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Atypical Neural Responses to Vocal Anger in Attention-Deficit/Hyperactivity Disorder

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Key points:

- Responses to expressions of hostility by others may be altered in children with ADHD because they have difficulties in recognising negative emotions.
- In this, the first study of its kind, we used electrophysiological methods to study brain event-related potentials of children with ADHD in response to angry, happy and neutral vocal expressions.
- Compared to controls, children with ADHD displayed significant N100 enhancement and P300 attenuation to angry relative to neutral voices.
- This pattern of results provides new evidence that very early stages of emotion processing are implicated in ADHD.
- Future research should test the hypothesis that the N100 component is a marker for automatic hyper-orientation to vocal threat stimuli in ADHD.

Abstract

Background: Deficits in facial emotion processing, reported in attention-deficit/hyperactivity disorder (ADHD), have been linked to both early perceptual and later attentional components of event-related potentials (ERPs). However, the neural underpinnings of vocal emotion processing deficits in ADHD have yet to be characterised. Here, we report the first ERP study of vocal affective prosody processing in ADHD.

Methods: ERPs of six to eleven year old children with ADHD (n=25) and typically developing controls (n=25) were recorded as they completed a task measuring recognition of vocal prosodic stimuli (angry, happy and neutral). Audiometric assessments were conducted to screen for hearing impairments.

Results: Children with ADHD were less accurate than controls at recognising vocal anger. Relative to controls, they displayed enhanced N100 and attenuated P300 components to vocal anger. The P300 effect was reduced, but remained significant, after controlling for N100 effects by rebaselining. Only the N100 effect was significant when children with ADHD and comorbid conduct disorder (n=10) were excluded.

Conclusion: This study provides the first evidence linking ADHD to atypical neural activity during the early perceptual stages of vocal anger processing. These effects may reflect pre-attentive hyper-vigilance to vocal anger in ADHD.

Keywords: attention-deficit/hyperactivity disorder, conduct disorder, emotion processing, vocal, ERP, prosody.

Introduction

Studies of attention-deficit/hyperactivity disorder (ADHD) pathophysiology have typically focused on cognitive (Konrad, Neufang, Hanisch, Fink & Herpertz-Dahlmann, 2006) and, more recently, motivational processes (Sonuga-Barke & Fairchild, 2012). However, emotion dysregulation is increasingly regarded as an important clinical feature of the condition (Shaw, Stringaris, Nigg & Leibenluft, 2014). Consequently there has been a renewed interest in how individuals with ADHD process negative emotional expressions, such as anger, in the faces and voices of others (Uekermann et al., 2010). Such expressions of hostility may act as triggers for negative emotional outbursts in children with ADHD and contribute to coercive cycles of parent-child interaction (Johnston & Jassy, 2007).

Building on the body of relevant behavioural evidence (Chronaki et al., 2013; Shapiro, Hughes, August & Bloomquist, 1993), recent electrophysiological research has demonstrated altered neural responses to facial expressions of anger in ADHD. Both early sensory and later attention-mediated cognitive processes have been implicated (Dennis, Malone & Chen, 2009; Eimer & Holmes, 2007). For example, Williams and colleagues found enhanced facial anger-related modulation of the N170 event-related potential (ERP) component followed by an attenuated P300 in adolescents with ADHD (Williams et al., 2008). These effects were interpreted as indicating deficits in both early perceptual and later context-related processing of angry faces (Williams et al., 2008). In contrast to the above findings, Ibáñez and colleagues (2011) found that controls showed modulation of the N170 component by valence but this pattern was not observed in adult ADHD patients in a task that involved classifying the valence of facial expressions. In addition, both child (Köchel, Leutgeb & Schienle, 2014) and adult ADHD samples (Köchel, Leutgeb & Schienle, 2012) have been reported to show attenuated late positive potentials during the processing of angry faces in an inhibitory task.

Emotional meaning in the expressions of significant others in our social environment is not solely conveyed by facial expressions, but also by voices – both in terms of content and also prosody, especially emotional tone (Banse & Scherer, 1996). While ADHD-related

deficits in emotion prosody recognition have been identified in behavioural studies (Chronaki et al., 2013; Corbett & Glidden, 2000; Norvilitis, Casey, Brooklier & Bonello, 2000), there have been no studies investigating their neural underpinnings. This is surprising given that in everyday life vocal anger is likely to be as critical as facial anger in terms of triggering inappropriate emotional responses in individuals with ADHD.

