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Inter-hemispherical asymmetry in default-mode functional connectivity and *BAIAP2* gene are associated with anger expression in ADHD adults

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is accompanied by resting-state alterations, including abnormal activity, connectivity and asymmetry of the default-mode network (DMN). Concurrently, recent studies suggested a link between ADHD and the presence of polymorphisms within the gene *BAIAP2* (i.e., brain-specific angiogenesis inhibitor 1-associated protein 2), known to be differentially expressed in brain hemispheres. The clinical and neuroimaging correlates of this polymorphism are still unknown. We investigated the association between *BAIAP2* polymorphisms and DMN functional connectivity (FC) asymmetry as well as behavioral measures in ADHD adults. Resting-state fMRI was acquired from 30 ADHD and 15 healthy adults. For each subject, rs7210438 and rs8079626 within the gene *BAIAP2* were genotyped. ADHD severity, impulsiveness and anger were assessed for the ADHD group. Using multivariate analysis of variance, we found that genetic features do have an impact on DMN FC asymmetry. In particular, polymorphism rs8079626 affects medial frontal gyrus and inferior parietal lobule connectivity asymmetry, lower for AA than AG/GG carriers. Further, when combining FC asymmetry and the presence of the rs8079626 variant, we successfully predicted increased externalization of anger in ADHD. In conclusion, a complex interplay between genetic vulnerability and inter-hemispherical DMN FC asymmetry plays a role in emotion regulation in adult ADHD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by marked impulsiveness and attentional deficits. It has a prevalence of 5–8% in childhood (Bush, 2010), and persists in adulthood in 60% of the cases with an established prevalence of 2.5–4.9%, (Simon et al., 2009). Depending on the presence and severity of ADHD cardinal symptoms (i.e., hyperactivity, impulsiveness and inattention), predominantly hyperactive/impulsive, inattentive and combined subtypes have been described (Biederman and Faraone, 2006; Fried et al., 2006; Babinski et al., 2011; Doshi et al., 2012; Chang et al., 2014; Ginsberg et al., 2014). Moreover, the poor regulation of emotions defines an additional dimension in ADHD characterized by a difficulty to control anger and tolerate frustration (Shaw et al., 2014). This latter dimension has undeniable consequences on the global functioning, quality of life, professional and social achievements, and interpersonal relationships of ADHD patients (Marx et al., 2011).

Etiologically, both environmental and genetic factors have been implicated in ADHD with an heritability estimated between 60% and 90% (Stergiakouli and Thapar, 2010). Several genes encoding neurotrophic factors and their receptors have been associated with ADHD (Ribases et al., 2008). In addition, previous lines of evidence supported a relationship between neurodevelopmental genes, characterized by an asymmetric expression in brain hemispheres, and vulnerability to ADHD (Ribases et al., 2009). Among these, adult ADHD was significantly associated with a haplotype constituted of two single

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nucleotide polymorphism markers, rs7210438 and rs8079626 (Ribases et al., 2009), located in *BAIAP2* (brain-specific angiogenesis inhibitor 1-associated protein 2), a gene known to be involved in neuronal proliferation, survival and maturation during early development (Knusel et al., 1990; Beck et al., 1993; Russo et al., 2007).

From a neuroimaging viewpoint, compelling evidence points to rather large-scale abnormalities in network organization in ADHD (Sergeant et al., 2006; Konrad and Eickhoff, 2010; Cao et al., 2013), affecting both functional (Cocchi et al., 2012; Colby et al., 2012; Fair et al., 2012; Tomasi and Volkow, 2012; Cao et al., 2013; Di Martino et al., 2013) and structural (Cao et al., 2013; Hong et al., 2014) connectivity. Moreover, an abnormal hemispheric asymmetry of brain structure and function was also consistently reported in ADHD (Dennis and Thompson, 2013; Shang et al., 2013; Cao et al., 2014; Hale et al., 2014, 2015; Keune et al., 2015; Silk et al., 2015), suggesting a possible neurodevelopmental scenario for this disorder.

