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Neurocognitive impairment in adolescent major depressive disorder: State vs. trait illness markers

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Abstract

Background—Current treatment outcomes of Major Depressive Disorder (MDD) in adolescents remain suboptimal. Discriminating between state and trait markers of MDD in adolescents would help identify markers that may guide choice of appropriate interventions and help improve longer-term outcome for individuals with the illness.

Methods—We compared neurocognitive performance in executive function, sustained attention and short-term memory in 20 adolescents with MDD in acute episode (MDDa), 20 previously depressed adolescents in remission (MDDr) and 17 healthy control participants (HC).

Results—There was a group difference that emerged for executive function with increasing task difficulty ($p = 0.033$). MDDa showed impaired executive function, as measured by using more

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Conflict of interest

Dr. Maalouf is on the speaker bureau of Eli Lilly. Dr. Brent receives research support from the National Institute of Mental Health, receives royalties from Guilford Press and is UpToDate Psychiatry Editor. Dr. Clark consults for Cambridge Cognition plc. Dr. Sahakian consults for Cambridge Cognition. She has consulted for Novartis, Shire, GlaxoSmithKline, Lilly Boehringer-Ingelheim and F Hoffman-La Roche Ltd. She has also received honoraria for Grand Rounds in Psychiatry at Massachusetts General Hospital (CME credits) (Boston, 27 April 2007) and for speaking at the International Conference on Cognitive Dysfunction in Schizophrenia and Mood Disorders: clinical aspects, mechanisms and therapy (Brescia, 17–19 January 2007). She was on the Medical Research Council Neurosciences and Mental Health Board (2010) and on the Science Co-ordination Team for the Foresight Project on Mental Capital and Wellbeing, 2008 (Office of Science, The Department of Innovation, Universities and Skills,). She is currently on Panel LS5 for the European Research Council. As an Associate Editor, she also receives an honorarium from Psychological Medicine. Dr. Phillips, Ms. Tavitian and Mrs. McHugh report no biomedical financial interests or potential conflicts of interest.

moves to solve 4-move problems on a forward planning task, relative to MDDr and HC ($p = 0.01$, $d = 0.94$ and $p = 0.015$, $d = 0.77$ respectively). MDDa showed more impulsivity as measured by lower response bias (B'') on a sustained attention task than both MDDr and HC ($p = 0.01$, $d = 0.85$ and $p = 0.008$, $d = 0.49$ respectively). Higher impulsivity was associated with more severe depression ($r = -0.365$, $p = 0.022$) and earlier age of onset of depression ($r = 0.402$, $p = 0.012$) and there was a trend for a correlation between more executive dysfunction and more severe depression ($r = 0.301$, $p = 0.059$) in MDDa and MDDr combined. The three groups did not differ significantly on short-term memory or target detection on the sustained attention task.

Limitation—These results need to be replicated in the future with a larger sample size.

Conclusion—Executive dysfunction and impulsivity appear to be state-specific markers of MDD in adolescents that are related to depression severity and not present in remission.

Keywords

Depression; Adolescent; Neurocognition; Executive function; Impulsivity

1. Introduction

Major depressive disorder (MDD) is a common condition in children and adolescents associated with significant medical and psychosocial morbidity and mortality (Kovacs, 1996; Lewinsohn et al., 1998). MDD is highly recurrent in children and adolescents, with 40% of patients experiencing a second episode within 2 years and nearly 75% within 5 years; almost all have a recurrence in adult life (Kovacs, 1996). Current treatments of pediatric depression lead to a sustained response rate of up to 80% and a remission rate of 60% by 6 months (Kennard et al., 2009; Vitiello et al., 2010) while response and remission rates remain moderate and low, respectively, in acute trials (Brent et al., 2008; Maalouf and Brent, 2010).

