

REVIEW ARTICLE

Regional Dysregulation and Aberrant Functional Connectivity in ADHD

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Abstract

The trajectory of neurodevelopmental adversity determining attention-deficit/hyperactivity disorder (ADHD) from childhood to adulthood which is recognized increasingly by the long-term impairment and the burgeoning persistence beyond childhood, through adolescence, to adulthood poses a prolonged history defined by a concatenation of symptom profiles and an underlying dysregulation accompanied by aberrant brain regional networks. Abnormalities within the “default mode network” and disharmonizing fluctuations afflicting brain regional connectivity, even inducing dysconnectivity, appear to be associated both with symptoms profiles and the relative efficacy of putative interventional outcomes. Co-morbidity in ADHD, a persistently debilitating and potentially regressive issue, is viewed from a perspective of eating disorders and substance use disorders although several other combinations proliferate. Among the factors contributing to dysregulation and aberrant connectivity in brain development are included genetic and epigenetic proclivities, neurotoxins and neurodegeneration, predisposing characteristics and environmental pressures. Finally, the likelihood of perinatal stress trauma and/or inflammation as contributory circumstances ought to be considered.

Keywords: ADHD; Childhood; Adolescence; Adulthood; Dysregulation; Aberrant connectivity; Default mode; Biomarkers; Co-morbidity; Perinatal

Attention-deficit/hyperactivity disorder (ADHD) prevalence appears, by most current accounts, to be steadily increasing, possibly due to greater diagnostic, parental and teacher awareness but also to the interactive effects of environmental stressors, chemical agents and a generally disharmonious and unhealthy lifestyles that major portions of the populations have adopted (Archer et al., 2011).[1] In many respects, the burgeoning incidence of ADHD and accompanying health problems is alarming (Archer and Garcia, 2016),[2] despite the in-roads that have been made pertaining to intervention (Archer and Kostrzewa, 2012)[3]. ADHD symptom profiles vary between children, adolescents and adults but basically incorporate an exaggerated level of impulsiveness, lack of attention and a high degree of distractibility, excessive thoughtlessness and forgetfulness, losing things and disability in ‘starting-and-finishing’ (Archer and Garcia, 2016)[2], as well as alterations of the processes determining decision-making and reinforcement learning. ADHD pathophysiology incorporates a concatenation of multiple, cohesive modality spanning deficits, with each deficit expressing marked spatial overlap within patterns of structural and functional dysregulation (Kessler et al., 2014; Metin et al., 2015)[4,5]. A growing consensus indicates that as ‘part-and-parcel’ to the ADHD condition impairments, the default network-ventral attention network interconnections, or dysconnections, present a key locus of dysfunction and neurodevelopmental derangement (Sripada et al., 2014a,b).[6] Kessler et al. (2016)[7a,ab] have identified parallel associations between intrinsic connectivity networks dysmaturation and ADHD diagnosis in a sample of youths. They observed a pattern depicting a consistent biomarker for severe attentional performance deficits concurrent with a ‘down-shifted’ expression of intrinsic connectivity network maturation, i.e. shallow maturation, as opposed to a right-shifted expression, i.e. ‘lagged’ maturation. ADHD children and adolescents demonstrated markedly reduced dorsal caudate functional connectivity with the superior and middle prefrontal cortices as well as reduced dorsal putamen connectivity with the parahippocampal cortex (Hong et al., 2015). [8] Estimations of connectivity correlated in diametrically opposite directions among the ADHD and healthy control individuals, respectively, through the assessment attentional performance by application of the Continuous Performance Test, despite a good response to methylphenidate. Remarkably, it seems the case that studies carried out on ADHD patients to a major extent target upon dopaminergic genes and the structure of basal ganglia using structural and functional Magnetic Resonance Imaging (MRI and fMRI) (Vilor-Tejedor et al., 2016).[9]