In terms of neural networks, whole brain resting-state functional imaging studies have reported abnormalities in the well-known Default Mode Network (DMN) (Sonuga-Barke and Castellanos, 2007; Castellanos et al., 2008; Fair et al., 2010; Tomasi and Volkow, 2012; Di Martino et al., 2013; Hale et al., 2014), a “task-negative” network including cortical areas that show temporally-coherent activity during the resting condition (i.e., posterior cingulate cortex (PCC), retrosplenial cortex, inferior parietal lobule, lateral temporal cortex, medial prefrontal cortex and hippocampal formation) (Buckner et al., 2008). These abnormalities included a decreased DMN functional activation (Hale et al., 2014), a delayed DMN maturation (Fair et al., 2010) and a structural/functional right-biased DMN asymmetry (Hale et al., 2014). Interestingly, a default-mode interference hypothesis in ADHD was firstly introduced by Sonuga-Barke and Castellanos (Sonuga-Barke and Castellanos, 2007), who postulated that the DMN fails to decrease its activity when switching to an active task in ADHD. In normal conditions, a fronto-parietal “task-positive” network (TPN), including dorsolateral prefrontal cortex, intraparietal sulcus, and supplementary motor area, antagonizes the DMN and is strongly activated during complex attentional tasks. Imbalances in the interplay between DMN and TPN have been thought to be at the origin of attentional deficits in ADHD (Castellanos et al., 2009). In terms of connectivity, an impairment between frontal brain regions and posterior DMN (precuneus and PCC) was observed (Castellanos et al., 2008) and converging results from voxel-based morphometry showed that decreased volume of the posterior DMN areas correlates with altered DMN connectivity (Castellanos et al., 2009).

The contribution of genetic factors in ADHD-related DMN dysfunction - in particular inter-hemispheric asymmetry - as well as their relevance in respect to clinical ADHD patterns are still poorly understood. To this purpose, the present work proposes a multivariate approach combining neuroimaging, genetics and behavioral information, to further elucidate the pathological mechanisms of ADHD (Dennis and Thompson, 2013). Using a cross-sectional design, we investigated the interactions between two polymorphisms within *BAIAP2* (rs7210438 and rs8079626) and DMN inter-hemispheric asymmetry in a sample of adult ADHD patients compared to controls. We also explored possible associations between the *BAIAP2* polymorphisms, DMN inter-hemispheric asymmetry and clinical parameters (overall disease severity, anger and impulsiveness) in our cohort.

2. Methods

2.1. Subjects

Thirty right handed adult ADHD patients (21 men; mean age ± SD = 38.7 ± 9.9 years) were recruited in a specialized program for adult with ADHD (Table 1). Diagnosis was made according to the Diagnostic and Statistical Manual (DSM) IV-TR criteria, based on clinical assessment by trained psychiatrists (NP and BP) in addition to using the French version of the Diagnostic Interview for Genetic Studies (DIGS) - a semi-structured interview including a detailed investigation of childhood ADHD and its persistence into adulthood (Preisig et al., 1999). The diagnosis was confirmed for all of the cases by a best estimate procedure. All subjects also filled out the Adult Self-Report Scale (ASRS-1.1) (Adler et al., 2006) exploring current ADHD symptoms, the Barrat Impulsiveness Scale (BIS-10) (Patton et al., 1995) investigating impulsivity (dimensions: attentional motor and non-planning impulsiveness), and the State-Trait Anger Expression Inventory (STAXI) (Spielberger, 1988), measuring the following anger dimensions: anger out, anger in, anger control, state anger and trait anger. All patients treated with methylphenidate stopped their medication 48 h before the fMRI recording.

A group of fifteen right handed healthy controls (4 men; mean age ± SD = 32.2 ± 5.5 years) was also recruited and screened for head trauma, neurological disorders, and crucially for current/past psychiatric disorders as well as subjective complaints of ADHD. Every participant was required to fill out the Adult ASRS-1.1 (Adler et al., 2006). All subjects were from European ancestry for at least two generations. The study was approved by the ethics committee of the University Hospitals of Geneva, Switzerland, and all subjects gave their informed written consent.

2.2. Genotyping

2.2.1. BAIAP2 rs8079626

Genomic DNA was extracted from peripheral blood using the Nucleon™BACC3Kit (Amersham plc, Buckingham shire, UK). Qualities of DNA were estimated by agarose gel electrophoresis and DNA was quantified with Maestro Nano Spectrophotometer (Maestrogen, LasVegas, NV, USA).

