Error-Related Brain Activity in ADHD: A Systematic Review and Meta-Analysis of Electroencephalography Markers of Cognitive Control Performance

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Abstract

Background. Deviant cognitive control performance is implicated in Attention-Deficit-Hyperactivity-Disorder (ADHD). It is also conjectured to be a potential diagnoser and differentiator between the Inattentive and Hyperactive-Impulsive ADHD types. Reliable measures have not been established due to the variation in published results.

Methods. We performed a systematic review and meta-analysis of the literature published up to May 2021 with data on electrophysiological correlates, that is, EEG correlates of cognitive control monitoring (error-related negativity, ERN; error positivity, Pe; correct-response negativity, CRN) in ADHD patients and the efficiency of EEG recordings in differentiating between ADHD types. Multiple databases including PubMed, Scopus, Google Scholar, bioRxiv, and medRxiv were searched for eligible literature. Meta-Analyses were performed through statistical tools provided by the open-source metafor package and separately using the Hedge's g standardized mean differences.

Results. Meta-Analyses were performed on a shortlisted set of 125 studies involving 7248 participants. To avoid extraneous variables, the sex ratio was maintained at 50:50, and the age groups of participants were equally varied between early teenagers (12-15 years), late teenagers (15-18 years), young adults (21-25), and middle-aged adults (29-37). The ADHD-afflicted group showed reduced ERN (Hedge's $g = -0.58$ [CIs: -0.76, -0.35]) and reduced Pe (Hedge's $g = -0.65$ [CIs: -0.79, -0.44). The Hyperactive-Impulsive ADHD types (2574/7248 participants) showed an increased CRN (Hedge's $g = 0.68$ [CIs: 0.71, 0.29]), while the Inattentive ADHD Types (4674/7248 participants) showed a slightly reduced CRN (Hedge's $g = -0.25$ [CIs: -0.31, -0.28]. The prevalence of counted task errors was higher in the teenagers' group (12-18 years) than the adults' group (21-37 years).

Conclusions. Results suggest that EEG Pattern Markers (especially Pe and CRN) can act as strong differentiators/diagnosers between the Hyperactive-Impulsive and Inattentive ADHD types. In further development, deep learning classifiers can be built for ADHD types using EEG Markers as Features and statistical values as weights.

Not Part of Abstract, Additional Notes. Pranjali Awasthi is a 14-year-old researcher working on the overlap of neuroimaging and machine learning at the Neural Dynamics of Control Lab, FIU. She is an avid speaker on topics of AI Awareness and Ethics. Here is a recent feature by the Analytics India Magazine: https://analyticsindiamag.com/how-this-15-year-old-created-a-research-career-in-machine-learning.

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Understanding Why Muscarinic Receptor Agonists Have Antipsychotic Properties

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Abstract

Background. All current antipsychotics have direct dopamine (DA) D_2 receptor activity, which is associated with problems such as dysphoria, EPS, or prolactin elevation. Muscarinic receptor agonists have shown antipsychotic-like activity across preclinical models and clinical trials. This poster reviews preclinical evidence as to how muscarinic receptor agonists, such as the M_1/M_4 preferring agonist xanomeline, might have clinically relevant antipsychotic effects.

Objectives. Highlight the novel mechanisms through which muscarinic receptor agonists are associated with antipsychotic effects without having any direct dopaminergic D_2 receptor activity.

Key Points. The muscarinic receptor family is composed of 5 G protein-coupled receptors (GPCRs). One of the leading hypotheses explaining the antipsychotic activity of muscarinic receptor agonists is preclinical studies of muscarinic receptor modulation of those DA circuits associated with psychosis. Both M_1 and M_4 receptors are expressed in DA neural circuits implicated in psychosis, and provide unique regulation of these circuits. Xanomeline has both functional M_1 and M_4 receptor agonist activity, and shows robust antipsychotic-like effects in several animal models that require the presence of functional M_1 and M_4 receptors. *M_4 receptors* are autoreceptors on cholinergic neurons that regulate DA circuits in two locations: ventral tegmental area (VTA) and nucleus accumbens (NAc). Cholinergic-rich neurons from the hindbrain at the VTA, where they release acetylcholine (ACh) into DA-rich synaptic spaces. M_4 autoreceptors are present on these neurons, and their activation reduces ACh release and lowers ambient synaptic ACh concentrations, leading to reduced DA cell firing. Cholinergic interneurons residing in the NAc also express M_4 autoreceptors. These ACh interneurons regulate ACh release with M_4 activation also turning off ACh release. Therefore, M_4 receptors serve as DA regulators at VTA and NAc, both key sites for dopamine's role in psychotic processes. *M_1 receptors* regulate DA circuits in a different, "top down" manner. M_1 receptors are found on cortical inhibitory interneurons. When activated, inhibitory drive onto excitatory output neurons is enhanced, which leads to reduced excitatory tone to VTA DA neurons.

Summary. Over the last 25 years, a growing body of evidence has shown potential for muscarinic receptor agonists to become a new class of medicines with potent antipsychotic activity. Preclinical data at micro-and macro-circuit levels suggest that the M_1 and M_4 receptor subtypes are most relevant in the regulation of DA circuits. The antipsychotic effects of muscarinic agonists effects may arise from influencing these key muscarinic receptor subtypes that are integral to the regulation of DA neural circuits. In summary, there has been great progress in understanding the potential for muscarinic receptor agonists for the treatment of psychosis.

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