

## A Biased Perspective on Brain Imaging of ADHD

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We ascend, in science, by tugging one another's bootstraps (p. ix).

Remotely plausible theories are better than no theories at all (p. 27).

—Jerry Fodor, *The Language of Thought*, 1975

As recently summarized in a consensus statement of 208 evidence-based conclusions (1), the hallmarks of the syndrome now known as attention deficit hyperactivity disorder (ADHD) were first described by the German physician Melchior Adam Weikard nearly 250 years ago. Progress since has come in fits and starts, but in some ways, ADHD enjoys an enviable position among common psychiatric disorders. The diagnostic criteria for ADHD, albeit still explicitly provisional, obtained “very good” test-retest reliability (intraclass kappa=0.61), the sine qua non of scientific inquiry, in the DSM-5 field trials (2). Effective short-term alleviation of symptoms with stimulant medications was first reported in 1937 (3), decades before the emergence of antimanic, antipsychotic, and antidepressant compounds, with large effect sizes that remain among the highest in the psychiatric pharmacopoeia. Nonpharmacologic, behavioral treatments boast a voluminous evidence base, and produce even greater symptom amelioration when they precede medication treatment (4).

Although ADHD was long thought to exclusively affect elementary-school-age boys, it is now recognized in both sexes and throughout adulthood. The substantial familiarity and heritability of ADHD is comparable to complex traits such as height, intelligence, and obesity (5). Breathtaking drops in genotyping costs, along with adoption of an open science data-sharing culture, have facilitated aggregation of a sufficiently large sample to yield the first genome-wide significant loci in ADHD (6), in addition to eight previously identified genes (*ADGRL3*, *ANKK1*, *BAIAP2*, *DAT1*, *DRD4*, *LRP5*, *LRP6*, and *SNAP25*) supported to varying degrees by meta-analyses, but not yet confirmed by genome-wide studies (1). As with all complex conditions, each of the probable genetic factors contributing to ADHD accounts for minuscule proportions of the phenotypic variance. Accordingly, genetic discoveries are unlikely to yield novel druggable targets in the near future. Still, genome-wide studies provide polygenic risk scores that succinctly capture broad genetic risk as a causal mediator (e.g., 7–9), at least for people of European ancestry.

In MRI studies of the brain in ADHD, the field in which I serendipitously landed nearly three decades ago, magnetic field strength has doubled from 1.5 to 3 tesla, bringing moderate improvements in spatial and temporal resolution. The unit costs of imaging have, unfortunately, remained stubbornly high (10), and this contributes to insufficient sample sizes and inadequate statistical power for most efforts (11). Accordingly, in this selective and admittedly biased overview, I focus on open science initiatives designed to take on this challenge and on emerging notions of mesoscale brain networks in psychiatric dysfunction with relevance to ADHD.

### BRAIN IMAGING IN THE ERA OF BIG DATA

A revolutionary and elegant response to the challenge of sample size was formulated just over a decade ago by Paul Thompson and colleagues in launching ENIGMA (Enhancing Neuro-Imaging Genetics Through Meta-Analyses) (12). As befits the original aim, the ENIGMA consortium identified genome-wide significant loci relating to hippocampal volume in a discovery sample of more than 9,000 healthy participants, confirmed in independent replication samples exceeding 9,000 more (13). In a companion paper including both healthy and psychiatrically ill participants (N=~21,000), another common intergenic variant was associated with bilateral hippocampal volume, and a variant within *HMGA2* (High Mobility Group AT-hook 2, a nonhistone chromosomal protein increasingly implicated in various cancers [14]) was associated with increased intracranial volume (15), although this clue has yet to be incorporated into neuropsychiatric pathophysiological models.

