

Misinterpreting Emotional Expressions in Attention-Deficit/Hyperactivity Disorder: Evidence for a Neural Marker and Stimulant Effects

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Background: In addition to cognitive impairment, there are disruptions to mood and emotion processing in attention-deficit/hyperactivity disorder (ADHD) but little is known about their neural basis. We examined ADHD disturbances in mood and emotion recognition and underlying neural systems before and after treatment with stimulant medication.

Methods: Participants were 51 unmedicated ADHD adolescents and 51 matched healthy control subjects rated for depressed and anxious mood and accuracy for identifying facial expressions of basic emotion. Brain function was recorded using event-related potentials (ERPs) while subjects viewed these expressions. ADHD subjects were retested after 4 weeks, following treatment with methylphenidate (MPH).

Results: ADHD subjects showed a profile of emotion-related impairment: higher depression and anxiety, deficits in identifying threat-related emotional expressions in particular, and alterations in ERPs. There was a pronounced reduction in occipital activity during the early perceptual analysis of emotional expression (within 120 msec), followed by an exaggeration of activity associated with structural encoding (120–220 msec) and subsequent reduction and slowing of temporal brain activity subserving context processing (300–400 msec). Methylphenidate normalized neural activity and produced some improvement of emotion recognition but had no impact on negative mood. Improvements in neural activity with MPH were consistent predictors of improvement in clinical features of emotional lability and hyperactivity.

Conclusions: Objective behavioral and brain function measures of emotion processing may provide a valuable addition to the clinical armamentarium for assessing emotional disturbances in ADHD and the efficacy of stimulants for treating these disturbances.

Key Words: ADHD, depression and anxiety, ERPs, event-related potentials, facial expressions of emotion, lability, methylphenidate, recognition

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder affecting 3% to 7% of children and adolescents (1). It is characterized by deficits in core cognitive functions such as sustained attention, inhibition, and executive planning (2). Yet, children and adolescents with ADHD also show deficits in social and emotional functions, including an inability to effectively appraise the emotional state of others (3,4). While cognitive deficits have been studied extensively, the nature and neural basis of emotional dysfunction in ADHD remain comparatively unknown.

Evidence from complementary behavioral and brain imaging measures has implicated the distributed frontotemporal-posterior and striatal systems in cognitive disruptions in ADHD and effects of stimulants on these disruptions (5–10). Corresponding distur-

bances in these cortical systems have been observed in first-degree relatives of individuals with ADHD (11), consistent with a potential marker of ADHD. Other theories have focused on neuromodulation of these systems, proposing that a dysregulation in excitatory catecholamines, such as norepinephrine, and their interaction with dopamine may contribute to cognitive disturbances in ADHD (12,13). Importantly, frontotemporal-posterior systems and associated neuromodulators are also involved in regulating emotional functions and may additionally contribute to emotion-related deficits in ADHD (14,15).

In this study, we brought together behavioral and brain function measures to assess emotional functions in individuals with ADHD before and after treatment with stimulant medication.

Facial expressions of emotion are innate and biologically salient signals of emotion central to human social interaction and pertinent to the study of emotional function (14). In healthy subjects, facial expressions elicit robust neural changes over frontotemporal and parieto-occipital cortices, indexed by event-related potentials (ERPs). Threat-related expressions in particular modulate the early P120/N120 complex, peaking around 120 msec poststimulus over frontal (N120) and temporo-occipital (P120) sites (16–18). Modulation of this complex reflects variations in early, low-level perceptual analysis of emotional valence. The subsequent N170, generated around 170 msec over the temporal cortex, is modulated specifically by face stimuli (19,20). These findings accord with the presence of neurons in the superior temporal cortex selective for facial expressions (21). The scalp-recorded N170, elicited over temporo-occipital sites, and concomitant vertex positive potential (VPP), elicited over frontocentral sites, are also enhanced by the valence of facial expressions (16,22). In the later period of 300 to 400 msec poststimulus, the P300 component associated with more con-

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trolled contextual evaluation is similarly enhanced by emotional expressions (16,22–24).

Of the few studies that have examined emotion processing in ADHD, the focus has been on behavioral measures. Compared with healthy children, individuals with ADHD are significantly poorer in identifying emotional expressions, especially negative expressions of fear, anger, and sadness (25–27). Since children with ADHD also make more random errors than control subjects, it has been suggested that their deficit reflects a failure to attend to salient emotional signals, originating from a primary deficiency in encoding these signals. This proposal accords with the focus of cognitive-behavioral theories on the inability to selectively attend and inhibit irrelevant information in ADHD (5,9,10,28). Yet, the neural timing of emotion processing deficits in ADHD remains unknown. It is also not known whether these deficits are present in ADHD independent of treatment.

We tested the hypothesis that ADHD would be associated with deficits in recognizing negative emotional expressions in particular. Using the high temporal resolution of ERPs, we expected the neural correlates of these deficits to implicate the temporal cortex P120 and N170 components associated with early perception and emotion encoding. Additionally, we expected emotional processing disturbances in ADHD to be reflected in greater anxious and depressed mood. Adolescents with ADHD were tested before and after treatment with stimulant medication to determine the trait-like nature of emotional disturbances.

Methods and Materials

Subjects

Participants were 51 unmedicated young male children and adolescents with attention-deficit/hyperactivity disorder (mean age = 13.79 ± 2.33 years; range 8–17) recruited from adolescent medicine clinics in Sydney and 51 age, sex, and years of education matched healthy control subjects (mean age = 13.09 ± 2.39 years) recruited from corresponding metropolitan regions. Testing and recruitment were in collaboration with the Brain Resource International Database (BRID; <http://www.brainresource.com>).

We confirmed that ADHD and control groups did not differ on number of stressful early life events ($\chi^2 = 3.179$, $p = .075$; control group mean = 1.27, ADHD group mean = 1.0), using an established scale (29,30), such that this factor could not account for group differences in emotional function.

