

In Quest of Pathognomonic/Endophenotypic Markers of Attention Deficit Hyperactivity Disorder (ADHD): Potential of EEG-Based Frequency Analysis and ERPs to Better Detect, Prevent and Manage ADHD

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Abstract: Attention deficit hyperactivity disorder (ADHD) is a chronic heritable developmental delay psychiatric disorder requiring chronic management, characterized by inattention, hyperactivity, hyperkineticity and impulsivity. Subjective clinical evaluation still remains crucial in its diagnosis. Discussed are two key aspects in the “characterizing ADHD” and on the quest for objective “pathognomonic/endophenotypic diagnostic markers of ADHD”. The first aspect briefly revolves around issues related to identification of pathognomonic/endophenotypic diagnostic markers in ADHD. Issues discussed include changes in ADHD definition, remission/persistence and overlapping-symptoms cum shared-heritability with its co-morbid cross-border mental disorders. The second aspect discussed is neurobiological and EEG-based studies on ADHD. Given the neurobiological and temporal aspects of ADHD symptoms the electroencephalograph (EEG) like NeuralScan by Medeia appears as an appropriate tool. The EEGs appropriateness is further enhanced when coupled with suitable behavior/cognitive/motor/psychological tasks/paradigms yielding EEG-based markers like event-related-potential (ERPs like P3 amplitudes and latency), reaction time variability (RTV), Theta:Beta ratio (TBR) and sensorimotor rhythm (SMR). At present, these markers could potentially help in the neurobiological characterization of ADHD and either help in identifying or lay the groundwork for identifying pathognomonic and/or endophenotypic EEG-based markers enabling its diagnosis, treatment and management.

Keywords: ADHD, EEG, event related potential, reaction time

Introduction

While attention deficit hyperactivity disorder (ADHD) carries the distinction of being among the most well-researched mental disorders still challenges remain regarding its diagnosis, management and treatment. For instance, to date diagnosis is based on subjective clinical examination using standard questionnaires and tests that capture impairments in behavior and cognition.¹⁻⁷

As ADHD traits (inattention, hyperactivity, hyperkineticity and impulsivity) have both a neurobiological and temporal aspect state-of-the-art electroencephalography (EEG) machines like NeuralScan by Medeia (Figure 1) with its easy-to-wear reusable 10/20 system EEG caps, user/clinician-friendly software and cloud-based reporting make neurobiological characterization of ADHD possible. However, while EEG-based confirmation of ADHD has received FDA approval, it has yet to be

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Figure I EEG-based frequency analysis using (A) NeuralScan by Medeia showing demo results of: (B) Resting EEG (Eyes Open and Eyes Closed) and Theta/Beta ratio, (C) Visual and Auditory processing, Working Memory and Attention and (D) Theta/Beta ratio, Visual and Auditory processing, Working Memory, Attention Reaction Time (RT) and Reaction Time Variability (RTV).

approved in instances where the clinical diagnosis of ADHD is negative, the aim being to prevent over-diagnosis and misdiagnosis.⁸ Recent features like quantitative electroencephalogram (qEEG) and low-resolution brain electromagnetic tomography (LORETA) have added both a power and spatial component to EEG analysis.^{9–11} With these new features, one can measure, capture and record from Theta:Beta ratio (TBR) to a whole range of EEG-based frequency analysis (alpha, α , beta, β , theta, θ , delta, δ , gamma, γ , mu, sensorimotor rhythm (SMR)) to event-related-potential (ERPs) components (P1, N1, P2, N2, P3, N3, ERN, Pe, CNV, RT, amplitudes and latency) to reaction time variability (RTV) to power and source analysis. Furthermore depending on the paradigms and tasks used to elicit these ERPs one can now achieve better neurobiological, behavioral and psychological characterization and guide management of ADHD. Thus, EEG machines like NeuralScan are fast becoming potential pathognomonic diagnostic tools.

Clinicians could easily study and assess

- (a) Neurobiological and EEG-based risk factors of cognitive impairment, hyperactivity and attention that will either be potential markers or modifiable traits,
- (b) responder and non-responders to treatment via medication/behavioral therapy/neurofeedback,
- (c) heritable brainwave alterations exclusive to ADHD or shared with it co-morbid psychiatric disorders and
- (d) tailor treatment.

Taken together the EEG-based findings could in turn add enormous value in the quest for brain-based pathognomonic and endophenotypic markers of ADHD. The benefit of endophenotypic markers of ADHD would be that diagnosis would be more objective and less symptom-based especially in light of symptom overlaps with other cross-border co-morbid mental disorders. However, endophenotyping ADHD comes with its own challenge is that ADHD also shares heritable traits with some of its co-morbid mental disorders. With this in mind we sought to consider together I) challenges in identifying markers of ADHD, current II) neurobiology and III) EEG-based aspects on ADHD in the hope of either identifying or laying the framework for identification of potential pathognomonic/endophenotypic markers of ADHD.

Challenges in Identifying Endophenotypic/Pathognomonic Markers of ADHD

Changes in Diagnostic Criteria

Changes in diagnostic criteria impact on: prevalence, incidence, conversion and remission rates, comparison across studies and long-term follow-up studies. The nosology of ADHD has changed from the “incapacity to attend” to a “Neurodevelopmental Neurocognitive Disorder”.^{12–15} Developments in neuropsychology, neuroimaging, epidemiology, genetics, and pathophysiology contributed to Diagnostic and Statistical Manual for Mental Disorders (DSM) DSM-VI/DSM-VI-TR’s classification of ADHD as ADHD with inattention (ADHD-I), hyperactivity (ADHD-H), and combined (ADHD-C) subtypes.⁵ Barkley further described ADHD.

as a disorder of executive dysregulation (in behavioral inhibition, working memory, motivation, and motor control) rather than simply of attention and hyperactivity¹⁶

Barkley worked to ensure it was distinct from concentration deficit disorder (CDD).^{16–19} Further developments in molecular biology, psychometrics, and cognitive and affective neurosciences led to ADHD being classified under “Neurodevelopmental Disorders” and “Neurocognitive Disorders” in DSM-V requiring symptoms to be present in two or more environments.⁶ Based on the current definition of ADHD its prevalence is 2.2% in children which translates to 1:45 children and 2.8% in adults, i.e. 1:36 adults. 50–65% of childhood ADHD persists into adulthood with the persistence rate of childhood ADHD being 47.4%. The higher adult prevalence rate seen is a reflection of conversion of children who were originally below the diagnostic thresholds and self-reported or new cases of adult ADHD.^{20–22}

Overlapping Symptoms of Cross-Border Cum Co-Morbid Mental Disorders

While symptoms/behavior manifesting as a spectrum of hues, tones, tints and shades, were originally used to frame the diagnostic criteria they have also added to the confusion due to symptom-sharing between cross-border cum co-morbid mental disorders.^{6,7,23,24} 80% of individuals with adult ADHD have at least one other co-morbid condition.^{23–27} While the general consensus is to treat the dominant functionally impairing illness the overlapping symptoms make clear-cut diagnosis, treatment and determination of the burden of disease challenging^{28–31} Figure 2A

