Altered Resting-state Functional Connectivity Patterns of Several Frontal and DMN Related Areas in Children with Attention Deficit Hyperactivity Disorder

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Attention Deficit Hyperactivity Disorder (ADHD) affects nearly 5% of school-aged children and generally it continues to adulthood. Neural basis of ADHD has been a matter of debate in recent decades. In this study a group independent component analysis based study has been done on 21 ADHD individuals and 21 control group. Spatial maps have been derived using dual regression method. Several differences have been found in frontal pole (specifically anterior cingulate cortex and inferior frontal gyrus). Posterior components of DMN, cerebellum and brainstem (pons) in the form of decreased activation compared to control group.

Key words: Children with attention deficit, DMN, Patterns of several frontal.

Age-inappropriate symptoms of inattention, impulsiveness and hyperactivity are main characteristic of Attention Deficit Hyperactivity Disorder (ADHD)[1]. It affects nearly 5% of school-aged children and generally it continues to adulthood[17]. Variety of studies has been conducted in order to understand neural basis of ADHD[10]. Structural and functional studies have been attributed to study underlying neural basis of ADHD. Earlier Positron Emission Tomography studies suggested general reduction in neural activity of brain[29]; however recent studies have shown differences in a variety of regions[2]. Underactivation of dorsal anterior cingulate cortex (ACC) and changeless network of fronto-striatal-insular have been suggested as an effective basis for inattention and impulsivity in patient with ADHD. Structural studies have suggested reduced volume and cortical thickness in several frontal brain regions, in parietal temporal areas, the basal ganglia, posterior cingulated (PCC), the cerebellum and the splenium of the corpus callosum[3,7,6,5,10,17,20].

Functional magnetic resonance studies provide a valuable technique for studying neural basis of ADHD. Several studies of fMRI have been dedicated to studying different regions of brain in task related paradigms. Children with ADHD have been studied during vigilant, selective and flexible attention[10,19], tasks with temporal processing[10,13], “hot” executive functions[20], reward expecting tasks and very few in emotion processing tasks[10]. In these task-related experiments brain activity patterns are derived by dynamic changes between task experiment and baseline. The differences of patterns caused by the disorder are then studied based on comparing ADHD patients with their age matched controls[17]. Various evidences have been provided to show under-activation in the DLPFC/IFC, ACC, Caudate, supplementary motor area (SMA) compared to control group[10,12&22]. Furthermore there are convergent evidence toward

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fronto-striatal network abnormalities[23].

FMRI studies which are done in rest state are quite different from task based experiments. This kind of fMRI studies provides further information about brain dynamics. In rest state studies results can be compared through different studies[17]. However few studies have been dedicated to study fMRI data of ADHD children in rest state[17, 28].

The purpose of this study was to compare functional connectivity network between ADHD individuals and control group using rest state fMRI images. We were looking for differences in patterns of neural activity underlying the disorder.

METHODS

Subjects

The subject group comprised 21 ADHD individuals in the age of 8.5±2 and 21 age matched controls from typically developing individuals. All participants had a Full Scale IQ of 80 or higher and were checked with the Symptom-Checklist-90-Revised (SCL-90 R) in order to avoid other psychiatric disorders[11]. The criteria for individuals evaluation included: 1.Lifetime history of psychotic, bipolar or substance use disorders, 2) current history of mood, psychotic, anxiety, or substance use disorders, 3) lifetime history of treatment with psychotropic other than stimulants (for ADHD group). They had no history of language disorder or a Reading Disability (RD) either screened out before a visit or based on school assessment completed within 1 year of participation. RD was based on a statistically significant discrepancy between a child's FSIQ score and his/her Word Reading subtest score from the Wechsler Individual Achievement Test-II [Wechsler, 2002], or a standard score below 85 on the Word Reading subtest, regardless of IQ score. Participants with visual or hearing impairment, or history of other neurological or psychiatric disorder were excluded. Psychiatric diagnoses were based on evaluations with the Diagnostic Interview for Children and Adolescents, Fourth Edition (DICA-IV, 1997), a structured parent interview based on DSM-IV criteria; the Conners' Parent Rating Scale-Revised, Long Form (CPRS-R), and the DuPaul ADHD Rating Scale-IV (Reid, 1998). Intelligence was evaluated with the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) and academic achievement was assessed with the Wechsler Individual Achievement Test-II [Wechsler, 2002]. Children assigned to the ADHD group met criteria for ADHD on the DICA-IV and either had a T-score of 65 or greater on the CPRS-R Long Form (DSM-IV Inattentive) and/or M (DSM-V Hyperactive/Impulsive) or met criteria on the DuPaul ADHD Rating Scale IV (six out of nine items scored 2 or 3 from Inattention items and/or six out of nine scored 2 or 3 from the Hyperactivity/Impulsivity items). Children with DSM-IV diagnoses other than Oppositional Defiant Disorder or Specific Phobias were excluded.

