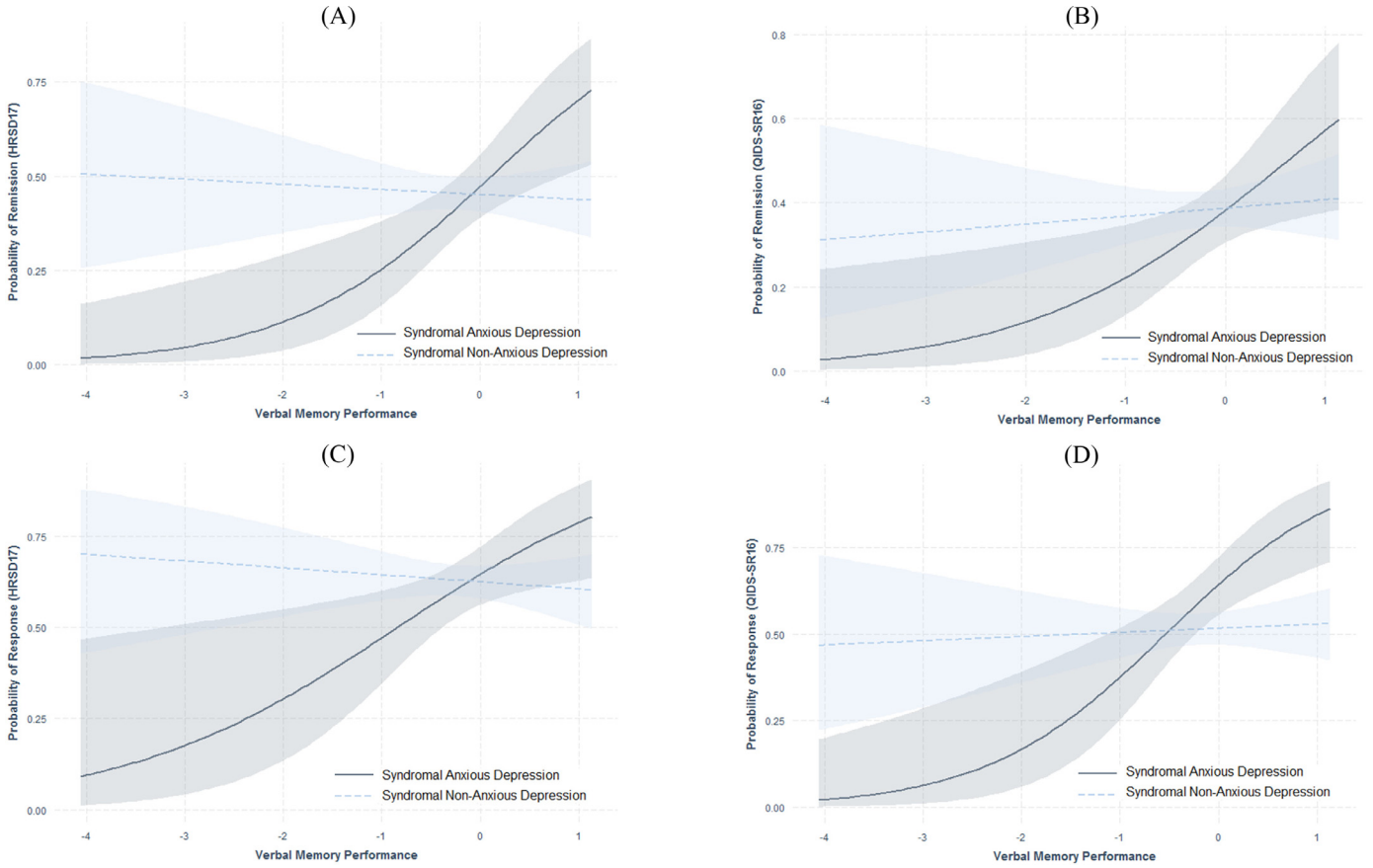

Fig. 2. Plots of the predicted probabilities of remission defined by the $HRSD_{17}$ (A), remission defined by the QIDS-SR_{16} (B), response defined by the $HRSD_{17}$ (C), response defined by the QIDS-SR_{16} (D), as a function of verbal memory in MDD with and without a comorbid anxiety disorder.
Note. 95% confidence intervals shown.

outcome, while no association was found in people with non-anxious depression.