A

Spectrum of ADHD Symptoms	Other Mental Disorders sharing shades/hues in the spectrum of symptoms seen in ADHD				Symptoms unique to the Other Mental Disorders not shared with ADHD
	Mood Disorders	Major Depressive Disorder			Poor concentration during depressive episode, low mood, weight loss, diminished interest in activities and suicidal thoughts
		Bipolar Disorder	Hypo-manic		Episodic symptoms, fluctuating between MDD & manic state.
			Depressed		Impulsivity/, Inattention accompanied by elevated mood, grandiosity
	Anxiety Disorders	Generalized AD			Inattentive due to worry, rather distractible Fatigue. Muscle tension, Sleep disturbance
	Personality Disorders	Anti-Social PD			Delinquent behavior, deceitfulness, disregard for self & others. Lack of remorse
		Borderline PD			Abandonment fears, unstable relationships & self-image. Suicidal thoughts, paranoia and self-injury
	Other	Substance-Use Disorder			Excessive use of substance irrespective of consequence. ADHD needs to precede SUD
		Sleep Disorders			Sleepiness, tiredness

B

Individuals (%) with Other Mental Disorders with ADHD (n=349)

Deberdt W et al, BMC Psychiatry. 2015

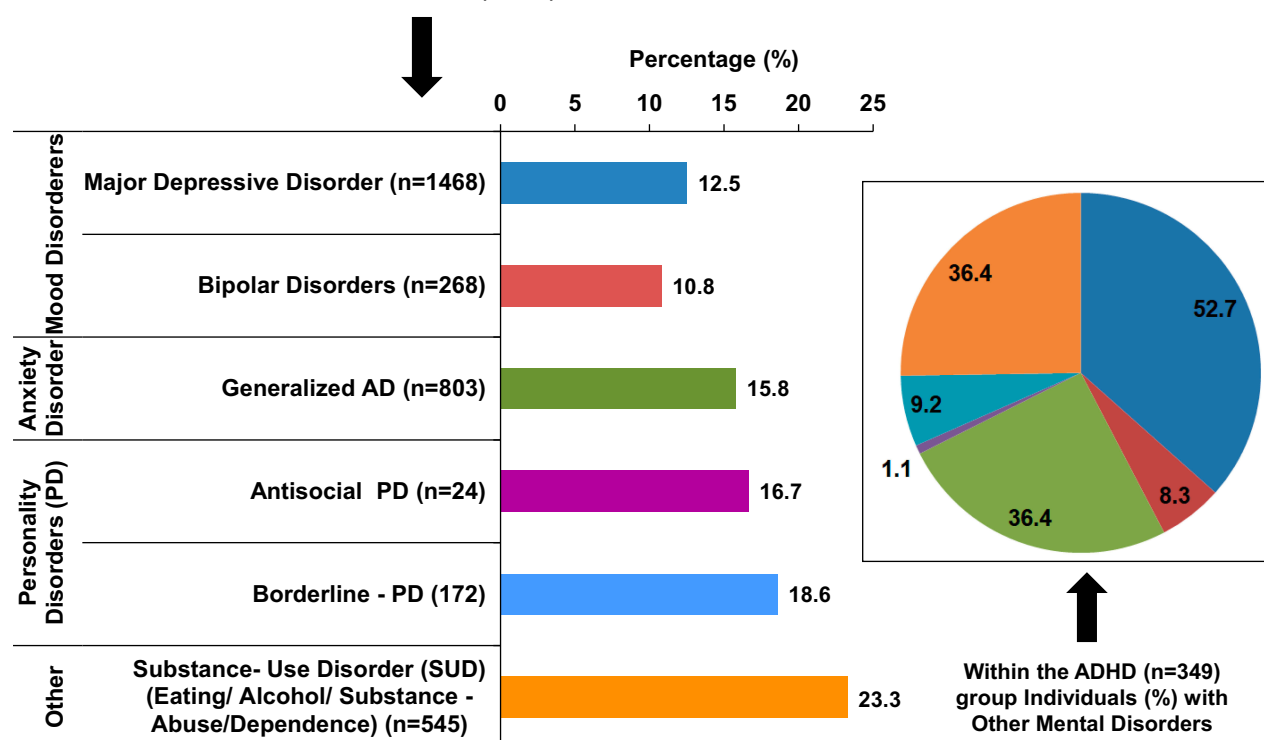


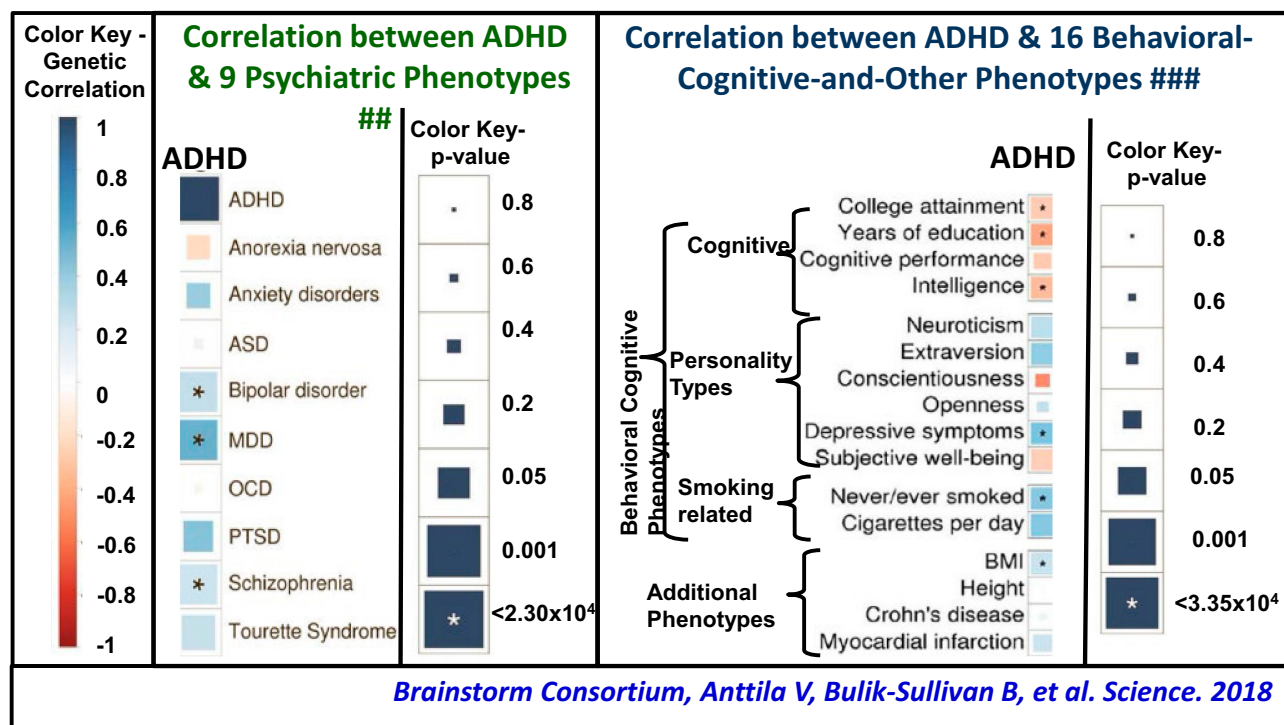
Figure 2 (A) ADHD and its cross-border co-morbidities: Illustration of symptom sharing and symptoms unique.^{6,7} Percentage of Individuals with ADHD and selected symptom sharing (cross-border) psychiatric comorbidities (32).

provides an illustration of symptoms shared by and symptoms that distinguish ADHD and other mental disorders.^{6,7} Figure 2B presents the results of a multinational cross-sectional study in Europe to estimate the prevalence of ADHD in adult outpatient psychiatric care facilities. Out of $n=2284$ individuals included in the study, 349 had ADHD (17.4%, $n=2009$ screened using DSM-V).³² Within the ADHD subgroup (pie diagram) major depressive disorder (MDD), generalized anxiety disorder (generalized AD) and substance use disorder (SUD) were the most common co-morbidities. Study results of the Regional ADHD Registry database at 18 tertiary care ADHD centers ($n=2861$) in Italy between 2011 and 2016 period were, 67% ($n=1919$) had ADHD, among whom 34% ($n=650$) had ADHD alone and the remaining had ADHD+≥1 mental health co-morbidity (learning disorders/sleep disorders/oppositional defiant disorder/anxiety disorders).³³ The implications for neurobiological and EEG-based studies on ADHD are overlapping symptoms that could extend to overlaps in neurobiological and EEG patterns.

