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Abnormal fear circuitry in Attention Deficit Hyperactivity Disorder: A controlled magnetic resonance imaging study

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ABSTRACT

We examined whether non-traumatized subjects with Attention Deficit Hyperactivity Disorder (ADHD) have dysfunctional activation in brain structures mediating fear extinction, possibly explaining the statistical association between ADHD and other disorders characterized by aberrant fear processing such as PTSD. Medication naïve, non-traumatized young adult subjects with (N=27) and without (N=20) ADHD underwent a 2-day fear conditioning and extinction protocol in a 3 T functional magnetic resonance imaging (fMRI) scanner. Skin conductance response (SCR) was recorded as a measure of conditioned response. Compared to healthy controls, ADHD subjects had significantly greater insular cortex activation during early extinction, lesser dorsal anterior cingulate cortex (dACC) activation during late extinction, lesser ventromedial prefrontal cortex (vmPFC) activation during late extinction learning and extinction recall, and greater hippocampal activation during extinction recall. Hippocampal and vmPFC deficits were similar to those documented in PTSD subjects compared to traumatized controls without PTSD. Non-traumatized, medication naive adults with ADHD had abnormalities in fear circuits during extinction learning and extinction recall, and some findings were consistent with those previously documented in subjects with PTSD compared to traumatized controls without PTSD. These findings could explain the significant association between ADHD and PTSD as well as impaired emotion regulation in ADHD.

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a common, early onset, treatable neurobiological disorder associated with high morbidity and dysfunction. Individuals with ADHD are at an increased risk for developing other psychiatric illnesses, including mood disorders, anxiety disorders (Herry et al., 2008; LeDoux, 2000; Likhtik et al., 2008; Myers and Davis, 2007; Spencer et al., 2016) and posttraumatic stress disorder (PTSD). Our recent meta-analysis documented a robust and bidirectional association between ADHD and PTSD in both referred and non-referred samples of adults and children (Spencer et al., 2016). This finding remained even among studies that examined traumatized cohorts, indicating that the association was not due to trauma exposure. Because the onset of ADHD was consistently earlier than the onset of PTSD in all studies examining temporality, we hypothesized that ADHD may be an antecedent risk factor for PTSD

and thus associated with a neurobiological vulnerability for PTSD.

Examining neurobiological vulnerability in high risk individuals is possible due to neuroimaging advances. Studies have begun to document a neurobiological basis for PTSD by studying fear extinction learning and extinction recall (i.e., the memory or retention of extinction learning). This work relies on a translational paradigm first studied in rodents (Herry et al., 2008; LeDoux, 2000; Likhtik et al., 2008; Myers and Davis, 2007; Quirk and Mueller, 2008; Sotres-Bayon et al., 2006). Extending this paradigm to humans, Milad et al. reported functional activation of amygdala during extinction learning and activation of vmPFC and hippocampus during extinction recall in healthy, normal subjects (Linnman et al., 2012; Milad et al., 2007). Using this paradigm to study PTSD, Milad et al. found that activation of the fear extinction network is impaired during extinction learning and recall in individuals with PTSD compared to traumatized individuals without PTSD (Bremner et al., 1999; Garfinkel et al., 2014; Kasai et al.,

2008; Linnman et al., 2012; Marin et al., 2016; Milad et al., 2007). These findings provide an opportunity to investigate fear circuitry in individuals at clinically high risk for acquiring PTSD, such as those with ADHD. If abnormalities in fear circuitry are present, the finding may not be specific to ADHD and could represent a vulnerability common to other high-risk individuals.

To this end, the goal of this study was to examine whether individuals with ADHD have abnormalities in fear circuitry resembling those found in PTSD. We studied medication naïve young adults with and without ADHD with no history of trauma exposure using the same validated fear conditioning and extinction neuroimaging paradigm pioneered by Milad et al. (Garfinkel et al., 2014; Linnman et al., 2011, 2012; Milad et al., 2008, 2005, 2009, 2006, 2007). Skin conductance response (SCR) was recorded as a psychophysiological index of fear conditioning, extinction and extinction recall as in previous studies (Phelps et al., 2004; Pitman and Orr, 1986). We hypothesized that non-traumatized, medication-naïve subjects with ADHD would demonstrate dysfunctional activation in brain structures that mediate fear extinction and learning, consistent with those previously reported in subjects with PTSD.

