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Assessing Neurocognitive Predictors of Treatment Response in Adolescents with Major Depression

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Abstract

Although various treatment approaches are available for MDD, 30 to 50% of patients fail to respond to those interventions[23]. Identifying pre-treatment biomarkers may give clinicians reliable estimates of whether patients will respond to a treatment. Such biomarkers can guide treatment selection, which may reduce costs relevant to unsuccessful treatments. Neurocognitive tasks are designed to tap into the functioning of critical neural networks that may highlight deficits associated with MDD, which may indicate biomarkers relevant to treatment response. in which deficits may be associated with MDD and which may indicate markers relevant to treatment responses. This study used Attention Network Task (ANT) and Iowa Gambling Task (IGT) to assess critical aspects of attention (alerting, orienting), executive control (conflict detection), and decision making in the context of rewards and punishments. Previous research has revealed that depressed adolescents show impairments in the ANT and IGT compared to their healthy counterparts. The deficits implicated in the task results were hypothesized to be the markers that can potentially predict treatment outcome in depressed adolescents (N = 15). Participants received 16 weeks of interpersonal psychotherapy (IPT-A) treatment. Pre-treatment ANT and IGT scores of treatment responders and non-responders were compared and correlated with the degree of remission achieved over the course of treatment. Overall for the ANT, conflict detection and alerting did not differentiate responders and non-responders. However, a significant positive correlation was found between orienting score and the degree of treatment response. For the IGT, on the other hand, analyses failed to report any significant group differences.

Keywords: adolescent depression, executive function, treatment biomarkers

1. Introduction

Adolescent depression is a significant growing public health problem requiring foremost attention. By the age of eighteen, 11% of the adolescent population experiences depression and it ranks as the number one cause of illness and disability for adolescents[42], which is associated with significant morbidity and mortality[31]. Adolescence is a critical period for prevention and treatment of depression. Early onset of the disorder is argued to result in great psychosocial impairments, which in turn, may link to other negative prognostic indicators including comorbid mental illnesses[6]. Because early onset is associated with important risks, intervening early is likely to be highly advantageous. When the key neurobiological disruptions associated with the disorder are targeted, the adolescent brain could potentially recover more easily due to its enhanced brain plasticity.

Fortunately, a variety of evidence-based treatments are available for adolescents suffering from depression and include psychotherapeutic and pharmacological interventions[8]. Yet many adolescents receiving these treatments (30-50%) fail to respond[23]. In part, the variability of treatment response is likely to be due to the heterogeneous nature of the disorder. This variety may require different and personalized intervention approaches for depressed individuals, in order to maximize the benefits received from therapy. Efforts to determine who might be more or less likely to

benefit from a particular treatment hold promise. Some researchers have examined characteristics of symptom presentation that might differentially predict treatment response[14-15]. Also in adults, there is preliminary evidence indicating that neurobiological anomalies evident in depression may one day be used to aid in treatment selection[25]. Therefore, investigating the link between those biomarkers of remission and specific interventions may be helpful for creating personalized treatment approaches for individuals or groups of individuals. Developing better insight about the underlying neurobiological and cognitive factors of adolescent depression could help with improving the effectiveness of interventions. Such biomarkers may provide clinicians with powerful tools to understand individual differences and specify what treatment should be provided to whom[25].

1.1. Neurobiological Disruptions in Depression

Experimental neuropsychology has used brain-imaging technology to identify brain regions and networks that associate with specific cognitive functions. This approach allows us to identify key associated cognitive processes that are disrupted in those suffering from depression that may potentially serve as predictors of treatment response.

1.1.1. anomalies in neural structure and activation and associated neurocognitive processes

Depression is associated with a disrupted interactional network between dorsal and ventral cortical regions and is characterized by decreased activity in the dorsal frontolimbic regions and increased activity in ventral compartments[24]. Lessened activity in the dorsal parts of the network including the dorsolateral prefrontal cortex, dorsal anterior cingulate cortex (dACC), inferior parietal cortex, and striatum was shown to be associated with cognitive symptoms of depression, resulting in impairments of executive function. Among other brain regions, the anterior cingulate cortex (ACC) is central for the cognitive processing "hub" and depression treatment[1]. ACC is thought to be the error detection and correction device of the brain[5-43]. Neuroimaging studies with depressed adults have shown that the dorsal part of ACC (dACC) is hypoactive[24-13] and performance in this brain region is associated with tasks involving selective and directed attention and executive function. In particular, a reduced performance was detected in tasks that require executive monitoring of conflict among different response options in depressed adults[18]. Among adolescents more specifically, Han et al.[16] investigated several different indexes of executive function in 30 depressed adolescents and 31 healthy controls. Depressed participants displayed marginally poorer performance than controls on the Attentional Network Task (ANT), which involves conflict monitoring, compared to a control group. This finding was recently replicated with a larger sample of adolescents in which group differences in the conflict monitoring performance was significantly poorer for depressed versus control adolescents[39].