In healthy controls, vocal emotional expressions modulate ERPs over a range of scalp regions in both adult (Schirmer & Kotz, 2006) and child samples (Chronaki et al., 2012). In a similar way to that seen in face processing studies, there are emotion specific effects at both early sensory and later attention-mediated components (Iredale, Rushby, McDonald, Dimoska-Di Marco & Swift, 2013; Schirmer & Kotz, 2006). For instance, the N100, an index of the initial extraction of information and sensory analysis of stimuli (Wunderlich & Cone-Wesson, 2001), has been shown to be affected by vocal emotional content (Iredale et al., 2013; Pinheiro et al., 2011). The auditory N100 (80-150 ms) shows a parietal distribution in young children which displays an anterior shift in the teenage years (Pang & Taylor, 2000). The N100 response to vocal anger, in particular, is prominent in parietal-occipital areas in 6-11-year-old children (Chronaki et al., 2012). The P300, reflecting attentional engagement and allocation of cognitive resources (Banaschewski & Brandeis, 2007; Nelson & McCleery, 2008), and the N400, reflecting cognitive evaluation (Schirmer & Kotz, 2006), are also modulated by emotion, especially for negatively-valenced stimuli (Broyd et al., 2012). The N400 to vocal emotion is evident in parietal-occipital scalp regions in healthy individuals (Toivonen & Rama, 2009). Research using Functional Magnetic Resonance Imaging (fMRI) has shown activation of the cuneus in medial occipital cortex in response to angry voices (Sander et al., 2005), which was suggested to reflect vivid visual mental imagery induced by hearing angry voices (Kosslyn & Thompson, 2003).

This paper reports the first ERP study of vocal prosody recognition in ADHD. Building on previous findings, we hypothesized that anger prosody recognition deficits observed behaviourally in ADHD would be reflected in ERP abnormalities, and specifically in attenuated P300 amplitudes to vocal anger. In addition, building on the face processing

literature showing exaggerated early perceptual face-specific components (i.e., N170) to anger, we expected increased N100 amplitudes to anger from vocal expressions in ADHD. The above would fit with a model of rapid initial hyper-orientation to threatening (angry) stimuli followed by deficits in later, cognitive evaluation of the emotional significance of these stimuli (Williams et al., 2008). As vocal signals of anger normally act as signals of social punishment, lower sensitivity to anger in children with ADHD at later, more evaluative stages of processing, may limit their ability to appropriately modify their behaviour in social interactions.

To test the above hypotheses we examined ERP differences between ADHD and controls in components related to early sensory processing (N100), later attentional engagement (P300) and cognitive evaluation (N400) in response to angry, happy and neutral prosodic stimuli. ADHD is frequently comorbid with conduct disorder (CD; (Biederman, 2005), and emotional dysregulation (Stringaris, Rowe & Maughan, 2012) and alterations in emotion recognition are also reported in CD (Fairchild, Van Goozen, Calder, Stollery & Goodyer, 2009). It is possible that difficulties in emotion processing in ADHD could be driven by co-occurring CD. Therefore, and contrary to previous ERP research which has not taken CD comorbidity in account (Williams et al., 2008), we sought to investigate whether CD comorbidity contributed to our behavioural and ERP results.

Methods and Materials

Participants

Thirty typically-developing children (2 girls) and 36 children with ADHD (1 girl), aged between 6 and 11 years, were recruited into the study. Informed written consent was obtained from the parent(s) and written assent from the child. Children with ADHD were recruited from local child and adolescent mental health clinics and all had a clinical diagnosis of ADHD. They all undertook a comprehensive clinical research assessment as part of the South Hampshire ADHD Register. This included the ADHD, CD and Oppositional Defiant

Disorder (ODD) scales of the parent version of the Diagnostic Interview Schedule for Children- NIMH (DISC-IV; Shaffer et al., 1993), the parent and teacher version of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) to establish the pervasiveness of the presentation and the 'sadness' scale of the Children's Behaviour Questionnaire (CBQ; Putman & Rothbart, 2006) to provide a measure of internalising problems. Full scale IQ was also assessed using the Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 2004). Patients were only included if they met criteria for ADHD on the DISC-IV. In addition, all but two scored above borderline thresholds on the hyperactivity subscales of the SDQ-teacher report. Results did not change after excluding these two patients. Controls were recruited from local mainstream schools. They completed the same measures as the ADHD patients apart from the DISC-IV. They also only completed the Block Design and Vocabulary sub-tests of the WISC-IV. General exclusion criteria were; a) IQ<75; b) hearing difficulties, as assessed with a clinical audiometer; and c) diagnosis of autism spectrum disorder or a neurological condition. In addition, two control children were excluded as they scored above borderline thresholds on the hyperactivity subscales of the SDQ. Nine children (six ADHD, three controls) were excluded due to excessive ERP artifacts. The final sample included 25 controls (mean age=9.04 years, SD=1.46 years, age range 6.83-11.67) and 25 children with ADHD (mean age=8.85 years, SD=1.47 years, age range 6.33-11.50). Ten children with ADHD also had a DISC-IV CD diagnosis and ten were taking methylphenidate medication but all were asked to withdraw their medication 24 hours prior to testing (5 half-lives). Participant characteristics are presented in Table 1. The study was approved by the University of Southampton Ethics Committee and the National Health Service (NHS) Research Ethics Committee.

