Cognitive behavior therapy for irritability in high-functioning ASD: Pilot study of neurobiological mechanisms.

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ABSTRACT

Background: In addition to the core symptoms, up to 50 percent of children with ASD exhibit irritability and disruptive behavior problems.(1) If present in childhood, these problems may persist in adolescence and adulthood and place considerable strain on individuals and their families. Psychotropic medication, notably risperidone and aripiprazole, and psychosocial treatments based on applied behavioral analysis have been used for irritability in ASD. There is also emerging evidence that Cognitive Behavioral Therapy (CBT) can be helpful for irritability in children with high-functioning ASD.(2) CBT teaches children to recognize antecedents and consequences of problem behavior and to use emotion regulation and problem-solving skills to reduce irritability, aggression and noncompliance. **Objectives:** We investigated the neurobiological mechanisms of CBT by evaluating functional magnetic resonance imaging (fMRI) and electrophysiological (EEG) markers of socioemotional functioning before and after treatment in a 16-year old girl with Asperger Syndrome. **Results:** Parent ratings revealed a decrease in the ABC irritability score from 17 at baseline to 5 at endpoint. The fMRI regions of interest analysis revealed significantly increased activation from pre- to post-treatment in the subgenual anterior cingulate cortex, right ventrolateral prefrontal cortex, and left ventrolateral prefrontal cortex in frustration vs. neutral conditions. The analysis of electrophysiological data revealed a reduction in the difference between NoGo and Go N2 ERPs at post-treatment versus pre-treatment in the frustration condition.

METHODS

Study Subject: The participant was a 16-year-old girl with Asperger Syndrome complicated by irritability. There was no history of communication delays but observations revealed somewhat formal language with a tendency to lengthy monologues. Over-encompassing interests included collecting stuffed animals, beanie babies and webkinz, and fascination with the movie Pirates of the Caribbean. The subject reported enjoying these activities and spending considerable time organizing her collections and looking up related topics on line. The irritability and disruptive behavior problems included being easily frustrated, yelling, arguing and insisting on having her demands met immediately. Anger outbursts occurred several times per day, were accompanied by yelling and crying, and persisted for 15-30 minutes at home or led to leaving class at inappropriate times in school. Most intensive outbursts occurred if the subject was interrupted when doing something on the computer or when organizing her collection of beanie babies.

Treatment: CBT was adapted from our work in typically developing children (3-5) and consisted of 10 weekly sessions. Sessions 1-3 included education about anger triggers, experience and expression followed by practice of common arousal management skills such as deep breathing, muscle relaxation and positive imagery. Sessions 4-6 included cognitive restructuring of hostile attributions and practicing problem-solving skills. For example, the participant was asked to identify and evaluate the consequences of various actions for herself and for the others involved in conflicts. Sessions 7-9 were dedicated to behavioral practice of skills for preventing or resolving potentially anger-provoking situations with friends, siblings, parents, and teachers. For example, the participant was asked to recall a situation in which she acted angrily and to role-play behaviors that would have prevented excessive anger. At the end of each session, the participant was asked to practice particular anger coping skills at home and to describe her experience in one-page logs.

Clinical Assessment: The *Irritability subscale of the Aberrant Behavior Checklist (ABC)* was used as the primary outcome measure.(6) The scale includes 15 items asking about aggression, self-injury, tantrums, agitation, and unstable mood. The total Irritability scale score ranges from 0 to 45, with higher scores indicating greater severity.

EEG and fMRI Procedures

EEG and fMRI data were collected during separate sessions while the subject performed the frustration-induction Go-NoGo task before and after treatment. The frustration-induction Go-NoGo task represents a mixed blocked/event-related design for fMRI and EEG studies (see Figure 1). Subjects are instructed to view a steady stream of common objects (balls, hats, chairs, etc.) and to press a button every time an object is presented in a green frame but to inhibit their response when an object appears in a red frame (66 of 200 trials). The opportunity to win a prize was manipulated across three conditions with known frustration-induction effects. (7,8)

Change in the amplitudes of N2 components in the Go versus NoGo ERP waves during frustration and neutral conditions of the Go-No/Go task was the primary EEG outcome measure. The main contrasts of interest for the blood oxygenation level dependent signal (BOLD) was the difference between: (1) neutral vs. frustration conditions of the task.