Heritability of ADHD and Shared Heritability of Its Co-Morbidities

Compounding the issue is the heritability and at times shared heritability of both ADHD and its co-morbidities and that ADHD is a heterogeneous disorder with many subtypes (ADHD-I, ADHD-H, and ADHD-C). Genetic studies on ADHD include a) family, b) twin, c) candidate genes, d) genome-wide approaches (GWAS), e) copy number variations (CNV), f) environmental risks and g) endophenotypes.^{34–47} Siblings of ADHD probands are at 9-times greater risk of ADHD with twins both monozygotic: MZ and dizygotic: DZ, sharing 100% and 50% genetic inheritance, respectively, as well as environmental exposure exhibit a heritability of ADHD of ~75%.^{34–36}

A GWAS study worth mentioning in detail is one carried out by the Brain Consortium (Figure 3) to quantify the degree of overlap of genetic risk factors involved in 10 psychiatric and 15 neurological disorders also looking at 17 behaviour-cognitive phenotypes among 265,218 patients and 784,643 control participants (total



Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Major Depressive Disorder (MDD), Anxiety disorders (generalized anxiety disorder, panic disorder, social phobia, agoraphobia, and specific phobias), Obsessive-Compulsive Disorder (OCD), Post-Traumatic Stress Disorder (PTSD) and Body Mass Index (BMI)

Data from 1,58,028 patients and 3,65,993 control participants totaling 5,24,021 participants

Data from 11,24,048 participants

Figure 3 Correlation illustrating the shared genetics of ADHD with selected psychiatric co-morbidities and behavioral-cognitive phenotypes.

of 1,191,588 individuals).⁴⁶ Results indicated that while neurological disorders appeared distinct from each other in terms of genetic risk, psychiatric disorders showed a high degree of genetic correlation with each other. Presented in [Figure 3](#) is the correlation between ADHD and the other psychiatric disorders and the correlation between ADHD and the behavioral-cognitive phenotypes. This shared genetic etiology highlights the need to re-define both clinical and diagnostic boundaries to prevent diagnostic misclassification. Further, endophenotyping strategies need to ensure they reflect phenotypic heterogeneity that correlates with genetic correlations where psychiatric disorders are concerned.

Neurobiological Studies on ADHD

Deficits in working memory, cognitive flexibility, attention and inhibition are seen in ADHD.^{48–50} Both magnetic resonance imaging (MRI) and fMRI had highlighted the role of

- (a) The frontoparietal, dorsal frontostriatal composed of the dorsolateral prefrontal cortex (PFC), dorsal striatum (DS), and the thalamus: attention and attention orientation),
- (b) mesocorticolimbic circuits composed of the orbitofrontal cortex (OFC), ventral striatum and nucleus accumbens (NAcc), ventral tegmental area (VTA), and anterior hippocampus: reward and emotional processes, ie, motivation, frustration tolerance, and reward anticipation and
- (c) the default mode network (DMN) that includes the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and lateral parietal cortex (LPC) and the cognitive control networks (CCN) that includes the dorsolateral prefrontal cortex (DLPFC), anterior insular cortex (AIC), and supramarginal gyrus (SMG) in ADHD.

Studies on whole-brain structural MRI showed volumetric reductions in the basal ganglia in children with this reduction attenuating by adulthood.^{51–53} These findings help establish ADHD as a disorder that involved delayed neurobiological development. Another finding that supported this view was a longitudinal study of 223 children with ADHD with 223 healthy controls which demonstrated that ADHD children were 2–5 years behind in achieving similar cortical thickness as healthy controls.^{54–56}

Studies on neural connectivity in ADHD using diffusion MRI (dMRI) showed decreased fractional anisotropy (anterior corona radiata, internal capsule, and forceps minor and reduced orbitofrontal white matter organisation (mesocorticolimbic circuits)).^{57–59} Resting-state functional connectivity showed reduced connectivity within the DMN and task-based functional connectivity revealed increased activity for rest or introspective thought/tasks; while in controls DMN deactivation occurred as they transitioned to extrospective tasks a reduction in deactivation was seen in ADHD, which is possibly the cause of lapses or errors in goal-directed behavior.^{60–64} In terms of inhibitory control, a study of 287 individuals with ADHD and 320 healthy controls found that those with ADHD exhibit reduced activation in frontostriatal regions including the right inferior frontal cortex, striatum, and supplemental motor cortex during tasks requiring response inhibition.^{64–66}

Functional MRI and diffusion tensor imaging studies have revealed impairments in prefrontal-striatal networks (inattention) and frontal-limbic networks (hyperactivity), over-activation of DMN-activation of fronto-striatal and fronto-parietal circuits, other frontal brain region and systems involved in executive function and attention to be implicated in ADHD.^{66–72} In terms of neurotransmitters, delayed maturation of certain dopaminergic neural pathways in children and adolescents with ADHD, lower levels of available dopamine receptor and transporter molecules in adults with ADHD and polymorphisms in the serotonin transporter gene (associated with differential response to ADHD treatment) and deficiencies in glutamate signaling characterize the disorder.^{73–77}

Electrophysiology and ADHD

[Figure 1](#) illustrates the facility with which EEG frequency analysis and ERP studies can be carried out using EEG machines like the NeuralScan by Medeia. Presented below are EEG-based studies on key aspects of ADHD.

Presented in [Tables 1](#) and [2](#) is a summary of the approach followed in a recent review of EEG-based studies between 2000 and 2017 that examined ADHD-specific cognitive aspects (allocation of attentional resources, performance monitoring, and processing).⁷⁸ Findings of the review were that in ADHD, in aspects of attention: orienting to cues, signaling response preparation, monitoring of conflict, rewarding feedback, and diminished inhibitory control were seen in young adulthood. The review also highlighted the need for studies between 16 and 26 age-group on ADHD.