Numerous adult studies have indicated neurocognitive impairments during the acute stage of MDD (Elliott et al., 1996; Maalouf et al., 2010). State markers, present only during the acute stage of MDD, may reflect pathophysiologic processes of the illness (Merriam et al., 1999; Siegle et al., 2007) that may in turn act as markers to help predict treatment response and guide treatment choice (Gorlyn et al., 2008; Mayberg, 2002). By contrast, persistent trait-like markers may represent vulnerability for, and/or longer-term secondary effects of MDD, and may therefore be less likely to help predict treatment response in the illness. Discriminating between state and trait markers of MDD is therefore an important first step toward identifying markers that may help guide choice of appropriate interventions, and help improve longer-term outcome for individuals with the illness.

Studies examining neurocognitive function in adult MDD have indicated that specific deficits in different neurocognitive domains may represent state or trait markers of MDD. These studies indicated impairment in executive function, sustained attention and short-term memory. These neurocognitive processes are an essential component of emotion regulation, which in turn is a core clinical feature of MDD (Mayberg, 2007; Phillips et al., 2008).

Executive function refers to higher-level cognitive functions that are involved in the control and direction of memory and attention in order to flexibly organize behavior and engage in forward planning (Clark et al., 2009; Stuss and Levine, 2002). Mounting evidence indicates that executive function is significantly impaired in adults with MDD in acute episode (Rogers et al., 2004). These impairments are also present in unmedicated adults with MDD (Taylor Tavares et al., 2007). While executive function may improve in remission relative to functioning during the acute episode, remitted adults still show some residual deficits relative to healthy controls (Clark et al., 2005b; Hammar et al., 2010). This feature could reflect pre-existing vulnerability or sequelae of the depressive episode itself. In support of the latter view, residual deficits in remitted adults correlate with both the number and severity of past episodes, even after controlling for residual symptoms (Bhardwaj et al., 2010).

Difficulties in the domain of attention is one of the earliest signs of MDD and the ability to sustain attention supports various cognitive functions such as short term memory and planning (Preiss et al., 2010). There have been reports of impaired sustained attention in depressed adults with MDD in some (Koetsier and et al., 2002; van der Meere et al., 2007) but not all studies (Maalouf et al., 2010). In addition, studies exploring attention deficits in remitted adults with MDD have yielded contradicting results. While impairments in sustained attention were found in remitted MDD patients as compared to healthy controls in some studies (Paelecke-Habermann et al., 2005; Paradiso et al., 1997), they were not confirmed by other studies (Clark et al., 2005a; Liu et al., 2002; Robertson et al., 2003). As such, whether sustained attention deficit is a state or trait marker for MDD is still unclear.

As a third relevant domain, studies also indicate impaired short-term memory in adult patients with MDD. Consolidation of short-term memory into long-term storage has been reported to be impaired in adults with MDD (Wolfe et al., 1987), although this has not been confirmed by all studies. The memory impairment may subside during remission (Clark et al., 2005b), increase with illness chronicity, and correlate with the total length of time spent in a depressed state (Gorwood et al., 2008).

The few studies examining neurocognitive function in adolescent MDD have provided evidence mainly for executive function deficits in acute state (Wilkinson and Goodyer, 2006) although this finding has not been confirmed in all studies (Favre et al., 2009; Korhonen et al., 2002; Kyte et al., 2005). Furthermore, executive function deficits have not been detected in high-risk children of mothers with MDD (Klimes-Dougan et al., 2006) suggesting that such findings are related to depressive state rather than trait markers of the illness.

Impairment in sustained attention have also been reported in adolescents with MDD during the depressed state (Cataldo et al., 2005; Wilkinson and Goodyer, 2006), but findings on memory impairment in depressed children and adolescents have been contradictory. While one study found no impairment in memory in adolescents with MDD in acute state (Korhonen et al., 2002), a recent study showed impairments on delayed verbal memory and delayed visual memory in a group of adolescents with MDD in acute state and/or remission as depression status was not clarified in this study (Brooks et al., 2010). Memory deficits

were not detected in high-risk children of mothers with MDD (Klimes-Dougan et al., 2006), suggesting that these deficits may be state markers of adolescent MDD.

