Comprehensive Psychiatry 94 (2019) 152113

Contents lists available at ScienceDirect

Comprehensive Psychiatry

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

Association between cognitive function and performance on effort based decision making in patients with major depressive disorder treated with Vortioxetine☆

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ARTICLE INFO

Keywords:
Motivation
Reward
Anhedonia
MDD
Major depressive disorder
Vortioxetine

ABSTRACT

Background: It is well established that deficits in motivation, reward, and cognition are common during and in between syndromal episodes of depression as part of Major Depressive Disorder (MDD). Informed by evidence indicating functional and structural interconnectivity between cognitive and reward brain circuits, we preliminarily evaluate the association between measures of cognitive performance and reward/motivation.
Methods: This is a post-hoc analysis of a primary study (i.e. the THINC-it sensitivity to change study). Adults (18–65 years of age) meeting DSM-5 criteria for MDD, single-episode or recurrent confirmed by M.I.N.I. with moderate severity or greater (i.e. Montgomery Asberg Depression Rating Scale ≥20). All eligible subjects received vortioxetine 10–20 mg open-label for 8 weeks. The Effort Expenditure Reward Task (EEfRT) was the principal measure of motivation and reward. We directly compare the effects of cognitive measures and depressive symptoms on effort-based decision-making using the THINC-it composite score and MADRS total score.
Results: Twenty-one participants with MDD (Mean age = 38.47, SD = 12.85) and 20 healthy volunteers (Mean age = 41.50, SD = 14.21) completed the optional EEfRT task. Amongst individuals with MDD, performance in processing speed, executive function (i.e. Trails B) and overall composite cognitive score was positively associated with the proportion of hard-task choices in the high reward condition (i.e. greater reward valuation). Across both groups, a greater probability ($\chi^2 = 1.137$) and magnitude of reward ($\chi^2 = 0.045$) was associated with increased effort (i.e. choosing the hard task more frequently). Using fully factored GEE models, we observed a positive association between performance on the Trails test ($\beta = 2.223$, SE = 0.928, $p = 0.017$) as well as the composite score ($\beta = 0.978$, SE = 0.0.459, $p = 0.033$), and greater effort for high rewards. In addition, it was observed that a positive association (i.e. greater effort for reward in higher probability) was observed with depressive symptoms and overall cognitive measures.
Conclusion: Herein, we observed that an association exists between overall cognitive function, notably processing speed and executive function and reward function. Specifically, a greater effort for hard task rewards (using the EEfRT task) was manifested in individuals exhibiting higher levels of cognitive performance in a well-characterized sample of MDD treated with Vortioxetine.

1. Introduction

Notwithstanding the availability of a large number of mechanistically dissimilar antidepressants, most individuals with Major Depressive Disorder (MDD) manifest residual symptomatology between episodes, notably in areas of motivation and anhedonia [1]. Residual

☆ ClinicalTrials.gov Identifier: NCT03053362.
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https://doi.org/10.1016/j.comppsych.2019.07.006

deficits in reward and motivation in MDD are common and are principal mediators of poor functional outcome, decreased quality of life, and belie acceptability of existing therapies [2]. Moreover, selective serotonin reuptake inhibitors (SSRIs) are not only insufficient at fulling abrogating residual depressive symptoms, but in some cases reported to engender and/or amplify measures of apathy, emotional blunting and disinterest. The foregoing observations provide the impetus for exploring the efficacy of alternative agents for reward measures. Towards this aim, further research is needed to parse possible associations between reward measures and other dimensions/domains of psychopathology in MDD [3].

Convergent evidence indicates that the neural substrates subserving anhedonia are discrete, yet interact with other brain circuits and networks [4]. For example, brain circuits subserving general cognitive functions are known to have functional as well as structural interconnectivity with reward/motivation circuits [5–7]. The foregoing observation, along with other evidence demonstrating overlap of motivation and cognition suggests that associations between cognitive performance and measures of reward motivation exist [8].