Children with ADHD taking psychoactive medications other than stimulants were excluded. Children who were taking stimulant medication were removed from these medications the day before and the day of testing.

TDC participants were required to have T-scores of 60 or below on the DSM-IV Inattention (L) and DSM-IV Hyperactivity (M) subscales of CPRS-R and no history of behavioral, emotional, or serious medical problems. Additionally, TDC individuals were not included if there was a history of school-based intervention services as established by parent interview, or if they met DSM-IV psychiatric disorder except specific phobia as reported on the DICA-IV[11].

MRI Scanning

Each participant underwent one resting state scan consisting of 128 contiguous whole-brain functional volumes using echo planar imaging on a Siemens 3.0 Tesla Allegra (TR=2500 ms; TE=30 ms; flip angle=90, 47 slices, matrix=84*81; FOV=256*256 , 141 mm; acquisition voxel size=3×3×3mm; 6.4 min). Each subject lay supine with the head snugly fixed by a belt and foam pads. Participants were verbally instructed to relax and during the resting-state fMRI sessions, the subjects were asked to remain still as much as possible, keep their eyes closed and try not to think systematically. A high-resolution T1-weighted magnetization prepared gradient echo sequence was also obtained.

Data Preprocessing

The first few fMRI image volumes of subjects were discarded and the rest were utilized for data analysis. Images were used for one level of motion correction using MCFLIRT using FSL (www.fmrib.ox.ac.uk/fsl). BET brain extraction and spatial smoothing using FWHM (5mm) and also a high pass temporal filtering were used. FMRI resting state images were first registered to their high resolution anatomical image by normal 6 DoF transformation and then registered to standard Montreal Neurological Institute (MNI152) template using 12 DoF affine transform by normal search using resampling resolution of 4mm. The registration phase is necessary in order to overcome the problem of different shapes of head through participants.

Functional Connectivity Analysis

Spatial connectivity maps and their relative time series were derived using group ICA method by MELODIC toolbox. Using this method spatial maps are assumed to be independent. Resulting independent components were used to derive results using dual regression method. The set of spatial maps from the group-average analysis was used to generate subject-specific versions of the spatial maps, and associated time series, using dual regression[14]. First, for each subject, the group-average set of spatial maps is regressed (as spatial regressor in a multiple regression) into the subject's 4D space-time dataset. This results in a set of subject-specific time series, one per group-level spatial map. Next, those time series are regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map. We then tested for group differences using FSL's *randomize* permutation - testing tool[22].

RESULTS

Between Group Resting State Network Comparison

Several Resting state networks resulted frm the group ICA which was done by the MELODIC toolbox. The aim was to find obvious differences between ADHD and control group. By using dual regression and randomizing the results several meaningful differences between patterns were found. Reduction in activity in different parts of frontal lobe including Subcallosal cortex and cingulate cortex were seen. Additionally reduced neural activity pattern was seen in ADHD group compared to controls in superior division of lateral occipital cortex in parietal lobe, angular gyrus, Inferior temporal gyrus, Cerebullum, Inferior Temporal gyrus, Occipital fusiform gyrus and Anterior Cingulate (Table 1). These areas were thresholded to have a minimum amount of voxels as well as meaningful value of p. X, Y and Z values are reported in MNI152 coordinates (Figure.1 , Table1).