Together the above findings indicate that while there is strong evidence of neurocognitive deficits in MDD in adults and emerging evidence of such impairments in MDD in adolescents, it is not clear whether these deficits are trait or state markers of MDD, particularly in adolescent MDD. Previous studies in adolescents were not designed to disaggregate state vs. trait markers of MDD, and did not therefore compare participants in acute and remitted phases of MDD. The present study compared performance in three neurocognitive domains (executive function, sustained attention and short-term memory) in acutely depressed adolescents (MDDa), adolescents with remitted depression (MDDr), and healthy controls (HC).

We hypothesized that MDDa would show impairments in executive function and sustained attention relative to HC. Existing data did not allow us to specify whether MDDr would show a similar level of impairment on executive function and sustained attention as MDDa. We also wished to examine the extent to which short-term memory impairment was evident in MDDa and MDDr relative to HC, given the conflicting findings in the extant literature regarding impairment in this neurocognitive domain in adolescent MDD.

2. Methods

2.1. Participants and measures

The study protocol was approved by the University of Pittsburgh Institutional Review Board. In total 57 adolescents were recruited. Forty participants meeting criteria for MDD, current or past, according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) and the Kiddie Schedule for Affective Disorders Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997) were classified into two groups, acutely depressed (MDDa) and remitted (MDDr), based on their scores on the Children's Depression rating Scale-revised (CDRS-R) (Poznanski et al., 1984) which was used as a measure of depressive symptoms severity. MDDa included 20 participants with CDRS scores ≥ 40 , and MDDr included 20 participants with CDRS scores ≤ 28 , a commonly used criterion for remission in pediatric depression trials (Emslie et al., 2002). In addition, 17 healthy control participants (HC) with no previous psychiatric history or psychiatric history in biological parents were recruited. The groups were balanced on age, gender, pubertal development level and estimated IQ (Table 1). The two depression groups did not differ significantly on total number of depressive episodes (mean: 1.2 and 1.4 and sd: 0.5 and 0.6 for MDDa and MDDr respectively), presence of comorbid anxiety disorders and number of participants receiving antidepressant treatment (Table 1). A full prorated IQ score was obtained through two subscales, verbal (vocabulary) and performance (matrix reasoning), of the Wechsler Intelligence Scale for Children-IV (WISC-IV). Participants also completed two self-report questionnaires: The Screen for Child Anxiety Related Disorders (SCARED) child and parent versions (Birmaher et al., 1997) and the Peterson Puberty Development Scale (PDS) (Petersen et al., 1988). Exclusion criteria included a history of head injury, epilepsy, developmental disorder, loss of consciousness for more than 10 min, IQ estimate of <80 , current psychotic symptoms, current history of alcohol and illicit substance abuse or

dependence and current or past history of Attention Deficit Hyperactivity Disorder. The sample reflected the demographic characteristics of Pittsburgh population and were recruited through the Western Psychiatric Institute and Clinic, Services for Teens at Risk (STAR) clinic, and local advertising. All participants and their parents were made aware of the purpose of the study and signed an informed assent/consent to participate. Clinical characteristics of each of the study groups are shown in Table 1.

2.2. Computerized tasks

We employed three computerized neurocognitive tasks from the Cambridge Neuropsychological Tests Automated Battery (CANTAB): (a) Stockings of Cambridge (SOC) task, as a measure of executive function; (b) Rapid Visual Processing (RVP) task, as a measure of sustained attention; and (c) the Delayed matching to Sample task (DMS), a measure of visual short-term memory. These tasks are appropriate for use in children and adolescents and their sensitivity to psychiatric disorders has been demonstrated previously (De Luca et al., 2003; Sahakian and Owen, 1992).