The inclusion criterion for both groups was an intelligence quotient (IQ) estimate of 80 or above, assessed using the Spot-the-Word test (31), which has been validated against Wechsler scales (32) and the full-scale Wechsler Intelligence Scale for Children-III (WISC-III) in a subset of 10 ADHD participants from this study ($r = .79$). Exclusion criteria for control subjects were symptoms of Axis I disorder, using BRID personal history and screening assessments, including SPHERES (33), Patient Health Questionnaire (PHQ-9) (34), and items screening for family history of psychiatric disorder defined as requiring medication and/or hospitalization. Exclusion criteria for both groups included physical brain injury, neurological disorder, other serious medical or genetic condition, and drug dependence, assessed using the Alcohol Use Disorders Identification Test (AUDIT) (15) and the Fagerstrom Nicotine Dependence Questionnaire (35).

Diagnosis of ADHD was based on DSM-IV criteria using a semistructured clinical interview and the Conners' Parent Rating

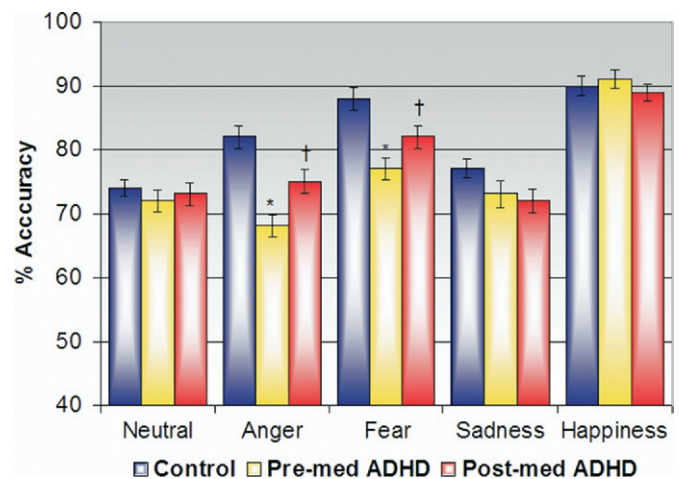


Figure 1. Mean percentage recognition accuracy (and standard error) for facial expression stimuli for unmedicated ADHD (gold), medicated ADHD (red), and matched healthy control (dark blue) subject groups. *indicates significantly reduced accuracy in unmedicated ADHD versus control subjects ($p < .0001$). †indicates a significant improvement in accuracy in ADHD following medication with methylphenidate ($p < .01$). ADHD, attention-deficit/hyperactivity disorder.

Scale-Revised: Long Version (CPRS-R:L) criteria (T-scores ≥ 65 or 1.5 SD, for inattentive or hyperactivity/impulsivity subscales). See Supplement 1 for additional details on assessment of ADHD and comorbid conditions.

Of the initial 51 ADHD participants, 33 (65%; mean age = 13.53 ± 2.71 years) completed postmedication retest. This subgroup did not differ from the total on demographic factors nor baseline CPRS-R:L ratings, negative mood, emotion recognition, or ERP components.

Informed assent/consent to participate in this study was provided by participants/parents or guardians.

Design

Testing was undertaken before and after stimulant treatment (methylphenidate [MPH]) using a naturalistic open-label design, as the first step toward future randomized controlled trials.

At baseline, we completed clinical ratings for the ADHD group. Both groups were tested on behavioral (negative mood and emotion recognition) and emotion-elicited ERP measures. Attention-deficit/hyperactivity disorder subjects returned for testing on these measures after 4 weeks, following treatment with a prescribed course of immediate-release methylphenidate.

Twenty-six of the ADHD individuals were medication naïve and were titrated to the maximum effective dose of .4 to 1.3 mg/kg per day over 1 week (10 mg increments), with a subsequent week of stable dose. The remaining 25 ADHD individuals underwent a washout from stimulant medication for at least 3 days prior to testing and resumed an optimal dosage of MPH after baseline testing.

The maximum effective dose of MPH was maintained until retest. According to medical and/or parental reports, all ADHD participants showed a positive response to the medication, based on efficacy and lack of adverse events. No participant was taking concurrent medications known to affect the central nervous system. At retest, the typical dose of MPH (mean 24.1 mg/day; range 10–60 mg/day) was taken 60 minutes before testing

