Literature Review

Development of MentisCura's unique, powerful and proprietary EEG-based biomarkers has been based on a large body of research into correlations of electrophysiological measures with clinically observable changes in the human brain. This review provides an introduction of key scientific papers directly related to our technologies.
The ADHD Brain

Studies on the neuroimaging, neurophysiology, neurochemistry and genetics of ADHD show significant differences in brain activity and function, but currently findings from neurobiological research do not have a direct application in daily practice.

Research on the cortical development in children with ADHD show a delay rather than deviance in the cortical maturation compared to typically developing controls.

The Neurobiology and Genetics of Attention-Deficit/Hyperactivity Disorder (ADHD): What Every Clinician Should Know.


Quote

"Insights from neuroscience have unequivocally shown that the brains of children with ADHD differ from those of controls. Recently, research on the neurobiological basis of ADHD has shifted from a model based on brain regional differences to a framework characterised by altered connectivity between several brain areas, and current research is focused on investigating individual elements of these networks." (p. 430)

Abstract

This review, addressed mainly to clinicians, considers commonly asked questions related to the neuroimaging, neurophysiology, neurochemistry and genetics of Attention-Deficit/Hyperactivity Disorder (ADHD). It provides answers based on the most recent meta-analyses and systematic reviews, as well as additional relevant original studies. Empirical findings from neurobiological research into ADHD reflect a shift in the conceptualisation of this disorder from simple theoretical views of a few isolated dysfunctions to more complex models integrating the heterogeneity of the clinical manifestations of ADHD. Thus, findings from structural and functional neuroimaging suggest the involvement of developmentally abnormal brain networks related to cognition, attention, emotion and sensorimotor functions. Brain functioning alterations are confirmed by neurophysiological findings, showing that individuals with ADHD have elevated theta/beta power ratios, and less pronounced responses and longer latencies of event-related potentials, compared with controls. At a molecular level, alterations in any single neurotransmitter system are unlikely to explain the complexity of ADHD; rather, the disorder has been linked to dysfunctions in several systems, including the dopaminergic, adrenergic, serotoninergic and cholinergic pathways. Genetic studies showing a heritability of ~60–75% suggest that a plethora of genes, each one with a small but significant effect, interact with environmental factors to increase the susceptibility to ADHD. Currently, findings from neurobiological research do not have a direct application in daily clinical practice, but it is hoped that in the near future they will complement the diagnostic process and contribute to the long-term effective treatment of this impairing condition.

Attention-deficit/hyperactivity Disorder Is Characterized by a Delay in Cortical Maturation


Quote

"Cortical development in children with ADHD lagged behind that of typically developing children by several years. However, the ordered sequence of regional development, with primary sensory and motor areas attaining their peak cortical thickness before high-order association areas, was similar in both groups, suggesting that ADHD is characterized by delay rather than deviance in cortical maturation.” (p. 19659)
**Abstract**

There is controversy over the nature of the disturbance in brain development that underpins attention-deficit/hyperactivity disorder (ADHD). In particular, it is unclear whether the disorder results from a delay in brain maturation or whether it represents a complete deviation from the template of typical development. Using computational neuroanatomic techniques, we estimated cortical thickness at >40,000 cerebral points from 824 magnetic resonance scans acquired prospectively on 223 children with ADHD and 223 typically developing controls. With this sample size, we could define the growth trajectory of each cortical point, delineating a phase of childhood increase followed by adolescent decrease in cortical thickness (a quadratic growth model). From these trajectories, the age of attaining peak cortical thickness was derived and used as an index of cortical maturation. We found maturation to progress in a similar manner regionally in both children with and without ADHD, with primary sensory areas attaining peak cortical thickness before polymodal, high-order association areas. However, there was a marked delay in ADHD in attaining peak thickness throughout most of the cerebrum: the median age by which 50% of the cortical points attained peak thickness for this group was 10.5 years (SE 0.01), which was significantly later than the median age of 7.5 years (SE 0.02) for typically developing controls (log rank test \( \chi^2 \) = 5,609, \( P < 1.0 \times 10^{-20} \)). The delay was most prominent in prefrontal regions important for control of cognitive processes including attention and motor planning. Neuroanatomic documentation of a delay in regional cortical maturation in ADHD has not been previously reported.