Table I Analytic Approach Followed to Review EEG-Based Cognitive Studies on ADHD from 2000 to 2017

Analytical Approach		Prominent Components & Proposed Functional Significance
ERP's	Sensory processing	P50: sensory gating, N1 (N100): Sensory processing of unexpected (auditory) stimulus, P1 (P100): Sensory processing of stimulus in the contralateral visual field, N170: Structural encoding of faces, Early posterior negativity (EPN): Selective visual attention toward emotional stimuli, Mismatch negativity (MMN): Detection of infrequent and odd deviant stimulus in a repetitive sequence of auditory or visual stimuli
	Stimulus evaluation	N2: Detection of mismatch and/or inhibition of competing response, N250: Storage of face representation in long-term memory, P2: Sensitivity to various stimulus features, P3a (novelty P3): Novelty processing and involuntary orienting of attention, P3b (classic P3): Attentional engagement and stimulus evaluation/decision-making, N3 (slow wave or late posterior negativity (LPN)), Enhanced attention to stimulus, particularly the nonautomatic, controlled part of the stimulus processing, Negative-going wave over centroparietal electrodes peaking at 250–500 ms poststimulus
	Response preparation	CNV Negative-going wave rising around 260–470 ms after a warning stimulus: Response and motor preparation to upcoming stimulus, Lateralised readiness potential (LRP) Negative-going wave over motor cortices contralateral to the responding hands: Motor preparation before action execution, Late positive potential (LPP): Salience of emotional stimuli
	Error detection	Error-related negativity (ERN) Negative-going wave rising 50–100 ms following erroneous response execution over frontocentral electrodes: Unconscious error processing Error-related positivity (PE) Positive-going wave over centro-parietal electrodes peaking around 200–500 ms post-error, after the occurrence of ERN: Conscious error processing
Quantitative EEG (qEEG)		Very-low frequency (VLF, 0.02–0.2 Hz): Default-mode network, Delta: Attention and inhibition, Theta: Cognitive control, learning and memory, Alpha (8–12 Hz, over occipital cortex): Alertness, attention and inhibition, Mu rhythms (8–13 Hz, over sensorimotor cortex): Action execution and observation of others' actions, Beta: Sensorimotor processing and sensory gating, Gamma: Sensory binding
Time-frequency analyses		Evoked power & Induced power: Dynamic changes in power of a given frequency band over time, Event-related phase-locking OR inter-trial coherence (ITC), Consistency of timing of ERPs across trials (eg, neural variability), Coherence & Cross-frequency coupling: Brain's regional connectivity and interregional interaction

With ADHD being a delay in neural development more studies that cover childhood and young adulthood (till 25 years) are warranted. The review also highlighted the need for genetically informed studies (family studies and twin studies), studies across lifespan in executive functions and/or decision-making processes, cross-border disorder diseases comparisons, whether ADHD was classified based on self-, parent- or teacher-reporting, neuroimaging and studies on remission and persistence of ADHD.

Another key aspect brought out by this review is ERPs subtypes exist based on the paradigm used to elicit them with the odd ball paradigm and its variations being used to study attention and ADHD. Paradigms used include;

- Stimuli (visual vs. auditory) cued continuous performance tasks (CPT), such as cue orienting (cue-trials), response execution (go-trials), response inhibition (no-go trials), trial conditions with inhibitory versus response demands.
- Performance monitoring (various facets of monitoring within the same task) including; conflict (errors and feedback), context monitoring (e.g., social vs. non-social),

- Face processing tasks (covering a range of positive and negative emotions), emotional conditions.
- Other paradigms used to evaluate cognitive ability include colour vision, orientation, brightness, pitch, motion, cross-modality integration, etc.

Such psychological, functional, and behavioral studies keeping in mind the structural, pathophysiological and environmental aspects of ADHD will certainly go a long way in clarifying the symptom and heritability sharing between ADHD, its comorbidities and cross-border disorders, aid in its endophenotyping and in identification of a diagnostic marker.^{79–81}

ADHD, Attention, Cognitive Performance, Default Mode Network (DMN) Deactivation

The default mode network (DMN) which includes the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC)/precuneus and medial, lateral and inferior parietal cortex medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC)/precuneus and medial, lateral and inferior parietal

Table 2 Neurocognitive Domains and the ERP Components Elicited via Appropriate Paradigms in EEG-Based Cognitive Studies on ADHD from 2000–2017

Neurocognitive Domain	Subprocesses Investigated	EEG/ERP Components	Paradigms Used to Elicit ERPs	ADHD
Attention Processing	Cue processing	P50, P1, N1, P2, N2, P3a, P3b, TF-PCA of P3b, LRP, CNV, VLF, delta, theta, alpha, beta, gamma	Visual oddball, Auditory oddball & go/no-go, Fast task, Cued CPT, Eriksen flanker task, Two choice reaction	
	Response preparation	CNV	Auditory oddball & go/no-go	
	Novelty processing			
	Sustained attention	VLF	Cued CPT	
	Perceptual binding			
Inhibition Control		P1, N1, P2, N2, P3b, LRP	Stop-signal Go/no-go	
Performance Monitoring	Conflict monitoring	N2, ERN, Pe, CNV, LPP, ITC, theta, early positivity,	Flankers task, Go/no-go, Incentive delay task	
	Error processing	ERN, Pe	Go/no-go	*
	Predictions			
Face Processing	Structural encoding	N170, P1	Visual oddball with faces	
Sensory Processing	Visual processing	P1, theta, alpha	cVEP, Light flash paradigm Tone processing during film. Brightness detection task	*
	Auditory processing	N1, theta, alpha	Tone processing during film	*
	Context modulation			
Memory and Language	Working memory	Alpha; P3b	Delayed match-to-sample task Modified I-back task	
	Semantic processing			
	Speech processing			

Note: EEG and ERP components where ADHD-autism spectrum disorder (ASD) shows an overlap. **Boxes shaded grey** indicates studies where the ERPs reflective of cognitive status in ADHD were elicited using appropriate paradigms. Blank cells indicate areas on EEG aspects of ADHD not yet studied. Note: Adapted from Lau-Zhu A, Fritz A, McLoughlin G. Overlaps and distinctions between attention deficit/hyperactivity disorder and autism spectrum disorder in young adulthood: Systematic review and guiding framework for EEG-imaging research. *Neurosci Biobehav Rev.* 2019;96:93–115. Creative Commons license and disclaimer.⁷⁸ Available from: <http://creativecommons.org/licenses/by/4.0/legalcode>"<http://creativecommons.org/licenses/by/4.0/legalcode>

cortex is active when the brain is at rest and deactivates with the onset of goal-directed tasks.^{82–90} Further, the DMN is comprised of both task-positive (extrospective attention) and task-negative (introspective attention) components with attenuation being directly correlated to the degree of complexity and cognitive challenge a task presents.^{82–90} DMN oscillations are very low frequency (VLF) oscillations with individuals with ADHD exhibiting reduced DMN deactivation when transitioning from rest to a specific task, ie, increased reaction time variability (RTV).^{91–93} In a study on adults with low and high levels of ADHD Broyd et al compared EEG at rest and during a task that demanded

attention.⁹⁴ While both groups exhibited equivalent attention and performance via sLORETA it was found that both groups showed atypical deactivation, ie, the DMN regions deactivated differed. Attention-induced DMN deactivation occurred in the medial prefrontal regions (mPFC) in those with low-level ADHD while in those with high ADHD the temporal regions were deactivated.

Inhibitory Control

A study on inhibition control and ADHD highlighted deficits in the ‘inhibition of interferences’ and ‘action inhibition’ via ‘Simon Tasks’ and ‘Go/Nogo tasks’.

