Brain response to facial expressions in adults with adolescent ADHD

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ABSTRACT

The symptoms of ADHD tend to have continuity to adulthood even though the diagnostic criteria were no longer fulfilled. The aim of our study was to find out possible differences in BOLD signal in the face-processing network between adults with previous ADHD (pADHD, $n = 23$) and controls ($n = 29$) from the same birth cohort when viewing dynamic facial expressions. The brain imaging was performed using a General Electric Signa 1.5 Tesla HDX. Dynamic facial expression stimuli included happy and fearful expressions. The pADHD group demonstrated elevated activity in the left parietal area during fearful facial expression. The Network Based Statistics including multiple areas demonstrated higher functional connectivity in attention related network during visual exposure to happy faces in the pADHD group. Conclusions: We found differences in brain responses to facial emotional expressions in individuals with previous ADHD compared to control group in a number of brain regions including areas linked to processing of facial emotional expressions and attention. This might indicate that although these individuals no longer fulfill the ADHD diagnosis, they exhibit overactive network properties affecting facial processing.

1. Introduction

Symptoms of excessive inattention, hyperactivity and impulsivity are characteristic to attention deficit hyperactivity disorder (ADHD), but the disorder has also been connected to a variety of other symptoms including deficits in social cognition and functioning (Nijmeijer et al., 2008; Kofler et al., 2018). Social cognition includes understanding others' feelings and emotions and recognizing them from facial expressions and body postures. In addition, empathy, humor, and understanding of social contexts belong to social abilities (Uekermann et al., 2010). Understanding other people's emotions is crucial to successful navigation in social interactions.

The processing of human faces is uniquely distinct from the processing given to other types of objects (Haxby et al., 2000). The recognition of emotional facial expressions involves visual cortex and limbic areas as well as associative cortical regions (Winston et al., 2003; Vuilleumier and Pourtois, 2007; Tahmasebi et al., 2012). Facial emotional recognition in individuals with ADHD has been of interest in a variety of behavioural studies (Borhani and Nejati, 2018), but studies using functional magnetic resonance imaging (fMRI) are still sparse.

However, there are a few fMRI studies that have examined functional brain network activation and connectivity in children and adolescents with ADHD in response to viewing facial emotional expressions. In a study by Brotman et al. (2010), ADHD patients (mean age 14) showed hyperactivity in left amygdala while rating subjective fear of neutral faces when compared to children with bipolar disease and healthy controls. Marsh et al. (2008) showed that ADHD patients (age 10–17) viewing angry faces expressed hyperactivity in frontal and posterior cingulate cortex when compared to controls. In a study by Malisza et al. (2011), ADHD patients (mean age 12) showed reduced

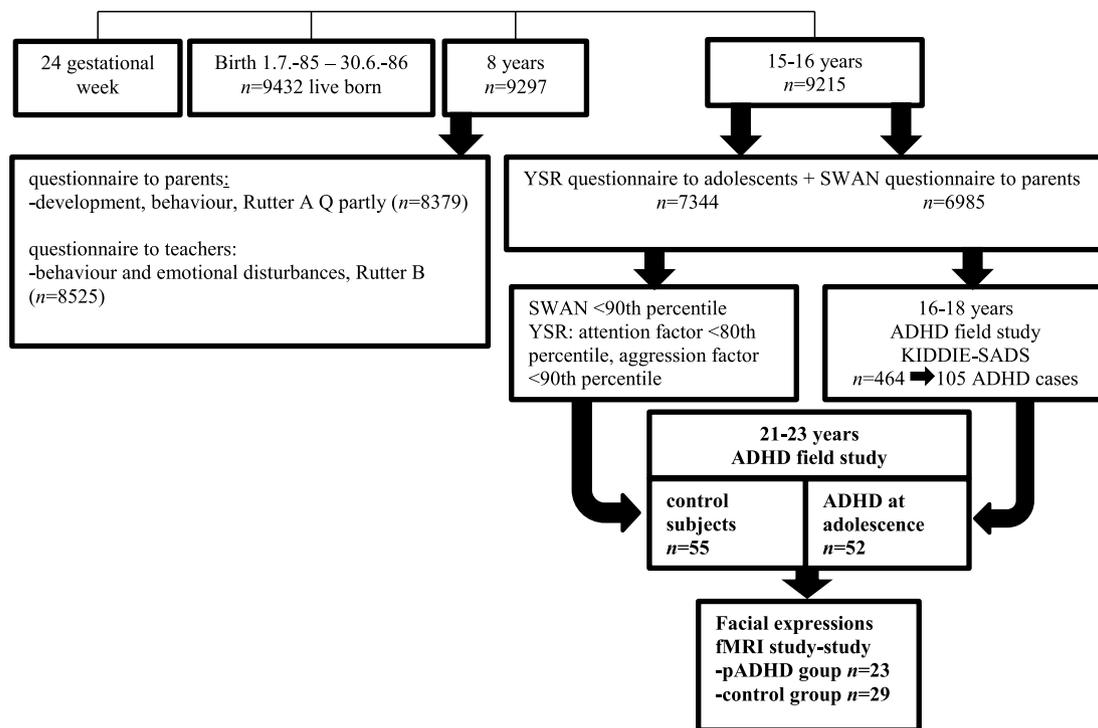**Fig. 1.** Data collection process. Youth self report (YSR) (Achenbach, 1991), The swan rating scale (SWAN) (Swanson et al., 2012), Schedule for affective disorders and schizophrenia for school-age children – present and lifetime version (K-SADS-PL) (Kaufman et al., 1997).