It is also established that dopamine signalling is a critical neurotransmitter involved across disparate measures of motivation. Emotional blunting, which overlaps with deficits in motivation and reward, has been reported with exposure to SSRI antidepressants [9]. A working hypothesis is that the compensatory decreased firing of catecholaminergic neurons in response to serotonergic enhancement may partially explain the emotional blunting/apathy phenomenon [10]. Moreover, the foregoing observation provides the impetus for considering agents that have indirect effects on dopamine and/or other neurochemical systems relevant to neuroplasticity as potential treatments for deficits in motivation [11,12]. Herein, we sought to preliminarily evaluate these associations by using a rigorous measure of reward, the Effort Expenditure for Reward Task (EEfRT). The conceptual background and validation of the EEfRT task have been reported elsewhere [13]. The antidepressant we chose to provide preliminary assessment of this association was Vortioxetine. Vortioxetine was selected in part due to its demonstrated pro-cognitive effects which have been replicated in short term studies in MDD [14]. Moreover, pre-clinical evidence (e.g. sucrose preference) as well as pharmacologic studies indicate that vortioxetine engages neurotransmitter systems relevant to reward, motivation and pleasure [15]. The pharmacological profile of vortioxetine provides the basis for hypothesizing that vortioxetine would improve measures of reward, motivation and anhedonia in adults with MDD.

The data set we chose for this analysis was obtained from a primary study that sought to determine sensitivity to change with a cognitive measure in MDD.

2. Methodology

2.1. Participants

The primary study was an 8-week, open-label, sensitivity to change study assessing alterations in cognitive function/performance, as measured by the THINC-it (ClinicalTrials.gov Identifier: NCT03053362). Eligible adults (18–65 years of age) meeting criteria for Diagnostic and Statistical Manual, Fifth Edition (DSM-5)-defined MDD were treated with vortioxetine (10–20 mg flexibly dosed) ($N = 100$) and ($N = 50$) age, and sex-matched, healthy controls. All subjects were enrolled at the Brain and Cognition Discovery Foundation (BCDF) in Toronto, ON. Institutional review board-approved consent was obtained prior to initiating the study and all eligible participants provided written informed consent.

Participants met the following eligibility criteria:(1) provide written informed consent, (2) male or female 18–65 years of age, (3) a current diagnosis of a major depressive episode (MDE) as part of MDD as per DSM-5 criteria, (4) current MDE is confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I. 5.0.), (5) outpatient of a psychiatric setting, (6) MADRS score ≥20 at screening and baseline, (7) history of at least one prior MDE formally diagnosed by a healthcare provider or validated by previous treatment (e.g., guideline-informed pharmacotherapy and/or manual-based psychotherapy).

The exclusion criteria were: (1) current alcohol and/or substance use disorder as confirmed by the M.I.N.I. 5.0, (2) presence of comorbid psychiatric disorder other than MDD that is a focus of clinical concern as confirmed by the M.I.N.I. 5.0, (3) medications approved and/or employed off-label for cognitive dysfunction (e.g., psychostimulants), (4) any medication for a general medical disorder that, in the opinion of the investigator, may affect cognitive function, (5) use of benzodiazepines within 12 h of cognitive assessments, (6) consumption of alcohol within 8 h of cognitive assessments, (7) inconsistent use or abuse of marijuana, (8) physical, cognitive, or language impairments sufficient to adversely affect data derived from cognitive assessments, (9) diagnosed reading disability or dyslexia, (10) clinically significant learning disorder by history, (11) electroconvulsive therapy (ECT) in the last 6 months, (12) history of moderate or severe head trauma (e.g., loss of consciousness for >1 h), other neurological disorders, or unstable systemic medical diseases that, in the opinion of the investigator, are likely to affect the central nervous system, (13) pregnant and/or breastfeeding, (14) received investigational agents as part of a separate study within 30 days of the screening visit, (15) actively suicidal/presence of suicidal ideation or evaluated as being a suicide risk (as per clinical judgment using the Columbia-Suicide Severity Rating Scale), (16) currently receiving treatment with Monoamine Oxidase Inhibitors (MAOIs) antidepressants, antibiotics such as linezolid, or intravenous methylene blue, (17) previous hypersensitivity reaction to vortioxetine or any components of the formulation, (18) patients with angioedema, (19) clinical worsening symptoms of depression and suicide risk, (20) serotonin syndrome, (21) abnormal bleeding, (22) previous history of mania/hypomania, (23) angle closure glaucoma, (24) hyponatremia, (25) moderate hepatic impairment, (26) and history of seizures and epilepsy were also excluded from this study.