2.3. Stockings of Cambridge (SOC)

Participants are shown two displays containing colored balls. The displays are described as stacks of colored balls held in socks suspended from a beam. Participants must use the balls in the lower display to copy the pattern shown in the upper one. The balls may be moved one at a time by touching the required ball then touching the position to which it should be moved. The primary outcome measures are mean number of moves for 2, 3, 4 and 5-move problems.

2.4. Rapid visual processing task (RVP)

A white box is displayed in the center of the computer screen, inside which digits, from 2 to 9, are displayed randomly at the rate of 100 digits per minute. Participants press the touch pad when they detect any of the following three sequences of digits (2–4–6, 3–5–7 and 4–6–8). The primary outcome measures are mean latency, total hits (target detection) and total false alarm (commission errors) and the duration of the task is 7 min. Because target detection may be confounded by a tendency to respond impulsively on the task, signal detection analysis is applied to derive independent estimates of target sensitivity (accuracy) and response bias (impulsivity) (Grier, 1971). Thus correct detections and commission errors are converted to target sensitivity (A') and response bias (B'') ranging from -1 to $+1$. A low RVP A' indicates that individuals have difficulty discriminating target from non-target stimuli suggesting an impairment in sustained attention whereas a low RVP B'' indicates that individuals respond in a disinhibited manner to target and to non-target stimuli suggesting a more impulsive response style.

2.5. Delayed matching to sample (DMS)

This is a test of immediate and delayed visual memory, in a four-choice simultaneous and delayed recognition memory paradigm. Participants are shown a complex visual pattern (the sample) and then four different patterns only one of which is identical to the sample. In some trials the sample and the choice patterns are shown simultaneously, whereas in others,

there is a delay of 0, 4 or 12 seconds. Participants are instructed to touch the pattern that matched the sample. The primary outcome measure is percentage of total correct responses.

2.5.1. Statistical analyses—Analyses were conducted using the Statistical Package for Social Sciences, Version 18. For SOC a repeated measure ANOVA was conducted where levels of difficulty (number of moves for 2, 3, 4 and 5-move problems) were entered as within subject variables, and group was entered as a between subjects variable. Group effect was further explored by comparing the three groups on number of moves for 2, 3, 4, and 5-move problems respectively using non-parametric tests (Kruskal–Wallis) and then pair-wise post hoc analysis using the Mann–Whitney *U* test. For RVP, we compared the three groups on total hits, total false alarms, latency, RVP *A'* and RVB' using Kruskal–Wallis test and then pair-wise post hoc analysis using the Mann–Whitney *U* test. To determine the extent to which abnormal performance on neurocognitive tasks in both MDDa and MDDr was associated with clinical variables, exploratory analyses were performed with Spearman correlation between abnormal measures on each task in MDDa and MDDr combined and relevant clinical data (CDRS, SCARED-C, SCARED-P, age of illness onset, total duration of depressive episodes, total number of depressive episodes). The potential confounding effect of medications, suicidality and comorbidities was examined using non-parametric Mann–Whitney *U* test to compare relevant dependent measures in MDDa and MDDr taking, versus those not taking Selective Serotonin Reuptake Inhibitors (SSRIs), those with vs. without history of suicidality (separate comparisons for suicide attempts and ideation) and those with vs. those without comorbid anxiety disorders. For the three-group comparisons and exploratory correlation analyses in combined MDDa and MDDr, statistical significance was set at $p < 0.05$, and for post-hoc pair-wise comparisons, statistical significance was set at $p < 0.017$ to correct for multiple comparisons (three pair-wise comparisons). Non-parametric tests were used due to deviation of data from normality. RVP data was missing on one participant in the MDDa group, this participant was excluded from the RVP analysis only.