2. Methods

2.1. Subjects

The study was approved by the Partners Human Research Committee (PHRC), and all subjects completed written informed consent in accordance with PHRC requirements. A total of 27 (13 male and 14 female) non-traumatized, right-handed, medication-naïve, young adult subjects age 19–33 (M =23, SD=5.2) with ADHD were compared to 20 (10 male and 10 female) non-traumatized, right-handed healthy controls (HC) age 21–34 (M =26, SD =3.6) described and reported elsewhere (Linnman et al., 2011). ADHD subjects were recruited from referrals to an adult ADHD program at Massachusetts General Hospital and through media advertisements. Controls were recruited from the community and free of current psychiatric disorders. All ADHD subjects were diagnosed with childhood onset, persistent DSM-IV-TR-defined ADHD combined type as determined by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS) ADHD Module and clinical interview by a psychiatrist with expertise in diagnosis and treatment of adult ADHD. All ADHD subjects had baseline severity of ≥ 24 on the Adult ADHD Investigator Symptom Report Scale (AISRS) (Adler et al., 2011). Subjects were excluded for (Seidman et al., 2011): 1) current (last month), non-ADHD Axis I psychiatric conditions; 2) Hamilton Depression Scale score > 16, Beck Depression Inventory score > 19, or Hamilton Anxiety Scale > 21; 3) trauma exposure endorsed on the PTSD module of the Structured Clinical Interview for DSM-IV (SCID-IV); 4) past treatment for ADHD; 5) severe medical illness, neurologic illness, or history of significant head trauma; 6) major sensorimotor handicaps; 7) inadequate English language skill or inability to understand informed consent; 8) Full Scale IQ < 80 (Wechsler, 1999); 9) positive urine toxicology screen or substance abuse in the past 6 months; 10) positive urine pregnancy test or possible pregnancy; 11) any other contraindications to MRI scanning.

Table 1 summarizes the sample demographics. ADHD and HC subjects did not significantly differ according to mean age, mean shock level, and sex distribution. ADHD subjects had significantly fewer years of education compared to HC subjects. This was not controlled for in the analysis since it is consistent with ADHD pathology. Due to excessive motion, fMRI data from 9 ADHD subjects during conditioning, 11 during extinction learning, and 6 during extinction recall could not be included in data analysis, resulting in final samples of 18 ADHD subjects during conditioning, 16 during extinction learning, and 21 during extinction recall. Due to excessive motion, data from one control subject was not usable during conditioning, extinction learning, or

Table 1
Group mean demographics and psychometric measures.

Demographics				
	ADHD n=27	HC n=20	Statistic	*p* value
Age (yrs)	23.3 ± 5.2	25.1 ± 3.6	z=1.70	0.09
Sex (male/female)	13/14	10/10	χ^2=0.02	0.90
Years of education	15.4 ± 7.3	17.3 ± 1.8	T=3.43	< 0.001
Shock Level (mA)	2.1	2.1	T=−0.37	0.71
AISRS Scores	39.0 ± 8.3	–	–	–

Note: ± designates standard deviation (SD).

extinction recall, resulting in a final control sample of 19 subjects during each phase.

2.2. Fear conditioning and extinction procedures

Participants underwent a 2-day fear conditioning and extinction paradigm in a 3-T fMRI scanner. The protocol was identical to that previously developed and validated in healthy subjects and clinical populations including PTSD, OCD, and schizophrenia (Holt et al., 2012; Linnman et al., 2011; McLaughlin et al., 2015; Milad et al., 2009)(Fig. 1). Two Ag/AgCl recording electrodes (9 mm diameter) were attached to the palm of the participant's non-dominant hand to measure skin conductance levels. Electrical stimulation was delivered through electrodes attached to the second and third fingers of the right hand. The shock intensity was previously determined by each participant to reach a highly annoying, but not painful, stimulation (Orr et al., 2000). Participants first viewed all paradigm images without receiving shocks. This was followed by the fear-conditioning phase, during which participants saw an image of a room (e.g., office) with an unlit lamp for 3 s. The lamp then turned on for 6 s with one of three colors: red, blue, or yellow. Two of these colors (CS+) were presented eight times each, 5 of which were followed by a 500 ms shock (62.5% reinforcement). The third color was presented 16 times and not followed by a shock (CS-). This fear-conditioning phase was followed by fear extinction learning in a new context (e.g., library) during which participants saw only one of the CS+ and the CS- (each cue was presented 16 times). These 32 trials were not reinforced and therefore led to the extinction of the CS +(CS+E). The next day, participants underwent extinction recall (in the extinction learning context, e.g., library) during which the CS+E and the non-extinguished CS+(CS+NE) were presented eight times each with sixteen presentations of the CS- interspersed. For all phases, the order of stimulus presentation was pseudorandom and the inter-trial intervals varied between 12 and 18 s.

2.3. Psychophysiological measures

The SCR score was calculated as previously described (Milad et al., 2005, 2007; Orr et al., 2000; Pitman and Orr, 1986): by subtracting the mean skin conductance level during the 2 s immediately before CS onset (during which context alone was presented) from the highest skin conductance level recorded during the 6-second CS. Therefore, all skin conductance responses to CS+E, CS+NE, and CS- reflect changes induced by the CS beyond any changes produced by the context. All SCR values were square-root transformed prior to analysis. For extinction learning, the 16 trials of CS+ were averaged in blocks of 2 trials, resulting in 8 blocks to investigate learning over time. The magnitude of extinction retention was measured as follows for each subject: 100 − (average SCR to the first two CS+E trials of extinction recall divided by their largest SCR to that same CS during conditioning) *100, yielding an extinction retention index (ERI) (Milad et al., 2005, 2007). The ERI was calculated to normalize each subject's SCR during extinction recall to that exhibited during conditioning, adjusting the SCR during recall for differences in CR magnitude during acquisition.