Converging evidence from studies using various methodologies suggest that the emotional/stress-response system also functions abnormally in depression. Dysfunctions in the neural circuitry of the reward-related system involving the ventral tegmental area (VTA), ventral medial PFC (VMPFC), amygdala, and ventral striatum lead to impairments in processing motivation and rewards in depressed adults[9]. A neural network composed of similar brain regions involving amygdala, DLPFC, nucleus accumbens (NAc), ventral striatum, and VMPFC was implicated in the functioning of decision-making mechanisms in adults, which is an another important domain of executive functioning in individuals. According to the triadic model of motivated behavior in adolescence, although these regions contribute to a healthy decision-making mechanism with the balanced engagement of reward, harm, and regulatory systems in adults, they are not yet mature in adolescence. The reward-driven system mediated by the ventral striatum is overactive in adolescents, while the harm-avoidant system involving the amygdala and the VMPFC that regulates the balance between those two systems functions poorly[11]. Such an imbalance drives adolescents to be over-reactive to rewards and less sensitive to risky and potentially harmful situations. This overlap between the areas implicated in developmental changes of motivated behavior and neural dysfunction evident in depression may possibly be related to the prevalence of depression in adolescence, however research is needed on this area[11.]

Unsurprisingly, past research have revealed abnormalities associated with the processing of rewards and punishments in depression by using the Iowa Gambling Task (IGT). Overall, depressed adults demonstrated altered sensitivity to rewards and punishments and impaired decision-making. Some studies displayed impaired performance in depression[29-30]. Individuals with depression are more likely to prefer immediate rewards in spite of the potential cost of higher losses and make disadvantageous choices. Also, they typically fail to adapt to changing environments[7]. In contrast, other studies suggested a better performance in depression group compared to healthy controls[21-37]. Taking into account the triadic model, one would expect to see a different pattern of IGT functioning in adolescents[11]. Han et

al.[16] reported no significant difference between depressed and healthy groups of adolescents on their performances of IGT. However, a group by gender interaction has been found. While the boys in a control group outperformed depressed boys, girls in depression group made more advantageous choices compared to healthy girls[39]. To my knowledge, there are no other studies investigating the affective decision making mechanisms in adolescent depression, even though it is critical to examine distinct patterns of processing in reward-related behavior in order to have an in depth understanding of underlying neurocognitive deficits.

1.2. Biomarkers of Depression Treatment

Although treatment effects are likely to lead to changes in the brain and body, I expect that the aforementioned key neurobiological processes that are disrupted at baseline in depressed adolescents may be useful baseline indexes to predict treatment response. In the past decades, investigations for determining such biomarkers have accelerated. Some neuroimaging studies reported promising results on various regions that may be associated with eventual treatment response. An influential study[24] displayed that resting glucose metabolism in rostral ACC differentiates the responders and non-responders in antidepressant treatment of depression. The results were replicated with various intervention strategies by many researchers[10-34-36]. Pizzagalli[33] conducted a meta-analysis of studies investigating the relationship between baseline characteristics and treatment response that centrally implicated the ACC. Overall, of 23 studies, 19 found significant positive association between rostral ACC activation and treatment success, implying that those who have less impairment in rostral ACC functioning would benefit more from treatment. Eleven of these studies investigated the rostral ACC activation before the onset of an antidepressant treatment, whereas seven of them used sleep deprivation, one used ECT, and four of them used rTMS treatments. Another study by Konarski et al.[20] examined the connection between pregenual and subgenual ACC activity and recovery in CBT and venlafaxine treatments. Overactive metabolism in pregenual and subgenual cingulate cortices characterized non-response to both treatments.

A promising strategy might be to identify more feasible neurocognitive tasks that largely map onto these critical brain functions. Specific regions associated with the ACC are involved in attention and conflict monitoring and have shown to predict treatment response in depressed adults[38]. Indeed, deficits in attention and executive control involve functional cooperation of several brain regions including ACC and prefrontal cortex. Baseline reaction levels to conflict could be an alternative biomarker for remission in depression treatment. Identifying a neurocognitive marker would help establish stronger treatment plans with reduced costs compared to neuroimaging. One commonly used executive control measure that is associated with ACC functioning is the Stroop test. There is preliminary evidence that indicates reduced pretreatment conflict scores measured by the Stroop test can anticipate poor response to pharmacotherapy in participants with late onset depression[38].