3. Results

3.1. SOC: a measure of executive function

3.1.1. Main findings—There was a group by difficulty effect on this measure; ANOVA ($F(3.5, 94.7) = 2.88$ and $p = 0.033$) (Fig. 1). We explored this effect further by comparing the groups at each level of difficulty. The three groups differed on the four-move problems ($p = 0.013$), with MDDa requiring more moves to solve these problems than both HC ($p = 0.015$) and MDDr ($p = 0.01$). There was a trend difference on the five-move problems among the three groups ($p = 0.057$), and no difference on the two and three-move problems ($p > 0.05$) (Table 2).

3.1.2. Exploratory analysis—There was a trend for a positive correlation between CDRS and number of moves for 4-move problems in the two combined MDD groups ($r = 0.301$ $p = 0.059$). There were no significant correlations between performance at the 4-move stage and SCARED (P), SCARED (C), age of illness onset, total duration of depressive episodes and number of depressive episodes ($p > 0.05$). In the combined MDD group, individuals with and without a history of suicide attempt and those with and without a

history of suicidal ideation did not differ in their performance at the 4-move stage ($p > 0.05$). There was also no difference in performance at this stage between subjects receiving SSRI and those not receiving SSRI and those with lifetime comorbid anxiety disorders and those without ($p > 0.05$).

3.2. RVP: a measure of sustained attention

3.2.1. Main findings—There was a significant effect of group upon RVP total false alarm ($p = 0.006$) which was substantiated by the signal detection analysis of B'' ($p = 0.009$). Post-hoc pair-wise comparisons showed that MDDa had more false alarms and more impulsive response style (lower RVP B'') than both MDDr ($p = 0.009$ for false alarms and $p = 0.01$ for RVP B'') and HC ($p = 0.004$ for false alarms and $p = 0.008$ for RVP B''). MDDr did not differ from HC on these measures. There were no group differences on latency, total hits and target sensitivity (RVP A') ($p > 0.05$; Table 2).

3.2.2. Exploratory analysis—There was a statistically significant positive correlation between CDRS and RVP false alarm ($r = 0.366$, $p = 0.022$) substantiated by a negative correlation between CDRS and RVP B'' ($r = -0.365$, $p = 0.022$) (i.e. higher impulsivity associated with greater depression severity) in the 2 combined MDD groups. There was also a negative correlation between age of illness onset and RVP false alarms ($r = -0.346$, $p = 0.033$) substantiated by a positive correlation between age of illness onset and RVP B'' ($r = 0.402$, $p = 0.012$) indicating higher impulsivity was associated with earlier disease onset. There were no significant correlations between SCARED (P), SCARED (C), age of illness onset, total duration of depressive episodes, number of depressive episodes and RVP B'' or false alarms in MDDa and MDDr ($p > 0.05$). There were no differences in the combined MDD groups on RVP B'' and RVP false alarms between individuals with and without a history of suicide attempt, and those with and without a history of suicidal ideation ($p > 0.05$). There were also no differences on RVP B'' and RVP false alarms between individuals on SSRI and those off SSRI. There was, however, a significant difference between individuals with and those without lifetime comorbid anxiety disorders suggesting that those with lifetime anxiety disorders were more impulsive ($p = 0.036$).

3.3. DMS: a measure of short-term memory

The three groups did not differ significantly on % correct answers ($p > 0.05$); hence no post-hoc pair-wise comparisons were conducted (Table 2).

4. Discussion

The aim of this study was to examine the extent to which impairments in neurocognitive domains represent state versus trait markers of pediatric depression. We assessed the performance of adolescent participants in a current MDD episode (MDDa), participants with MDD, tested in remission (MDDr) and healthy controls (HC) on well-validated neurocognitive tasks of executive functioning, sustained attention, and short-term memory taken from the CANTAB assessment.

Our findings revealed that executive dysfunction and impulsivity appeared to be state markers of depression in adolescents: they were present in the acutely depressed group but

not in the remitted group. Our data also indicated that target sensitivity on a sustained attention task and short-term memory were not impaired in adolescent depression.