Genotyping was identified by high-resolution melt (HRM) assay on a Rotor-Gene 6000 instrument (Corbett Life Science, Australia). In each HRM assay, we used three controls as standards of each possible genotype determined by capillary sequencing at the Genomic platform of Geneva university after PCR amplification using the following conditions: a 370 bp PCR product was obtained by PCR amplification on DNA samples using forward primer 5′- TTTGGCTGTTGTTGTGTGTG-3’ and reverse primer 5′-GTGCAGCAGGCAGAATACAA-3′. PCR reactions were performed in 25 µl final volume containing 100 ng of DNA, 1× ThermoPOL Reaction Buffer (New England Biolabs, cat.num: M0267L), 1.6Mm MgCl2 (New England Biolabs, cat.num: B9021S), 200 µM Dntp (New England Biolabs, cat.num: N0447L), 0.20 Mm of each Forward and Reverse primers, 2 units of HotStart Taq DNA polymerase (Biolabs, cat.num: M0267L). PCR amplification were perform ed as follows: 95 °C during 3 m in, 30 cycles of 95 °C during 30 s, 58 °C during 30 s and 72 °C during 30 s.

PCR and HRM conditions were as follows: PCR reaction was carried out with 100 ng of genomic DNA using Kappa 2 G Robust Hot Start Kit (Kappa Biosystem, Cape Town, South Africa) in a final volume of 20 µl containing 1x buffer A, 0.02 mM dNTPs, 7.5 µM of each primer (designed with Primer3 site) 5′- TTGTTGTGTGTGCCTGTTTTT-3’ forward type and 5′-CGTGCCAAGATCAGCAGTT -3′ reverse type, 0.01 mM Hot Start polymerase and 0.04 µM Eva Green fluorescent intercalating dye (Quantace, London, United Kingdom). Amplification conditions were as follows: 95 °C for 3 min, 45 cycles of 95 °C for 5 s, 60 °C for 30 s and 72 °C for 20 s. Immediately following PCR cycling, the HRM was set from 68 °C to 90 °C, with the temperature rising by 0.2 °C per second. Each sample was tested in duplicate and each of our experimental runs included the three standards.

2.2.2. BAIAP2 rs7210438

Genotyping was identified by capillary sequencing at the Genomic platform of Geneva university after PCR amplification using the following conditions: a 426 bp PCR product was obtained by PCR amplification on DNA samples using forward primer 5′ -

Table 1
Clinical and demographic characteristics of controls and ADHD subjects.

		Controls (N = 15)		ADHD (N = 30)		
		Mean	SD	Mean	SD	t; p
Age		32.2	5.5	38.7	9.9	2.77; 0.008
ASRS v1.1		20.9	9.5	47.7	10.1	8.70; 1.1×10^{-9}
STAXI	**Anger in**	–	–	18.7	5.6	–
	Anger out	–	–	15.4	4.4	–
	Anger control	–	–	21.7	4.6	–
	Trait anger	–	–	25.3	6.7	–
	State anger	–	–	18.5	6.5	–
Bis-10 total		–	–	70.8	16.3	–
		N	**%**	**N**	**%**	**Odds ratio; p**
Gender	**Female**	11	73%	9	30%	6.12; 0.01
	Male	4	26%	21	70%	
rs8079626	**AG + GG**	4	27%	12	40%	1.91; 0.51
	AA	11	73%	17	57%	
rs7210438	**CT**	5	33%	14	47%	1.72; 0.52
	CC	10	67%	16	53%	

Abbreviations: ASRSv1.1 = Adult ADHD Self-Report Scale; STAXI = State-Trait Anger Expression; BIS-10 = Barrat Impulsiveness Scale.

CTCTGATTTGCAGCTGAGCA -3′ and reverse primer 5′-ACAGCCTGCCTCTGTCTGAT-3′. PCR reactions were performed in 25 µl final volume containing 100 ng of DNA, 1× ThermoPOL Reaction Buffer (New England Biolabs, cat.num: M0267L), 1.6Mm MgCl2 (New England Biolabs, cat.num: B9021S), 200 µM Dntp (New England Biolabs, cat.num: N0447L), 0.20 Mm of each Forward and Reverse primers, 2 units of HotStart Taq DNA polymerase (Biolabs, cat.num: M0267L). PCR amplification were performed as follows: 95 °C during 3 m in, 30 cycles of 95 °C during 30 s, 58 °C during 30 s and 72 °C during 30 s.

All files of sequences received have been analyzed with the APE software.