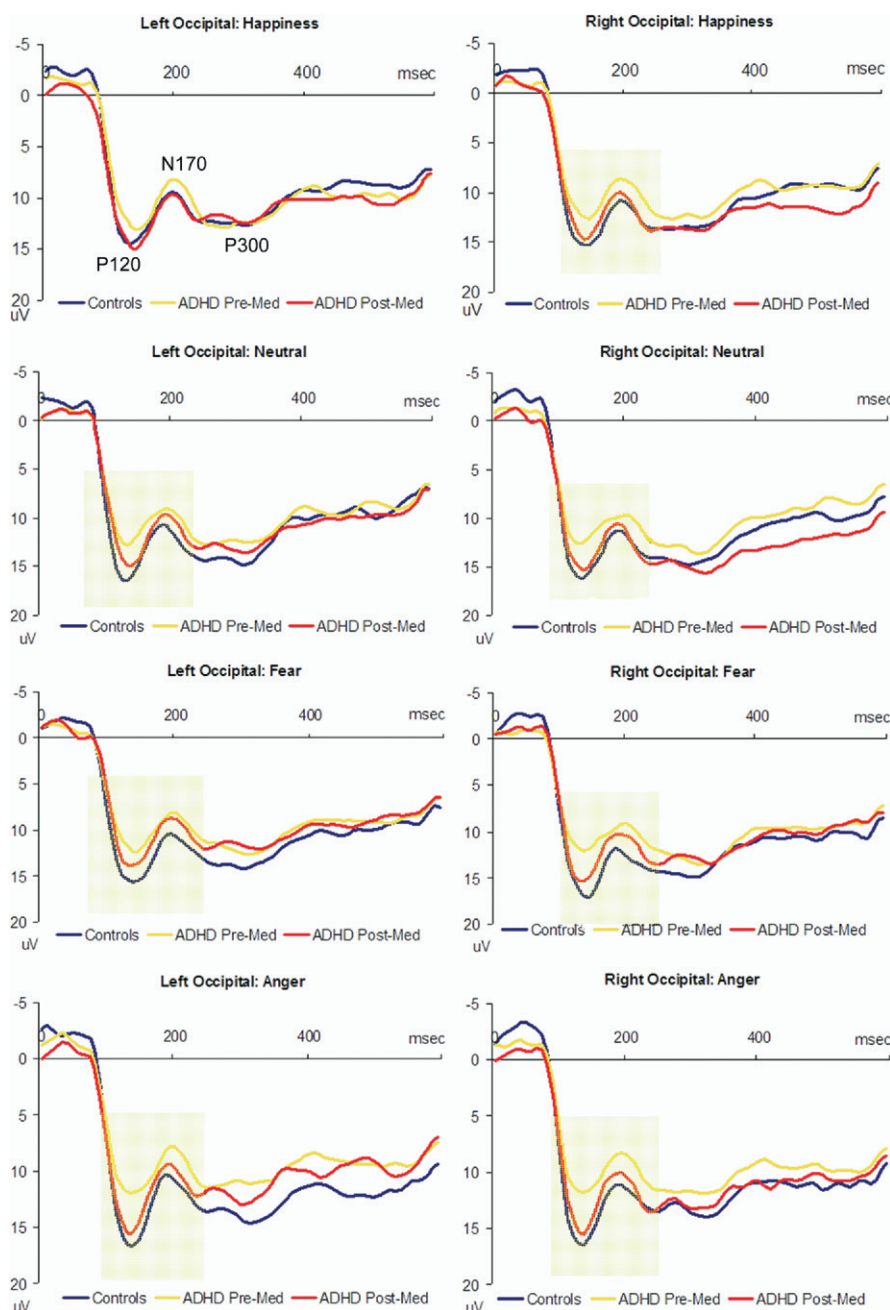


Figure 2. Event-related potential waveforms for the occipital brain regions (depicted for left occipital O1 and right occipital O2 sites) elicited by facial expressions of anger, fear, neutral, and happiness in unmedicated ADHD (gold), medicated ADHD (red), and matched healthy control (dark blue) subject groups. Yellow shading indicates significant reductions in the P120 ERP component (peaking around 120 msec poststimulus) and exaggeration of the N170 component (peaking around 170 msec poststimulus) in unmedicated ADHD versus control subjects and the significant improvement of these effects following medication with methylphenidate in ADHD. ADHD, attention-deficit/hyperactivity disorder; ERP, event-related potential.

commenced, consistent with the clinical effects and half-life (2–3 hours) of the drug (36).

Using the same electroencephalogram (EEG) system employed in this study, we have found ERP measures to have sound reliability for this 4-week test-retest period (37).

Clinical Ratings

In addition to CPRS-R:L T-score ratings used for confirmation of ADHD diagnoses, we also documented ratings for other clinical features assessed by this scale: ADHD index, restless-impulsive, emotional lability, oppositional, cognitive problems/inattentive, hyperactivity, anxious-shy, perfectionism, social problems, and psychosomatic features.

Assessment of Negative Mood. Both ADHD and control participants were assessed for anxiety and depression using the

21-item Depression, Anxiety and Stress Scale (DASS) (38), which has been validated against the Beck Depression and Anxiety Inventories and includes Australian norms (38).¹

Emotion Recognition. Evoked expressions of facial emotion (eight different individuals; four male individuals, four female individuals) from a standardized series (39) were presented in black and white. Participants selected the verbal label corre-

¹Testers used standardized phrases in simpler language to explain DASS and early life stress items to younger participants where needed. The correlation between responses of participants under and over 14 years was .84, pointing to the consistency of this approach. There were also no mean differences between those who completed scales independently and those who had questions explained in simpler language.