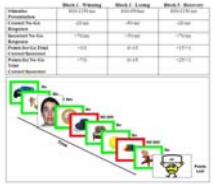

Figure 1. Frustration-induction Go-No/Go task. Upper panel shows latency windows for stimulus presentation and correct responses by 3 task blocks. Lower panel shows a sample of the task stimuli.

ERP results

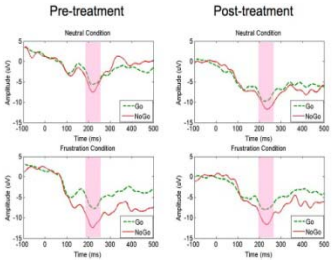

Figure 2. ERPs to the frustration induction Go-No/Go task at pre- and post-treatment. Highlighted areas mark the latency of the N2 ERP peak ± 50 milliseconds.

fMRI results

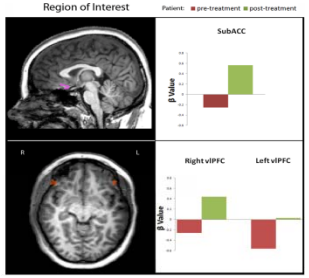

Figure 3. Region of interest analysis of brain activation pre- and post-treatment in the contrast of neutral vs. frustration conditions of the Go-No/Go task. Beta values represent the magnitude and direction of activation in the regions of interest. Results are depicted on the anatomical brain of the subject.

RESULTS

Parent ratings revealed a decrease in the ABC irritability score from 17 at baseline to 5 at endpoint. Both the EEG and fMRI procedures were well-tolerated and there was no difficulty in obtaining full cooperation with the subject. Figure 2 shows evoked response potentials (ERPs) in the N2 latency window for the Go and NoGo trials of the task in the neutral (top panels) and frustration (bottom panels) condition at pre-treatment (left) and post-treatment (right). The magnitude of the difference in the amplitudes between N2 ERPs is believed to reflect cognitive effort involved in the monitoring of conflicting information. There was a 25% reduction in the difference between NoGo and Go N2 ERPs at post-treatment (3.60 μV) versus pre-treatment (4.86 μV) in the frustration condition. In contrast, this difference remained virtually unchanged in the neutral condition. This suggests a more efficient cognitive control during performance of a response inhibition task when frustrated. Figure 3 shows the results of the fMRI during frustration-induction task collected with the pilot subject before and after treatment. Regions of Interest (ROI) were first defined in three healthy subjects using the false discovery rate procedure controlling for multiple comparisons and then used for the ROI analysis in the patient. This analysis revealed significantly increased activation from pre- to post-treatment in the subgenual anterior cingulate cortex (β=0.86), right ventrolateral prefrontal cortex (β=0.65), and left ventrolateral prefrontal cortex (β=0.60) in frustration vs. neutral conditions. These results suggest that brain regions which are recruited in a cognitive task requiring emotion regulation following a period of frustration were hypoactive in the subject before treatment but showed increased activation following treatment with CBT for irritability.

CONCLUSIONS

The 12-point change in the ABC irritability score represents a meaningful decline in irritability which is similar to the mean improvement in the medication trials(9). fMRI results suggest that brain regions which are recruited in a cognitive task requiring emotion regulation following a period of frustration showed increased activation following treatment with CBT for irritability. ERP results suggests more efficient cognitive control of frustration when performing a response inhibition task after CBT. Thus, reduction of irritability was paralleled by changes in the neural circuitry of emotion regulation. This pilot study supports the feasibility of using fMRI and EEG technology to investigate neurobiological mechanisms of CBT in adolescents with high-functioning ASD.

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