activity compared to healthy controls in putamen, insula, inferior frontal gyrus, occipital gyrus, anterior cingulate gyrus and fusiform gyrus when they were shown pictures of happy or angry faces and were asked if they saw happy faces. Passarotti et al. (2010) found in their study that ADHD patients (mean age 13.4) viewing angry faces had reduced activation compared to healthy controls in ventral and medial prefrontal cortex, pregenual anterior cingulate cortex, striatum and temporoparietal regions and increased activation in right dorsolateral prefrontal cortex. When viewing happy faces, ADHD patients showed increased activation in the same regions. The fMRI studies have shown activation differences between ADHD patients and healthy controls in various brain areas connected to facial emotion processing supporting thus the results of behavioral studies indicating the difficulties of ADHD patients in facial emotional recognition (Borhani and Nejati, 2018).

Face processing has been shown to be partially modulated also by attention to the presented stimulus (Vuilleumier and Pourtois, 2007). The attention network comprises both dorsal and ventral attention networks that work in synergy with other networks such as default mode network (DMN) (Kim, 2014). Dorsal frontoparietal network includes frontal eye field (FEF), intraparietal sulcus and implements orienting of attention via top-down signaling to subsequent networks (Corbetta and Shulman, 2002). Ventral frontoparietal network comprises temporoparietal cortex and inferior frontal cortex and is involved in detecting salient changes in the environment (Corbetta and Shulman, 2002). Deficits in sustained attention and inhibition have been suggested to have significant influence on emotion recognition in children with ADHD (Sinzig et al., 2008). From this perspective, the attention networks are worth including in fMRI studies of neural responses to facial expressions.

The core symptoms of ADHD tend to have continuity to adulthood even though the diagnostic criteria are no longer fulfilled. Up to 65% of children with ADHD have been indicated to have some ADHD symptoms as adults while only 15% still meet full diagnostic criteria (Faraone et al., 2006). In a review article by Borhani and Nejati (2018), they suggested that facial emotion recognition in ADHD does not alleviate across development and is partially distinct from core symptoms

of ADHD. Across the reviewed literature, the most deficient facial expression to be recognised was fear. Schulz et al. (2014) have shown in their study comprising 14 adults with childhood ADHD (7 of them still fulfilling the diagnostic criteria of ADHD) functional anomalies in limbic networks for response execution in face emotion go/no-go task when compared to control subjects.

The aim of our study was to find out whether there are differences in functional brain activity of adults with previous ADHD in their childhood/adolescence versus controls in blood oxygen level dependent (BOLD) signal in the face-processing network when viewing dynamic facial expressions of opposing valences of fear and happiness. For this purpose, we administered fMRI to measure brain response to faces in a sample of young adults drawn from the Northern Finland 1986 Birth Cohort (NFBC1986). Furthermore, given the importance of attention in face-processing and as a core symptom of ADHD, we also investigated the group differences in connectivity of the attention and face network during visual exposure to faces. For this purpose, we used a priori regions of interest (ROI) from meta-analyses by Neurosynth (http://neurosynth.org). The analysis was conducted in January 2019.