The eligibility criteria for the healthy controls were: (1) no current or history of mental disorder as evidenced by the M.I.N.I. 5.0 for DSM-IV, (2) no first-degree relative with an established diagnosis by a healthcare provider of a mood or psychiatric disorder, (3) no unstable medical disorders. Healthy volunteers were excluded if any of the following criteria was met: (1) use of any medication for a general medical disorder and/or condition that, in the opinion of the investigator, may affect cognitive function (e.g., corticosteroids, beta-blockers), (2) pregnant and/or breastfeeding, (3) consumption of alcohol within 8 h of THINC-it tool administration, (4) inconsistent use or abuse of marijuana.

2.2. Clinical and cognitive assessment

The primary outcome measure in the study was sensitivity to change with the THINC-it tool [16]. The THINC-it tool has been previously validated in adults with MDD. The THINC-it tool is digitalized and completed by the respondent on a tablet and includes variants of four objective, previously validated tests, Spotter (Choice Reaction Time), Symbol Check (1-back test), Trails (Trails Making Test B), and Codebreaker (Digit Symbol Substitution Test) as well as a self-reported cognitive measures (i.e., Perceived Deficit Questionnaire, 5-item). The secondary measures relevant to the report herein were the Montgomery Åsberg Depression Rating Scale (MADRS), Snaith-Hamilton Affective Pleasure Scale Questionnaire (SHAPS), and the Effort Expenditure for Rewards Task (EEfRT).

The EEfRT measures participants' willingness to make efforts to obtain a monetary reward under different conditions of reward probability and magnitude [13]. In each EEfRT trial, participants were given an opportunity to choose between two tasks with different levels of difficulty: a “hard task” and an “easy task.” Participants were aware that successful trial completion did not guarantee winning the monetary reward.

Before making a choice, participants were provided with information that varied from trial to trial regarding: (1) the probability (12%, 50%, and 88%) of winning the money if the task was successfully completed; and (2) the monetary reward magnitude of the hard tasks. The reward magnitude was set at $1.00 for easy tasks and higher amounts that varied per trial within a range of $1.24–$4.30 for hard tasks. Probability levels always applied to both the hard task and easy task, and there were equal proportions of each probability level across the experiment. Successful completion of the easy task trials required 30 button presses using the dominant index finger within 7 s, whereas the hard task trials required 100 button presses using the non-dominant little finger within 21 s. Participants were given 20 min to perform the task; thus, the number of trials varied across the participants.

2.3. Statistical analysis

Participants performed the EEfRT within 20 min, and the number of trials completed during that time varied amongst them (Table 1). Consistent with previous studies and the original validation of the EEfRT task, only the first 50 trials were used [13]. We used generalized estimating equation (GEE) models to test the effects of group and the interactions between group, reward magnitude and probability, as well as clinical and cognitive variables, on the willingness to expend effort for rewards. We used an independent matrix, which best fit our data, and a binary logistic distribution to model the dichotomous outcome of choosing the hard versus the easy task. All GEE models included reward magnitude, probability, and expected value (EV, defined as the interaction between reward probability and magnitude). In addition, each model included a trial number as a covariate to control for possible effects of fatigue over the course of the task. The groups systematically differed in the time of the day in which they were assessed (Table 1), as we observed an effect of this variable on the outcomes, we then considered it as a covariate included in all models. Reward magnitude was categorized in three groups: low (<$2.30), medium ($2.31–$3.29), and high (>$3.30). To assess correlations between EEfRT and clinical and cognitive data, we calculated the mean proportions of hard-task choices across each level of reward magnitude for all subjects. To minimize the number of GEE models tested, only clinical and cognitive variables that correlated with proportions of hard-task choices were included in the GEE analysis. Moreover, all models were fully factorial, as done previously by McCarthy et al. (2015). We adjusted for multiple comparisons using the Bonferroni method.

Table 1
Sample characteristics.