Using fMRI to ascertain expectancy in children presenting ADHD symptoms through assessment of between-group differences in brain activity related to expectations concerning ‘when’ (i.e. timing), but not ‘what’ events will occur (i.e. cognitive control). Explicitly, Van Hulst et al. (2016)[10] obtained timing-related hypoactivity which was shown to be partially related to those children presenting a primary diagnosis of ADHD (left hemisphere pallidum) and partially shared by those children presenting similar levels of ADHD symptoms and a primary diagnosis of autism spectrum disorders (left hemisphere subthalamic nucleus). Furthermore, they obtained a poorer task performance that was related to timing, but only in the autism spectrum disorder children and symptoms of ADHD. It would seem to be the case that the presence of these neurobiological changes in children presenting ADHD symptoms may be linked to a failure to construct or monitor expectations thereby hindering the efficiency/efficacy of the child’s reciprocal interactions with environmental stimuli. Resting-state fMRI analysis of 56 child and adolescent ADHD patients and 56 normal controls (aged matched) the frontoparietal network which is associated with hyperactivity and impulsiveness expressed marked interactive effects of patient age and symptom profiles predictive for IQ scoring (Park et al., 2016) [11]. Using 3.0 Tesla fMRI scanner, and estimating the Korean ADHD Rating Scale, the Wisconsin Card Sorting Test, the 7- and 14-ring drill test with hop jumps, it found that childhood ADHD patients expressed an extended distance-traveled estimate and a decreased-speed on the 14-ring hop jump task whereas on the Wisconsin Card Sorting Test task, ADHD children demonstrated decreased activation within right gyrus brain region with total distance on the 14-ring hop jump task was negatively correlated with the mean β value of Cluster 2 in ADHD children according to the Korean ADHD Rating Scale (Kang et al., 2016)[12]. Despite these indications, using task-based fMRI to assess functional connectivity alterations between key reward processing regions in adolescents and young adults presenting ADHD (Oldehinkel et al., 2016)[13], it appears some manner of ‘developmental normalization’ occurred or that the reward-processing deficits earlier observed emanated from particular functional connectivity alterations in general task-related networks.

The “default mode network”, a regional brain interlocking nexus distinct from other networks, represents a confluence of interacting brain regions, expressing more-or-less synchronically correlated activity, and pathways under activation at times when individuals are unfocused upon the surrounding environment and their brains remain in a state of wakeful rest (Bellana et al., 2016)[14]. It has been found that abnormalities in the intrinsic activity of resting state networks may contribute to the etiology of conduct disorder and poor prognosis of ADHD in combination with conduct disorder (Uytun et al., 2016)[15]; whereas reduced default mode functional connectivity is associated with expressions of conduct disorder (Broulidakis et al., 2016)[16], individuals presenting ADHD present disproportionately high expressions of default mode network activity related to goal-directed tasks accompanied by ‘switch-specificity alterations in the right insula region (Sidlauskaitė et al., 2016)[17]. Moreover, adult ADHD patients demonstrated markedly stronger resting-state functional connectivity in the anterior cingulate gyrus of the executive control network, as well as in the cerebellar network, than healthy control adults (Moster et al., 2016)[18]. Opposing patterns of functional variability changes have been established for patients presenting schizophrenia spectrum disorders in contrast to those presenting ADHD: the former express lower variability in regions of the default mode network whereas the latter, with autism spectrum disorders, express higher levels of variability; on the other hand, within subcortical regions the former expressed higher variability and the latter lower levels of variability with symptoms scores related to variability levels in each case (Zhang et al., 2016) [19]. In a comparison with age-, gender-, and performance IQ-matched typically developing children, ADHD children showed weaker levels of functional connectivity between the right anterior prefrontal cortex and the right ventrolateral prefrontal cortex, as well as between the left anterior prefrontal cortex and the right inferior parietal lobule (Lin et al., 2015)[20]. In this context, aberrant connectivity represented an etiopathogenic expression of the altered frontoparietal control network in ADHD that are related particular to symptoms of impulsiveness and opposition-defiance (see above); these deficits ought to be observed with reference to those deficits pertaining to response inhibition and attentional control. Nevertheless, this observation renders it somewhat problematic to resolve the greater activated network-wise amplitude of low frequency fluctuations and enhanced functional connectivity variants between the intrinsic connectivity networks together with a temporal pattern within posterior default mode network that correlated positively with inattention scores among ADHD children (Wang and Li, 2015)[21]. Among ADHD adolescents, their unaffected siblings and healthy controls, it was shown that the former two groups presented weaker functional connectivity within the response inhibition network (van Rooij et al., 2015)[22], whereas the latter group showed lesser connectivity between default mode network nodes. Greater response inhibition network connectivity related to lower ADHD severity concurrent with higher levels of default mode connectivity related to elevated ADHD severity.