2. Methods

The Northern Ostrobothnia Hospital District Ethical Committee has approved the study, and informed consent was obtained from each participant according to the Helsinki declaration.

2.1. Participants

The study population and controls were derived from the Northern Finland Birth Cohort 1986 (NFBC1986) (Järvelin et al., 1993). The invitation letter to participate in an adult ADHD field study was sent to all 105 subjects who had been given a definite diagnosis of current ADHD as part of a population-based ADHD study at the age of 16–18 (Smalley et al., 2007; Hurtig et al., 2007). 52 subjects participated the adult ADHD field study. The adult ADHD field study is part of the larger Oulu Brain and Mind study (Veijola et al., 2013) and due to imaging

schedule limitations, the facial expressions fMRI was done only for a randomly selected subgroup of participants. The data collection process is presented in Fig. 1.

The study group for the facial expression fMRI analysis consisted of 23 individuals with a history of ADHD (17 male and 6 female) forming the group with previous ADHD (pADHD group) and 29 controls (23 male, 6 female) forming the control group. The mean age in the pADHD group was 22.7 y (SD 0.6) and in the control group 22.9 y (SD 0.9).

The present status of ADHD symptoms was assessed by trained interviewers using a semi-structured interview adjusted for adult life based on diagnostic symptom criteria of the ICD-10 Classification of Mental and Behavioral Disorders (WHO 1993) and covering the 18 diagnostic symptoms of ADHD from the Manual of Mental Disorders DSM-5 (APA, 2013). Symptoms were rated ADHD positive if they were reported to occur often or very often. None of the pADHD group or of the control group fulfilled DSM-5 (APA, 2013) diagnostic criteria for present ADHD (≥ 5 inattention symptoms and ≥ 5 hyperactivity-impulsivity symptoms). The mean number of all ADHD symptoms together was 1.78 (SD 2.13) for the pADHD group and 0.34 (SD 0.90) for the control group. The difference in the number of ADHD symptoms between the groups was statistically significant (Mann-Whitney U test: $p = 0.004$, $Z = -2.898$). None of the participants had any current or life-time ADHD medication or current other psychoactive medication or a positive drug test (urine sample).

The Full Scale Intelligence Quotient (FSIQ) was estimated with verbal and non-verbal subtests from Wechsler Adult Intelligence Scale III (WAIS III) (Wechsler, 1997) Finnish version: Vocabulary and Matrix Reasoning. Global Assessment of Functioning (GAF) (Endicott et al., 1976) was completed as part of the interview protocol. The demographic data is presented in Table 1.

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1996) was conducted to assess present and lifetime major mental disorders. One of the control group and 5 of the study group had one or more present DSM-IV (APA, 1994) axis I disorders (Table 2). None of the participants had any significant neurological or other somatic disorders.

Groups did not differ in their framewise displacement, although pADHD tended to have a higher head motion during scanning (p-value = 0.06). Average framewise displacements are provided in Table 1.

2.2. Emotion recognition test

Participants of the present study completed a test of emotion recognition. The same test has been used in previous NFBC1986 analysis (Pulkkinen et al., 2015; Lieslehto et al., 2017). The test involved the viewing of 16 facial expressions on a computer screen: six happy, five fearful and five neutral facial expressions presented in a pseudo-random order contrasted to scrambled images having the same luminescence

Table 1
Demographic data.

	pADHD	Controls
Number of subjects	23	29
Mean age in years (± SD)	22.7 (0.6)	22.9 (0.9)
Mean IQ (± SD)	96,1 (22.8)	112,8 (22.7)*
Mean GAF (± SD)	80.7 (5.0)	86.7 (8.1)**
Lefthanded	6	3
Average frame wise displacement	0.044	0.064

Attention deficit hyperactivity disorder (ADHD), Intelligent quotient (IQ), Global assessment of functioning (GAF), Standard deviation (SD).