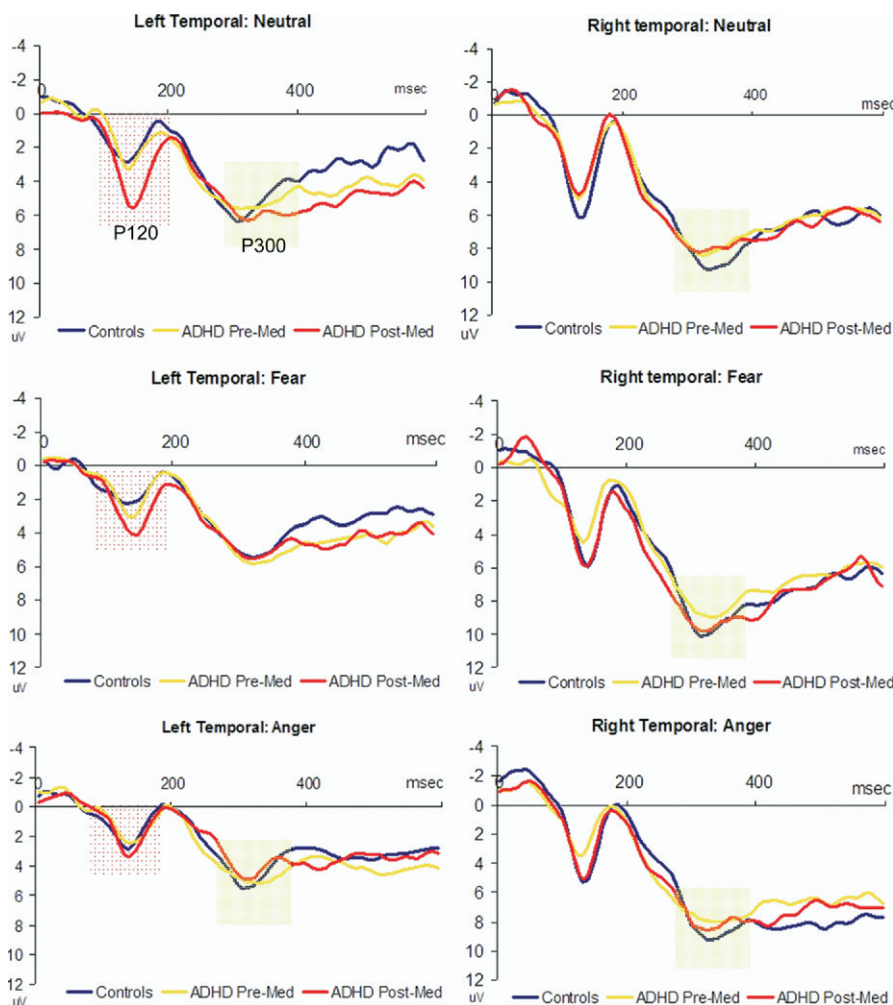


Figure 3. Event-related potential waveforms for the temporal brain regions (depicted for left temporal T5 and right temporal T6 sites) elicited by facial expressions of anger, fear, and neutral in unmedicated ADHD (gold), medicated ADHD (red), and matched healthy control (dark blue) subject groups. Yellow shading indicates significant reduction and slowing of the P300 ERP component (peaking around 360 msec poststimulus) in unmedicated ADHD versus control subjects and the improvement of these effects following medication with methylphenidate in ADHD for P300 amplitude (nonsignificant pre-post medication difference but no longer different to control subjects) and P300 latency (significant pre-post medication difference). Pink shading indicates the additional enhancement of the left occipital P120 component following medication. ADHD, attention-deficit/hyperactivity disorder; ERP, event-related potential.

sponding to each facial expression (fear, anger, sadness, disgust, happiness, or neutral) and percentage accuracy was recorded.

Emotion-Elicited ERP Recording. Participants were tested in a sound- and light-attenuated room, with ambient temperature 24°C. During ERP recording, the same facial expression stimuli were presented. In a previously established pseudorandomized, event-related design (16), there were 32 repeats of each expression, with stimulus duration 500 msec and interstimulus interval 700 msec. Luminance and contrast were equivalent across stimuli, and each face was centered by eye level on a black background.

Event-related potential data were recorded using a Quik-Cap (Compumedics Neuroscan, Abbotsford, Victoria, Australia) according to the 10-10 electrode International system. At occipital (O1, O2) and temporal (T5, T6) sites, the following peak ERP components (with respective latency windows) were quantified for peak amplitude and latency: P120 (80–150 msec), N170 (150–220 msec), and Late P300 (300–400 msec).² These compo-

nents were polarity reversed at frontomedial (Fz, Cz) sites, producing the corresponding N120 (80–150 msec), VPP (150–220 msec), and N300 (280–450 msec).

There were no differences between groups in amount of missing or replaced ERP data (see Supplement 1 for additional information on ERP protocols).

Statistical Analyses

At baseline, unmedicated ADHD and control groups were compared on depression and anxiety using independent *t* tests. Repeated measures analysis of variance (ANOVA) was used to examine group differences in emotion recognition accuracy, with group (unmedicated ADHD versus control group) as the between-subjects factor, emotion as the within-subjects factor, and planned contrasts at $p < .05$. Corresponding ANOVAs were used to examine emotion-elicited ERPs (amplitude and latency), with planned contrasts at $p < .01$ (given multiple regions). For ADHD participants, Pearson bivariate correlation analysis was used to explore relationships between ERPs that differentiated them from control subjects and clinical and behavioral measures.

Paired *t* tests were used to evaluate pre-MPH versus post-MPH changes in clinical ratings and depression and anxiety in ADHD. Repeated measures ANOVA was used to assess the effect of medication on emotion recognition, with emotion and medication (pre-MPH versus post-MPH) as within-subjects factors and planned

²The P230 (180–250 msec) and N250 (230–330 msec) observed over temporal and occipital sites and concomitant bipolar N200 (150–250 msec) and Early P300 (220–330 msec) observed over frontocentral sites were less prominent in this late childhood/adolescent sample than in previously studied adult samples (16,40). Thus, these ERP components were not included in the focal components for this study. However, we confirmed that ADHD did not differ from control subjects on amplitude for these latency windows.

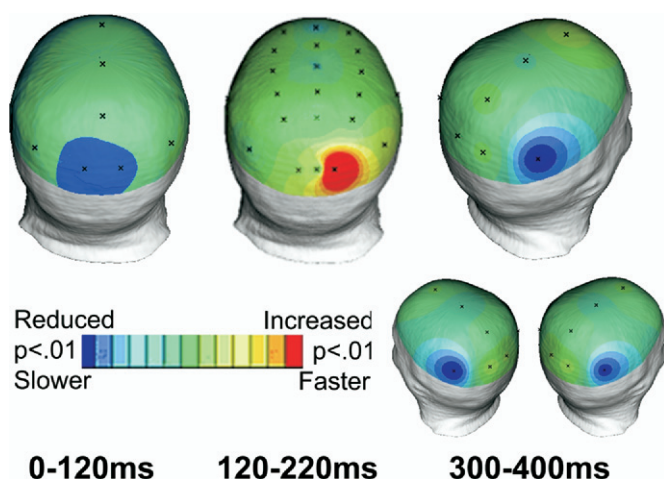


Figure 4. Topographical statistical parameter maps illustrate the distribution of neural alterations in unmedicated ADHD relative to control subjects in response to expressions of anger as the exemplar. There were reductions in bilateral occipital activity within 120 msec poststimulus (P120 ERP component), followed by enhancements of right occipital activity within 120 to 220 msec (N70 ERP component) and a reduction and delay in subsequent temporal cortex activity (P300 ERP component; right temporal reduction with bilateral temporal delay). Parameter maps for the 0 to 220 msec period are viewed from the back of the head and those for 300 to 400 msec are viewed from the side. Regions colored blue indicate a significant reduction or delay in activity, those colored red a significant enhancement, in ADHD versus control subjects. ADHD, attention-deficit/hyperactivity disorder; ERP, event-related potential.

contrasts at $p < .05$. Corresponding repeated measures ANOVAs were used to assess the effect of medication on ERPs, which showed significant group differences at baseline, with planned contrasts at $p < .01$. Regression analyses were used to determine

whether changes in emotion recognition and ERPs following MPH predicted changes in clinical ratings over and above the contribution of age and estimated IQ.