Our findings regarding executive function indicated a group by difficulty interaction whereby MDDa performed worse than HC with increased SOC task difficulty. Three-group comparisons showed that MDDa were impaired relative to MDDr and HC groups at the moderately difficult 4-move stage of the task, with an effect approaching statistical significance on the most difficult 5-move-problems. MDDr performance did not differ from HC on this task. These findings therefore suggest that executive dysfunction may be a state-marker of adolescent MDD, i.e., an impairment that is present in MDDa but not in MDDr. This finding is consistent with previous work in adolescents (Wilkinson and Goodyer, 2006) although other studies have found no such deficits in depressed adolescents (Favre et al., 2009; Kyte et al., 2005). Kyte et al. (2005) studied a group of adolescents who were tested up to one year after their first depressive episode. The group included participants who were in remission as well as in the acute phase of MDD, which may explain the negative findings in their study. Our data also indicated that there was a statistical trend for a positive correlation between executive function deficits and depression severity, a finding that is consistent with adult studies and that has not been thus far shown in adolescents. The association of impaired executive function with depressed mood state may reflect an impaired ability to perform cognitive control processes necessary for emotion regulation (Phillips et al., 2008). The deleterious impact of depressed mood because of the load associated with depression-related, negative self-focused cognitions may further impact executive dysfunction.

Our study also highlights a disparity in executive function performance between remitted MDD adolescents and previous studies of remitted MDD adults (Hammar et al., 2010). One possibility is that the trait-related nature of the effect in adults reflects a debilitating pathophysiological process during the depressive episodes. The adolescents in the present study have also experienced more than one episode on average, and there was no association between number of episodes and executive ability. Thus, the adolescent brain may be better able to recover from executive function deficits associated with depression, highlighting the importance of early intervention to prevent recurrence of depression which may lead to “scarring” and persistence of associated cognitive deficits.

Our findings regarding sustained attention revealed no group differences in terms of target sensitivity (RVP A') and total number of hits. Instead, MDDa tended to respond more impulsively on the RVP task than both MDDr and HC, as measured by a lower RVP B'' in MDDa relative to MDDr and HC. Our negative finding regarding target sensitivity during sustained attention is compatible with our previous findings in adults, although there are other studies indicating impairment in this domain in depressed children and adolescents (Cataldo et al., 2005; Wilkinson and Goodyer, 2006). The difference between our findings and the other pediatric study findings is probably due to patient selection criteria and choice of attention task. For instance, while ADHD was an exclusion criterion in the present study, it was not an exclusion criterion in the study by Wilkinson and Goodyer (2006) (Wilkinson and Goodyer, 2006). Furthermore, while we recruited adolescents in acute episode MDD, Cataldo et al.'s (2005) (Cataldo et al., 2005) sample included youth with acute episode

MDD and/or dysthymia. Our findings regarding impulsivity indicate that impulsivity may be a state-dependent factor for depression in adolescents that is associated with depression severity. This is consistent with other studies exploring impulsivity in children with MDD whereby depressed youth tended to respond more impulsively than healthy controls on behavioral tasks (Palladino et al., 1997) and make more impulsive decision on a decision-making task (Kyte et al., 2005) although a recent study that included a sample of adolescents with MDD and/or dysthymia showed no indication of impulsive responding on an attention task (Cataldo et al., 2005). The role of impulsivity in depressed youth could explain the association between depression and increased participation in health risk behaviors (Testa and Steinberg, 2010). Our data also indicate that impulsivity is associated with earlier onset of illness although not associated with number of depressive episodes. This suggests that the developing adolescent brain is more vulnerable to this type of cognitive deficit the earlier the deleterious effect of depression occurs and may explain the disparity between this positive finding in adolescent MDD and our negative finding on the RVP task in adult MDD (Maalouf et al., 2010). While previous studies reported an association between impulsivity and suicide attempts (Corruble et al., 2003; Dumais et al., 2005), we did not show this association in our sample. Future studies with larger sample sizes need to further explore this potential association. Our data also indicated that impulsivity was associated with the presence of lifetime anxiety disorders in the combined MDD groups. Although anxiety has been conceptualized as having a negative relationship with impulsivity (Askénazy et al., 2003; Caci et al., 1998), our findings are compatible with the few adult studies that have shown increased rates of impulsivity among samples of adults with specific anxiety disorders (Summerfeldt et al., 2004).