* Statistically significant difference between pADHD and cotrol groups (ANOVA: $F = 5.02$, $df = 1$, $p = 0.029$ p = 0.029).

** Statistically significant difference between pADHD and cotrol groups (Mann-Whitney U test: $p < 0.001$ $Z = -3801$).

Table 2
Current DSM-IV Axis I disorders according to the structured clinical interview for DSM-IV Axis I Disorders (SCID)# in pADHD and control groups.

DSM-IV Axis I disorder	pADHD	controls
Dysthymic disorder	1	0
Specific phobia	2	1
Alcohol abuse	1	0
Adjustment disorder with depressed mood + alcohol dependence	1	0
No DSM-IV Axis I disorder	18	28
Total	**23**	**29**

[#]First et al., 1996.

and colours. These facial expressions were the same as those presented during fMRI. Facial expressions were shown on a computer screen and participants were instructed to answer based on their first impression by pressing the response button. Participants were given five options: happy, fearful, angry, surprised and neutral facial expression. Emotional facial expressions (happy and fearful) were dynamic, and the neutral facial expression was a static image.

2.3. Imaging methods and analyses

The imaging was performed using a General Electric Signa 1.5 Tesla HDX with an 8-channel head-coil utilizing parallel imaging with an acceleration factor of 2.0 (TR 3200 ms, TE 45 ms, 37 oblique axial slices with 2.9 mm slice thickness and 0.3 mm space between the slices covering the whole brain, FOV 25.6 × 25.6 cm, with a 128 × 128 matrix, i.e. $2 \times 2 \times 2.9$ mm voxels, and flip angle of 90°). Due to T1 equilibrium effects, the first three images were excluded. The anatomical images for co-registration of fMRI data to Montreal Neurological Institute (MNI) standard space coordinates were obtained using T1-weighted 3D FSPGR sequence (TR 12.4 ms, TE 5.2 ms, slice thickness 1 mm, FOV 24.0 cm × 24.0 cm, 256 × 256 matrix, and flip angle 20°). The subjects were asked to lie still and relax and to look at the stimuli on a translucent screen that was seen through a mirror system installed in the head-coil. Hearing was protected with earplugs and motion was minimized with soft pads fitted over the ears.

2.3.1. Facial expression stimuli

Dynamic facial expression stimuli included happy and fearful expressions. The videos were selected from the "Helsinki University of Technology (TKK) video sequence collection" (Kätsyri, 2006). In order to remove the effect of primary visual activations, we used changing dynamic mosaic images of the same faces between randomly alternating video clips of happy and fearful facial expressions (Fig. 2). The dynamic part of each video clip lasted 1.2 ± 0.3 s (range 0.7–1.8 s) and the last frame was shown for 1–1.5 s so that the total duration of each video clip was 2.5 s. The stimuli were shown in 30 s blocks of 12 times 2.5 s video clips. Videos of happy expressions consisted of video clips of six actors and videos of fearful expressions consisted of video clips of five actors.

2.3.2. Pre-processing and analysis of imaging data

Pre-processing and the analysis of the structural and functional data were conducted using FSL software version 5.07 (FMRIB Center, University of Oxford, www.fmrib.ox.ac.uk/fsl). The following pre-processing steps were conducted before contrast modeling: brain extraction with 3dSkullstrip (Smith, 2002; Cox, 1996), motion correction with MCFLIRT (Jenkinson et al., 2002), spatial smoothing using a Gaussian kernel of FWHM 5.0 mm, linear co-registration and nonlinear normalization to the 2 mm MNI-152 template (Jenkinson et al., 2001, 2002) and FSL´s high-pass filtering (cutoff = 120 s) and prewhitening.