	HC $N = 20$	MDD N = 21	p-Value
Age, mean (SD)	41.50 (14.21)	38.47 (12.85)	0.433[a]
Gender (female), n (%)	10 (50.0)	12 (57.1)	0.647[b]
Years of education, mean (SD)	17.35 (2.23)	16.26 (2.68)	0.060[a]
Time of assessment	13:20 (1:59)	10:31 (2:09)	< 0.001[c]
BMI, mean (SD)	25.88 (4.01)	28.93 (6.16)	0.159[a]
Overweight/obese, n (%)	11 (55.0)	12 (57.1)	0.890
MADRS, mean (SD)	0.75 (1.58)	20.61 (10.50)	< 0.001[a]
SHAPS, mean (SD)	0 (0)	3.71 (4.40)	< 0.001[a]
Spotter	0.02 (0.99)	0.14 (1.22)	0.727[c]
Symbol check latency	0.07 (0.94)	0.05 (0.70)	0.934[c]
Symbol check accuracy	0.07 (1.03)	0.44 (0.71)	0.190[c]
Codebreaker	0.30 (0.84)	0.36 (0.79)	0.799[c]
Trails	0.35 (0.18)	0.24 (0.28)	0.156[c]
Thinc-it composite score	0.18 (0.55)	0.25 (0.63)	0.735[c]
Total number of EEfRT trials, mean (SD)	69.65 (13.97)	70.32 (12.07)	0.875[c]
Total amount of monetary rewards, mean (SD)	70.84 (12.51)	67.27 (18.90)	0.486[c]

HC: healthy controls; MDD: major depressive disorder; SD: standard deviation; BMI: body mass index; MADRS: Montgomery–Åsberg Depression Rating Scale; SHAPS: Snaith-Hamilton Affective Pleasure Scale; SDS: Sheehan disability scale; EEfRT: effort expenditure for rewards task.
[a] Mann-Whitney test.
[b] Chi-square test.
[c] t-Test.

Table 2
Correlations between clinical and cognitive data, and mean proportions of hard-task choices overall, and across each level of reward magnitude.

	% Hard task	
	r	p-Value
Healthy controls		
MADRS	−0.076	0.749
SHPS	−0.051	0.832
Spotter	0.212	0.369
SC latency	−0.165	0.488
SC accuracy	−0.096	0.686
Codebreaker	0.399	0.082
Trails	0.004	0.987
Composite	0.177	0.456
Major depressive disorder		
MADRS	0.129	0.576
SHAPS	−0.147	0.526
Spotter	0.477	0.029
SC latency	0.387	0.083
SC accuracy	0.478	0.029
Codebreaker	0.377	0.092
Trails	0.476	0.029
Composite	0.533	0.013

3. Results

3.1. Sample description

Twenty-one participants with MDD (Mean age = 38.47, SD = 12.85) and 20 healthy volunteers (Mean age = 41.50, SD = 14.21) completed the optional EEfRT task. Participants' characteristics, and between-group differences in socio-demographic, clinical and cognitive measures are described in Table 1. Zero-order correlations between clinical and cognitive data, and mean proportions of hard-task choices across each level of reward magnitude, are described in Table 2. In healthy controls, there was no association between proportions of hard-task choices and clinical/cognitive measures. In individuals with MDD, performance in the Spotter, Symbol Check Accuracy, Trails and the composite score were positively associated with proportions of hard-task choices, particularly in the high reward condition.

3.2. Effort-based decision-making

3.2.1. Group effects

Consistent with previous studies, we observed strong effects of reward probability, magnitude and expected value on the probability on

Table 3
Fully factorial GEE model of group effects.