Table1. Areas of different connectivity patterns in ADHD individuals

Regions	Brodman's area BA	P value	No. of Voxels	X	Y	Z
ADHD<Controlol						
Frontal pole/Right cerebral cortex	10 , 11	>.02	570	34	45	16
Frontal medial cortex	10,11	0.01	511	22	43	12
Inferior temporal gyrus/superior parietal lobule/Precuneus	7	0.01	484	25	9	28
Cerebellum	-	0.05	385	22	18	4
Occipital pole/lateral occipital cortex inferior division/ Occipital fusiform gyrus	17,18	0.01	160	29	8	13
Temporal pole/Temporal fusiform gyrus/ inferior temporal gyrus	20 , 38	>0.01	141	15	33	8
Frontal pole	6,8	0.02	122	15	47	26

DISCUSSION

By analyzing and comparing the functional connectivity of control and ADHD group, the activity patterns underlying whole brain neural activity were used to find the differences between

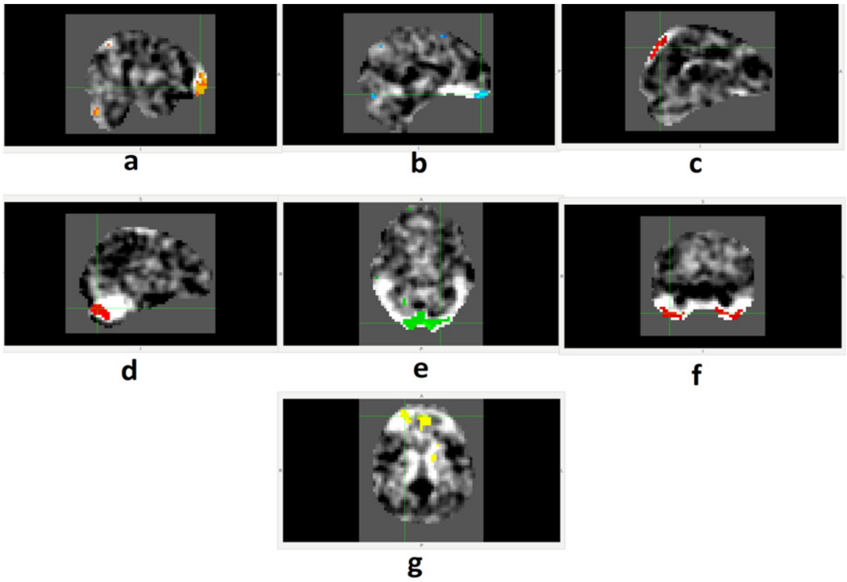

Fig. 1. Areas of difference: a) Frontal pole/Right cerebral cortex b) Frontal medial cortex c) Inferior temporal gyrus/superior parietal lobule/Precuneus d) Cerebellum e) Occipital fusiform gyrus f) Temporal fusiform gyrus g) Frontal pole

two groups. Frontal areas have been widely implicated in the control of attention[26] the right inferior frontal gyrus has been proven to participate in stimulus - driven modulating the attention[8] and right middle frontal gyrus has effective rule in manipulating the contents of working memory in attention process[27]. Furthermore the anterior cingulate cortex has effects on detecting and resolving processing conflicts[26,27].

Default mode network has been considered as one of important resting state networks which affect brain activity in rest state[22]. Our findings support the decreased activity in default mode network related areas both in frontal areas including anterior cingulate cortex (ACC) and posterior parts. Precuneus, one of the well-known areas of DMN, has also been found to have different activity pattern between two groups. Our results are congruous with literature[4] and also morphometric findings of decreased cortical thickness in precuneus[4, 18].

The ADHD individuals showed decreased connectivity in cerebellum compared to typically growing control group. Cerebellum has been found to be involved in a number of autonomic cardiovascular response representation and conditioned cardiovascular control[15], and performs the major role acting as a functional mediate between cortex and brainstem to perform cortical modulation of brainstem autonomic nuclei[9,25].