Dynamic happy and fearful facial expression blocks were used as stimuli paradigms and dynamic mosaic blocks between them as
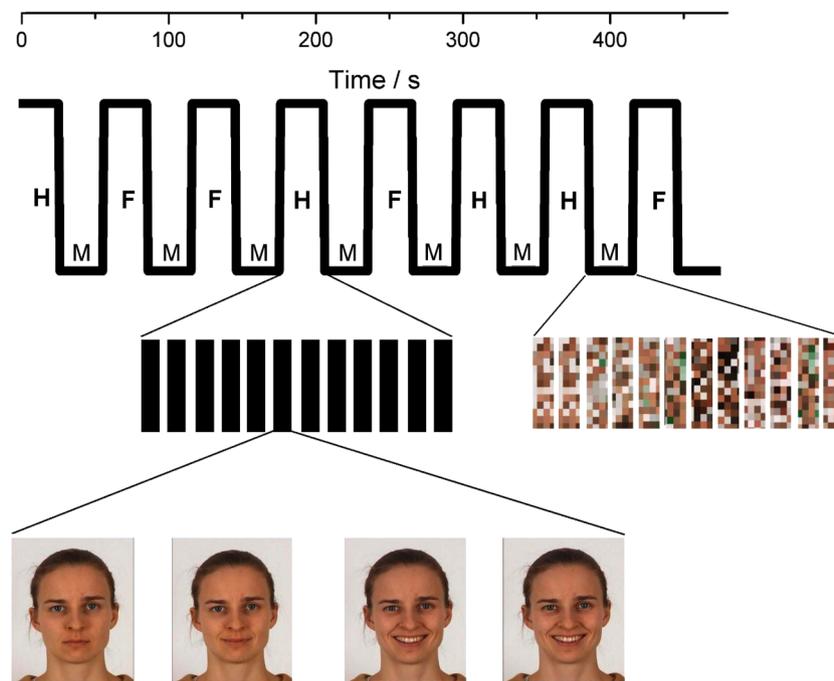
Fig. 2. Example of dynamic facial expression stimuli.

baseline stimuli. Data processing was performed using FEAT version 6.00. FILM with local autocorrelation correction (Woolrich et al., 2004) was used for Individual time-series general linear modeling. Group level analysis was conducted using FLAME 1 (Beckmann et al., 2003; Woolrich et al., 2004) and Z (Gaussianized T/F) statistic images were thresholded using Z-score >3.1 with cluster significance threshold of $p < 0.05$. IQ was used as a nuisance regressor in the model as there was a group difference in IQ (Table 1). Group difference in GAF was ignored as it would possibly relate to the clinical condition of interest. To define brain regions where study groups differed in blood oxygen level dependent (BOLD) responses to happy and fearful facial expressions FSLView (Harvard-Oxford, Juelich, MNI) was utilized.

2.3.3. Functional connectivity in attention network during visual exposure to happy and fearful faces

First, we conducted an automated meta-analysis of 1831 attention-related brain imaging studies and 864 face related studies in Neurosynth (http://www.neurosynth.org/) (Yarkoni et al., 2011) to further test the link of the neuronal correlates of attention to the processing of faces. The meta-analysis assessed the brain regions more strongly associated with the term "attention" and "faces" than with the other terms. This method yielded 20 regions of interest (ROIs) that are described in supplementary Table 1.

Second, for each individual and each ROI, the mean BOLD signal time-series was calculated by averaging the BOLD signal from all voxels constituting the ROI at every time point (150 time points in total). The BOLD time-series for each face condition were realized by concatenating the BOLD signal from the corresponding blocks (4 blocks per facial expression, 37 time points for happy and 38 time points for fearful facial expressions). We did not use BOLD signal during control condition (i.e. mosaic) in our functional connectivity analysis. Nuisance covariates including white matter (WM) signals, and cerebrospinal fluid (CSF) signals and six motion parameters were regressed out of the BOLD signals. WM and CSF voxels were identified by FSL's FAST and six motion parameters with MCFLIRT. For each participant and facial expression condition, we then created 20×20 correlation matrices by calculating Pearson's correlation coefficient between each pair of ROIs.

Third, Network Based Statistics (NBS) was used to identify ROI–ROI pairs that revealed group differences (pADHD vs. Controls) in

functional connectivity per face condition. NBS approach tests whether a set of multiple pairwise correlations in BOLD signal associated with an effect of interest (e.g. group differences) forms a connected component cluster of ROI–ROI pairs that would be unlikely to have occurred at random (Zalesky et al., 2010). NBS was conducted with Graphvar (Kruschwitz et al., 2015). For each face condition, we used an initial cluster-forming threshold of FDR-corrected p-value, generated randomized data with 5000 permutations, and considered network components statistically significant at an FWE-corrected threshold of p-value <0.05. NBS results are visualized with BrainNet Viewer (https://www.nitrc.org/projects/bnv). In addition to IQ, which differed between groups, we added average BOLD response within the explored network as a covariate in the model to control for the effect of mean activation of each face emotion type (separately for happy and fearful facial expressions).