Beyond leveraging the unassailable test reliability of structural MRI data (intraclass correlations reaching 0.98–1.00 [16]) to identify associated genomic loci, ENIGMA projects have transformed psychiatric neuroimaging. ENIGMA studies, conducted by volunteering workgroups, avoid the ethical and practical challenges of sharing raw structural imaging data, which are as uniquely identifiable as fingerprints. Instead, contributing sites process their brain images locally with the same freely available software, FreeSurfer (17). FreeSurfer computes subcortical volumes (18) as well as areas and thickness of 34 Desikan-Killiany cortical parcels per hemisphere, along with average thickness and area for each

hemisphere and intracranial volume (19). These derived values, or features, can be aggregated without risking violations of confidentiality or privacy. This innovation has made it possible to amass samples in the tens of thousands for mega-analyses, in which individual participants' values are entered into statistical analyses, instead of meta-analyses that combine group means and standard deviations or summary effect sizes. ENIGMA papers are currently emerging at the rate of more than one per week, encompassing a vast range of topics (20).

The first ENIGMA effort in ADHD focused on subcortical regions (accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus) and intracranial volume, contrasting 1,713 patients with a categorical diagnosis of ADHD to 1,429 age-matched healthy comparison participants shared by 23 sites (18). Participants ranged in age from 4 to 63 years. To stratify by age, children (53% of the sample) were defined as being age 14 or younger, adolescents (18%) were ages 15–21, and adults (29%) were age 22 and older. In mega-analyses encompassing the entire sample, patients had significantly smaller intracranial volume (Cohen's  $d = -0.10$ ) after adjusting for sex, age, and site. Other analyses, adjusting for sex, age, site, and intracranial volume, found smaller volumes in the ADHD group for amygdala ( $d = -0.19$ ), accumbens ( $d = -0.15$ ), caudate ( $d = -0.11$ ), hippocampus ( $d = -0.11$ ), and putamen ( $d = -0.11$ ) (18). In age-stratified analyses, these differences were all present in children, whereas adults did not differ on any measure. Adolescents differed significantly only in the hippocampus ( $d = -0.24$ ) while also exhibiting the widest confidence intervals on all measures. Though intriguing, the age differences cannot be interpreted definitively given the cross-sectional nature of ENIGMA studies (21). Additional analyses did not find any evidence that the observed effects could be ascribed to past or current exposure to stimulant medications; although results differed by sex, sex differences did not interact with diagnosis (18). Lessons from this first ADHD ENIGMA study include 1) confirmation that the categorical diagnosis of ADHD in children is associated with reduced intracranial volume, consistent with an overall reduction in total brain volume, which we first noticed in 1996 in the National Institute of Mental Health (NIMH) ADHD sample (22, 23); 2) confirmation of smaller volumes in basal ganglia structures (caudate, putamen, and accumbens), long linked to models of ADHD (24); 3) surprising findings of smaller amygdala and hippocampus volumes, which have been generally neglected in ADHD (with a rare exception [25]), and which may relate to increasing awareness that emotional dysregulation (26), although not included in the diagnostic criteria, is a major contributor to poor outcomes in ADHD (27); and 4) the humbling observation that effect sizes are small (Cohen's  $d$  values  $< 0.20$ ), confirming the underpowered nature of most prior work (11).

The next ADHD ENIGMA initiative examined cortical surface area and thickness in an expanded sample from 36 cohorts comprising 2,246 patients with ADHD and 1,934 comparison participants, with the same covariates, including intracranial volume (19). Case-comparison differences were

observed exclusively in children and were most pronounced in the youngest third. The largest case-comparison difference was in mean cortical surface area ( $d = -0.21$  for all children;  $d = -0.35$  in the youngest tertile, ages 4–9 years). Among the 34 parcels examined, smaller surface areas in children with ADHD were found in 24, whereas thinner cortex in ADHD was observed only in four regions (temporal pole and in fusiform, precentral, and parahippocampal gyri). Analyses of familiarity incorporated 211 patients with ADHD, their 175 unaffected siblings, and 120 healthy comparison participants from two NeuroIMAGE study sites (28). Several frontal features were significantly smaller in unaffected siblings than in healthy comparison participants, consistent with familial effects. The expanded ENIGMA sample again produced 1) whole brain reductions in mean cortex surface area even after adjusting for significantly smaller intracranial volume; 2) strongly age-related effects, with the strongest results in the youngest children; 3) relatively few differences in cortical thickness, in contrast to widespread smaller surface areas (cortical surface area and thickness differ in their genetic determinants [29], validating the importance of distinguishing them in studies of cortical volume [30]); and 4) once again, small effect sizes.