Brain connectivity assessments cover three basic areas of research: (i) anatomical connectivity, (ii) functional connectivity and (iii) effective connectivity referring to structural aspects of connections between neighboring neurons, the temporal dependency of neuronal activation patterns of anatomically separated brain regions and the particular type of influence that one neuronal system brings to bear upon another type of neuronal system thereby emulating causal interactions between the associated activated brain areas (Lang et al., 2012)[23]. Among the methods applied for studying connectivity may be listed several neuroimaging and neuroanatomical techniques, including: fMRI (see above), diffusion-weighted MRI tractography (Yo et al., 2009)[24], EEG (Zaric et al., 2016)[25], magnetoencephalographic analysis (MEG, Liuzzi et al., 2016)[26], PET (Trotta et al., 2016; Vanicek et al., 2016) [27] and SPECT (Jann et al., 2015)[28]. The quantification of brain connectivity proceeds through the encoding of neighborhood relations into a connectivity matrix by which whose rows and columns correspond to the different brain regions. Functional connectivity is commonly deduced from intervoxel cross-correlations and is often assumed to reflect also the interregional coherence of fluctuations in activity of the underlying neuronal networks within the different brain regions implicated. Currently,

the separations between anatomical neuronal connections and related functional connectivity and/or effective connectivity remain the focus of much study.

The intimate role of dopaminergic neurotransmission, both due to hereditary and environmental influence, as well as from drug-treatment studies is well-established (Hung et al., 2016; Schranke et al., 2016; Ziegler et al., 2016)[29,30,31] while more recent approaches point to the importance of dopamine-glutamate interactions (Miller et al., 2014)[32]. Several lines of evidence have implied that sporadic disturbances in the signaling of glutamate receptors during a critical period of brain development may contribute to the ADHD pathophysiology (Archer and Garcia, 2016)[2]. It seems likely that the various symptom profiles expressed through behavioral deficits in ADHD are linked to alterations within the global cortico-striatal functional architecture of brain, or whether or not ADHD-related alterations are limited to local, intrastriatal functional connections. Ketamine and other glutamate antagonists have been applied as animal models for ADHD (Fredriksson and Archer, 2002, 2003, 2004; Fredriksson et al., 2004)[33,34,35,36]; in this context, it ought to be considered that ketamine caused specific connectivity alterations within and between resting-state consciousness networks with frontoparietal default mode connectivity disruption together with default mode anti-correlation and sensory plus sensory-motor network connectivity preservation unfolding (Bonhomme et al., 2016)[37]. In adult ADHD patients, impaired/altered cerebellar areas of the default mode network have been observed (Hove et al., 2015; Kucyi et al., 2015)[38,39]. A consistent feature of childhood ADHD are the aberrant, dysregulated, cross-network interactions between the salience network, central executive network, and default mode network (Cai et al., 2015)[40]. Serotonergic modulation of functional connectivity appears to be implicated in the resting-state default mode network since acute tryptophan depletion with subsequent losses of serotonin availability to ADHD patients induced reduced functional connectivity in the right superior premotor cortex and left somatosensory cortex, whereas the reverse was observed in the healthy controls (Biskup et al., 2016)[41]. Regarding the serotonin transporter, Vanicek et al. (2016)[42] obtained significant differences in the interregional correlations between the precuneus and the hippocampus in patients with ADHD compared to healthy controls, using the serotonin transporter binding potential, "SERT BPND", of the investigated regions-of-interest under study. Acute methylphenidate administration caused marked functional connectivity alterations between regions of the default mode network with marginal increases in the anterior-posterior connectivity location of the network (Battel et al., 2016)[43].