3. Results

3.1. Emotion recognition test

There were no statistically significant differences between pADHD and control groups in the emotion recognition test as shown in the Table 3.

3.2. The fMRI results

The fMRI results are presented in Figs. 3 and 4. Fig. 3 and Table 4

Table 3
Emotion recognition test.

Variable	pADHD	Controls	Statistical testing (p-values)
Emotion recognition [M (SD)]			
Happy[b]	5.86 (0.47)	5.93 (0.37)	0.58[a]
Fearful[c]	4.27 (1.03)	4.00 (1.07)	0.36[a]

SD = standard deviation.
[a] *t*-test.
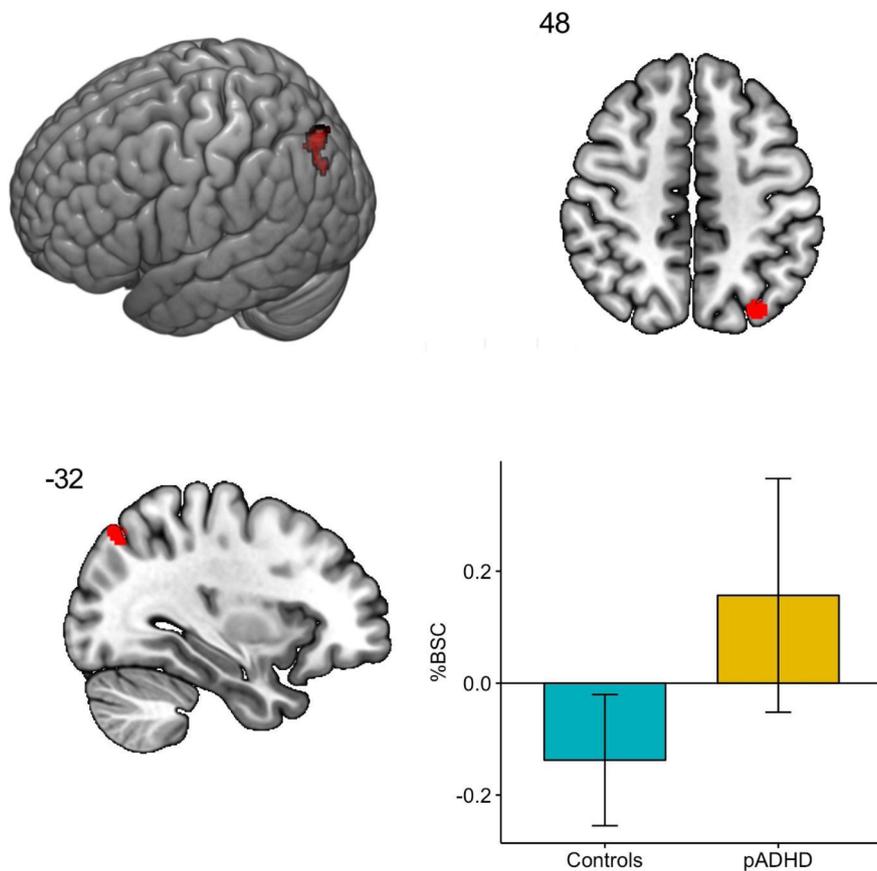[b] max score was 6.
[c] max score was 5.

Fig. 3. Group differences in BOLD response to fearful faces (warm color) and %BSC (percent BOLD signal change) in the significant clusters.
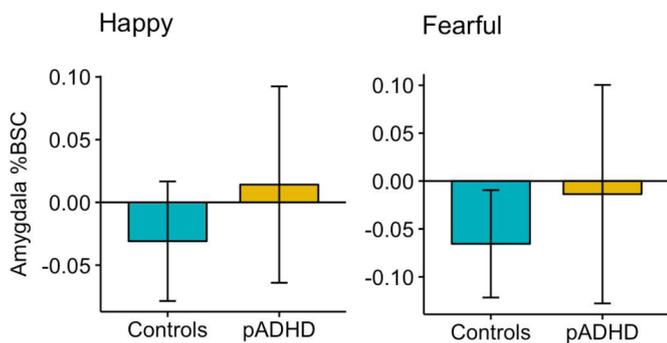

Fig. 4. BOLD response to happy and fearful facial expressions in the Amygdala.