2.3. MRI acquisition

Imaging data was acquired for all subjects on a MR 3 T scanner (TRIO, Siemens medical systems, Erlangen, Germany) with the following protocols: 1) 3D T1-weighted image: voxel size 1 mm^3 isotropic, 256 × 256 × 176 matrix, TE = 2.27 ms, TR = 2300 ms; 2) multi-echo echo-planar imaging (EPI) covering the entire brain, 74 × 74 × 45 matrix, voxel size 3 mm^3 isotropic, TE = 30 ms, TR = 3000 ms, 180 repetitions for 9 min duration. Simultaneously, a carbon dioxide (CO_2) challenge was used during the fMRI acquisition, in order to measure vascular reactivity and exclude alterations of the neurovascular coupling in the ADHD population, which might cause differences between groups in the fMRI and connectivity. CO_2 was administered via a nasal canula in a concentration of 7% mixed in synthetic air, following a block-based paradigm of 1 min OFF, 2 min ON, 2 min OFF, 2 min ON, 2 min OFF. Subjects were asked to breathe normally through the nose and lie still keeping their eyes closed without thinking at something particular, following the standard resting-state acquisition practice (Fox and Raichle, 2007).

2.4. Functional MRI preprocessing

The preprocessing of functional volumes was carried out using a combination of in-house MATLAB scripts and functions from SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/) completed with the DPARSF (Chao-Gan and Yu-Feng, 2010) and IBASPM toolboxes (Alemán-Gómez, 2006). Functional images were first spatially realigned to the mean image and then spatially smoothed by convolution with a Gaussian kernel (8 mm FWHM). To extract the FC matrices, we adapted a previously published pipeline (Richiardi et al., 2011, 2012). The high-resolution T1 image was linearly registered to the mean functional volume (SPM8 coregistration) and segmented with the SPM8's New Segment algorithm, an extension of the unified segmentation algorithm (Ashburner and Friston, 2005), in order to obtain individual tissue maps (white matter, gray matter, cerebrospinal fluid). A modified version of the IBASPM toolbox and the AAL atlas (Tzourio-Mazoyer et al., 2002) were then used to obtain a subject-specific parcellation of the gray matter (individual structural atlas), including 90 cortical and subcortical regions. Each individual structural parcellation was mapped back onto the native resolution of the functional images, yielding the functional atlas in the subject's native space that was further used in the analysis. The fMRI voxel time courses were detrended and nuisance variables were regressed out using the DPARSF toolbox (6 head motion parameters, average cerebrospinal fluid and white matter signal from segmentation masks mapped to fMRI resolution). A CO_2 challenge regressor introduced in previous literature (Richiardi et al., 2014) was defined and regressed out for the functional connectivity estimation in order to exclude the contribution of the CO_2 administrated during the experiment. Then, the preprocessed voxel time courses were spatially averaged within the cortical regions of the functional atlas, yielding 90 regional time courses. A wavelet transform was used to filter these regional time courses into frequency sub-bands and at the same time remove slow polynomial trends. We kept the third scale, for which the associated wavelets have a center frequency at 0.03 Hz and thus allows focusing on typical resting-state fluctuations (Achard et al., 2006; Richiardi et al., 2012). Finally, the pairwise Pearson correlations between all time courses were computed and entered in a 90 × 90 FC matrix. To quantify the CO_2 response at different brain locations, the beta maps of the CO_2 regressor were parcellated into 90 regions using the above-mentioned atlas and the beta values were spatially averaged within the regions, yielding 90 coefficients for every individual.

2.5. Inter-hemispherical asymmetry measures of the DMN connectivity

We selected DMN regions reported by Buckner and colleagues (Buckner et al., 2008). This procedure led to 28 AAL atlas regions (14 right and 14 left) out of 90; only the FC values between these regions were retained from the initial FC matrices. This yielded a reduced 28 × 28 FC matrix for every subject referred to as the DMN FC matrix, which can be viewed as the adjacency matrix of an undirected, weighted graph, in which DMN regions are the nodes and the FC values represent the edge weights. For every node, we computed the nodal strength as the sum of the correlation of all its connections, taken in absolute value. This yielded a measure of the global connectivity of each DMN region

Table 2
Results of multivariate analysis of variance (MANOVA) between Asym-FC and genetic variants show one significant model including three factors. Individual analysis of variance (ANOVA) tests for the model which yielded significant results are also reported.