The current study did not show any differences in visual short-term memory among the three groups. This finding is in contrast with the results of a recent study whereby MDD adolescents performed worse on measures of delayed visual and verbal memory (Brooks et al., 2010). Our finding is, however, consistent with studies exploring memory functions in adult samples with first episode major depression (Basso and Bornstein, 1999; Fossati et al., 2004). These studies showed impairment in memory functions in recurrent MDD patients while no such impairment was noted for first episode MDD patients. These results highlight the debilitating effects of long term recurrent depression on cognitive functions (Basso and Bornstein, 1999; Fossati et al.) and may explain our negative results as the mean numbers of depressive episodes in our sample were 1.2 and 1.4 for MDDa and MDDr respectively.

One strength of our study was the rigorous clinical characterization of the MDD cases, and the use of well-validated neurocognitive probes. Although a major limitation of our study, however, was a relatively modest sample size, we were able to detect a moderate effect size for impulsivity ($d = 0.49$ for MDDa vs. HC) and moderate to large effect size for executive dysfunction ($d = 0.77$, MDDa vs. HC) with our current sample size. Future studies should aim at recruiting a larger number of participants to confirm our findings. A second limitation is that participants were assessed at just one point in time. Demonstrating that neurocognitive differences during depressive state recede once remission is attained in the same participants would allow us to draw even stronger causal inferences than our current design. A further limitation is our choice of neurocognitive tasks which was limited in an effort not to overburden our participants: The visual planning task (SOC) that we employed

in the present study measures one aspect of executive function, and our choice of memory assessment was limited to spatial short-term memory.

In summary, this is the first study to examine the extent to which impairment on three neurocognitive domains may represent state vs. trait markers of depression in adolescents, by measuring performance on well-validated tasks of sustained attention, executive function and memory in both MDDa and MDDr relative to HC. We showed that impaired executive function and impulsivity appeared to be state-specific markers in adolescent depression that were present in MDDa and did not persist in MDDr. Furthermore, we showed that these deficits were associated with depression severity in adolescents with a history of MDD – i.e., in MDDa and MDDr combined. The neurocognitive tasks we employed in our study are easily administered and transportable tasks that can be used in a variety of different clinical settings. Employment of these tasks is therefore a promising first step towards identifying state markers of MDD in adolescents that may reflect pathophysiologic processes of acute illness and predict response to SSRIs and to psychotherapy as compared to trait markers that persist in remitted state or confer vulnerability to the illness. Given the importance of executive function in psychotherapy, possible applications of these measures in the future may be in the personalization of the timing and focus of psychotherapy and cognitive rehabilitation (Calkins et al., 2011).

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Fig. 1.

Performance on Stockings of Cambridge Task. There was a group by difficulty effect when number of moves for 2, 3, 4, and 5-move problems were entered as within subjects variables, and group as a between subject variable in a repeated measures ANOVA ($F(3.5, 94.7) = 2.88$ and $p = 0.033$). In addition, there was a between-subjects group effect $F(2, 54) = 3.94$ and $p = 0.025$ and a within-subjects difficulty effect $F(1.7, 94.7) = 332$ and $p = 0.00$.

Table 1

Demographic and clinical data.