One of the major benefits of the promulgation of the NIMH Research Diagnostic Criteria (RDoC) project (31), to which I will return, has been to free investigators from rigid allegiance to diagnostic categories in the name of scientific rigor. Contrasts and comparisons across diagnoses are now not just “allowed,” but actively encouraged. ENIGMA has examined group case-comparison interregional differences in cortical thickness in six disorders: ADHD, autism spectrum disorder, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, and schizophrenia ( $N \sim 28,000$ ), drawn from 145 ENIGMA cohorts, ranging from ages 2 to 89 years (32). Principal component analysis applied to the interregional variations in cortical thickness across the 34 Desikan-Killiany cortical parcels (averaged across the hemispheres) explained 48% of the variance. “Virtual histology” was then conducted by filtering data from the gene-expression data of six donors in the Allen Human Brain Atlas, mapped to the same 34 regions. To optimize interdonor similarity, two-stage filtering reduced the number of genes interrogated from 20,737 to 2,511. The interregional profile of the first principal component in cortical thickness was associated with pyramidal-cell gene expression patterns (explaining 56% of interregional variation). Coexpression analyses showed two clusters enriched with genes associated with all six disorders: a prenatal cluster of genes involved in neurodevelopmental processes such as axon guidance, and a postnatal cluster of genes involved in synaptic activity and plasticity-related processes (32). This innovative approach suggests that the increasingly recognized commonalities among psychiatric disorders derive from shared genetic factors affecting processes during early brain development, highlighting the neurodevelopmental nature of most psychopathology (33, 34).

The substantial genetic overlap among psychiatric disorders (35, 36) was confirmed by an analysis of 25 brain disorders utilizing genome-wide association studies of 265,218 patients and 784,643 comparison participants in relation to 17 phenotypes from 1,191,588 individuals. Psychiatric disorders exhibited common risk variants, in contrast to neurological disorders, which were more distinct from one another and from the psychiatric disorders. The Brainstorm Consortium also identified significant genetic correlations among psychiatric disorders and a number of brain phenotypes, including cognitive measures. They concluded that their results “indicate that the clinical boundaries for the studied psychiatric phenotypes do not reflect distinct underlying pathogenic processes” (37). Supportive findings from ENIGMA data, based on 24,360 patients and 37,425 comparison participants, also found that correlations among psychiatric disorders, including ADHD, “were correlated with the corresponding pairwise correlations among disorders derived from genome-wide association studies ( $r=0.494$ )” (38).

These commonalities at the levels of genomics and brain structure parallel the hypothesis that a common factor underlies much of psychopathology—the “*p* factor” (39). Parkes et al. tested the hypothesis that the *p* factor involves neurodevelopmental deviations by examining age-related decreases in brain regional volumes (40) across 400 cortical parcels in the Philadelphia Neurodevelopmental Cohort (41) in relation to six orthogonal dimensions, including overall psychopathology (*p* factor), anxious misery, and positive psychosis symptoms (42). They confirmed that analyses of volumetric deviations from normality outperformed analyses using raw cortical values; that overall psychopathology was associated with lower than normative cortex volumes in three of their four hypothesized areas (ventromedial prefrontal/medial orbitofrontal cortex, inferior temporal, and dorsal anterior cingulate cortex); and that correlations in deviation from normative neurodevelopment in case-control contrasts of individuals with ADHD versus those with major depressive disorder diminished markedly when overall psychopathology was controlled for (42).