		F-value	p-value
MANOVA	rs7210438	1.94	0.0822
	Group*rs8079626	**1.66**	**0.0071****
	Age*rs7210438	**1.98**	**0.0206***
Inferior Parietal Lobule (ANOVA)	rs7210438	1.33	0.2561
	Group*rs8079626	**4.41**	**0.0033****
	Age*rs7210438	2.84	0.0724
Medial Frontal Gyrus (ANOVA)	rs7210438	3.94	0.0552
	Group*rs8079626	**3.69**	**0.0089****
	Age*rs7210438	**4.08**	**0.0259***

** $p < 0.01$.
* $p < 0.05$.

with the other DMN areas. To evaluate the asymmetry in connectivity between the two hemispheres, we then computed the symmetry index SI = (L − R)/0.5*(L + R) between the left and right nodal strengths (L and R respectively) of homologous regions, and thus obtained 14 asymmetry measures (referred to as FC-Asym) for each subject. Positive FC-Asym values indicate asymmetry with the region in the left hemisphere having higher connectivity than the corresponding region in the right hemisphere, while negative values relate to the opposite effect.

2.6. Dependency between connectivity asymmetry and genetics

In order to explore the relationship between FC-Asym values and genetic variants expressed by the individuals for the two BAIAP2 polymorphisms, we performed a multivariate analysis of variance (MANOVA), in which the 14 FC-Asym values were set as dependent variables, while genes (presence or absence of polymorphism), diagnostic group, sex, and the interactions between these variables were included as independent variables. Having several dependent variables (FC-Asym values), the MANOVA appears here as the best option, as it summarizes all FC-Asym values in a single aggregated measure that takes into account the dependencies between them. Then, backward selection was used to highlight the best model in terms of Bayesian Information Criterion (BIC) criterion. Individual analyses of variance (ANOVAs) were conducted as follow-up (post-hoc) tests to detect the potential influence of genetics on individual region asymmetries.

2.7. Predicting ADHD severity, anger and impulsivity from brain connectivity and genetics

We relied on linear regression models to explore relationships between imaging data, genotypes, and intermediate dimensions. Different linear regression models were fitted, with the aim of predicting the following clinical dimensions in the ADHD group: ADHD severity (ASRS-v1.1 score), impulsivity (BIS-10 score measuring attentional, motor and nonplanning impulsiveness) and anger (STAXI scores measuring anger in, anger out, anger control, trait anger and state anger) (one model for each behavioral variable). Throughout this paper the term “prediction” should be understood from the machine-learning perspective, instead of its clinical interpretation. We evaluated the quality of each model in terms of prediction performance under the leave-one-out cross-validation (LOOCV) framework. We computed the Pearson correlation between the actual behavioral scores and the predicted ones. In case of limited samples, LOCCV is the recommended approach to estimate the validity of the results in an independent dataset (McShane et al., 2013). To assess the potential contribution of genetics data in the prediction, the full procedure was repeated twice: in a first attempt, only FC-Asym values were set as regressors for the prediction of behavioral dimensions, while the second time genetics data were introduced as well. We used the backward selection technique to keep the most relevant variables. The models with highest BIC were chosen for each variable.

2.8. Vascular contribution

We excluded the presence of vascular differences between groups by comparing the regional response to the CO2 challenge in the two groups. To this aim, an independent two-sample *t*-test on the 90 region-averaged CO2 beta values of ADHD and controls was performed.

3. Results

3.1. Clinical characteristics

Table 1 displays the clinical and demographic characteristics of the subjects, as well as the genotyping results. *rs7210438* and *rs8079626* were in linkage equilibrium (LD = 0.004) and were both at Hardy-Weinberg equilibrium among patients and controls. ADHD subjects were older than controls (38 years old ± 10 vs. 32 years old ± 5; p = 0.008), and more often males (70% vs. 26%; p = 0.01). Also, as expected, their ASRS score was significantly higher than that of controls ($p = 1.1 \times 10^{-9}$).

3.2. Dependency between connectivity asymmetry and genetics

Asym-FC average values in the different clinical groups and in the presence of the different polymorphisms are reported in Supplementary Table S1.

The MANOVA demonstrated the presence of a dependency of Asym-FC values on specific genetic polymorphisms, this dependency changing according to the clinical group or age (see Table 2). In particular, a dependency of Asym-FC values on the interaction between the polymorphism *rs8079626* and the group belonging (F = 1.66, p = 0.007), and on the interaction between the polymorphism *rs7210438* and age (F = 1.98, p = 0.02) was found. Subsequent individual ANOVA tests allowed for detecting two DMN regions significantly driving this relationship, namely the inferior parietal lobule (F = 4.41, p = 0.0033 for *rs8079626*, Table 2), and the medial frontal gyrus (F = 3.59, p = 0.0089 for *rs7210438,* F = 4.08, p = 0.026 for *rs7210438*, Table 2).