Secondary analyses of MPH effects and ADHD subtype are outlined in Supplement 1.

Results

Relative to control subjects, ADHD subjects showed higher levels of depression and anxiety, deficits in recognizing emotional expressions (Figure 1), and disruptions to ERPs (Figures 2–4). Methylphenidate produced a significant improvement in ERPs (Figures 2 and 3), some improvement in emotion recognition, but no impact on depression and anxiety. These results are presented in turn.

Baseline Clinical Profile

The unmedicated ADHD group had a profile of restless-impulsivity and emotional lability, with oppositional behavior, cognitive problems/inattention, and hyperactivity/impulsivity ($T \geq 65$), while anxiety-shyness, perfectionism, social problems, and psychosomatic features were within one standard deviation of average (Table 1).

Baseline Negative Mood. Unmedicated ADHD subjects had significantly higher depression ($t = 6.18$, $p < .0001$) and anxiety ($t = 4.91$, $p < .0001$) than control subjects (Table 1).

Baseline Emotion Recognition. There was a significant interaction between group and emotion recognition accuracy [$F(5,500) = 49.35$, $p < .0001$], due to a reduction in recognition of anger [$F(1,100) = 173.36$, $p < .0001$] and fear [$F(1,100) = 107.02$, $p < .0001$] in particular, in ADHD (Figure 1). These expressions tended to be misidentified as neutral or sadness.

Table 1. Means and Standard Deviations for ADHD on Mood Measures and Clinical Ratings, Before and After Treatment with Methylphenidate (MPH)

Scale	ADHD pre-MPH		ADHD post-MPH		Difference	
	Mean	SD	Mean	SD	<i>t</i>	<i>p</i> Value
DASS ^a						
Depression	10.16	10.43	8.54	9.68	ns	
Anxiety	5.36	6.35	5.06	6.08	ns	
CPRS-R:L Ratings						
ADHD index	72.65	9.70	64.00	10.99	2.78	.013
Global index	75.88	9.71	62.71	12.02	2.65	.020
Restless-impulsive	74.10	10.18	64.11	14.12	2.06	.030
Emotional lability	70.20	12.76	62.43	12.84	2.58	.030
Oppositional	72.33	13.06	62.83	12.32	3.15	.006
Cognitive problems/ inattentive	71.74	8.26	61.44	8.49	4.86	.001
Hyperactivity	74.49	12.96	61.21	13.48	4.75	<.0001
Anxious-shy	58.66	12.88	56.89	13.07	ns	
Perfectionism	54.07	11.62	57.11	12.35	ns	
Social problems	61.20	15.88	57.33	13.54	ns	
Psychosomatic	60.10	15.44	58.11	14.97	ns	
DSM-IV inattentive	71.76	9.31	62.56	12.01	2.57	.030
DSM-IV hyperactive-impulsive	73.44	12.74	64.44	13.89	2.15	.030
DSM-IV total	74.99	9.69	60.89	12.76	3.25	.008

DASS categories and range of scores (with % of ADHD participants in each category) are as follows (30): Depression: normal 0–9 (51.0%); mild 10–13 (13.7%); moderate 14–20 (19.6%); severe 21–27 (5.9%); extremely severe 28+ (9.8%). Anxiety: normal 0–7 (64.7%); mild 8–9 (5.9%); moderate 10–14 (17.6%); severe 15–19 (7.8%); extremely severe 20+ (3.9%).

The proportion of ADHD participants in severe and extremely severe categories accords with the proportion who met criteria for comorbid generalized anxiety and depression (details in Methods).

ADHD, attention-deficit/hyperactivity disorder; CPRS-R:L, Conners' Parent Rating Scale-Revised: Long Version; DASS, Depression, Anxiety and Stress Scale; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.*; MPH, methylphenidate; ns, nonsignificant; SD, standard deviation.

^aControl group means for DASS scales were: Depression 1.34 (SD = 2.50); Anxiety 1.00 (SD = 1.55).

Table 2. Summary of ANOVA Contrasts Showing Significant Differences in ERP Components Elicited During Emotion Processing for ADHD Compared with Healthy Control Subjects

Emotion	Region	F Value	p Value ^{a,b,c}	Direction of Effect
P120 Amplitude				
Anger	Right occipital	7.54	.003	Reduced
	Left occipital	6.54	.009	Reduced
Fear	Right occipital	6.50	.012	Reduced
	Left occipital	4.24	.018	Reduced
<i>Disgust</i>	<i>Right occipital</i>	3.84	.053	<i>Reduced</i>
Sadness	Right occipital	7.21	.008	Reduced
Neutral	Right occipital	8.80	.004	Reduced
	Left occipital	3.79	.050	Reduced
Happiness	Right occipital	6.393	.013	Reduced
N170 Amplitude				
Anger	Right occipital	7.890	.006	Increased
	Left occipital	5.19	.010	Increased
Fear	Right occipital	8.072	.005	Increased
	Left occipital	5.09	.011	Increased
<i>Disgust</i>	<i>Right occipital</i>	4.830	.030	<i>Increased</i>
Neutral	Right occipital	6.584	.012	Increased
	Left occipital	4.96	.019	Increased
<i>Happiness</i>	<i>Right occipital</i>	3.812	.054	<i>Increased</i>
P300 Amplitude				
Anger	Right temporal	6.28	.031	Reduced
Fear	Right temporal	6.15	.032	Reduced
<i>Neutral</i>	<i>Right temporal</i>	4.88	.055	<i>Reduced</i>
P300 Latency				
Anger	Right temporal	6.535	.012	Delayed
	Left temporal	7.870	.006	Delayed
Fear	Right temporal	6.578	.013	Delayed
	Left temporal	6.76	.010	Delayed
<i>Neutral</i>	<i>Left temporal</i>	3.982	.049	<i>Delayed</i>

ADHD, attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; ERP, event-related potential.

^aBolding indicates effects significant at the corrected alpha level of $p < .01$.