So, how do these observations fit with the RDoC agenda? RDoC was launched in 2010 based on the conclusion that the enhancements in psychiatric nosological reliability obtained by incorporating the Research Diagnostic Criteria (43) into DSM-III and its subsequent editions had failed to provide an adequate framework to incorporate potential insights from genetics and neuroscience. This eloquent declaration, announced in the *Journal* (31), was built on three assumptions: “First, the RDoC framework conceptualizes mental illnesses as brain disorders. In contrast to neurological disorders with identifiable lesions, mental disorders can be addressed as disorders of brain circuits. Second, RDoC classification assumes that the dysfunction in neural circuits can be identified with the tools of clinical neuroscience, including electrophysiology, functional neuroimaging, and new methods for quantifying connections in vivo. Third, the RDoC framework assumes that data from genetics and clinical

neuroscience will yield biosignatures that will augment clinical symptoms and signs for clinical management” (31).

The primary focus for RDoC is on neural circuitry, and the workhorse for identifying neural circuitry remains functional neuroimaging, particularly functional MRI (fMRI) methods. What remains an open question is whether fMRI methods are sufficiently precise to delineate the putative neural circuits underlying interindividual differences in behavior and psychiatric symptoms. Considering the sheer magnitude of the problem—86 billion neurons interacting with and influencing each other throughout the lifespan, adapting to a limitless number of stimuli and settings—concluding that brain function remains inscrutable would not be surprising. To compound the problem, the universal phenomenon of effect sizes deflating over time as scientific fields mature (44) has also held here, accompanied by incontrovertible evidence of vastly inflated false positive rates in many fMRI studies (45, 46).

### SO HOW DOES AN INVETERATE OPTIMIST RESPOND?

I begin by celebrating the first major neuroscientific discovery of the 21st century, the default mode network (47–49). In 2001, Marcus Raichle and colleagues described a baseline brain state during quiet rest by measuring the brain oxygen extraction fraction with positron emission tomography, which, unlike fMRI, is quantitative (50). Despite the lack of active tasks, the investigators observed consistent patterns of deactivation in the posterior cingulate and precuneus and in the medial prefrontal cortex (47). Independently, Bharat Biswal and colleagues had earlier reported that task-free fMRI data could yield correlational maps—that is, evidence of “functional connectivity” (51)—that aligned with task-based activation maps in the sensorimotor cortex (52, 53). However, these two lines of investigation were not joined until Michael Greicius, then a neurology resident, and Vinod Menon and colleagues accomplished the feat for the first time (54). Their key innovation was to identify default mode network regions of interest from task-associated deactivations, in a paper handled by Raichle as editor (54). From that moment on, Raichle’s colleagues at Washington University in St. Louis, led by Steve Peterson, became leading proponents of what has come to be known as resting-state functional connectivity (55). Still, the approach evoked substantial resistance (56). In response, Michael Milham and Biswal collected 1,414 de-identified data sets from 35 imaging centers and made them easily downloadable on the Neuroimaging Tools and Resources site (<https://www.nitrc.org/>), even before the manuscript describing the effort was accepted for publication (57). Within 3 months, Nora Volkow and Dardo Tomasi had tested this novel method, mapping functional connectivity density, on these data (58). As they confirmed independently, this collection of unharmonized data from throughout the world, obtained on multiple types of magnets, exhibiting every form of demographic heterogeneity, still illustrated profoundly universal aspects of the brain’s intrinsic functional architecture (57).

Those were exhilarating days, as it briefly seemed that reclining in a scanner for just a few minutes could yield stable indices of interindividual variations in traits across nearly all conditions and throughout the brain (59) as well as providing robust indices of brain age (60). That resting-state fMRI correlations are exquisitely sensitive to the effects of even minor head motion in the scanner was first noticed by Jonathan Power and colleagues, and almost immediately confirmed by colleagues at the University of Pennsylvania and our group (61–63). Ever since, the field has had to work to minimize the effects of in-scanner head motion, a particular challenge for ADHD, a disorder characterized by excessive motoric activity (64).