**Clinical Utility of EEG in Attention-Deficit/Hyperactivity Disorder: A Research Update.**


**Quote**

"Currently, no single diagnostic test for ADHD exists. A proper diagnostic evaluation for ADHD (and all other childhood psychiatric disorders) generally involves a process of collecting data on the history, course, and duration of symptoms, both at home and at school, using clinical interviews and behavior rating scales. Because inattention is pathognomonic to nearly all childhood psychiatric disorders, it is often difficult to make differential diagnoses between ADHD and other disorders that can have a similar presentation, including autism spectrum disorders, mood and anxiety disorders, and learning disabilities. Thus, a biologically based diagnostic test or biological marker (i.e., biomarker) that is sensitive and specific to ADHD would be of great assistance. Based on the findings previously reviewed, EEG measures have been viewed as a promising biomarker for ADHD." (p.573)

**Abstract**

Psychiatric research applications of electroencephalography (EEG), the earliest approach to imaging human cortical brain activity, are attracting increasing scientific and clinical interest. For more than 40 years, EEG research has attempted to characterize and quantify the neurophysiology of attention-deficit/hyperactivity disorder (ADHD), most consistently associating it with increased frontocentral theta band activity and increased theta to beta power ratio during rest compared to non-ADHD controls. Recent reports suggest that while these EEG measures demonstrate strong discriminant validity for ADHD, significant EEG heterogeneity also exists across ADHD-diag-
nosed individuals. In particular, additional studies validating the use of the $\theta/\beta$ power ratio measure appear to be needed before it can be used for clinical diagnosis. In recent years, the number and the scientific quality of research reports on EEG-based neurofeedback (NF) for ADHD have grown considerably, although the studies reviewed here do not yet support NF training as a first-line, stand-alone treatment modality. In particular, more research is needed comparing NF to placebo control and other effective treatments for ADHD. Currently, after a long period of relative stasis, the neurophysiological specificity of measures used in EEG research is rapidly increasing. It is likely, therefore, that new EEG studies of ADHD using higher density recordings and new measures drawn from viewing EEG as a 3-dimensional functional imaging modality, as well as intensive re-analyses of existing EEG study data, can better characterize the neurophysiological differences between and within ADHD and non-ADHD subjects, and lead to more precise diagnostic measures and effective NF approaches.

Examining the Diagnostic Utility of EEG Power Measures in Children with Attention Deficit/Hyperactivity Disorder


Quote

The current results are supportive of the use of resting state EEG in the diagnosis of AD/HD (p. 1138).

Abstract

Objective: This study investigated the diagnostic utility of EEG power during eyes-closed resting conditions for children with attention-deficit/hyperactivity disorder (AD/HD).

Methods: Subjects consisted of 253 boys with AD/HD combined type and 67 age-matched controls. EEG was recorded from 21 sites during an eyes-closed resting condition and was Fourier transformed to provide estimates for total power and absolute and relative power in delta, theta, alpha and beta bands. Factor analysis was used to group sites into frontal, central and posterior regions, with these data subjected to cluster analysis. Logistic regression was performed on the entire AD/HD sample versus control, for AD/HD clusters versus control, and then for each AD/HD cluster independently versus control, using total, absolute and relative power measures.

Results: Logistic regression performed on the clusters independently produced the best classification results, with a sensitivity of 89.0% and a specificity of 79.6%, with an overall classification accuracy of 87.0%

Conclusions: The obtained classification results are supportive of an independent diagnostic test for AD/HD based on EEG power at rest.

Significance: This is the first study to investigate sensitivity and specificity of EEG power for AD/HD in a resting condition.

Eeg Phenotypes Predict Treatment Outcome to Stimulants in Children with Adhd.