	HC N = 17	MDDr N = 20	MDDa N = 20	Statistics
Age Mean (SD)	15.2 (1.8)	15.4 (1.3)	15.3 (1.6)	F (2,54) = 0.095 p = 0.910
Female: Male	9:8	15:5	17:3	Chi-Square = 4.82, df = 2 p = 0.09
IQ Mean (SD)	112 (11)	113 (12)	105 (11)	F (2,54) = 2.94 p = 0.061
PDS Mean (SD)	2.7 (0.8)	2.8 (0.5)	2.8 (0.4)	F (2,54) = 0.311 p = 0.73
CDRS Mean (SD)	19.1 (2.3)	23.7 (3.4)	58.6 (10.9)	F (2,54) = 188.92 P = 0.00 HC vs. MDR: p = 0.139 HC vs. MDD p = 0.00 MDD vs. MDR p = 0.00
SCARED-child Mean (SD)	4.9 (6.2)	17.4 (14.9)	32.4 (18.2)	F (2,54) = 17.10 P = 0.00 pairwise Bonferroni All S with p<0.05
SCARED-Parent Mean (SD)	4.9 (5.8)	14.8 (9.8)	27.0 (14.8)	F(2,53) = 18.58 P = 0.00 pairwise Bonferroni All S with p<0.05
Total episodes duration Mean (SD) ^a		19.2 (21.7)	24.8 (22.2)	T = -0.789, df = 37, p = 0.435
Total number of episodes Mean (SD)		1.2 (0.5)	1.4 (0.6)	T = -1.37, df = 36.4, p = 0.178
Age of illness onset Mean (SD) ^a		159.8 (23.6)	140.2 (36.2)	T = 1.99, df = 37, p = 0.054
Age of Onset of current MDD Mean (SD) ^a			163.1 (19.4)	
Age of Offset of last MDD Mean (SD) ^a		180.4 (16.5)		
Time since offset of last MDD Mean (SD) ^a		4.28 (9.6)		
Presence of Lifetime Anxiety Disorders N(% Yes)		10 (50%)	15 (75%)	Chi-Square = 2.67 df = 1 p = 0.10
Receiving SSRI/SNRI N (% Yes)		13 (65%)	13 (65%)	Chi-Square = 0.0 df = 1 p = 1.0

^a In months.

Table 2

Neurocognitive measures: 3-group comparisons.

	HC n = 17	MDDr n = 20	MDDa N = 20	Statistics test Kruskal-Wallis test	Significant post-hoc Mann-Whitney U test and effect size (Cohen's d)
RVP total hits mean (SD)	15.4 (6.4)	14.9 (5.6)	12.9 (4.6)	p = 0.298	
RVP false alarms mean (SD)	1.3 (2.4)	1.4 (1.9)	3.8 (3.4)	p = 0.006	MDD>HC, p = 0.004, d = 0.85 MDR vs. HC, p = 0.598 MDD>MDR, p = 0.009, d = 0.87
RVP A' target sensitivity mean (SD)	0.89 (0.07)	0.88 (0.05)	0.86 (0.05)	p = 0.193	
RVP B' mean (SD)	0.95 (0.08)	0.95 (0.06)	0.88 (0.10)	p = 0.009	MDD<HC, p = 0.008, d = 0.49 MDR vs. HC, p = 0.801 MDD<MDR, p = 0.010, d = 0.85
RVP latency mean (SD)	437 (105)	420 (62)	445 (96)	p = 0.618	
DMS % correct mean (SD)	86.2 (10.5)	87.7 (10.6)	85.0 (15.0)	p = 0.834	
SOC # moves for 2-move-problems mean (SD)	2.1 (0.2)	2.0 (0.2)	2.0 (0.0)	p = 0.571	
SOC # moves for 3-move-problems mean (SD)	3.3 (0.5)	3.3 (0.6)	3.5 (0.7)	p = 0.526	
SOC # moves for 4-move-problems mean (SD)	5.1 (1.0)	5.0 (0.9)	5.8 (0.8)	p = 0.013	MDD>HC, p = 0.015, d = 0.77 MDD>MDR, p = 0.01, d = 0.94 MDR vs. HC, p = 0.9
SOC # moves for 5-move-problems mean (SD)	6.1 (1.4)	6.6 (1.2)	7.5 (2.0)	p = 0.057	