There remain a number of important gaps in the literature. First, given that neurocognitive processes function differently in adolescents and adults[40], findings of treatment response documented with adult literature may differ for adolescents. It is particularly important that the pivotal work examining cognitive predictors of treatment response and non-response in adolescents is undertaken due to the enhanced neuroplasticity that is evident in the brain networks until early adulthood. Second, studies examining treatment response mostly consisted of pharmacotherapy studies (e.g., Pizzagalli[33]). Evidence-based psychotherapies have also been validated for adolescent depression and thus require further investigation[41]. Determining various neurocognitive and biomarkers for different interventions would provide evidence-based guidance for mental health professionals to determine the right first-line treatment for individual patients, which would help increase remission rates[26].

The aim of this current study was to identify whether impairments in various domains of executive function evident in depression could be used as reliable markers for treatment response in adolescents. In the study, Attention Network Test (ANT) and Iowa Gambling Task (IGT) were administered at baseline to evaluate if distinct cognitive alterations would predict improvement made in interpersonal psychotherapy (IPT). Based on the evidence that tasks involving the ACC are associated with treatment response[38], I predicted that a specific component of executive attention involved in conflict detection would be related to treatment responses. Specifically, I hypothesized that MDD adolescents who responded successfully to treatment would perform better in these conflict detection tasks at baseline as compared to treatment non-responders. However, due to the lack of evidence on the other two components of attention (alerting and orienting) and the mixed results reported on affective decision-making, I did not make specific predictions regarding the IGT and the alerting and orienting components of the ANT.

2. Method

2.1. Participants

Participants included 15 adolescents diagnosed with MDD with ages ranging from 12 to 17 years (M=14.8). The majority of the participants were female (67%). Thirteen participants identified themselves as Caucasian (87%), while there was one American Indian and one with more than one race (see Table 1). Treatment seeking participants with current or partially remitted depression were eligible to participate in this intervention trial. Inclusion criteria consisted of English fluency; DSM–IV diagnosis of major depressive disorder, dysthymic disorder, or depressive disorder NOS; Children's Depression Rating Scale-Revised raw score ranged from 36 to 75; Children Global Assessment Scale score < 65; and a primary caregiver who was capable of giving consent on behalf of the subject. Participants were excluded if they had any neurological and chronic medical condition, bipolar disorder, psychosis, substance abuse, OCD, conduct disorder, eating disorder, PDD, mental retardation, schizophrenia, or a severe episode of depression with CDRS-R raw score more than 75. Further, a medical illness that can possibly influence treatment, current risk for suicide, concurrent active treatment for another mental illness, previous non-response to an adequate trial of fluoxetine or IPT-A, and medication usage for a psychiatric condition other than ADHD were among exclusion criteria. Non-English speaking patients and families, and females who were pregnant, breastfeeding, or having unprotected sexual intercourse were also eliminated from the study.

Table 1. Demographic characteristics of the sample

Demographic Characteristics	**Remission** N=6	**Non-Remission** N=9
Age $\bar{x}$ (SD)	15.5 (1.76)	14.33 (1.66)
Gender N(%)		
Female	3 (20)	7 (46.67)
Male	3 (20)	2 (13.33)
Race N(%)		
White	5 (33.33)	8 (53.33)
American Indian	0	1 (6.67)
More than one race	1 (6.67)	0

2.2. Procedures

Participants were recruited from flyers posted at community postings, and inpatient and outpatient clinical services at the University of Minnesota and the surrounding. Diagnostic interviews were conducted when participants came in for the first visit. In their second visit, participants completed a set of cognitive tasks including the ANT, IGT, questionnaires, and intelligence test. This study is a part of a larger study approved by the Institutional Review Board of the University of Minnesota in which neuroimaging, neuroendocrine, and neuropsychological measures were featured. All participants signed informed consent and/or assent (if under 18) and for each visit they received a monetary compensation.

2.3. Measures

2.3.1.diagnosis and symptom assessment.