Findings revealed that inhibitory control operates on a hierarchical “first come, first serve” basis which is not integrated in ADHD. The defect was attributed to dysfunctions at the response selection level and fronto-parietal cortices. The clinical benefit of this finding is that it indicated that ADHD children required to be given simple step-wise instruction arranged in priority rather than complex situations requiring “if-then” decisions. Findings are also suggestive that behavioural, pharmacological and neurofeedback might help in this area.⁹⁵

Cognitive and Neurophysiological Markers of ADHD Persistence and Remission

Childhood ADHD tends to persist into adulthood.^{96–98} In a six-year follow-up study of 279 individuals, 169 were controls, all with IQ>70; 23 (21%) were remitters and the remaining were individuals in whom ADHD persisted among 110 individuals with childhood ADHD.⁹⁹ Tests administered included; i) diagnostic (Diagnostic Interview for ADHD in adults, DIVA, Barkley Functional Impairment Scale, BFIS, ii) IQ (Wechsler Abbreviated Scale of Intelligence, WASI-III and digit span subtest for adults and children) and iii) activity level (Actigraphy).^{100–107} Neurophysiological tests using the i) the fast task, ii) Go/No-Go (GNG) task, and iii) cued flanker continuous performance task (CPT-OX) paradigms to elicit and measure EEG-based RTV, CNV, cue-P3, nogo-P3, commission error (CE) and omission error (OE) as well as delta, theta, alpha and beta power following Fast Fourier Transform (FFT) to evaluate attentional and inhibitory processes.^{102,108–113}

The study was able to identify key markers of i) remission: preparation-vigilance measures (CNV, delta activity, RTV and OE) ii) moderator/s: IQ and iii) cognitive factors that did not influence the outcome of remission or persistence: executive control measures of inhibition or working memory (nogo-P3, CE and digit span backwards, DSB).²¹ Among the findings, preparation-vigilance processes have enormous clinical impact and potential in designing non-pharmacological interventions (cognitive training and neurofeedback) for individuals with ADHD.²¹ In terms of replication of results, this lack of association of executive control measures with ADHD remission was seen in some studies while in others no similar association was seen.^{114–121}

Studies carried out to further examine factors influencing ADHD remission by Cheung et al, Michelini et al and James et al used the Fast Task with incentive paradigm and measured hypoarousal via skin conductance level

(SCL).^{122–124} ADHD remitters were similar to controls in baseline allocation (P3) and fast-incentive CNV amplitude both of which were found to be malleable components under fast task conditions. However, ADHD remitters differed to controls and were similar to ADHD persisters in terms of baseline peripheral arousal (SCL) which was also found to be modifiable under fast-task conditions. Thus, baseline SCL levels could prove as an enduring marker both in ADHD remitters and persisters. Here too treatment with MPH is found to improve both ADHD symptoms and peripheral arousal.^{125–127}

Cheung et al, Du Reitz et al and Michelini et al worked on other aspects pertinent to diagnosis of ADHD persistence and remittance studies.^{123,128,129} Du Rietz et al examined cognitive-neurophysiological and movement correlates of ADHD diagnosis of persisters and remitters based on parent/teacher reporting (common practice for childhood ADHD diagnosis) versus self-reported (common practice for adult ADHD diagnosis) among the same study population (6-year follow-up study).^{123,128} By DSM-V, ADHD persisters were 47% for self-reporting and 79% for parent-reporting. A key finding of the study was that self-report of ADHD persistence and remission did not correlate with neurophysiological and movement results obtained. The implications for follow-up studies of childhood ADHD are that both self-reported and parent/teacher reporting might need to be obtained.¹²⁸

Michelini et al examined cognitive-performance measures and ERP's involved in conflict monitoring: N2 and error processing: error-related negativity, ERN, and positivity, Pe, from an arrow flanker task with low-conflict and high-conflict conditions. N2 is a frontocentral negative deflection obtained at 200–400ms following a high conflict/incongruent stimulus (two competing responses and evaluation) when a correct response is made.^{129–131} If the subject makes an error, the ERN is recorded (frontocentral response-locked negative deflection at 0–150 ms) followed by the Pe (centroparietal positive enhancement at 200–400 ms after response), ie, the ERN reflects unconscious response-monitoring system following a mistake while Pe represents conscious error processing to adjust response strategy.^{132–135} While N2 (for flanker task) showed no difference between persisters and remitters, enhancement of Pe (for Go/NoGo tasks) and ERN (for performance-monitoring tasks) was seen both in this study and has been reported in ADHD remitters.^{130,136–141} The findings of this study also illustrated the malleability of Pe and ERN and

in turn the possibility of nonpharmacological interventions via Neurofeedback and behavioral training.¹²⁹

Reaction Time (RT), Reaction Time Variability (RTV), Malleability of RTV and Response Speed – ERP

The EEG's and ERP's temporal precision was used by Cheung et al to study the relationship between cognitive performance via RTV both a heritable and malleable trait and response speed.¹²² The group examined P3 amplitudes (attention allocation) and contingent negative variation (CNV) a marker of preparation in 174 controls and 93 individuals with ADHD at baseline and following fast-incentive conditions of a four-choice reaction time task. P3 amplitudes were attenuated in ADHD individuals and RTV increased, with both ERP components proving malleable to fast-paced reward conditions. Twin studies have highlighted both heritability and the relationship between theta oscillations, RTV and ADHD.¹⁴² The CNV, reflecting cognitive anticipation and motor preparation, has been shown to be another heritable trait reduced in ADHD, neuro-developmentally delayed based on topographical studies.^{108,109,143-147} A key aspect worth noting is that the CNV calculated as the mean amplitude at Cz or Pz, in milliseconds, varies in site and interval depending both on the age group studied and the paradigm used to elicit it.^{144,146,147}

Studies have demonstrated the possibility of normalization of P3 and CNV amplitudes in ADHD following stimulant medication and methylphenidate (MPH) respectively.¹⁴⁸⁻¹⁵¹ Studies using go/no-go tasks in combination with either neurofeedback or rewards/incentives have also shown them to be malleable to non-pharmacological techniques.¹⁵²⁻¹⁵⁷ One aspect to be kept in mind when considering comparison and efficacy studies is that while these interventions did help normalize response speeds in ADHD individuals, the use of rewards/incentives further also increases CNV amplitudes and reduces RTV/response times in healthy adults.¹⁵⁸ Further as the mode of action of MPH which normalize CNV amplitudes is via the catecholaminergic pathway; the converse also applies, ie, CNV could serve as a catecholaminergic system marker.^{108,158} Cheung et al also looked at the relationship between P3, CNV, RTV and intellectual quotient (IQ) between controls and individuals with ADHD. While IQ exhibited a negative association with P3 amplitude such an association was absent among ADHD individuals.^{122,159}

Reaction time variability (RTV) another candidate neurocognitive marker of ADHD refers to the degree of intra-individual variation in responding to a target stimulus, and increased reaction time variability on attention tasks has been commonly reported in ADHD youths.^{65,160,161} Frontal lobe damage increases RTV, while individual differences in RTV predict inhibitory success, subjects with increased RTV show greater activation during response inhibition tasks.^{162,163}

A recent study (n=1538 youths) examined the relationship between ADHD symptoms, maps of dopaminergic gene expression (DRD1 and DRD2 gene), brain structure (ventromedial prefrontal cortex, vmPFC), and reaction time variability – an index of lapses in attention. It also tested for associations between brain structural correlates of ADHD symptomatology and maps of dopaminergic gene expression. Parent ratings, adolescent self-reports, and reaction time variability were negatively associated with gray matter volume (GMV), while DRD1 and DRD2 gene expression were associated with brain structural correlates of ADHD symptoms. Increased RTV on tasks of vigilant attention is common when comparing children with ADHD versus typically developing controls.^{65,161} The hypothesis is that increased RTV is linked to default mode network (DMN) activity typically attenuated during goal-directed tasks, can persist into periods of task-related processing and, as a result, compete with task-specific neural processing, eg, like working memory tasks.⁶³ The vmPFC is a primary hub in the brain's DMN – a network posited to play a central role in mind-wandering and task-unrelated thought. Although speculative, it is possible that the volumetric reductions in the vmPFC may be linked to DMN dysfunction.