3.3. Predicting ADHD severity, impulsivity and anger from brain connectivity and genetics in ADHD

The regression models predicting clinical dimensions from Asym-FC values alone did not yield any significant results. On the contrary, including the genetics data together with the Asym-FC values yielded one model able to significantly predict the *anger-out* score in the ADHD population (corr = 0.78, p = 8e-07, significant after multiple comparisons correction for the number of models tested).

Fig. 1 displays the measured variables against the predicted ones under LOOCV framework, showing the satisfactory performance of the model.

The coefficients of the model are reported in Fig. 2, together with their p-values. The variables contributing more significantly to the model (showing a p-value < 0.05 with multiple comparison correction for the number of variables included) are the FC-Asym values of supramarginal gyrus, hippocampus, superior and middle frontal gyrus and angular gyrus, together with the presence of the genetic variants *AG* and *GG* of *BAIAP2 rs8079626*.

The sign of model coefficients are important in order to interpret the direction of asymmetry and due to the symmetry index construction, they have the following interpretation: i.e. a leftward (L > R) asymmetry correlating with *anger-out* in case of positive coefficient, or a rightward (R > L) asymmetry correlating with *anger-out* in case of negative one. All the significant variables contributed to the model with a

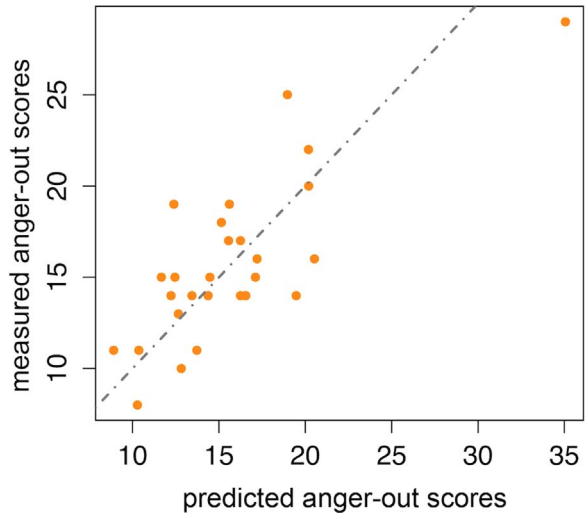

Fig. 1. Scatterplot of measured versus LOOCV predicted *anger-out* scores. The line indicating perfect prediction (diagonal with slope 1) is shown. Full model statistics: corr = 0.78, p-value = 8e−07.

negative sign, highlighting a rightward asymmetry of connectivity leading to a higher level of anger in the patients' cohort.

3.4. Vascular contribution

The CO_2 challenge was effectively regressed out, which is a necessary preprocessing step to remove the overall effect induced by the CO_2 challenge on the timecourses of all brain regions and the consequently non-specific increase in functional connectivity. Further, the two groups did not show a significant difference in the CO_2 beta values ($p > 0.1$, non corrected), excluding any vascular contribution in the group characterization.

4. Discussion

This study provides first evidence supporting a relationship between the presence of *BAIAP2 rs8079626* polymorphism, inter-hemispheric DMN asymmetry, and anger expression in adult ADHD.

The DMN as the hallmark of resting state has been found altered in many neurological and psychiatric disorders, such as, among all, schizophrenia (Stephan et al., 2009; Woodward et al., 2011; Guo et al., 2014), mild cognitive impairment (Sinanaj et al., 2015) and ADHD (Sonuga-Barke and Castellanos, 2007; Castellanos et al., 2008; Fair et al., 2010; Tomasi and Volkow, 2012; Di Martino et al., 2013). Based on previous reports of abnormal laterality of the ADHD brain (Dennis and Thompson, 2013; Shang et al., 2013; Cao et al., 2014; Hale et al., 2014, 2015; Keune et al., 2015; Silk et al., 2015), we could postulate that the asymmetric expression of neurodevelopmental genes might be at the origin of structural and functional changes in this disorder. However, these changes are not clear yet, as both a dysfunctional activity of the right hemisphere (Vance et al., 2007; Smith et al., 2008; Chamberlain et al., 2009; Bush, 2011) and the opposite (Cao et al., 2014; Hale et al., 2014, 2015) have been reported in literature. Moreover, the reflections of these unilateral activation deficits on functional connectivity are not trivial and require dedicated analyses focused on network properties (Dennis and Thompson, 2013; Cao et al., 2014).