The presence or absence of a DSM-VI-TR Axis I disorder(s) was confirmed by a semi-structured diagnostic interview. Participants under 18 years of age and a legal guardian completed independent interviews using the Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime Version[19](KSADS-PL). The KSADS-PL interviews were conducted by highly trained individuals who were clinical psychologists, child psychiatrists or advanced trainees enrolled in graduate clinical psychology doctoral programs under the direct supervision of a clinician.

Besides KSADS-PL, clinicians completed the Children's Depression Rating Scale[35] (CDRS) on participants. The CDRS-R is a semi-structured interview that assesses 17 symptom areas related to depression, including those that

serve as criteria in the DSM-IV. After the first interview, CDRS-R was completed during weeks 4, 8, 12, and 16 of treatment. Even though CDRS-R was completed in every four weeks for a larger study, only the interviews conducted during diagnostic and week 16 visits were considered for current assessments. In addition, the study used The Beck Depression Inventory – II[4] (BDI) to measure the self-reported symptom expression.

At week 16, participants were considered remitted if they had a CDRS-R raw score less than or equal to 28. For correlational analyses, the amount of the improvement a participant made was calculated by subtracting post-treatment CDRS-R and BDI-II scores (at week 16) from the baseline scores.

Table 2. Baseline measures

Baseline Measures	**Remission** N=6	**Non-Remission** N=9
BDI $\bar{x}$ (SD)	28.33 (13.5)	29.33 (10.75)
CDRS $\bar{x}$ (SD)	49.33 (10.48)	52.44 (8.76)
CGI $\bar{x}$ (SD)	3.67 (.82)	4.44 (1.02)
C-GAS $\bar{x}$ (SD)	53.33 (5.85)	53.33 (7.89)

2.3.2. therapy

All participants who qualified for this study started Interpersonal Psychotherapy for Depressed Adolescents[27-28] (IPT-A), an evidence-based treatment for adolescent depression. IPT-A is a time-limited psychological intervention that aims to decrease depression symptoms by improving interpersonal functioning. Adolescents learn specific communication and interpersonal problem-solving skills that can address the interpersonal difficulties that are most closely related to their depression.

Participants were drawn from a 16-week sequential multiple assignment randomized trial examining the effectiveness of four adaptive treatment strategies for adolescent depression that begin with IPT-A. Within the 16-week trial, the initial treatment plan was 12 IPT-A sessions. Insufficient responders at week 4 or week 8 had their treatment augmented by adding four additional IPT-A sessions or prescribing the anti-depressant medication, fluoxetine. The time point and augmentation strategy were randomized.

2.3.3. neurocognitive assessments.

Although all participants underwent a battery of computerized neurocognitive tasks, only the Attention Network Task (ANT) and Iowa Gambling Task (IGT) were considered for current assessments.

The Attention Network Task (ANT) is a cognitive reaction time test, designed to measure the processing efficiency of three attentional networks: alerting, orienting, and executive control. The main purpose of the test is to detect delays in reaction time during three flanker conditions in the presence of four different cues. Participants were instructed to press either the left or right button to indicate the direction of center arrowhead. The flankers in the task might either be congruent, incongruent, or neutral. In the congruent flanker stimulus, the central arrow appears with two arrowheads on each side flanked in the same direction, while they point in the opposite direction in the incongruent stimulus. In the neutral stimulus, the arrowhead appears with two dash lines on both sides. These flankers are present either above or below the fixation point. They are preceded by four cue conditions: no cue, center cue (the cue appears on the fixation point), double cue (two cues appear on above and below the fixation point), and spatial cue (the cue indicates the location of upcoming stimulus). A block of stimuli is shown starting with a fixation period, followed by one of the four cue conditions, one more fixation period, and finally ends with flankers. Compared to the congruent condition, incongruent flankers create conflict, typically leading to longer reaction times (conflict score is based on the participant's relative reaction time for consistent and inconsistent flanker trials). The orienting score, on the other hand, is based on one's reaction to the spatial cues. It measures the ability to choose information from perceptual input. Finally, the alerting score is measured by the no cue/double cue conditions, in which the participant is required to maintain an alerted state[13]. Three summary scores from this task (conflict, alerting, orienting) were considered in the analysis.

The Iowa Gambling Task (IGT), is a neuropsychological task assessing affective decision-making mechanisms in the context of rewards and punishments. During the task, a participant is instructed to earn as much money as possible

by freely choosing among the four decks of cards at a time. Each card comes with a regular reward, while some cards bring punishments. Unknown to participant; the first two decks (A and B) are disadvantageous, choosing more from those two results in high immediate reward but higher punishments and an overall loss. In contrast, the last two decks (C and D) are advantageous and associated with lower immediate gain but a net gain with smaller punishments. The decks A and C produce small punishments frequently, while the decks B and D confer large but infrequent punishments. There are 5 blocks, each consisting of 20 cards with a total of 100 trials. It takes approximately 5 minutes to administer the task. The performance on IGT has been shown to be associated with activity in VMPFC[3].