Vocal Emotion Recognition Task

Pure tone audiometric testing was conducted at the beginning of the experimental session with a standard clinical audiometer to establish whether participants' hearing threshold was

within the average range defined as 25 dB following the British Society of Audiology Recommended Procedures (2004).Task stimuli consisted of standardised and previously validated in children (Chronaki et al., 2012) vocal prosodic stimuli (an interjection 'ah' sound) developed by Maurage and colleagues (Maurage, Joassin, Philippot & Campanella, 2007). These were angry and happy emotions (both at high intensity) along with neutral control stimuli (Maurage et al., 2007). Vocal stimuli were the same as in our previous work (see Table S1, Chronaki et al., 2012). To rule out stimulus-specific variation in the ERP components, we also used two different versions of each vocal stimulus that were recorded by different female actors. Children were instructed to identify the type of emotional prosody by pressing one of the three response box buttons with the labels 'angry', 'happy' or 'neutral'. Each trial began with the presentation of a central fixation cross (500 ms), which was replaced by a blank screen and the simultaneous presentation of the prosodic stimulus. The screen remained blank until the participants responded and there was a 1000 ms interval before the onset of the next trial. Button presses were logged via Presentation software (Neurobehavioral Systems, Albany, CA). The session consisted of a practice block (12 trials - four of each emotion) and 360 experimental trials (120 trials per emotion type/60 trials per actor) were presented in two blocks of 180 trials. Emotional stimulus presentation order was randomized. There was a 5-minute rest between blocks. The task lasted approximately one hour. Children did not receive any feedback about their responses.

Electrophysiological recording and processing

Electroencephalographic (EEG) data were recorded from an electrode cap (Easycap, Herrsching, Germany) containing 66 equidistant silver/silver chloride (Ag/AgCl) electrodes using Neuroscan Synamps^2 70 channel EEG system. Cap electrodes were referenced to the nose. The EEG data were sampled at 250 Hz with a band pass filter at 0.1 to 70 Hz using an AC procedure and recorded from 19 sites (see Figure S1). A ground electrode was fitted midway between the electrode at the vertex and frontal site (number 32). Vertical electro-

oculogram (vEOG) was recorded from four electrodes: two bipolar electrodes were placed directly beneath the left and right eyes, while the two electrodes placed above the right and left eye were included within the electrode cap. Impedances for vEOG, reference and cap electrodes were kept below 5 kΩ. The ERP epoch was defined as 100 ms pre-stimulus to 1000 ms post-stimulus and was filtered with a low-pass filter down 48 dB at 32 Hz. An ocular artifact reduction procedure (Semlitsch, Anderer, Schuster & Presslich, 1986) based on vEOG activity was used to remove the influence of blinks and other eye movements; epochs were rejected if amplitudes exceeded ±150 μV at any EOG or scalp sites included in analyses or if participants responded incorrectly. Average ERPs were calculated for each emotion type (Angry, Happy, Neutral).

A minimum of 20 artifact-free epochs out of a total of 60 epochs for each emotion type (and a minimum of 10 artifact free epochs per actor) were used for calculating ERP averages for each block. The mean and SD of the number of epochs included in the analyses for each emotion type were as follows: Controls: Angry: M=48.64, SD=7.61, Neutral: M=49.50, SD=5.44, Happy: M=46.80, SD=8.14; ADHD group: Angry: M=40.90, SD=11.75, Neutral: M=39.80, SD=12.94, Happy: M=38.30, SD=12.90. There was no significant effect of emotion condition or actor on the number of correct and artifact free epochs in the healthy controls and ADHD group (ps >.17). The groups differed in the number of correct and artifact free epochs for angry ($F(1,48)=7.60, p<.01$), happy($F(1,48)=7.80, p<.05$) and neutral stimuli ($F(1,48)=11.90, p<.01$), with fewer artifact-free epochs for children with ADHD than controls. However, mean amplitude is not biased by the mean number of trials (Luck, 2010). Grand average ERP waveforms were displayed for each stimulus for the purpose of defining each component's latency range. A baseline-to-peak mean amplitude method was used to calculate the N100 (80-180 ms), P300 (260-380 ms) and N400 (380-500 ms) components. Peaks were confirmed by visual inspection and clearly visible in all individual waveforms. In line with our earlier work (Chronaki et al., 2012) and previous literature (Schirmer & Kotz, 2006), the ERP analyses focused on parietal (sites 12, 13, 14, 24, 26) and occipital (sites 37, 38, 39, 40) regions. To increase measurement reliability (Dien

& Santuzzi, 2005) mean amplitudes for each ERP component were calculated as an average for a number of defined groups of electrode sites (see Figure S1).