ADHD is characterized by greater intra-individual RTV during cognitive tasks. One commonality among these various populations with increased RTV are problems with attention, although there seems to be considerable variability in the types of attentional difficulties across populations (such as: selective, sustained and divided attention, and combinations of these).¹⁶⁴⁻¹⁶⁷ Studies on RTV and ADHD subtypes show poor correlation, RTV and reduced white matter volume show high correlation and RTV has been shown to improve with both stimulant medication and cognitive training.¹⁶⁸⁻¹⁸⁶

Theta Beta Wave Power (TBR) and ADHD

EEG studies on frequency analysis revealed an increase in theta wave power and/or decrease of beta wave power

(TBR) in frontal areas, or a decrease in sensorimotor rhythm (SMR) power in the central area.^{187–210} Theta and TBR studies between 1930 and 1970 led to TBR to being a candidate diagnostic marker both in children and adults. However, TBRs variability with age, ADHD subtypes, its 63% sensitivity and 58% specificity when compared with clinical diagnosis of ADHD (gold standard) and its poor correlation with ADHD symptoms ($r = 0.10$ for children and $r = -0.14$ for adults) have raised questions on its candidature.^{187–210} While some studies have revealed THBR to be a reliable marker of ADHD resulting in it being cleared by the FDA and the BlueCross others have had contrary results.^{211–213} No consistent theta or theta/beta increases to diagnostically useful levels were found with ADHD. Thus, in order to prevent over diagnosis and misdiagnosis the TBR has been advocated only as an add-on tool following clinical diagnosis. However, TBR has been very used successfully both as a tool to determine treatment efficacy and as a neurofeedback, NFB tool.^{187,191,208,209}

The effects of an acute dose (0.7 mg/kg) of methylphenidate (MPH), known to improve home, school and cognitive task performance were evaluated via quantitative electroencephalography (QEEG) study following a one-week washout period.²¹⁴ The chief reason for use of QEEG was that it enabled both temporal and spatial study of attention using the continuous performance test (CPT) and test of variables of attention (T.O.V.A.).^{196,211,212,215,216} Results of the study ($n=20$, 6–12 years) were; for TOVA measures: omission error (oe, $p < 0.01$), commission errors (not-significant at $p > 0.05$), response time (RT, $p < 0.05$) and standard deviation ($p < 0.01$) for MPH-washout versus MPH-single-dose. MPH showed no brain wave frequency changes in the resting EEG state. However following CPT, increase in α (right and left frontal and occipital areas), β activity (all areas except temporal brain region) and θ/β ratio (right frontal and parieto-occipital, and left temporal areas) was seen with decrease in θ (occipital and right temporo-parietal areas), and δ activity (occipito-parietal areas).¹⁹⁶

Another controlled, randomized, multigroup design, with pre-, post- and follow-up treatment phase study evaluated treatment efficacy of Neurofeedback, NFB ($n=19$) versus pharmacological, Rx ($n=19$, MPH: 1 mg/kilo/day) therapy versus behavioral therapy, BT ($n=19$) and ADHD.^{177,191} NFB: 30 sessions of θ/β training at 4/sessions week (30-s initial baseline + 24-min, ie, six 4-min runs, with a choice of 5 different screens like games, puzzles,

etc., with rewards to ensure reinforcement). BT: 15 one-on-one 50-min sessions of cognitive-behavioral therapy. Parents training: 10 weekly 90-min sessions and teachers training: 5 group sessions, 90 min each.^{197–199} Evaluators were blinded to which child received which therapy. All three therapies showed similar TBR improvements ($p > 0.05$) indicating that they were equally effective (Hypothesis (H), $H_{Rx} = H_{NFB} = H_{BT}$). While global attention ($p = 0.002$), auditory attention ($p = 0.017$) and visual attention ($p = 0.028$) were significant during treatment phase with the group on medication (Rx) showing the most improvement, the differences reached non-significance (NS) post-treatment. Classic resting-EEG patterns for children ADHD versus healthy developing controls indicate elevated θ and reduced α and β . A study to determine if these resting-EEG patterns were seen in adults evaluated 18 college students with ADHD and 17 controls.¹⁹⁹ Adults with ADHD also exhibited the same neural abnormalities as children with ADHD with decrease in α and β , increase in θ and θ/β when relative power computation was carried out and this was more marked for eyes closed than eyes opened condition. vi.P3: In terms of P300 and ADHD, a recent meta-analysis observed that while P3b amplitude declines with age in non-ADHD controls, this decline was more marked in individuals with ADHD.^{78,217,218} The neurobiological aspects linked with this finding are that cortical maturation in ADHD is delayed.²¹⁹ The prefrontal cortex provides input signals for the ventral attention network, which is in turn linked with the P300b ERP component.²²⁰ Thus, if one wanted to examine the contributions of the prefrontal cortex to P3 generation it would be best to study prefrontal cortical maturation and P3 both in adolescence and young adulthood;²²¹ P3 indexes attention and memory processes, updating of mental representations stored in working memory based on novel incoming stimuli, attentional orienting either rapid, or passive attentional shifts to new/unexpected stimuli, or active attention shift due to a task.^{222–227} Auditory P3 amplitude increases across childhood-till 20 years whereas its latency decreases across lifespan.²²⁵ P3 amplitude also shows variations in terms of electrode regions for which it is at peak across development.^{223,224} P300 variations have also been associated with, externalizing problems which are genetically mediated, social information processing style and high levels of aggression. P300 variations have also been associated with the distributed neural circuit including the lateral prefrontal cortex, both of which have shown impairments in externalizing disorders.^{228–236} P3 amplitudes have been also shown to

vary depending on the paradigm used to elicit them.^{237–241} One study examined P3 amplitudes and topographical maps among the ADHD subtypes following the Go/NoGo task.¹⁴¹ The chief findings are (Figure 4) individuals with ADHD showed deficits in the anterior (frontal site) attentional system. ADHD-I and ADHD-H groups showed impairments for attention-demanding Go/NoGo respond-to-target task, while the ADHD-H and ADHD-C exhibited slightly less impairment for inhibition-demanding Go/NoGo suppress-to-target task.¹⁴¹

Sensori-Motor Rhythm (SMR) and ADHD

Several sleep disorders (sleep apnea and restless legs syndrome, idiopathic “sleep-onset insomnia” (SOI), also called “delayed sleep phase syndrome”) are associated with ADHD.^{242,243} Sensori-motor rhythm (SMR) Neurofeedback studies revealed that this intervention normalized sleep and thus improved ADHD symptoms such as inattention and hyperactivity/impulsivity, demonstrated the role of sleep in cognition, reported that adult ADHD is characterized by a higher prevalence of “evening types”, characterized by a delayed circadian phase.^{242–246} Arns et al demonstrated an association between high sunlight intensity and low ADHD prevalence in ADHD.²⁴² Several studies have demonstrated that Sensori-motor rhythm neurofeedback (SMR) results in increased sleep spindle density during sleep, decreased sleep latency and increased total sleep time.^{247,248} Research has also demonstrated that melatonin results in an increased sleep spindle density and decreased sleep latency, suggesting overlap in the working mechanisms of SMR neurofeedback and melatonin.²⁴⁹ Sleep spindles are generated by the GABA-ergic thalamic reticular neurons and are synchronized through glutamatergic cortico-thalamic projections.²⁵⁰ SMR neurofeedback had its most specific effect on decreasing SOL. For TBR neurofeedback no association between clinical improvement and change in SOL or PSQI were found. Clinically, TBR and SMR neurofeedback had similar effects on symptom reduction in ADHD (inattention and hyperactivity/impulsivity); therefore, these results suggest differential effects and different working mechanisms for TBR and SMR neurofeedback in the treatment of ADHD.