ADHD predisposes patients to several conditions, e.g. narcolepsy and hypersomnia, but even more important there appears to persist a shared pathophysiology with various addictive syndromes incorporated in the Reward Deficiency Syndrome, such as drug abuse and eating-intake disorders (Modestino et al., 2015)[44]. Furthermore, it has been proposed over a series of reports that genetic variants of dopaminergic genes and other "reward genes" are important common determinants of reward deficiency syndrome (RDS), which we hypothesize includes ADHD as a behavioral subtype (cf. Blum et al., 1996, 2000, 2008a,b, 2010)[45,46,47,48,49]. ADHD symptom profiles, particularly regarding the hyperactivity syndromes, attentional problems and impulsiveness, may present surprisingly high levels of co-morbidity to a range of 'parallel' disorders, including eating disorders and drug-related disorders; yet, there has been found to be an uncertain variability in the diagnostic rate of both ADHD and its co-morbidities. For example, a clear positive relationship between responsiveness-to-food and the total ADHD symptom index, especially impulsiveness, lack of attention and the hyperactivity subscales, separately, has been observed (Leventakou et al., 2016)[50]. In a similar context, they obtained also marked positive associations between emotional overeating and ADHD symptoms; those children linked to the highest tertile of the emotional overeating scale presented higher total ADHD index and hyperactivity subscale scores. As an indication of, ADHD children's food avoidant behaviors, 'food fussiness' was shown to be associated significantly with the impulsiveness subscale. The authors found also marked dose-response associations between the expressions of food approach and the ADHD symptoms. Medium level and the highest tertile ADHD children pertaining to the food responsiveness subscale presented elevated scoring on the ADHD total scale, in comparison with those on the lowest tertile. Across gender, individuals presenting lifetime and previous 12-month binge eating and binge eating disorder showed significantly higher prevalence for ADHD diagnosis than individuals without binge eating and binge eating disorder, respectively (Brewerton and Duncan, 2016)[51]. Female ADHD patients presenting lifetime and previous 12-month bulimia nervosa and lifetime anorexia nervosa also showed markedly higher prevalence for ADHD diagnosis in comparison with female patients not presenting these diagnoses. In view of the situation that ADHD expression was invariably initiated earlier than the eating disorder expression, ADHD condition offers an important risk factor for subsequent binge eating and related eating disorder. Co-morbidity with cocaine abuse among adult ADHD diagnosed individuals presented the highest level of effect size for global cognitive impairment compared with cocaine-naïve ADHD patients and healthy controls (Wunderli et al., 2016)[52]. Compared with adult ADHD patients without substance use disorders, patients presenting ADHD together with cocaine/crack showed markedly lower mean IQ levels and higher levels of motor impulsiveness as well as performing more poorly on tasks that assessed verbal skills, vigilance, implicit learning during decision making (Miguel et al., 2016)[53]. The former group of patients (no substance abuse) displayed a worsened level of performance on selective attention, information processing, and visual search tests. Taking converging trends together, Capusan et al. (2016)[54] have collected evidence demonstrating that ADHD symptoms and their associated subtypes derived from the general population were related to increased risks for all types of substance use/abuse disorder outcomes, without any differences between the ADHD subtypes, without substance preferences, and in the absence of gender differences for the presented co-morbidity. Finally, levels of estimated ADHD-symptom severity, co-morbid presence of conduct disorder and major depressive disorder tendency, and treatment-efficacy for ADHD remain the main predictors of ADHD persistence over the childhood-to-adulthood trajectory (Caye et al., 2016)[55].

Laboratory animal models of ADHD imply that several factors contribute to the dysregulation and dysconnectivity observed in the expressions of disorder, including:- (i) genetically- and/or epigenetically-based models, e.g. spontaneously hypertensive rats (Kim et al., 2016)[56] or Naples High-excitability rats (Ruocco et al., 2015)[57], SNAP-25-deficient mutant coloboma mice (Baca et al., 2013)[58] or Cadherin-13, risk gene for ADHD (Rivero et al., 2015)[59]; further, Nr3c1-Bhlhb2, transcription factor silencing, axis dysregulation was involved in the development of ADHD through a disruption of prefrontal cortex functioning (Wu et al., 2016)[60]. In a pair-matching case-control study of ADHD children, it was found that Aberrant DNA methylation and histone acetylation was established in ADHD by applying the combination of p300, MYST4 and HDAC1 to obtain an accuracy of 0.9338 (Xu et al., 2015)[61]. (ii) Neurotoxicity- and/or neurodegeneration-based models, e.g. pesticide and perfluoroalkyl substances (Lien et al., 2016; Mostafalou and Abdollahi, 2016)[62,63], that implicate both neurons and glial cells (Motaghinejad et al., 2016; Shah and Lahiri, 2016)[64,65]. (iii) N-methyl-D-aspartate (NMDA) neonatally-injected antagonist models in rodents, e.g. NMDA blockade during the brain growth spurt period (Oliveira-Pinto et al., 2015)[66], and single unit recordings of basal and glutamate-induced excitability of pyramidal neurons in the prefrontal cortex of anaesthetised rats coupled with microiontophoresis (Di Miceli and Gronier, 2016)[67], as well as biomorphic electrode concurrent evaluations of glutamate in aligned networks of the frontal cortex that involve the cingulate, prelimbic, infralimbic and dorsal peduncle regions (Miller et al., 2015)[68] (iv) Models based upon changes induced by the environment, e.g. exposure to 'greenhouse gas' (Fluegge, 2016)[69], genetic and environmental overlap during development (Brikell et al., 2016; Homberg et al., 2016)[70,71], childhood trauma history (Ferrer et al., 2016)[72], familial aggregation driven by environmental factors (Chen et al., 2016; Yin et al., 2016)[73,74], peer influence as a magnifier of ADHD diagnosis (Aronson, 2016)[75], second-hand smoking exposure and low blood lead levels (Joo et al., 2016)[76], preschool hyperactivity expression and developmental trajectories (Lopez-Vicente et al., 2016; Smith et al., 2016)[77,78] and susceptibility risk factors (Vilor-Tejedor et al., 2016)[79].