	χ^2	p-Value
Reward probability	48.354	<0.001
Reward magnitude	49.216	<0.001
Expected value	9.959	0.041
Trial number	0.059	0.808
Time of the day	6.894	0.009
Group	3.131	0.077
Group x magnitude	0.045	0.978
Group x probability	1.137	0.566
Group x EV	8.596	0.072

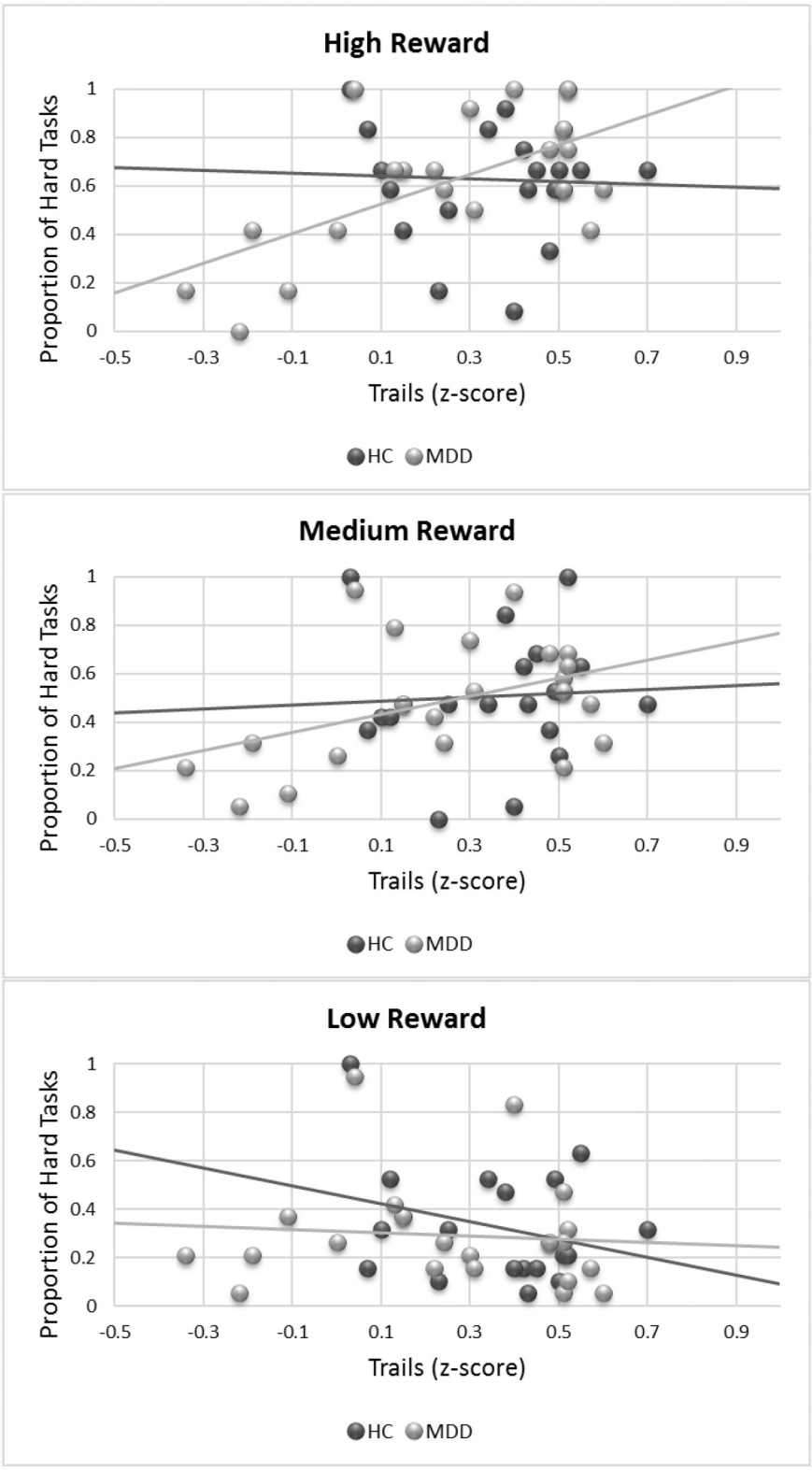

Fig. 1. Correlations between proportion of hard tasks within groups, according to reward magnitude, and Trails performance (z-score).

the tendency to choose the hard task (Table 3), indicating that greater probability and magnitude of reward was associated with more effort (choosing the hard task more frequently) across all groups. There was a trend for a main effect of group and a group x EV interaction, indicating that there was a numerical, but not statistical, difference in the proportion of hard task choices in the MDD group (M = 0.38, SE = 0.05), relative to the HC group (M = 0.57, SE = 0.07).