^bRegular text indicates effects of marginal significance at the corrected alpha level of $p = .01$.

^cItalics indicate trend level effects at $p = .02$ – $.06$.

Baseline ERPs

ERP Amplitude. Right occipital P120 was generally reduced in unmedicated ADHD versus control subjects across emotions [$F(1,100) = 6.84, p = .01$]. Contrasts confirmed the reductions for individual emotions (Table 2; Figures 2 and 4).

For the left occipital P120, a group by emotion interaction [$F(1,100) = 3.88, p = .045$] was due to reductions in unmedicated ADHD subjects for anger and at trend level for fear and neutral but no effects for other expressions (Table 2; Figures 2 and 4).

The right occipital N170 showed a group main effect [$F(1,100) = 4.11, p = .04$] due to a comparative enhancement across emotions in ADHD subjects. Contrasts confirmed this enhancement for individual emotions (Table 2; Figures 2 and 4).

There was a group by emotion interaction for the left occipital N170 [$F(1,100) = 3.96, p = .042$] due to a corresponding enhancement in ADHD subjects for anger and fear and at trend level for neutral but not other expressions (Table 2; Figures 2 and 4).

The subsequent right temporal P300 showed a significant group by emotion interaction [$F(5,500) = 3.65, p = .006$] due to a reduction in ADHD versus control subjects for anger and fear in particular and at trend level for neutral but not other expressions (Table 2; Figures 3 and 4).

ERP Latency. Effects for ERP latency were limited to the temporal P300. There was a group by emotion interaction for both left [$F(5,500) = 4.34, p = .04$] and right [$F(5,500) = 5.33,$

$p = .02$] temporal P300 latency due to delayed latency in ADHD for anger and fear in particular (Table 2; Figures 3 and 4).

Relationships Between Baseline Clinical Profile, Negative Mood, Emotion Recognition, and ERPs

Poorer emotion recognition in unmedicated ADHD subjects was related to the reduction in right occipital P120 for anger ($r = .45, p = .008$), fear ($r = .42, p = .016$), and sadness ($r = .35, p = .045$) and at trend level for neutral ($r = .34, p = .061$).

Poorer recognition of anger was also correlated with higher anxiety ($r = -.35, p = .009$) and depression ($r = -.29, p = .013$), as was recognition of fear at trend level (anxiety, $r = .21, p = .07$; depression, $r = .26, p = .027$).

Greater depression in ADHD was related in particular to the reduction in bilateral occipital P120 and anxiety to the reduction in left occipital P120 (Table 3). Reductions in occipital P120 were also correlated with greater CPRS-R:L ratings of hyperactivity and emotional lability (Table 3). There were no significant correlations between P120 and CPRS-R:L ratings of DSM-IV hyperactivity and DSM-IV inattention, relevant to defining ADHD combined and inattentive subtypes.³

³Attention-deficit/hyperactivity disorder inattentive and combined subtypes also did not differ on these measures of emotion recognition, mood, and emotion-elicited ERPs (we did not include the hyperactivity/impulsivity subtype given the small size, $n = 2$).

Table 3. Summary of Correlations, with Pearson *r* and (*p* Values), Between Negative Mood, Clinical Features of ADHD, and Emotion ERP Deficits

ERP Component	DASS		CPRS-R:L Ratings ^a				
	Anxiety	Depression	Emotional Lability	Oppositional	Inattention/Cognitive Problems	Hyperactivity	Anxiety-Shy
Right Occipital P120 Amplitude							
Anger	-.20 (.046)	-.33 (.001)	-.44 (.005)	-.29 (.050)	–	-.36 (.014)	-.32 (.042)
Fear	–	-.26 (.008)	-.48 (.002)	-.37 (.008)	–	-.42 (.004)	-.34 (.032)
Disgust	–	–	-.41 (.010)	–	–	–	–
Sadness	–	-.25 (.010)	–	–	–	–	–
Neutral	–	-.28 (.005)	-.40 (.010)	–	–	-.30 (.041)	-.31 (.040)
Happiness	–	-.24 (.017)	-.33 (.037)	–	–	-.36 (.014)	–
Left Occipital P120 Amplitude							
Anger	-.20 (.043)	-.33 (.001)	-.36 (.012)	–	–	-.32 (.032)	–
Fear	-.21 (.040)	-.28 (.004)	-.40 (.010)	–	–	-.36 (.012)	–
Neutral	-.21 (.035)	-.31 (.002)	-.35 (.029)	–	–	-.36 (.012)	–
Right Occipital N170 Amplitude							
Anger	–	.26 (.011)	.53 (.001)	.33 (.032)	.36 (.019)	–	.33 (.044)
Fear	–	–	–	.41 (.006)	–	–	–
Disgust	–	–	.33 (.040)	–	.35 (.028)	–	–
Neutral	–	–	–	–	–	–	–
Happiness	–	–	–	–	–	–	–
Right Temporal P300 Amplitude							
Anger	–	–	–	–	–	–	–
Fear	–	–	–	–	–	–	–
Neutral	–	–	–	–	–	–	–
Right Temporal P300 Latency ^b							
Anger	.26 (.013)	–	–	–	–	–	–
Fear	–	.29 (.004)	–	–	–	–	–

Bolded correlations are significant at the corrected *p* value of .008.

ADHD, attention-deficit/hyperactivity disorder; CPRS-R:L, Conners' Parent Rating Scale-Revised: Long Version; DASS, Depression, Anxiety and Stress Scale; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.*; ERP, event-related potential.

^aThere were no significant correlations for CPRS-R:L ratings of DSM-IV hyperactivity and DSM-IV inattention. Similarly, there were no significant correlations for subscales of Restless-Impulsive, Perfectionism, Social Problems, or Psychosomatic Problems.

^bThere were no significant correlations for left temporal P300 latency.

There were comparatively few correlations involving N170 and P300 components. The most consistent pattern was between the abnormally enhanced right occipital N170 and higher depression, along with CPRS-R:L ratings of hyperactivity, cognitive problems/inattentiveness, anxiety-shyness, and emotional lability (Table 3).