We report here evidence supporting an association between DMN connectivity asymmetry and genetic markers in a population of ADHD and controls. Our results, in fact, suggest that the polymorphism rs8079626 has a different effect on the DMN FC asymmetry, in particular of the inferior parietal lobule and the medial frontal gyrus, depending on the clinical group (ADHD or controls). This confirms the importance of integrating the information yielded from imaging and genetics for a comprehensive analysis of the pathophysiological mechanisms underlying ADHD.

In addition, we were able to significantly predict the level of externalized anger (measured by *anger-out* score, reflecting the tendency to engage in aggressive or confrontational behavior) (Spielberger, 1988) in the population of adult ADHD, but only when combining the Asym-FC and genetic data together, further confirming the relevance of a multimodal analysis in this context. Anger management may be difficult for ADHD adults, as impulsivity and mood changes in this pathology often lead to very abrupt and intense anger expressions (Lubke et al., 2015). These symptoms may reflect emotion dysregulation processes that represent a key diagnostic feature of ADHD (Shaw et al., 2014).

Our data suggest that having the AG or GG variant of *rs8079626* instead of the AA, together with a specific connectivity asymmetry pattern, favors increased *anger-out* in ADHD patients, and this might appear in line with the more frequent occurrence of the AG and GG variants in the ADHD cohort with respect to the healthy group. Consistently with these results, *BAIAP2* has already been implicated in diverse psychiatric disorders where anger plays an important role, including autism (Celestino-Soper et al., 2011; Levy et al., 2011; Toma et al., 2011) and schizophrenia (Fromer et al., 2014). The BAIAP2 polymorphisms possibly modulate the development of brain regions associated with emotion regulation, as also shown in previous findings where BAIAP2 was associated to left parahippocampal cortex sensitivity to emotional arousing memory stimuli (Luksys et al., 2014).

Consistently, in our case the connectivity asymmetry of the hippocampus -a key structure for intrinsic affective and emotion regulation

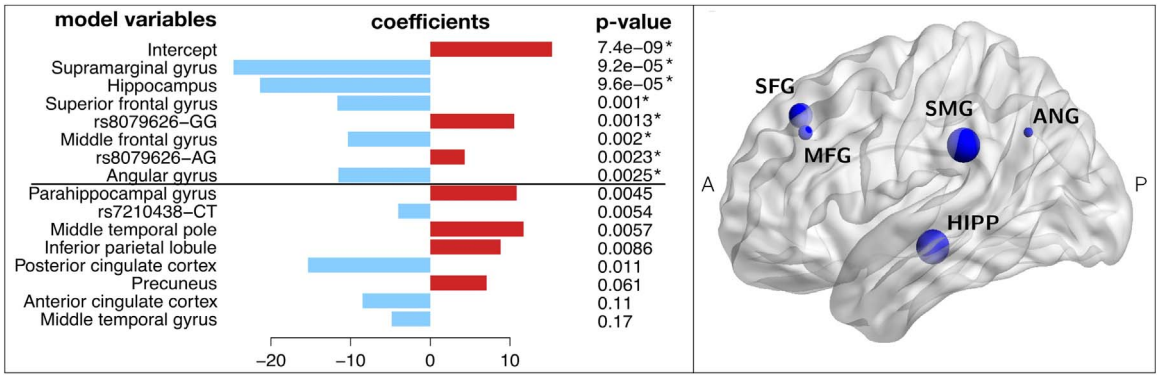

Fig. 2. Left: coefficients of the model predicting *anger-out*, ordered by increasing p-values; positive (red)/negative (blue) values = magnitude of the effect positively/negatively correlating with *anger-out*. p-values are reported on the right. (*) Bonferroni corrected significant p-values (alpha-level = 0.05, $p < 0.0031$). Right: The regions with significant coefficients are displayed on a brain graph, with node size inversely proportional to their p-values. Abbreviations: SFG = superior frontal gyrus; MFG = middle frontal gyrus; SMG = supramarginal gyrus; ANG = angular gyrus; HIPP = hippocampus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

networks-, the parietal (supramarginal and angular gyri) and the frontal lobe (superior and middle frontal gyri) showed to have a major influence on anger manifestation in ADHD, when associated with a specific BAIAP2 polymorphism. In all these regions, a rightward asymmetry was found to favor a higher *anger-out* score.