To examine whether any differences between the ADHD group and controls found for later components (i.e., P300, N400) reflected differences in prior components, as altered exogenous processing were driven by differences in earlier components (Johnstone, Barry & Clarke, 2013), we repeated all analyses for the P300 after rebaselining the waveforms to an N100 anchor and all N400 analyses after doing this with respect to P300. Following Luck and colleagues (Woodman, Arita & Luck, 2009), we assessed P300 activity by rebaselining the ERPs to the 100-ms interval overlapping with the N100 component (80-180 ms).

Data Analysis

Performance data: Discrimination accuracy was computed for each target emotion using 'hits' -i.e., number of angry, happy or neutral expressions classified correctly (Corwin, 1994). Kolmogorov-Smirnov tests indicated that discrimination accuracy values were not normally distributed – probably because of ceiling effects ($p<.01$). Because of this, group effects were examined using Mann-Whitney tests. Correlations between child age, hearing, IQ, internalising problems and accuracy were assessed using Spearman's Rho tests.

ERP data: Initial models were run to examine the effects of (i) actor and (ii) task period (first half versus second half; see Figure S2). This second analysis was especially important because the current task was run with twice as many trials in each emotion condition as the original study using this task (Chronaki et al., 2012) because in this study we used two actors per emotion**.** Effects of emotion on ERPs were only found in the first half of the task - equivalent to the length of the whole task in our previous study (Chronaki et al., 2012). All children in this study successfully completed the whole task; however, as our objective was to investigate changes in prosody processing in ADHD, we restricted our analyses to the first half of the task in which typically-developing children showed emotion effects. Pearson's correlations examined the relationship between ERPs and child symptoms.

Repeated-measures ANOVA with group (ADHD, controls) as the between-subjects factor, emotion type (angry, happy, neutral) as the within-subjects factor and child sadness as the covariate were performed with planned contrasts comparing angry to neutral and happy. N100, P300 and N400 amplitudes over each scalp region were the dependent variables. Child sadness was included as a covariate because ADHD and controls significantly differed on this measure (see Table 1). In addition, when examining correlations in the two groups separately, we found that sadness was negatively associated with N100, P300 and N400 amplitudes to angry and neutral voices over parietal and occipital regions (Pearson's r = -.40 to -.54, $p<.01$). Because sadness influenced the neural response to vocal affect we added it as a covariate in the analyses. We also re-ran all analyses excluding the 10 ADHD patients with comorbid CD. Apart from conduct problems (as expected) ADHD patients with and without CD did not differ on background or behavioural characteristics. A detailed comparison between these two groups is provided in the supplementary materials.

Results

Performance data

The mean accuracy for all emotions was generally high in both groups (see Table 2). However, children with ADHD were less accurate at recognising anger compared with controls ($U=210$, $Z=-2.00$, $p=.047$, $r=-0.28$). Children with ADHD tended to err by miscategorising angry voices as neutral. Both controls and children with ADHD showed a tendency to classify vocal expressions as neutral than happy ($p<.05$). The group difference in accuracy did not persist when the 10 participants with comorbid CD were excluded ($U=160$, $Z=-.76$, $p>.05$, $r=-0.10$). ADHD children with CD did not significantly differ in accuracy from ADHD children without CD (see Table S2 for details). Age, mean hearing threshold, IQ, and internalising problems were not significantly associated with accuracy for any emotion type for either group (ps > .05).

-------Insert Tables 1-2 here-------

ERP data

There were no associations between ERPs and child age, hearing threshold or IQ (Pearson's r =from .03 to .25, ps > .11). Correlations between ERPs and child symptoms are presented in the supplementary materials. ADHD children with CD did not differ significantly with regard to any ERP components from ADHD children without CD (see Table S2).

Grand mean averages for each emotion are presented in Figure 1. The mean amplitudes for the N100, P300 and N400 components are presented in Figures 2-4.