3. Results

In the present study, a series of one-way ANOVAs were conducted to evaluate the validity of several different neurocognitive markers for predicting remission and non-remission in IPT-A treatment of adolescent depression. For the ANT, the analysis failed to document a significant relationship between pre-treatment conflict score and treatment response [$F(1,13) = 2.75$, $p = .12$]. These results do not support the hypothesis that reaction times of depressed adolescents to a conflicting stimulus might be used to determine whether the patient will remit by week 16 of those participating in IPT-A treatment. The results also failed to show an association between the other indexes of attention at baseline and treatment response status at week 16. That is, the results failed to show a group difference for alerting [$F(1,13) = .27$, $p = .61$] and only a marginally significant difference for orienting score [$F(1,13) = 4.14$, $p = .06$] of ANT. Correlational analyses were also conducted to assess dimensional relationships between neurocognitive performance and degree of treatment response in this small sample. The findings indicated a significant positive association between pre-treatment ANT orienting score and symptom improvement when undergoing treatment for both with CDRS-R [$r = .731$, $p = .001$] and BDI [$r = .518$, $p = 0.024$].

For the IGT analyses, two participants from the initial sample were excluded due to several errors in data processing. Overall, no significant group differences were found for choosing from the good decks [$F(1,11) = .049$, $p = .773$] or in total winnings [$F(1,11) = .66$, $p = .347$].

4. Discussion

This study attempted to expand our knowledge of how neuropsychological indexes that map on to brain functioning might be important in predicting response to a standard treatment. Contrary to my predictions, executive control functions generally failed to predict treatment response status. However, exploratory analysis showed some evidence that some components of regulatory control were associated with IPT treatment response. Specifically, the adolescent's ability to efficiently orient attention and to respond to reward contingencies was related to improvement.

While conflict detection on the ANT did not predict treatment response as hypothesized, other components of impaired attention, as demonstrated by poor performance on orienting on the ANT, were associated with degree of improvement in depressive symptoms, and should continued to be evaluated as possible biomarkers of treatment response with interpersonal psychotherapy. Orienting is the ability of selecting input among diverse sensory stimuli. Good performance on ANT requires that the participant is able to disengage attention from its current target, move it to another location, and engage attention at the new focus. Orienting is also involved when there is an unexpected stimulus out of current focus; it helps the person to reorient the gaze. It can be reflexive as well as voluntary. In the brain, orienting is known to activate parietal and frontal regions[12]. Previous literature has documented difficulties in disengaging attention from threat-related stimuli in individuals with anxiety disorders[32].

There has been some research suggesting orienting may be useful for personalization of interventions. For instance, people who have difficulties with disengaging attention from threat-related facial stimuli were shown to have a better treatment response to CBT for anxiety disorders[2]. Similar results have been documented with early-onset anxiety disorders as well. Difficulties with disengaging attention from severe threat predicted poor treatment prognosis for CBT in participants aged 8 to 16 years. Also, treatment responders had a tendency to not engage attention significantly with pictures displaying severe threat[22]. In studies with social phobia, training participants on disengaging attention from threat-related stimuli was shown to diminish behavioral symptoms of anxiety[17].

In the case of depression treatment, orienting ability may be an indicator of behavioral capabilities of depressed individuals in real life. When a patient encounters a traumatic situation, he or she may have difficulties disengaging

focus from a problematic situation and moving on to a new target. More specifically in interpersonal psychotherapy, the central theme of the intervention is to identify the problem by pointing one's attention to the difficulties in interpersonal relationships and addressing those using communication and problem solving skills that they learn[27]. Thus, the patient becomes more aware of his/her problems and malfunctioning relationships. If there is a deficit in orienting ability, it may interfere with disengaging focus from a specific problem and shifting to attempting to solve it. In this way, IPT may not help them solve the problems, but rather it fixates the attention on them. Therefore, individuals with reduced orienting ability may find it more difficult to move on with their lives and those with more improved pre-treatment orienting ability benefit more from IPT.