CONCLUSION

In summary we found different connectivity patterns in the areas of frontal pole (specifically anterior cingulate cortex and inferior frontal gyrus), posterior components of DMN, cerebellum and brainstem (pones) in the form of decreased activation compared to control group. These areas have been proven to have relatively high relationship with attention.

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REFERENCES

1. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association, 1994.
2. Banich, Marie T., Gregory C. Burgess, Brendan E. Depue, Luka Ruzic, L. Bidwell, Sena Hitt-Laustsen, Yiping P. Du, and Erik G. Willcutt. "The neural basis of sustained and transient attentional control in young adults with ADHD." *Neuropsychologia* 2009; **47**(14): 3095-3104.
3. Batty, Martin J., Elizabeth B. Liddle, Alain Pitiot, Roberto Toro, Madeleine J. Groom, Gaia Scerif, Mario Liotti, Peter F. Liddle, Tomáš Paus, and Chris Hollis. "Cortical gray matter in attention-deficit/hyperactivity disorder: a structural magnetic resonance imaging study." *Journal of the American Academy of Child & Adolescent Psychiatry* 2010; **49**(3):229-238.
4. Castellanos, F. Xavier, Daniel S. Margulies, Clare Kelly, Lucina Q. Uddin, Manely Ghaffari, Andrew Kirsch, David Shaw et al. "Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder." *Biological psychiatry* 2008; **63**(3): 332-337.
5. Castellanos, F. Xavier, Patti P. Lee, Wendy Sharp, Neal O. Jeffries, Deanna K. Greenstein, Liv S. Clasen, Jonathan D. Blumenthal et al. "Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder." Jama 2002; **288**(14): 1740-1748.
6. Carmona, Susanna, Erika Proal, Elseline A. Hoekzema, Juan-Domingo Gispert, Marisol Picado, Irene Moreno, Juan Carlos Soliva et al. "Ventro-striatal reductions underpin symptoms of hyperactivity and impulsivity in attention-deficit/hyperactivity disorder." *Biological psychiatry* 2009; **66**(10): 972-977.
7. Carmona, S., O. Vilarroya, A. Bielsa, V. Tremols, J. C. Soliva, M. Rovira, J. Tomas et al. "Global and regional gray matter reductions in ADHD: a voxel-based morphometric study." *Neuroscience letters* 2005; **389**(2): 88-93.
8. Corbetta, Maurizio, and Gordon L. Shulman. "Control of goal-directed and stimulus-driven attention in the brain." *Nature reviews neuroscience* 2002; **3**(3): 201-215.
9. Critchley, H. D., D. R. Corfield, M. P. Chandler, C. J. Mathias, and R. J. Dolan. "Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans." *The Journal of physiology* 2000; **523**(1): 259-270.
10. Cubillo, Ana, Rozmin Halari, Anna Smith, Eric Taylor, and Katya Rubia. "A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention." *Cortex* 2012; **48**(2): 194-215.
11. Derogatis, L. Manual for the Symptom Checklist 90 Revised (SCL-90-R). Baltimore: 1992. Available from author
12. Durston, Sarah, Martijn Mulder, B. J. Casey, Tim Ziermans, and Herman van Engeland. "Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for attention-deficit hyperactivity disorder." *Biological psychiatry* 2006; **60**(10): 1062-1070.
13. Durston, Sarah, Matthew C. Davidson, Martijn J. Mulder, Julie A. Spicer, Adriana Galvan, Nim Tottenham, Anouk Scheres, F. Xavier Castellanos, Herman Van Engeland, and B. J. Casey. "Neural and behavioral correlates of expectancy violations in attention deficit hyperactivity disorder." *Journal of Child Psychology and Psychiatry* 2007; **48**(9): 881-889.
14. Filippini, Nicola, Bradley J. MacIntosh, Morgan G. Hough, Guy M. Goodwin, Giovanni B. Frisoni, Stephen M. Smith, Paul M. Matthews, Christian F. Beckmann, and Clare E. Mackay. "Distinct patterns of brain activity in young carriers of the APOE-å4 allele." *Proceedings of the National Academy of Sciences* 2009; **106**(17):7209-7214.
15. Ghelarducci, Brunello, Domenico Salamone, Alfredo Simoni, and Laura Sebastiani. "Effects of early cerebellar removal on the classically conditioned bradycardia of adult rabbits." *Experimental brain research* 1996; **111**(3): 417-423.
16. Greicius, Michael D., Ben Krasnow, Allan L. Reiss, and Vinod Menon. "Functional connectivity in the resting brain: a network analysis of the default mode hypothesis." *Proceedings of the National Academy of Sciences* 2003; **100**(1): 253-258.
17. Mackie, Susan, Philip Shaw, Rhoshel Lenroot, Ron Pierson, Deanna Greenstein, Tom Nugent, Wendy Sharp, Jay Giedd, and Judith Rapoport. "Cerebellar development and clinical outcome in attention deficit hyperactivity disorder." *American Journal of Psychiatry* 2007; **164**(4): 647-655.
18. Makris, Nikos, Joseph Biederman, Eve M. Valera, George Bush, Jonathan Kaiser, David N. Kennedy, Verne S. Caviness, Stephen V. Faraone,

