

Novel in silico multivariate mapping of intrinsic and anticorrelated connectivity to neurocognitive functional maps supports the maturational hypothesis of ADHD.

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Abstract

From childhood to adolescence, strengthened coupling in frontal, striatal and parieto-temporal regions associated with cognitive control, and increased anticorrelation between task-positive and task-negative circuits, subserve the reshaping of behavior. ADHD is a common condition peaking in adolescence and regressing in adulthood, with a wide variety of cognitive control deficits. Alternate hypotheses of ADHD emphasize lagging circuitry refinement versus categorical differences in network function. However, quantifying the individual circuit contributions to behavioral findings, and relative roles of maturational versus categorical effects, is challenging in vivo or in meta-analyses using task-based paradigms within the same pipeline, given the multiplicity of neurobehavioral functions implicated. To address this, we analyzed 46 positively-correlated and anticorrelated circuits in a multivariate model in resting-state data from 504 age- and gender-matched youth, and created a novel in silico method to map individual quantified effects to reverse inference maps of 8 neurocognitive functions consistently implicated in ADHD, as well as dopamine and hyperactivity. We identified only age- and gender-related effects in intrinsic connectivity, and found that maturational refinement of circuits in youth with ADHD occupied 3-10x more brain locations than in typical development, with the footprint, effect size and contribution of individual circuits varying substantially. Our analysis supports the maturational hypothesis of ADHD, suggesting lagging connectivity reorganization within specific subnetworks of fronto-parietal control, ventral attention, cingulo-opercular, temporo-limbic and cerebellar sub-networks contribute across neurocognitive findings present in this complex condition. We present the first analysis of anti-correlated connectivity in ADHD and suggest new directions for exploring residual and non-responsive symptoms.