N100: There was no significant main effect of group on N100 amplitudes (all *p*s >.11). Overall, N100 amplitudes were larger to angry than to neutral stimuli (F (1, 47) = 3.90, p= .050, ηp^2 =.08). There was a significant group x emotion interaction effect on N100 amplitude in the occipital (F (2, 94) = 6.25, p=.003, ηp^2=.11) and parietal (F (2, 94) = 5.22, p= .007, ηp^2=.10) regions; ADHD participants showed larger amplitudes to angry compared to neutral voices compared to controls (see Table 3 and Figure 2). These effects persisted after excluding comorbid CD cases (ps: Occipital = .007; Parietal: = .025) and, in a separate analysis, medicated participants (ps: Occipital = .009; Parietal: = .040). There were also larger amplitudes to happy compared to neutral voices in the ADHD group compared to controls (see Table 3 and Figure 2) but this effect was no longer significant when the comorbid CD cases were excluded (p=.10). Mean N100 amplitude values for ADHD children with and without comorbid CD are provided in supplementary material (see Table S2).

P300: Occipital P300 amplitudes were larger to neutral than angry (F (1, 47) = 8.35, p= .006, ηp^2=.15) and happy stimuli (F (1, 47) = 9.30, p= .004, ηp^2=.16). There was no significant main effect of group (p >.25). There was a significant group x emotion interaction effect on P300 amplitude in the occipital (F (2, 94) = 6.12, p= .003, ηp^2=.11) and parietal (F (2, 94) = 6.01, p= .003, ηp^2=.11) region. P300 amplitudes were significantly reduced to angry compared to neutral voices in ADHD participants compared to controls (see Table 3 and Figure 3). These effects persisted when CD cases were excluded (ps: occipital = .032;

parietal = .023). After rebaselining for N100 amplitudes, the group x emotion interaction effect at P300 remained significant, although it was somewhat weaker (F (2, 96) = 4.00, p= .022, ηp^2=.07); the P300 remained significantly reduced to angry compared to happy voices in ADHD participants compared to controls in both the occipital (F (1, 48) = 5.47, p= .024, ηp^2=.10) and parietal (F (1, 48) = 4.63, p= .036, ηp^2 =.09) regions (see Figure 3). After excluding participants on medication, these effects remained for the occipital and parietal P300 after rebaselining (p<.01). These effects did not persist when the CD cases were excluded (ps >.20). Mean P300 amplitude values for ADHD children with and without comorbid CD are provided in supplementary material (see Table S2).

N400: Parietal N400 amplitudes were generally higher for controls than participants with ADHD, as shown by a main effect of group (F (1, 47) = 5.01, p= .030, ηp^2=.09). Occipital N400 amplitudes were larger for angry (F (1, 47) = 5.36, p= .025, ηp^2=.10) and happy (F (1, 47) = 9.30, p= .004, ηp^2 =.16) compared to neutral stimuli. Emotion effects on parietal N400 were limited to the comparison of happy versus neutral voices (F (1, 47) = 6.20, p= .016, ηp^2=.12). There was a significant group x emotion interaction effect on N400 amplitude in the occipital (F (2, 94) = 5.22, p= .007, ηp^2=.10) and parietal (F (2, 94) = 4.75, p= .011, ηp^2=.09) region. There were larger amplitudes to angry compared to neutral voices in ADHD participants compared to controls (see Table 3 and Figure 3). When the 10 participants with CD were excluded these effects persisted (ps: occipital = .050; parietal = .044). There were no significant effects of group or group x emotion interaction effects on the N400 amplitudes following rebaselining for P300 (ps >.15, see Figure 3). Mean N400 amplitude values for ADHD children with and without comorbid CD are provided in supplementary material (see Table S2).

-------Insert Table 3 and Figures 1-4 here-------

Discussion

Here we report the first evidence of altered neural responses during vocal prosody

processing in ADHD. The strongest and most robust group effects were found for the early sensory N100 component for anger, with the ADHD group showing larger amplitudes to angry relative to neutral voices whereas the control group showed no differences between these emotions at this stage of processing. We also found attenuated P300 amplitudes and increased N400 amplitudes to anger versus neutral stimuli in the ADHD group compared to controls, although these effects were reduced in magnitude or rendered non-significant, respectively, after rebaselining for earlier components suggesting that they may reflect 'flow-on' effects.