Findings associated with cognitive functioning in people with anxious depression have been mixed, with some showing cognitive deficits compared to their non-anxious counterparts, while others have found no differences (Basso et al., 2007; Lyche et al., 2010; Nelson et al., 2012). Our finding of poorer working memory, cognitive flexibility, and information processing in people with syndromal anxious depression suggests that deficits in these areas of functioning seen individually in both anxiety disorders (Castaneda et al., 2011; Ferreri et al., 2011) and MDD (Gotlib and Joormann, 2010; Hammar and Ardal, 2009; Snyder, 2013) are compounded in people with syndromal anxious depression. Given these tasks gauge functioning that includes frontal areas such as the pre-frontal cortex and anterior cingulate cortex (Badre and Wagner, 2006; Barbey et al., 2013; Leber et al., 2008; Milham et al., 2003), with some evidence of laterality (Badre and Wagner, 2006; Milham et al., 2003), these results are also consistent with the approach-withdrawal model whereby comorbid depression and anxiety results in a frontal asymmetry. However, given other measure that required frontal functioning were not impaired, such as executive functioning and response inhibition, the approach-withdraw model was only partially supported. Furthermore, it is unclear whether the valence-arousal model was supported as anxious apprehension and arousal have been suggested to vary depending on the specific anxiety disorder (Heller and Nitschke, 1998), and the syndromal anxious depression definition combines various anxiety disorders.

When compared to healthy controls, people with syndromal anxious depression showed greater impairments marked by larger effect sizes across most measures of cognitive functioning. Furthermore, after controlling for covariates, people with syndromal anxious depression maintained verbal memory, cognitive flexibility, and information processing deficits, whereas people with non-anxious depression did not. In comparison, people with HRSD anxious depression showed similar effect size deficits across measures of cognitive functioning when compared to healthy controls as people with non-anxious depression. Surprisingly, some measures of cognitive functioning only remained impaired in people with HRSD non-anxious depression, and not those with HRSD anxious depression, after controlling for covariates. These findings are consistent with previous research showing greater impairments in people with syndronal anxious depression, but not people with non-anxious depression, in executive and working memory functions when compared to healthy controls (Basso et al., 2007; Lyche et al., 2010).

Syndromal anxious depression moderated the relationship between verbal memory and antidepressant treatment outcome. Poorer baseline verbal memory performance predicted poorer antidepressant treatment outcome in people with syndromal anxious depression only, and not in those with non-anxious depression. Verbal memory has been shown to rely on functioning in the medial temporal lobe and the PFC, with verbal memory encoding shown to rely more on left PFC functioning and retrieval on right PFC functioning (Habib et al., 2003). Poorer verbal memory functioning in people with anxious depression, which is reflective of impaired neurobiological across these areas, may therefore prevent individuals from benefitting as strongly to antidepressant treatments. Conversely, verbal memory functioning in people with non-anxious depression that is less impaired may reflect neurobiological functioning capable of benefitting from treatment. These findings suggest people with syndromal anxious depression and poor verbal memory may represent as a subgroup of people with MDD that may require complimentary treatments (including cognitive remediation or

verbal memory training) to facilitate better outcomes.

This study has several limitations. iSPOT-D was designed as a practical study and recruited participants who were actively seeking antidepressant treatment to reflect real-world practise (Williams et al., 2011). While this increases the generalisability of results, future studies using more severe populations may find greater cognitive impairments compared to those found in the current study. Furthermore, findings related to treatment outcome are limited to the three antidepressants used in the study (i.e., escitalopram, sertraline, and venlafaxine-XR), and other classes of antidepressants require further investigation. Treatment outcome was assessed at a single time point, and assessment of further time points would clarify whether successful remission and response persisted beyond the 8-week treatment period. Lastly, due to participants being diagnosed using the MINI-Plus with DSM-IV criteria, the DSM-5 anxious distress specifier characterisation of anxious depression could not be assessed (Gaspersz et al., 2018).

In conclusion, our results suggest that people with syndromal anxious depression are characterised by poorer executive functions compared to people with non-anxious depression. Furthermore, better baseline verbal memory performance in people with syndromal anxious depression predicted better antidepressant treatment outcomes. Neurocognitive tests are easily accessible online and offer a practical and scalable method for predicting antidepressant treatment outcome. Future research should investigate how verbal memory interacts with other clinical and biological markers of anxious depression to further elucidate this relationship and develop more effective targeted therapies.

Acknowledgements

We thank all the patients and volunteers who agreed to participate in this study. We acknowledge Brain Resource as the sponsor for the iSPOT-D study (NCT00693849). We acknowledge the roles of Evian Gordon, Ph.D. MD, as sponsor Principal Investigator, Leanne Williams, Ph.D., for help on earlier versions of the manuscript and as the cross-site academic Principal Investigator for iSPOT-D (2008–2013), Claire Day, Ph.D., as the global trial coordinator for iSPOT-D (2008–2014), and the iSPOT-D Publication Team.

Funding

TAB was supported by a NSW Health PhD scholarship.

CRediT authorship contribution statement

Taylor A. Braund: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Gabriel Tillman:** Conceptualization, Writing - review & editing. **Donna M. Palmer:** Conceptualization, Writing - review & editing. **Anthony W.F. Harris:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

TAB and DMP report salaries from Brain Resource Ltd outside the submitted work. LMW and AWFH report non-salary research costs as iSPOT-D investigators. AWFH personal fees from Janssen Australia, Lundbeck Australia, Sumitomo Dainippon Pharma, and grants from Takeda Pharmaceutical Company, outside the submitted work. GT reports no conflict of interests.

Role of funding source

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

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.09.028.

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