Quote:

“Investigating EEG phenotypes provides a promising new way to approach EEG data, explaining much of the variance in EEGs and thereby potentially leading to more specific prospective treatment outcomes” (p. 436)
**Abstract**

This study demonstrates that the EEG phenotypes as described by Johnstone, Gunkelman & Lunt are identifiable EEG patterns with good inter-rater reliability. Furthermore, it was also demonstrated that these EEG phenotypes occurred in both ADHD subjects as well as healthy control subjects. The Frontal Slow and Slowed Alpha Peak Frequency and the Low Voltage EEG phenotype discriminated ADHD subjects best from controls (however the difference was not significant). The Frontal Slow group responded to a stimulant with a clinically relevant decreased number of false negative errors on the CPT. The Frontal Slow and Slowed Alpha Peak Frequency phenotypes have different etiologies as evidenced by the treatment response to stimulants. In previous research Slowed Alpha Peak Frequency has most likely erroneously shown up as a frontal theta sub-group. This implies that future research employing EEG measures in ADHD should avoid using traditional frequency bands, but dissociate Slowed Alpha Peak Frequency from frontal theta by taking the individual alpha peak frequency into account. Furthermore, the divergence from normal of the frequency bands pertaining to the various phenotypes is greater in the clinical group than in the controls. Investigating EEG phenotypes provides a promising new way to approach EEG data, explaining much of the variance in EEGs and thereby potentially leading to more specific prospective treatment outcomes.

**EEG Coherence in Children with Attention-deficit/hyperactivity Disorder: Differences Between Good and Poor Responders to Methylphenidate.**


**Quote**

“This study investigated the EEG coherence profiles between good and poor MPH responders in children with the Combined type of AD/HD. The AD/HD participants showed consistent coherence differences compared with controls, notably increased interhemispheric frontal theta coherences and enhanced left intrahemispheric coherences” (p.118)

**Abstract**

This retrospective study investigated differences in regional derivations of EEG coherence between good and poor responders to methylphenidate (MPH) in children (aged 8–12 years) with the combined type of attention-deficit/hyperactivity disorder (AD/HD). Participants included groups of good and poor male MPH responders and an aged-matched group of male controls. An eyes-closed, resting electroencephalogram (EEG) was recorded from 21 electrode sites. Coherence was calculated from eight intrahemispheric and eight interhemispheric electrode pairs, for the delta, theta, alpha and beta frequency bands. Compared with controls, the AD/HD participants had enhanced laterality over short-medium inter-electrode distances, and elevated frontal interhemispheric coherences, in the theta band. Good MPH responders had higher intrahemispheric coherences than poor MPH responders over short-medium and long inter-electrode distances in the beta band. Enhanced laterality at short-medium inter-electrode distances suggests that the AD/HD children may have a developmental lag in short-axonal connections in the left hemisphere. Elevated frontal interhemispheric theta coherence consistently indicates some frontal dysfunction in AD/HD. The beta coherence differences found between good and poor MPH responders could indicate that good MPH responders have some type of structural dysfunction associated with cortical connections involved in attention/arousal.
Statistical Pattern Recognition of EEG

In the last decade, the methods to analyse EEGs have improved greatly with more powerful computer solutions, making the EEG a reliable biomarker. Mentis Cura has found a way to construct classifiers using the statistical pattern recognition technique, automatically analyse the data and make it available to medical doctors.

Diagnostic Accuracy of Statistical Pattern Recognition of Electroencephalogram Registration in Evaluation of Cognitive Impairment and Dementia.


Quote

“Taking these strengths and weaknesses into consideration, EEG registration with SPR analysis seems to be a simple, inexpensive, and reasonably robust method for separating the various groups of patients that are referred to a memory clinic. The clinician needs to take into account the comorbidity that exists in some patients and the possible mixture of disorders that might be relevant. This is a method that could be an indicator of a biological marker and as such could be a valuable tool to come to a conclusion in the diagnostic process.” (p.58-59)

Abstract

Background: There is still a need for simple, noninvasive, and inexpensive methods to diagnose the causes of cognitive impairment and dementia. In this study, contemporary statistical methods were used to classify the clinical cases of cognitive impairment based on electroencephalograms (EEG). Methods: An EEG database was established from seven different groups of subjects with cognitive impairment and dementia as well as healthy controls. A classifier was created for each possible pair of groups using statistical pattern recognition (SPR). Results: A good-to-excellent separation was found when differentiating cases of degenerative disorders from controls, vascular disorders, and depression but this was less so when the likelihood of comorbidity was high. Conclusions: Using EEG with SPR seems to be a reliable method for diagnosing the causes of cognitive impairment and dementia, but comorbidity must be taken into account.