Table 4
Between group deviation clusters.

Anatomical region (s) corresponding cluster	Stimulus	MNI-coordinates			Voxels	Z-scores	p-value
		X	Y	Z			
Inferior parietal lobule L/	Fearful	− 28	− 74	50	105	4.35	0.0271

shows group differences in brain response to fearful faces. The pADHD group demonstrated elevated activity in the left inferior parietal lobe. No group differences in BOLD response were observed during happy facial expression. There were no group differences in Amygdala BOLD response to faces during happy (t-test, *p* = 0.32) or during fearful (t-test, *p* = 0.40) facial expressions. Fig. 4 represents percent BOLD signal change (%BSC) between groups in the Amygdala. The core symptoms of ADHD did not correlate with the %BSC in the left inferior parietal lobe

(Spearman's rho = 0.1, *p*-value = 0.5).

3.3. NBS

NBS revealed that pADHD (vs. controls) demonstrated higher functional connectivity during visual exposure to happy faces (two-tailed *p* = 0.0146, FWE corrected). This network component included Posterior Cingulate Cortex, Right Ventral Frontal Cortex, Right Dorsal Parietal Cortex, Left Temporoparietal Junction and is depicted in Fig. 5.

4. Discussion

In this study, we used both data driven and a priori ROI approaches in a population-based birth cohort sample (NFBC1986). Young adults with previous ADHD appear to differ from control individuals in the BOLD response to dynamic faces and in the degree of functional connectivity. Specifically, we found that pADHD group demonstrates higher BOLD response to fearful faces in left inferior parietal lobe. Furthermore, pADHD participants demonstrated higher functional connectivity in the links of the attention network during visual exposure to happy faces but not during fearful videos. Amygdala emotion areas showed no differences.

Inferior parietal lobule is the representational domain for perceived events and planned actions (Chong et al., 2008). Sarkheil et al. (2013) have indicated based on their study using dynamic emotional facial expression stimuli that inferior parietal lobules have a role in processing spatially relevant facial information, and a role in processing emotional contents of facial expressions. The results suggested a top-down role for action encoding networks in inferior parietal lobe in evaluation of facial expressions and support the idea that simulation of emotional display is involved in recognition of another individual´s emotion (Sarkheil et al., 2013; Adolphs et al., 2000). The elevated
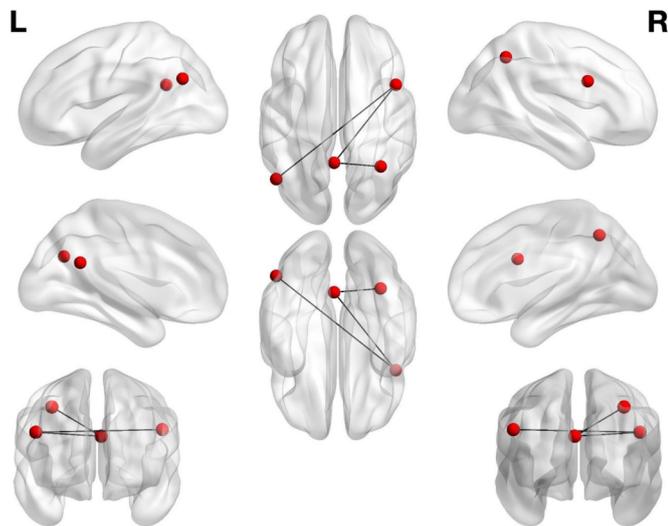
Fig. 5. Group differences in interregional connectivity. Figure represents those "connections" that were higher in pADHD group during visual exposure happy faces.

activation in inferior parietal lobule during fearful facial expression in pADHD group found in our study could refer to the need of more active use of the simulation process helping pADHD subjects to recognize the emotional contents of facial expressions.