It has been observed that low circulating levels of omega-3 are linked to conditions presenting CNS-related disorders, including cognitive deficit disorders, depression and anxiety disorders, poor anger and conduct control, ADHD and related syndromes, and accelerated neurodegeneration in the elderly individuals (Grant and Guest, 2016)[80]. Similarly, neuroimmune dysregulation occurs among a variety of CNS conditions with interactions involving central and peripheral immune mechanisms that have been found to be disrupted as observed through a series of neuroimmune biomarkers, such as CD3, CD4, CD7, HLA-DR, CD25, CD28, and CD56, which display variability in brain disorders as indicated in anxiety, depression, psychosis, stroke, Alzheimer's disease, Parkinson's disease, attention-deficit hyperactivity disorder, migraine, epilepsy, vascular dementia, mental retardation, cerebrovascular encephalopathy, multiple sclerosis, brain tumors, cranial nerve neuropathies, mental retardation, and posttraumatic brain injury (Cacabelos et al., 2016)[81]. In a functional magnetic resonance imaging study of a cohort of ADHD adolescents compared with matched healthy controls, Von Rhein et al. (2016)[82] did not confirm the notion that ADHD was associated with brain alterations in cortico-striatal networks but rather alterations within local regional striatal functional connectivity thereby implicating aberrant development of local regional functional connectivity of the putamen complex, which could generate eventually the augmentation of functional segregation between the anterior and posterior putamen in the disorder. Higher levels of functional connectivity, particularly within the frontal regions (anterior cingulate cortex) of the brain, linked to the executive control network were observed to correspond to reductions in ADHD symptoms with regard to hyperactivity-impulsiveness but not inattention (Francx et al., 2015)[83]. The presence of diverse co-morbidity encompasses regional dysregulation of both structural and functional expression that may, or may not, both exacerbate and/or render 'staging-progression' to the disorder.

Conclusions

Finally, Beare et al. (2016)[84] have observed that ADHD was linked to local proximal regions seen to be more modular and interconnected than in the case of the control groups wherein a decrease in the global, long-range connections, was observed depicting a reduced interchange between local, specialised networks in the ADHD condition. The disorder presents a sub-network of more substantial connectivity embracing bilateral frontostriatal connections in addition to the left occipital, temporal, and parietal regions in which the white matter microstructure was related to with ADHD symptom severity. Under normal conditions, successful neurodevelopmental outcomes emerge from the synchronized and determinative organization of converging neural elements into complex structural and functional networks, the connectome or "wiring-diagram", is a comprehensive map of neural connections in the human brain. Perinatal stress-related/inflammatory symptoms are common in women during pregnancy and are risk factors for neurobehavioral disorders and associated co-morbidities, including ADHD (Flinkkilä et al., 2016; Scheinost et al., 2016)[85,86]. The final outcome of ADHD diagnosis is accompanied by a complex, and discouraging heterogeneous, expression of symptom profiles emerging from altered functional connectivities, default mode network, biomarker identities, absence of necessary dietary ingredients, neuroimmune biomarkers, epigenetic pressures, reward deficiency syndrome and co-morbid complications that underlie serious reductions in the quality-of-life and aspirations of the ADHD child and its siblings. As adolescent and adult, the childhood complexities and disruptions may persist to hinder the health trajectory.

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