While in some ways the N100 component occurs at a surprisingly early stage to show modulation by emotional valence, there is a growing literature implicating early sensory processes in vocal emotion processing (Bostanov & Kotchoubey, 2004; Iredale et al., 2013). Furthermore, the N100 and other early components have previously been implicated in emotional processing in a range of psychiatric disorders. For example, Pinheiro and colleagues recently found abnormally enhanced N100 amplitudes during a negative relative to positive mood induction using emotional pictures in schizophrenic patients (Pinheiro et al., 2013). The same authors found reduced N100 for prosodic sentences with semantic content in children and adults with Williams syndrome (Pinheiro et al., 2011). Asperger's syndrome (Korpilahti et al., 2007) and childhood anxiety (Hogan, Butterfield, Phillips & Hadwin, 2007) are also associated with altered N100 responses to auditory stimuli. Interestingly, while some researchers have suggested impairments in auditory processing of non-emotion stimuli at the very earliest sensory stages in ADHD (Loiselle, Stamm, Maitinsky & Whipple, 1980; Zambelli, Stamm, Maitinsky & Loiselle, 1977), most studies suggest that N100 components are normal in most paradigms (Johnstone & Barry, 1996; Oades, Dittmann-Balcar, Schepker, Eggers & Zerbin, 1996). This is consistent with the results of the current study where alterations revealed no general deficit in the N100 component but rather an emotion-specific increase, while amplitudes were normal for neutral stimuli. The N100 findings are consistent with the idea that angry vocal expressions by others lead to a rapid and almost automatic hyper-orientation in children with ADHD. The auditory N100

component has been proposed to reflect a rapid 'early selection' mechanism underlying auditory attention (Woldorff et al., 1993). The N100 in the posterior auditory cortex is described as a preattentive gating mechanism that determines to what degree auditory stimuli capture awareness (Jaaskelainen et al., 2004). Early sensory ERPs (e.g., N100, P50) have been shown to reflect inhibition deficits related to vigilance to environmental stimuli (Cullum et al., 1993) in schizophrenia (Olincy et al., 2000) and ADHD (Bruckmann et al., 2012; D'Agati et al., 2013; Gonzalez-Trejo et al., 2011). Early hyper-vigilance to angry faces as reflected by increased P100 amplitude has also been shown in anxiety disorders (Mueller et al., 2009). The possibility of early pre-attentive hyper-vigilance to vocal anger in ADHD requires further investigation.

We also found significant, but less robust, anger-specific attenuation of the P300 component in children with ADHD. Our findings are consistent with previous research using facial stimuli showing P300 reductions to anger in ADHD (Williams et al., 2008). The P300 has been implicated consistently in both visual and vocal emotion processing as an index of attentional allocation to emotional stimuli prior to cognitive evaluation (Banaschewski & Brandeis, 2007; Schirmer & Kotz, 2006). Difficulties in attending to or perceiving others' emotions and especially signals of social punishment such as vocal anger may explain impaired social functioning in some children with ADHD. More generally, P300 abnormalities have been shown across a wide range of both social and non-social tasks in individuals with ADHD (Barry, Johnstone & Clarke, 2003; Johnstone et al., 2013), although these appear to be normalized by motivational manipulations and stimulant medication (Williams et al., 2008). Once again, no evidence for a fundamental deficit in P300 amplitudes was observed in ADHD in this study, given that the pattern of attenuation was specific to anger prosody. This finding of reduced P300 amplitudes to angry voices in children with ADHD mirrors to some extent the behavioural findings showing that children with ADHD were significantly less accurate in recognising vocal expressions of anger compared to typically developing children. This suggests lower sensitivity to social signals of punishment (i.e., anger) in some children with ADHD.

Taken together, the pattern of increased N100 amplitudes followed by reduced P300 amplitudes to vocal anger is consistent with a model of initial hyper-orientation to anger followed by attentional gating, perhaps suggesting an emotion-specific attempt to regulate the excitatory effects of experiencing anger from others. Whether such effects generalise to other emotionally-arousing or threatening stimuli and situations or are instead specific to angry voices will require further research. For instance, delayed rewards led to reduced N100 amplitudes due to their lower emotional salience in healthy individuals (Blackburn, Mason, Hoeksma, Zandstra & El-Deredy, 2012). It is interesting to note that while the N100 effects were robust when excluding patients with comorbid CD, the residual, and admittedly smaller, P300 effects were partly accounted by the presence of comorbid CD although this may be due to lack of power to detect a significant effect. Given the specific association between CD, neuropsychological deficits and emotional lability in ADHD (Banaschewski et al., 2012), one possibility worth investigating is that this attentional gating to anger may be especially important in children with ADHD who are vulnerable to developing antisocial behaviour.

While providing the first evidence of neural abnormalities to vocal anger prosody in ADHD, further study is required in a number of areas. First, only one class of positive (happy) and one class of negative (anger) stimuli was used. These findings could be extended in future studies by including a wider range of emotions, male and female actors and both social and non-social stimuli, to explore the specificity of the effects to anger and vocal expressions. The ecological validity of the stimuli could be improved by using cross-modal presentation of emotion (faces and voices), as in real life situations. In the current study, potential physical differences between the stimuli are unlikely to have affected the anger specific findings given the fact that ERPs in controls were similar for all emotions and only differed in ADHD for anger. Second, longitudinal studies are required to understand the developmental changes in ERPs. For instance, there are major developmental changes in the N100 component (Pang & Taylor, 2000). Recent work in children has demonstrated emotional prosody effects on the N100 in parietal-occipital areas (Chronaki et al., 2012).