Not only does our work complement several lines of evidence converging to hippocampal implication in patients with ADHD (Plessen et al., 2006; Posner et al., 2013, 2014; Ho et al., 2015; Rivero et al., 2015), but also it extends these findings with respect to functional connectivity. In line with our asymmetry results, Posner and colleagues (Posner et al., 2014) found reduced volume and functional connectivity in the left hippocampus of ADHD children with respect to controls, and associated these modifications with depressive symptoms.

A second region showing major contribution to our prediction model was the supramarginal gyrus that together with the involvement of the angular gyrus, suggests a rightward connectivity asymmetry of the parietal lobe favoring increased anger expression in ADHD in the presence of BAIAP2 specific polymorphisms. Functional deficits of the ventral attentional network (including the supramarginal and angular gyri) are well known in ADHD (Helenius et al., 2011; Cortese et al., 2012; McCarthy et al., 2013; McLeod et al., 2014) and right-ward hyperactivation of the angular gyrus (Cortese et al., 2012) and a left-ward hypoactivation of the ventral attention system (McCarthy et al., 2013) were previously observed in ADHD adults and could be in line with our connectivity results.

Finally, our study showed a rightward connectivity asymmetry in the middle and superior frontal gyri related to increased anger. Together with the amygdala and the ventrostriatal cortex (which were not the focus of this study), the prefrontal cortex is a key region in emotion regulation, and its abnormal functional activation in ADHD has been well documented (Dalwani et al., 2014; Shaw et al., 2014). The frontal cortex was found to be asymmetrically involved in the expression of positive/negative emotions related to approach/withdrawal motivational behaviors (Harmon-Jones et al., 2006). In particular, a left-lateralized increase of resting-state frontal activation was correlated with higher externalized anger, a negative but approach-oriented emotion (Harmon-Jones et al., 2003; Carver, 2004; Hewig et al., 2004). The rightward connectivity asymmetry found in DMN frontal regions can be consistent with the abovementioned findings, suggesting that the persistent engagement of the left frontal cortex could prevent frontal regions from normally interacting with the rest of the DMN, resulting in a modified resting-state connectivity pattern. This finding corroborates the “restless brain” model of ADHD, proposed by Castellanos and collaborators (Castellanos et al., 2009), suggesting that the interference on the DMN would prevent ADHD subjects from experiencing a normal resting-state condition, and that this would contribute to promote behaviors characterizing ADHD, such as impulsivity and anger.

Certain limitations should be considered when interpreting these data. First, the *ASRS-v1.1* score - representing the ADHD severity by measuring inattention and hyperactivity in adulthood - could not be predicted from genetic and FC-Asym data. Other ADHD-related dimensions, such as impulsivity and anger externalization, which was successfully predicted, are instead not specific to ADHD and may also be found in borderline personality or schizophrenia (Stephan et al., 2009; Prada et al., 2014). Second, the relative small sample size and the different proportion between men and women in the two groups based on clinical sample do not necessarily reflect population-based ADHD series. To account for the small size of controls in the rs8079626 AG + GG group and in the rs7210438 CT group and preserve the validity of results, we adopted the very conservative LOOCV method, which computes a non-biased estimation of the generalization error. Concerning the male/female different proportion, we observed the absence of significant correlation between gender and the variables of our predictive model. Third, our FC asymmetry analysis concerned the DMN network and did not take into account the emotion regulation circuit; e.g. the amygdala and the frontostriatal network. Lastly, the changes in FC should be regarded as the covariance between z-scored time courses. Therefore, FC can increase/decrease not only due to more/less covariance, but also due to lower/higher variance in respective regions.

For future studies, it would be useful to look into the dynamics of DMN. In fact, recent data showed that subsystems of the DMN have clearly distinct interactions with task-positive networks (Karahanoglu and Van De Ville, 2015).

On a related note, the contribution of vascular and neuronal effects in case of pathological alterations is still matter of debate (Hillman, 2014). The acquisition of resting-state fMRI with the CO_2 challenge may allow for elucidating this issue, e.g., the beta maps of the CO_2 regressors obtained and compared between groups could be inserted as covariates in the fMRI analysis and potentially calibrate the BOLD time courses with a measure of vascular contribution (Murphy et al., 2011). This would also allow to reduce inter-subject variability of FC measures, not related to neural effects.

In sum, we conclude that by adopting a multivariate predictive approach, our study offers new insights into altered DMN connectivity and its links with genetics and behavioral scores, opening the avenue for developing innovative surrogate functional markers in adult ADHD.

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Conflict of interest

None.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2017.09.004.

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