3.2.2. Interactions with cognitive measures

We then assessed separate, fully factored GEE models with the Spotter, Symbol Check Accuracy, Trails and the composite score. There was an interaction between Spotter and magnitude (χ^2 (2) = 6.811, p = 0.033), indicating a stronger correlation between performance in the Spotter and hard tasks choices in the higher reward scenarios; but there were no interactions with group, indicating that this effect was

similar between individuals with MDD and HCs. Similarly, there were interactions between Symbol Check Accuracy, magnitude (χ^2 (2) = 23.748, $p < 0.001$), and EV (χ^2 (4) = 9.581, $p = 0.048$), but no interactions involving group.

There were as well interactions between Trails, magnitude (χ^2 (2) = 12.067, $p = 0.002$), and EV (χ^2 (4) = 11.307, $p = 0.023$). In addition, we observed interactions between reward magnitude, Trails and group (χ^2 (2) = 8.066, $p = 0.018$), indicating a positive association between Trails performance and more effort for high rewards in individuals with MDD ($\beta = 2.223$, SE = 0.928, $p = 0.017$), but not in HCs ($\beta = -0.218$, SE = 1.26, $p = 0.863$). This difference was not seen in the low or medium reward conditions (all $p > 0.05$). Fig. 1 illustrates the correlations between Trails and mean proportions of hard-task choices across each level of reward magnitude. Conversely, there was an interaction between EV, Trails and group (χ^2 (4) = 9.545, $p = 0.049$).

The composite score had interactions with reward magnitude (χ^2 (2) = 15.737, $p < 0.001$), probability (χ^2 (2) = 19.992, $p < 0.001$) and EV (χ^2 (4) = 13.538, $p = 0.009$). There was as well a reward magnitude, composite score and group interaction (χ^2 (2) = 6.388, $p = 0.041$), indicating a positive association between the composite score and proportion of hard task choices in the high reward condition in individuals with MDD ($\beta = 0.978$, SE = 0.0.459, $p = 0.033$), but not in HCs ($\beta = 0.326$, SE = 0.415, $p = 0.432$).

3.2.3. Comparison with depressive symptoms

To directly compare the effects of cognitive measures and depressive symptoms on effort-based decision-making, we tested GEE models with a cognitive measure (i.e. Trails and composite score only, as these where the ones we observed significant group interactions) and MADRS total score in the MDD subgroup. Table 4 shows the results of the model with the composite score, indicating that this cognitive measure, but not the MADRS was positively associated with more effort for rewards in higher probability and magnitude conditions. Similarly, the model with the Trails indicated an interaction between Trails and magnitude (χ^2 (2) = 30.270, $p < 0.001$) and EV (χ^2 (4) = 9.505, $p = 0.049$), but no interactions involving the MADRS (all ps > 0.05).

4. Discussion

Herein, we preliminarily demonstrate that performance on cognitive measures highly correlates with a rigorous measure of reward/motivation. These data represent proof of principle data insofar as a well-characterized cohort of adults with MDD after receiving 8 weeks of treatment, demonstrate improvement in cognitive functions as well as depressive symptoms. Using a single end-point evaluation, we demonstrate that an antidepressant treated cohort (i.e. vortioxetine) manifest cross-sectional positive correlations between general cognitive measures and reward measures. In addition, we found that improvement on a self-reported measure of anhedonia (i.e. SHAPS) did not correlate with performance on the EEfRT task indicating that these two measures are evaluating different domains of psychopathology. We did not find any relationship between EEfRT task performance and cognitive performance in the HC sample. The interpretation of this finding in HC's is unclear but could be a consequence of the multiple factors independent of motivation that influence cognition.

Unequivocal statements regarding Vortioxetine's efficacy as a pro-motivation/reward intervention cannot be made in light of the study design we adopted (i.e. a single end-point evaluation of reward). Vortioxetine has demonstrated pro-cognitive effects on both subjective and objective measures of cognitive function of MDD. We have previously published evidence that Vortioxetine is capable of improving measures of anhedonia [17]. We add to the literature by preliminary reporting that improvements in cognition in a Vortioxetine-treated sample were associated with improvement (in a single end-point visit) in a rigorous measure of reward and motivation. Our preliminary results suggesting an association between measures of cognition and reward is in accordance with a prevailing framework that neural substrates subserving general cognitive functions are in interplay with substrates subserving reward and motivation [17]. It was noteworthy that the SHAPS, an integrated measure of anhedonia, does not correlate with performance on the EEfRT task suggesting that the two scales are evaluating dissociable domains.