Furthermore, a number of fMRI studies have shown activation of occipital regions specifically to anger prosody (Johnstone, van Reekum, Oakes & Davidson, 2006; Sander et al., 2005), suggesting visual imagery processes (Sander et al., 2005). In addition, only males were tested in this study. Future studies should include both males and females. Another limitation of the study was that the task was not optimized to show differences in performance between the groups but rather to have sufficient trials for ERP analyses. A final limitation is that some demographic information was not available for the participants in this study (i.e., parent education). Future studies should consider collecting this information in a uniform way if the two groups are recruited from different sources.

Finally, while we were able to repeat the analyses excluding participants with comorbid CD and show that most of the findings were independent of CD diagnosis, the influence of externalizing comorbidity cannot be ruled out as the majority of ADHD participants had comorbid diagnoses of oppositional defiant disorder (ODD). Further research using a systematic approach comparing pure and comorbid ADHD and CD/ODD cases would help clarify the extent of altered vocal emotional processing in these disorders.

From a clinical perspective our results highlight the need to take account of the way in which patients with ADHD respond to negative affect in the voices of others and how this might impact on their ability to listen and follow instructions. The use of a non-threatening tone may therefore represent an important treatment goal in parent training. Furthermore, given our evidence of very early, possibly pre-attentive, hyper-orientation to angry voices some form of desensitization training may be called for.

In summary, we provide the first evidence for altered neural processing of affective prosody in children with ADHD relative to typically-developing children. These effects were most pronounced for vocal expressions of anger and were most robust during the early stages of perceptual processing. Further research needs to establish whether these effects are specific to vocal anger or represent a more general early hyper-orientation to cues signalling potentially aversive and threatening social and non-social events at early stages of sensory processing in individuals with ADHD.

Supplementary material

Table S1. Results of the acoustic analysis of the stimuli, including fundamental frequency (f0) in Hz and intensity in dB.

Figure S1. Montage with 19 sites used in EEG recording and sites per region.

Figure S2. Grand Averages to angry, happy and neutral voices in parietal and occipital regions in the first half and second half of the task in controls.

Table S2. Mean accuracy and ERP amplitude values for ADHD children with and without CD.

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Table 1. Sample Characteristics.

	ADHD (n=25)		Controls (n=25)		Comparison	
	Mean	S.D.	Mean	S.D.	F	p Value
Child age (years)	8.85	1.46	9.04	1.47	.20	*ns*
Full Scale IQ	99.04	10.82	102.60	10.20	.00	*ns*
Hearing threshold (dB)	9.70	3.08	9.60	3.70	1.55	*ns*
Strengths and Difficulties Questionnaire						
Hyperactivity	8.80	1.86	2.80	2.60	87.55	**.001**
Conduct Problems	6.00	2.70	1.30	1.50	57.80	**.001**
Emotional Problems	5.00	2.14	1.80	2.00	29.50	**.001**
Children's Behaviour Questionnaire						
Internalising (Sadness)	3.20	.68	2.36	.56	23.60	**.001**

Table 2. Mean percentage (SD) of correct trials (in bold) and misattributions in the two groups.

	Vocal Expression presented		
Identified as	Angry	Happy	Neutral
Controls			
Angry	**93.50(12.20)**	4.20(6.80)	3.40(3.20)
Happy	3.90(10.00)	**87.30(13.40)**	2.40(3.00)
Neutral	2.50(2.80)	8.30(7.90)	**94.20(4.30)**
ADHD			
Angry	**84.50(18.90)**	9.70(14.30)	9.20(11.67)
Happy	7.26 (9.20)	**75.87(23.70)**	11.90(14.95)
Neutral	8.10(10.30)	14.20(15.40)	**78.90(22.80)**

Table 3. Summary of 2 (group) x 3 (emotion) effects on event-related potential amplitudes

	Contrast	Details	F-value	Significance
Occipital				
N100	A vs. N	ADHD:-2.40 vs. 1.30 Controls:-0.60 vs. -2.70	13.40	.001
	H vs. N	ADHD:-1.60 vs. 1.30 Controls:-1.80 vs. -2.70	4.60	.040
P300	A vs. N	ADHD:-0.90 vs. 8.12 Controls: 2.80 vs. 2.78	9.90	.003
N400	A vs. N	ADHD:0.68 vs. 8.30 Controls:1.70 vs. 0.50	7.30	.010
Parietal				
N100	A vs. N	ADHD:-1.65 vs.1.30 Controls:-0.20 vs -2.60	10.70	.002
P300	A vs. N	ADHD:2.36 vs. 7.86 Controls:3.90 vs. 1.90	10.30	.002
N400	A vs. N	ADHD:2.00 vs. 7.98 Controls:2.90 vs. -0.41	7.00	.010

Note 1: Emotion: A= Angry, H=Happy, N=Neutral. The units in the 'details' column represent amplitude in μV. *Note 2:* After rebaselining for effects at earlier ERP components, the P300 effects became weaker, whereas the N400 effects were non-significant.