In the case of the IGT, although results did not reveal significant group differences, it could still be a potential candidate for further investigation of displaying different important patterns of response between remission and no remission groups. The number of advantageous choices each group made from one experimental block to another could suggest an important pattern of reward-related processing in people who did and did not achieve remission. The performance on each block was calculated by subtracting the number of bad choices from good choices. Although there is no significant difference between the overall performances of the two groups, the difference in the shapes of task performance from block to block could give important clues about how they process reward and risk over time and how it is related to the benefit they receive from the treatment. The remission group did make more advantageous choices compared to non-remission group in the first block of the task. Moreover, the change between the first and second blocks is steeper for remission group compared to the non-remitters. The significant difference between groups in the second block, but not in the first block could be indicative of better learning abilities and more adaptive strategies of remitters to a new environment. Therefore, such adaptive patterns might point out the success of an individual in IPT-A at the baseline.

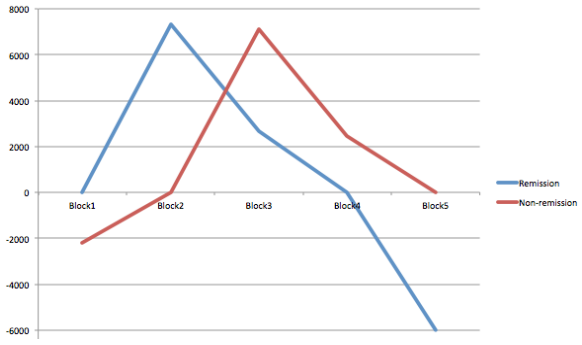

Figure 1. IGT scores by experimental blocks

The confidence in these findings is reinforced because converging results were noted across diverse indexes of treatment response. The findings for the ANT were supported by two different depression rating scales: the BDI and the CDRS-R. The BDI is a self-report index, while the CDRS-R is a clinical rating scale based on an unstructured clinical interview with the youth and their parents. By contrast, the adolescents' performance on the orienting tasks of the ANT failed to significantly predict dichotomous indexes of treatment response based on the CDRS-R. Future research will need to address this question with larger samples.

The present study has a number of strengths including baseline neurocognitive assessments and adolescent participants in a validated treatment. However, some limitations may have also affected the findings. One of the major concerns is the sample size. Replication of study with a larger sample is needed, since the findings of this pilot study are underpowered to detect group differences. Similarly, it is premature to determine whether conflict detection performance on the ANT is associated with treatment response. Despite the fact that conflict has been suggested to be associated with treatment outcome with patients with late-onset depression[38], neural networks function differently in adolescents and conflict monitoring ability may not be as mature as late-onset patients. More research is needed in this area.

Small sample size could also be a potential reason for the failure to find a significant difference between treatment response groups for conflict detection. Replication of the results with a larger sample could provide more statistical

power and reliability. Also, there is some variability in the nature of the treatment that was not addressed here. For example, although all participants received IPT-A for the first 4 to 8 weeks of this study, some of the ones who had not improved enough were given additional treatments (e.g., fluoxetine or twice weekly IPT-A sessions). Even though no association was observed between treatment response and the additional treatments, including distinct experimental groups receiving only specific interventions may help produce more reliable results. Another potential limitation would be the selection of the neurocognitive tasks. Considering the length of each test, participants might have become tired or bored while completing the ANT or the IGT, which would impair their task performance. While representative of attention under high resource load conditions, taking the test under more relaxed conditions may have yielded other results.

5. Conclusion

The findings of the current study contribute to the growing body of research on the biomarkers of depression treatment. However, replication of the study with a larger sample that has distinct therapy groups is needed. Neurocognitive abilities and impairments including executive control and disengagement in depressed adolescents might be an index of response to many other treatment modalities. The facilitative or impeding effects of those skills should be investigated with various other evidence-based practices. Along with predicting response to a specific treatment, future studies should address additional methods to treat cognitive disabilities evident in adolescent depression, which would be an alternative way of increasing treatment efficacy and preventing relapses.

The results of this study suggest that baseline neurocognitive abilities of depressed youth might be a likely indicator of treatment prognosis. Attentional bias, and more specifically impairments with disengagement, could have major implications in terms of personalization of treatment approaches. Better investigation of affective decision-making mechanisms is also promising. If future studies demonstrate meaningful links between pre-treatment cognitive impairments and treatment response, evidence-based clinical guidance may one day be used to develop personalized interventions. Such studies might be the critical next step for choosing the most effective first-line treatment by taking the individual differences into account[25] and developing personalized intervention plans with added trainings or treatment options targeting specific cognitive and behavioral impairments[17].

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