Sleep and ADHD

A meta-analysis of sleep (polysomnographic and EEG) studies carried out over the last 15 years to examine macro- and microstructural alterations of sleep in ADHDs. Higher slow-wave activity (SWA) and theta

oscillations were found to occur in ADHD during Non-REM (NREM) and REM sleep. Higher theta activity is harmful to memory, performance and inhibitory control in ADHD. These changes in brainwave patterns could be due to delay in cortical maturation. Poor sleep quality in turn is known to affect cognitive function.¹⁸⁷

Resting State Studies and ADHD

A meta-analysis on resting state condition (eyes open and closed) to examine the reliability of spectral analysis in studying psychiatric disorders identified 67 out 184 studies were ADHD. In the eyes closed condition for ADHD-children power increases for delta and theta and decreases across alpha, beta and gamma and increase in absolute power for both delta and theta was seen. In the eyes open condition, an increase was dominant in both delta and theta for ADHD-children and in the delta band for ADHD-adults. Decreases in absolute power were dominant in the beta band for ADHD-children. Meta-analysis revealed that diametrically opposite results for absolute power vs relative power were only seen in the delta band for ADHD-children in the eyes closed condition. Relative power comparisons of controls to ADHD in children with eyes closed yielded a highest consistency score of 7.0 while the highest consistency scores for absolute power with eyes closed was 2.8 for ADHD in children.²⁵¹

Neurofeedback (NFB) and ADHD

Meta-analysis of studies on neurofeedback where standard neurofeedback protocols revealed three main factors impacted NFB efficacy: first, a intensity of treatment, but not treatment duration, second, using parent rating was better than teacher rating and third, using high-quality EEG equipment.^{188,189}

Stimulant Medication and ADHD

A study was carried out to predict clinical gain and assess the risk of acute side effects of stimulant medication between without treatment (T1) and T2 on a single dose of stimulant medication groups using resting EEG (3-min eyes-closed, 3-min eyes-open), and 20 min cued visual GO/NOGO. EEG spectra, ERPs, omissions, commissions, RT, and RTV variability were computed. Excess theta in the ADHD group on treatment (T2) indicated positive treatment response and increased level of posterior alpha indicative of posterior hypoarousal were seen in non-responders.¹⁹¹

A Peak Amplitude and Latency of the P3a and P3b components associated with Go/NoGo targets

Groups			Control	ADHD-IA	ADHD-HI	ADHD-Combined
Items Endorsed (Mean)	Inattention		3.06	15.18	6.43	14.87
	Hyperactivity/Impulsivity		1.75	4.62	11.25	15.87
Respond-To-Target Task (Mean)	P3a	Amplitude (μ V)	3.29	1.33	1.31	2
	P3a	Latency (ms)	329	307	294	290
	P3b	Amplitude (μ V)	1.09	0.77	0.86	0.59
	P3b	Latency (ms)	577	538	565	542
Suppress-To-Target Task (Mean)	P3a	Amplitude (μ V)	4.11	3.11	2.5	3.04
	P3a	Latency (ms)	290	283	299	267
	P3b	Amplitude (μ V)	2.07	0.83	1.33	1.26
	P3b	Latency (ms)	332	349	348	354

B Topographical Maps associated with Go/NoGo targets

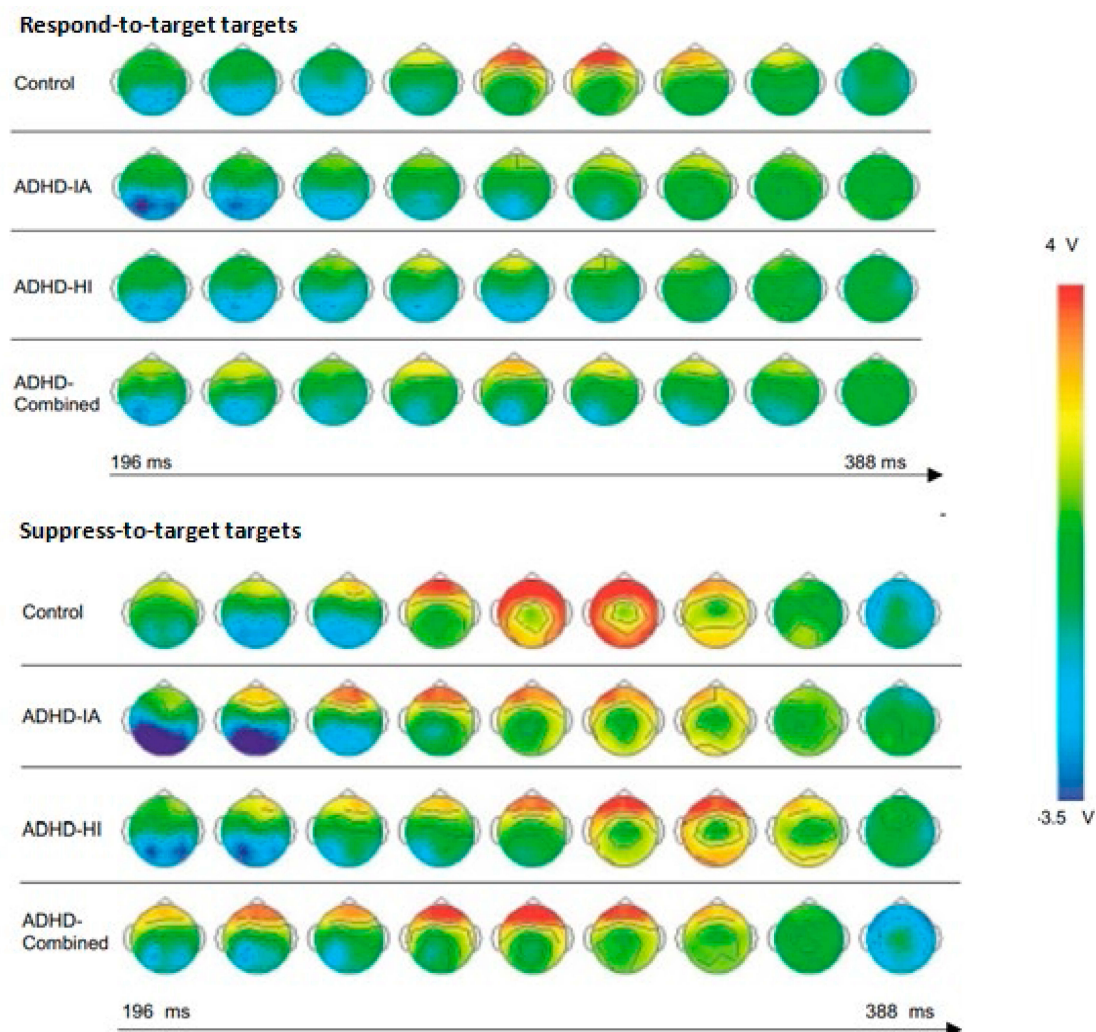


Figure 4 Attention among controls and individuals with self-reported ADHD captured via P3 following Go/NoGo Task Note: Adapted from Rodriguez PD, Baylis GC. Activation of brain attention systems in individuals with symptoms of ADHD. *Behav Neurol*. 2007;18(2):115–30. Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>."http://creativecommons.org/licenses/by/4.0/legalcode".¹⁴¹

Pathognomic/Endophenotyping Markers of ADHD ... Are We There Yet?