and Larry J. Seidman. "Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder." *Cerebral Cortex* 2007; **17**(6): 1364-1375.

19. Rubia, Katya, Rozmin Halari, Ana Cubillo, Abdul-Majeed Mohammad, Mick Brammer, and Eric Taylor. "Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naive children with ADHD during a rewarded continuous performance task." *Neuropharmacology* 2009; **57**(7): 640-652.

19. Scheres, Anouk, Michael P. Milham, Brian Knutson, and Francisco Xavier Castellanos. "Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder." *Biological psychiatry* 2007; **61**(5): 720-724.

21. Shaw, Philip, Jason Lerch, Deanna Greenstein, Wendy Sharp, Liv Clasen, Alan Evans, Jay Giedd, F. Xavier Castellanos, and Judith Rapoport. "Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder." *Archives of General Psychiatry* 2006; **63**(5): 540-549.

22. Suskauer, Stacy J., Daniel J. Simmonds, Brian S. Caffo, Martha B. Denckla, James J. Pekar, and Stewart H. Mostofsky. "fMRI of intrasubject variability in ADHD: anomalous premotor activity with prefrontal compensation." *Journal of the American Academy of Child & Adolescent Psychiatry* 2008; **47**(10): 1141-1150.

23. Swanson, James, F. Xavier Castellanos, Michael Murias, Gerald LaHoste, and James Kennedy. "Cognitive neuroscience of attention deficit hyperactivity disorder and hyperkinetic disorder." *Current opinion in neurobiology* 1998; **8**(2): 263-271.

24. Tian, Lixia, Tianzi Jiang, Meng Liang, Yufeng Zang, Yong He, Manqiu Sui, and Yufeng Wang. "Enhanced resting-state brain activities in ADHD patients: a fMRI study." *Brain and Development* 2008; **30**(5): 342-348.

25. Tian, Lixia, Tianzi Jiang, Yufeng Wang, Yufeng Zang, Yong He, Meng Liang, Manqiu Sui et al. "Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder." *Neuroscience letters* 2006; **400**(1): 39-43.

26. Weissman, D. H., K. C. Roberts, K. M. Visscher, and M. G. Woldorff. "The neural bases of momentary lapses in attention." *Nature neuroscience* 2006; **9**(7): 971-978.

27. Weissman, D. H., L. M. Warner, and M. G. Woldorff. "The neural mechanisms for minimizing cross-modal distraction." *The Journal of Neuroscience* 2004; **24**(48): 10941-10949.

28. Yu-Feng, Zang, He Yong, Zhu Chao-Zhe, Cao Qing-Jiu, Sui Man-Qiu, Liang Meng, Tian Li-Xia, Jiang Tian-Zi, and Wang Yu-Feng. "Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI." *Brain and Development* 2007; **29**(2): 83-91.

29. Zametkin, Alan J., Thomas E. Nordahl, Michael Gross, A. Catherine King, William E. Semple, Judith Rumsey, Susan Hamburger, and Robert M. Cohen. "Cerebral glucose metabolism in adults with hyperactivity of childhood onset." *New England Journal of Medicine* 1990; **323**(20): 1361-1366.