The mechanistic substrates mediating Vortioxetine's pro-cognitive effects are unknown but are conjectured to involve both serotonergic and catecholaminergic targets [18]. Moreover, vortioxetine also modulates glutamatergic activity which may also be relevant to its pro-cognitive effect [19]. Preclinical studies indicate that Vortioxetine targets proteins [e.g. brain derived neurotrophic factor (BDNF)] as well as behaviours (e.g. sucrose consumption) predictive of pro-cognitive and pro-reward effects respectively [20].

There are methodological limitations that affect the inferences and interpretations of our study. First, the results are post-hoc and the primary aim of the study was not to evaluate effects of vortioxetine on motivation and reward. Second, included in this post-hoc analysis was a subsample ($n = 21$) of a larger sample set that agreed to do the EEfRT at a single time point (i.e. at end point), suggesting that the level of motivation in this subsample may not be representative of the full analysis set. Furthermore, there was a drop-out rate in persons receiving open label vortioxetine (21%). Consequently, the persons who agreed to participate in the secondary analysis represent persons (i.e. a subsample of the 79%) who remained motivated to complete the 8-week open label study, and also were motivated to participate in the procedures of the EEfRT task. Furthermore, the EEfRT was not a repeat measure so we are unable to ascertain change across time and instead were only able to look at correlational outcomes.

Notwithstanding, the strengths of the study are that all subjects were well-characterized and received identical treatment (i.e. vortioxetine). The enrolled patients were representative of adults with MDD utilizing health care services at an academic health science center. Moreover, this study was the first to our knowledge to evaluate an antidepressant's effect on the EEfRT which is a highly rigorous measure of reward motivation. Taken together, this data represents pilot data and provide the impetus for larger, more rigorous studies evaluating reward outcomes in adults with MDD with a rigorous measure of motivation and reward (e.g. EEfRT) receiving antidepressant treatment.

In summary, we preliminary report evidence herein that a general measure of cognitive function as well as select subdomain measures (e.g. information processing speeding, executive function) correlate with measures of reward and motivation using a rigorous reward paradigm (i.e. EEfRT). Persisting deficits in motivation and reward amongst remitted adults with MDD provide the impetus to refine measures of motivation in adults with MDD and to identify viable and effective treatment strategies for affected individuals.

Table 4
Fully factorial GEE model of MADRS and cognition composite score effects, in individuals with MDD only.

	χ^2	p-Value
Reward probability	23.877	<0.001
Reward magnitude	2.841	0.242
Expected value	14.741	0.005
Trial number	1.249	0.264
Time of the day	9.354	0.002
MADRS	2.133	0.144
Cognition composite score	3.716	0.0541
MADRS x magnitude	0.723	0.697
Composite x magnitude	21.421	<0.001
MADRS x probability	3.204	0.201
Composite x probability	11.723	0.003
MADRS x EV	2.043	0.728
Composite x EV	12.729	0.013

Declaration of Competing Interest

Mehala Subramaniapillai has received an honoraria for publication of a review article unrelated to the current article by Institut La Conference Hippocrate (AICH).

Dr. Roger McIntyre has received research grant support from Stanley Medical Research Institute, CIHR/GACD/Chinese National Natural Research Foundation; speaker/consultation fees from Lundbeck, Janssen, Shire, Purdue, Pfizer, Otsuka, Allergan, Takeda, Neurocrine, Sunovion, Minerva.

Dr. Rodrigo Mansur, Hannah Zuckerman, Caroline Park, Yena Lee, Michelle Iacobucci, Bing Cao, Roger Ho, Kangguang Lin, and Lee Phan have no conflicts of interest to disclose.

Acknowledgements

This study was supported by an investigator initiated grant to the Brain and Cognition Discovery Foundation by Lundbeck, Denmark.

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