Meta-analytical approach in Neurosynth yielded several regions that are known to be involved in the dorsal and ventral attention networks (Kim, 2014). Specifically, using the results from a total of 2 695 studies, we identified 20 brain regions that robustly engage during attention or face tasks. Functional connectivity in these regions appeared to differ between groups during happy faces. We speculate that this result indicates that a previous ADHD diagnosis may over-engage the attention network during visual exposure to faces. This is interesting since fear often elicits stronger signals and between-group differences than happy facial valence (Rahko et al., 2012). This might indicate that valence of the facial expression does not need to cause bigger signal changes but rather elicit more widely distributed connectivity increase.

The precuneus/posterior cingulate cortex (PCC) has an important role in the integration of posterior association processes and anterior executive functions (Cavanna and Trimble, 2006). Precuneus/PCC along with medial prefrontal cortex and temporo-parietal junction have been connected to affective mentalizing processes e.g. inferring another´s affective state (Corradi-Dell'Acqua et al., 2014). Precuneus/PCC has been connected to long-term memory and retrieval of previous social knowledge when interpreting emotional expressions and integrating other possible affective cues (e.g. tears with sad facial expressions) (Takahashi et al., 2015). Precuneus/PCC together with other parts of default mode network (DMN) have been connected also to mind wandering, which can lead to retrieval of an episodic memory (Spreng et al., 2009) affecting thus the interpreting process as well. Failure in suppressing DMN activation during goal-directed processes has been associated with momentary lapses in attention (Weissman et al., 2006). In ADHD, altered DMN connectivity has been related to attention lapses, working memory deficits and task performance variability (Broyd et al., 2009).

In this study using dynamic facial videos, elevated activity connectivity in the pADHD group was seen only in precuneus and not in other parts of DMN. This might refer to the more active retrieval of previous social knowledge from the long-term memory helping the social recognizing process, but it might also refer to mind wandering and more quickly happening retrieval of information from episodic memory. The latter possibility might include a risk of hasty interpretations and impulsive reactions.

In our study, we used dynamic happy and fearful facial expression stimuli. The tasks connected to facial expressions have varied, which possibly explains at least partly the differences of the results between different studies. E.g. in our study, we did not find differences between the pADHD group and control group in the activation of amygdala region. It has been suggested that over large time scales of dynamic stimuli and under habituation effect of trial repetitions subcortical BOLD responses (e.g. amygdala response) might be less traceable (van der Gaag et al., 2007; Sarkheil et al., 2013). On the other hand, there were also no statistically significant differences between the study group and controls in emotion recognition test.

Our work has several strengths. The study is part of a population-based birth cohort study (NFBC1986), and thus, the participants were recruited from the general population representing the same age group from the same area. The population-based sample is likely to represent the natural course of ADHD, whereas the samples recruited from special clinics are likely to be biased to more severe cases. The other DSM-IV (APA, 1994) Axis I Disorders were mostly one-off cases and were considered meaningless as regarding the results. Due to statistically significant difference in IQ between the study group and control group, IQ was used as a nuisance factor to eliminate the possible effect to the results. We utilized dynamic facial expressions. We consider this as an advantage as there is evidence that dynamic facial expressions elicit a stronger response in different face processing regions compared to static images of facial expressions (Trautmann et al., 2009).

This study also has limitations that should be addressed in future studies. First, our fMRI study was cross-sectional, which prevented us from exploring the developmental aspects of previous ADHD diagnosis on brain response to faces. In addition, our sample sizes were relatively modest.

5. Conclusions

In our study, we found stronger response and connectivity in subjects with previous ADHD in number of brain regions including those linked to processing emotional facial expressions and those linked to attention. This might indicate that although these individuals no longer fulfill the ADHD diagnosis, they exhibit overactive face network properties compared to controls. This is in line with former studies that have suggested that facial emotion recognition in ADHD does not alleviate across development and is partially distinct from core symptoms of ADHD (Borhani and Nejati. 2018).

Disclosure statement

No competing financial interests exist.

Web references

Platform for large-scale, automated synthesis of functional magnetic resonance imaging (fMRI) data. http://neurosynth.org
FMRIB Software Library v5.0www.fmrib.ox.ac.uk/fsl
The source for neuroimaging tools and resources https://www.nitrc.org/

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.09.003.

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