Postmedication Clinical Profile

Treatment with MPH was found to significantly improve CPRS-R:L ratings of DSM-IV inattention and hyperactivity (Table 1). There were also significant improvements in ratings of oppositional behavior, cognitive problems/inattention, hyperactivity, ADHD index, impulsivity, and emotional lability but not anxiety-shyness, perfectionism, and social and psychosomatic problems (Table 1).

Postmedication Negative Mood. Methylphenidate did not significantly reduce depression or anxiety in ADHD, consistent with the lack of change for CPRS-R:L anxiety-shyness. Depression ($t = 5.62, p < .0001$) and anxiety ($t = 4.08, p < .0001$) at retest remained significantly higher than in control subjects (Table 1).

Postmedication Emotion Recognition. There was a medication by emotion interaction [$F(5,160) = 3.53, p = .018$], due to significant improvements in recognition of anger [$t(31) = 2.811, p = .008$] and fear [$t(31) = 2.66, p = .01$] with MPH but not other expressions (Figure 1). Nonetheless, recognition remained impaired in medicated ADHD relative to control subjects for anger [$t(82) = 3.53, p < .001$] and fear [$t(82) = 2.89, p = .01$] (Figure 1).

Postmedication ERPs

ERP Amplitude. There was an increase (indicating improvement) in right occipital P120 with MPH [$F(1,32) = 4.26, p = .009$]. Contrasts confirmed this increase for individual emotions (Figure 2; Supplement 1). Analysis of variance confirmed that medicated ADHD subjects did not differ from control subjects on the right occipital P120.

For left occipital P120, there was a medication by emotion interaction [$F(5,160) = 3.92, p = .030$] due to a significant increase (indicating improvement) with MPH for anger in particular ($p < .01$), lesser effects for fear and neutral ($p < .05$), and no difference for other expressions (Figure 2; Supplement 1).

Methylphenidate was also found to enhance the left temporal P120 [$F(5,160) = 49.56, p < .0001$], such that the medicated ADHD group had a larger P120 than control subjects [$F(5,160) = 16.42, p < .0001$] (Figure 3). Contrasts confirmed this effect for individual emotions (Supplement 1).

Methylphenidate produced a marginally significant reduction (indicating improvement) in right occipital N170 amplitude [$F(1,32) = 2.96, p = .05$] (Figure 2; Supplement 1), and ANOVA confirmed that medicated ADHD subjects no longer differed from control subjects.

While there were no significant effects for medication for right temporal P300, ADHD subjects did not differ from control subjects on right temporal P300 amplitude following MPH, suggesting a mean trend in the direction of improvement (Figure 3).

Table 4. Summary of Regression Analyses with $F(df = 32)$ and (p Values and R^2 Effect Size) for Prediction of Change in ERP Data, by the Improvement in Clinical Features of ADHD

Change: ERP Components	Change: CPRS-R:L Ratings						
	ADHD Index	Restless-Impulsive	Emotional Lability	Oppositional	Hyperactivity	DSM-IV Inattentive	DSM-IV Hyperactive
Right Occipital P120 Amplitude							
Anger	–	–	10.18 (.001, 46%)	5.22 (.040, 25%)	7.74 (.016, 37%)	7.63 (.015, 36%)	7.77 (.013, 37%)
Fear	–	–	9.93 (.003, 44%)	7.94 (.012, 38%)	7.04 (.019, 34%)	–	7.13 (.020, 34%)
Left Occipital P120 Amplitude							
Anger	6.25 (.035, 30%)	–	9.85 (.005, 42%)	–	6.31 (.025, 31%)	–	–
Fear	–	–	9.80 (.007, 41%)	–	5.39 (.039, 27%)	–	7.69 (.016, 35%)
Neutral	5.98 (.04, 22%)	–	10.07 (.002, 45%)	7.85 (.020, 30%)	7.10 (.019, 35%)	8.04 (.011, 38%)	7.42 (.021, 33%)
Right Occipital N170 Amplitude							
Anger	–	7.02 (.023, 24%)	8.56 (.010, 41%)	4.35 (.06, 19%)	4.99 (.05, 20%)	–	–
Fear	6.59 (.021, 31%)	6.61 (.032, 31%)	10.47 (.002, 46%)	8.01 (.011, 32%)	6.35 (.025, 31%)	8.24 (.010, 39%)	–
Disgust	6.15 (.037, 24%)	–	8.82 (.009, 40%)	8.81 (.009, 41%)	8.74 (.012, 42%)	8.65 (.008, 40%)	–
Neutral	6.33 (.035, 23%)	–	7.75 (.015, 38%)	5.13 (.040, 21%)	9.79 (.008, 43%)	–	–
Happiness	–	–	–	–	–	–	–

Bolded results are significant at the corrected p value of .008.

ADHD, attention-deficit/hyperactivity disorder; CPRS-R:L, Conners' Parent Rating Scale-Revised: Long Version; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.; ERP, event-related potential.

ERP Latency. There was a significant medication by emotion interaction for both right [$F(5,160) = 5.33$, $p = .02$] and left [$F(5,160) = 5.33$, $p = .02$] temporal P300 latency (Figure 3). Methylphenidate was found to speed P300 latency (indicating improvement) for anger ($p < .01$) and fear ($p < .05$) bilaterally and neutral ($p < .01$) for the left temporal region (Supplement 1).

Postmedication Change in ERPs and Prediction of Change in Clinical Features

The most consistent associations were for improvements in CPRS-R:L ratings of emotional instability and hyperactivity, predicted by changes in occipital P120 and N170, across each expression except happiness (Table 4). Improvement in CPRS-R:L ratings of inattention and oppositional features were predicted by more specific changes in right-sided P120 and N170 amplitude (Table 4). There were no significant contributions from age or estimated IQ.

In contrast, changes in P300 amplitude and latency with MPH did not predict clinical change, suggesting that the impact of stimulants on the first 200 msec of emotion processing is important for clinical improvement. Changes in emotion recognition with MPH were also unrelated to changes in clinical features.