Figure captions

Figure 1. Grand Averages to angry, happy and neutral voices in occipital and parietal regions in the two groups. Group x Emotion interactions at N100, P300 and N400, with enhanced N100 and N400 amplitudes to angry and happy versus neutral stimuli in ADHD relative to controls, but reduced P300 amplitudes to angry versus neutral stimuli in ADHD relative to controls. Scale is -4 to +16 microvolts. Angry Happy Neutral

Figure 2. Bar graphs with error bars for the occipital (A) and parietal (B) N100 amplitudes to angry, happy and neutral voices in the two groups. Group x Emotion interactions (A, B) with enhanced N100 amplitudes to angry versus neutral stimuli in ADHD relative to controls (***p* <.01, ****p* <.001). Error bars represent standard error of the mean. Topographic maps (C) for the mean change in voltage distribution for angry, happy and neutral voices. Scalp values represent the ends of the colour scale in μV for the N100. Dark blue=negativity, red=positivity. The bar graphs plot the N100 in an adjusted positive scale to capture the amount of the amplitude change per emotion and group.

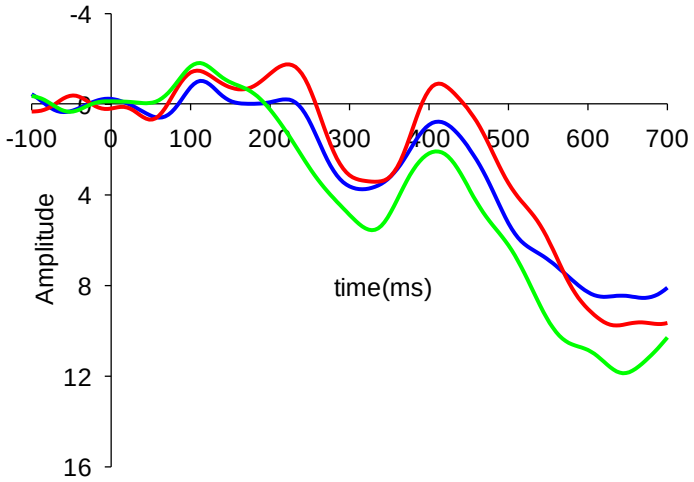
Figure 3. Bar graphs with error bars for the parietal and occipital P300 and N400 amplitudes to angry, happy and neutral voices. Group x Emotion interactions at P300 before rebaseline (A, C) and after rebaseline (B, D) with reduced P300 amplitudes to angry compared to neutral and happy stimuli in ADHD relative to controls. Group x Emotion interactions at N400 before rebaseline (E, G) and after rebaseline (F, H) with enhanced N400 amplitudes to angry relative to neutral stimuli in ADHD relative to controls before rebaselining (* *p*<.05, ***p* <.01, ****p* <.001). The bar graphs plot the N400 in an adjusted positive scale to capture the amount of the amplitude change per emotion and group.

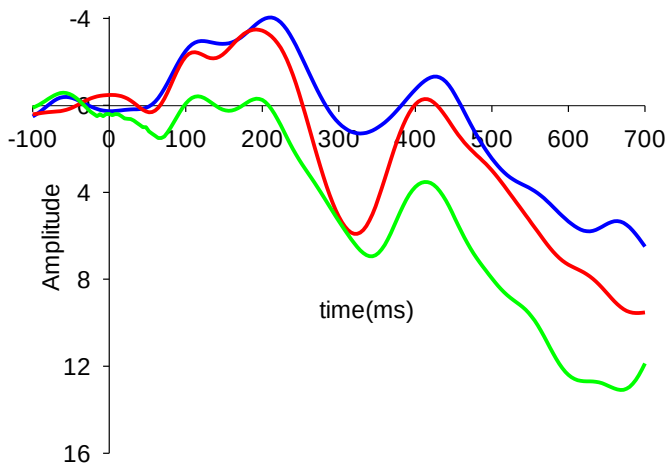
Figure 4. Topographic maps for the mean change in voltage distribution for angry, happy and neutral voices. Scalp values represent the ends of the colour scale in μV for the P300. Dark blue=negativity, red=positivity.

Controls

ADHD

Occipital





Parietal