With the shared heritability and symptom overlap seen in ADHD EEG-based endophenotyping holds promise in defining the etiology of ADHD.^{80,81,252,253} A recent study on heritability/genotyping of attention and inhibition processes in twins (67 male-only twin pairs) concordant and discordant for ADHD via ERPs and flanked CPT was carried out. ERPs were obtained for cue (P3, CNV or contingency negative variation), go (P3, N2) and nogo trials (P3, N2). No phenotypic associations were found between CPT-derived ERPs and ADHD.⁷⁸ Do these findings imply that the quest for pathognomic/endophenotyping markers of ADHD is a futile one?

The present paper looked at EEG-based studies of ADHD on attention, cognitive performance, default mode network (DMN) deactivation, inhibitory control, cognitive and neurophysiological markers of ADHD persistence and remission, reaction time (RT), reaction time variability (RTV), malleability of RTV and response Speed – ERP, Theta Beta wave power (TBR), P3, sensori-motor rhythm (SMR), sleep, resting state studies, neurofeedback (NFB) and stimulant medication. Study findings illustrated distinct patterns in ADHD versus normal individuals. We also looked at key challenges in identifying potential

pathognomic/endophenotyping markers of ADHD. Taken together the present work points at a framework, a step-wise systematic approach in the search for potential markers of ADHD (Figure 5):

- Step-1: Defining the ADHD population and sub-groups if required,
- Step-2: Symptom grouping (psychological phenotyping),
- Step-3: Carrying out appropriate EEG-based studies (neurobiological phenotyping) for each symptom,
- Step-4: Genotyping,
- Step-5: Environmental risk factor grouping,
- Step-6: Looking for patterns, association or causation depending on the study design.

Questions This Step-Wise Approach Will Help Raise and Answer

- * Could one predict persisters/remitters and responders/non-responders via neurobiological/EEG-based studies?
- * Could overlapping symptoms among the cross-border co-morbid mental disorders extend to overlap in neurobiological and EEG patterns?
- * If these psychiatric disorders share a common genetic risk then what causes a particular psychiatric disorder to dominate and clinically present? There are possibly distinct precipitating factors (genetic and non-genetic)

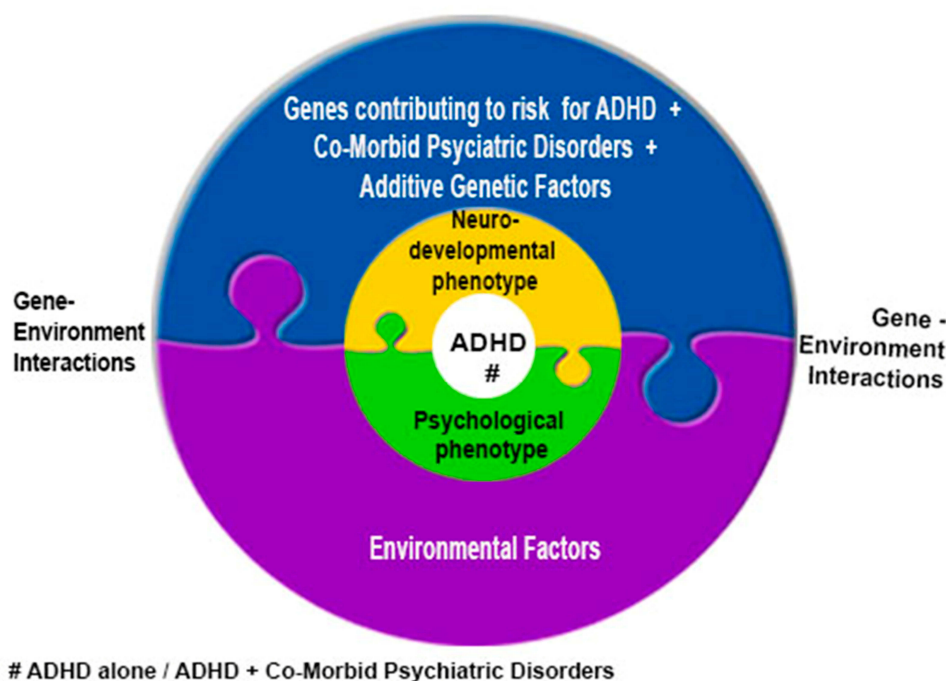


Figure 5 Diagrammatic illustration of the contributing factors to clinical phenotypic presentation of ADHD.

perhaps environmental) yet unknown that eventually contribute to the clinical dominant outcome (Figure 5).

- * **Should shared genetic etiology highlight the need to re-define clinical and diagnostic boundaries to prevent diagnostic misclassification?**
- * **Should endophenotyping strategies need to ensure they reflect phenotypic heterogeneity that correlates with genetic correlations where psychiatric disorders are concerned?**
- * Could another possible strategy be symptom-based-endophenotyping given the challenges in successful endophenotyping, diagnosing and treating psychiatric disorders with shared genetic heritability? For example, studying executive functioning in schizophrenia and ADHD or studying shared mechanism underlying cognitive biases in anorexia nervosa, obsessive-compulsive disorder (OCD) and schizophrenia.⁴⁷

Conclusion

The quest for a pathognomonic marker for ADHD seems challenging when one considers the overlapping symptoms and shared heritability between its psychiatric co-morbidities and cross-border disorders. For the same reasons, endophenotyping has also proved challenging. With deficits in neurobiology via developmental delay being the core factor contributing to behavioural and clinical symptoms seen, it seems logical that neurobiological characterization of ADHD might hold the answer to a pathognomonic marker for ADHD. The interplay of heritable, developmental and environmental factors that cause ADHD to manifest as a fully developed condition while related disorders possessing the same risk factors do not remain to be fully explained (Figure 4). However, among the neurobiological tools available, EEG machines like NeuralScan by Medeia are a cost-effective tool providing an accurate temporal resolution which is vital in studying attention and inhibition and fast task responses in ADHD. Through these new state-of-the-art technologies it is now possible to achieve both temporal and spatial (sLORETA) resolution and power analysis (QEEG) which will enable and facilitate step-wise neurobiological characterization, diagnosis and management of ADHD. In addition, the EEG could help in identifying potential EEG-based pathognomic/endophenotyping markers of ADHD if a step-wise approach is followed. The framework for identifying potential EEG-based pathognomic/endophenotyping markers of ADHD is described in the present paper that takes into consideration the psychological and neurobiological phenotypes seen, the EEG-patterns observed, the genotype expressed and the environmental factors at play.

Disclosure

Dr Slav Danev is an employee of Medeia Inc, which makes the Neuralscan product.

The authors report no other conflicts of interest in this work.

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