Discussion

This study provides new evidence to show that ADHD in young male adolescents is distinguished by emotion-related disturbances in occipitotemporal brain systems. These disturbances were apparent within 200 msec poststimulus and associated with both negative mood and emotional lability. Treatment with MPH brought an improvement in brain activity, which predicted improvements in emotional lability, while negative mood persisted after treatment.

Along with defining clinical features—hyperactivity, impulsivity, oppositional behavior, and cognitive problems/inattentiveness—the ADHD group was characterized by emotional lability and significantly higher levels of depression and anxiety

than healthy participants. ADHD adolescents also had difficulties in recognizing expressions of emotion. Recognition was particularly impaired for threat-related (anger, fear) expressions, which extends on previous reports (3,25–27) to suggest a specific deficit in recognizing social signals of potential threat in ADHD.

At the neural level, the most pronounced disturbance was a reduction in the occipital P120 in ADHD relative to healthy control subjects. This reduction was apparent across both left and right occipital cortices for anger and fear perception. These P120 reductions were associated specifically with poor emotion recognition and the constellation of depression, anxiety, emotional lability, and hyperactivity. The P120 is associated with early, feasibly automatic perceptual analysis of emotion (15,16). At this early stage, neural pathways, including early visual association areas, provide direct sensory input to the amygdala (36). In ADHD, impairments in these early visual pathways may disrupt the initial perceptual analysis of salient, particularly threat-related, signals and in turn contribute to negative mood and poor emotion regulation. In adults, reductions in the frontal concomitant of the P120 (i.e., the N120) contribute to higher depression and anxiety (40), suggesting a distinctive pathway for negative mood in adolescent ADHD.

Subsequent alterations in the N170 and P300 in ADHD feasibly reflect a general shift in the ERP waveform as a flow-on effect from the earlier P120. Consistent with this possibility, these components showed only isolated correlations with negative mood and clinical features. The right occipital N170 (120–220 msec) was exacerbated in ADHD, suggesting an overprocessing and encoding of emotional input, which nonetheless does not compensate for early disruptions. In the following period (300–400 msec), the reduction and delay in the temporal cortex P300 may reflect flow-on difficulties with contextual processing of this emotional input, particularly threat-related signals (11,16,19,20). A slowing of the P300 with negative mood in adults is again most apparent in frontal systems (36), consistent with the possibility that there is a distinctive temporo-occipital pathway for mood disturbances in ADHD.

Treatment with MPH brought the expected improvement in clinical features in ADHD, assessed by CPRS-R:L ratings. While emotion recognition also showed mean trends in the direction of improvement following MPH, recognition remained poorer in medicated ADHD subjects than in control subjects. For ERPs, the right occipital P120 showed the greatest increase (indicating improvement) with MPH, while there was only a minimal decrease for the N170 and no change for the temporal P300. The increase in right occipital P120 was coupled with an exaggeration of the left temporal P120, suggesting that stimulant treatment may also contribute to a mechanism of compensation for emotion processing disturbances. By contrast, there was no shift in depressed and anxious mood for ADHD subjects, which remained at a consistently high level compared with control subjects following MPH.

The shifts in occipital P120 with MPH were found to predict the improvements in clinical features of ADHD, most consistently for hyperactivity and emotional lability. These findings indicate that stimulants may have an effect on stabilizing emotional brain activity, which may not only contribute to improvements in the defining clinical profile of ADHD but also to regulation of emotional behaviors.

Methylphenidate has been found to improve ERP disturbances elicited by cognitive tasks in ADHD (41–44). It is possible that stimulant-related improvements in generalized cognitive functions contribute to improvements in emotion-related neural activity. For instance, the positive effect of stimulants on engaging brain systems for selective attention may also facilitate systems for appraising emotionally significant input. Studies examining both emotional and cognitive tasks would help elucidate the specific effects of MPH on emotional brain systems in ADHD.

The less effective impact of stimulants on behavioral measures of emotion recognition may reflect the fact that these measures capture the output of stimulus processing and are therefore less direct, while ERPs provide a direct and real-time index of neural processing (45). Alternatively, the apparent lack of stimulant impact on recognition might reflect the additional task requirements to categorize and select responses compared with ERP recording. Future studies might employ additional, finer-grained behavioral measures of emotion recognition, including ones with lesser task demands, to tease apart these issues.

Future research might also address some limitations of this study. Given the limited spatial resolution of ERPs, functional magnetic resonance imaging (MRI) would provide valuable complementary evidence for the role of temporo-occipital networks in emotional disturbances in ADHD and their improvement with MPH. Functional MRI might also help confirm if anxiety and depression in ADHD are associated with distinct neural systems compared with temporolimbic and frontal systems implicated in primary affective disorder (46).

A number of additional clinical and demographic factors might be considered in future research. This study was limited by the reliance on a self-report measure of anxiety and depression, and future studies might employ supplementary clinician ratings. The potential role of comorbid conditions such as learning disorders also needs systematic investigation. While emotion-related disturbances did correlate with DSM-IV subtype ratings in this study, the generality of these disturbances might be confirmed with a direct comparison of the three ADHD subtypes. Precise measures of puberty, a time of significant change in emotional and brain function (47), would elucidate its contribu-

tion to the present findings in adolescent ADHD. Relatedly, given sex differences in both emotional brain function (48) and in stimulant effects in ADHD (49), it would be valuable to extend the present research to female subjects with ADHD.

This study was also limited to one open-label treatment intervention. Given the promising results, additional studies are warranted to compare the effects of different treatment types (such as stimulants versus nonstimulants) on emotional function in randomized, controlled designs, with direct tests of medication level to ensure compliance. These designs would also enable comparison of responders versus nonresponders to treatment.

Our findings provide new evidence that ADHD is characterized by a profile of disturbances in emotional brain function and behavior. Disruptions to emotional brain function may be improved with MPH. Objective measures of emotional function may therefore provide valuable additional tools for use in clinical assessment of ADHD and treatment outcomes.

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Supplementary material cited in this article is available online.

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