With regard to the effect of scan duration on test-retest reliability, data from a single individual who was scanned twice weekly for nearly a year have provided a benchmark, suggesting that about 27 minutes of blood-oxygen-level-dependent (BOLD) data is adequate for obtaining reliable indices of brain function, with returns diminishing after 100 minutes (65). A similar estimate of 25 minutes emerged from scanning 13 individuals for 12 sessions, each including four types of scans, including resting state (66, 67). Fortunately, it is feasible to concatenate multiple sessions to improve reliability, although some caveats pertain (68). Between resting-state and task-based scanning, movies provide an intermediate alternative that improves tolerability, reduces motion, and can be combined with other forms of BOLD data to obtain individually relevant indices of connectivity (69). Still, most studies do not come close to obtaining the requisite quantity of data.

Besides longer scan durations with less motion, multiecho acquisition of the BOLD signal facilitates removing artifactual effects of motion from non-motion sources (70, 71). This method was implemented in an accelerated longitudinal design that differentiated two modes of developmental trajectories across adolescence: “conservative development” was characteristic of the primary cortex, which was strongly connected at age 14 and became even more strongly connected from ages 14 to 26; “disruptive development” was found in the association cortex and subcortical regions, where connections that were weak at 14 became stronger, and connections that were strong at 14 became weaker (72). Application of this type of approach to conditions such as ADHD would be of great interest. Unfortunately, the logistics of implementing a novel acquisition sequence across multiple types of scanners prevented it from being included in the Adolescent Brain Cognitive Development (ABCD) study.

ABCD represents the new model of prospectively harmonized data collection by consortia addressing a broad major issue such as adolescent development (73) rather than testing a specific hypothesis (74), thereby lending itself to multiple analytical strategies and scientific aims. A total of 11,875 participants have been enrolled, at ages 9–10, with the expectation of longitudinal follow-up for a decade. In an initial examination relevant to ADHD, dimensional analysis of ADHD symptoms used the attention problems scale of the

Child Behavior Checklist, which has been shown to converge on the clinical syndrome (75). In this case, Owens and colleagues studied 8,596 participants with analyzable structural MRI data and between 5,020 and 5,959 data sets for three fMRI tasks (76). A rigorous approach found that only the *N*-back working memory task was able to predict ADHD symptomatology even when accounting for potential confounders (age, sex, race, pubertal status, handedness, internalizing score, parental education, and family income), accounting for just 2.0% of the variance in out-of-sample prediction (76). As the authors noted, such small effects are consistent with ENIGMA results and are often meaningful in daily life. At any rate, the features that best predicted ADHD symptomatology were decreases in activations in task-positive regions (dorsolateral prefrontal cortex, posterior parietal cortex, and caudal anterior cingulate cortex) and increased activations in task-negative regions (ventromedial prefrontal cortex, posterior cingulate cortex, lateral temporal cortex, and precentral and postcentral gyri). These results are wonderfully convergent with hypotheses implicating the default mode network and task-positive regions in ADHD (77). Structural features were mostly consistent with functional results and the published literature, although at best they accounted for 1% of the out-of-sample variance and did not survive adjustment for covariates (76).

These small advances will not yield biomarkers, biosignatures, or improved diagnostic criteria, which constitute RDoC's third assumption and its overriding objective (31). But they are beginning to provide foundations for delineating the physiological principles of brain function and dysfunction. Understanding physiology has always been the royal road in medicine, essentially unattainable in psychiatry until recently. Fortunately, it appears that mesoscale indices of brain function and structure capture relevant facets of how the brain operates. This might not have been the case. If the fundamental unit of cognitive processing (construed broadly to include affective and social computations) was as small as a cortical column or its subunits, then the problem would be nearly hopeless. Instead, substantially sized brain regions seem to function as units in sufficiently enduring ways, with substantial spatial overlap across individuals.

We are not there yet, but signs abound of possible clues. Besides Raichle, Biswal, and Greicius, consider the contributions of Vinod Menon, the senior author of the seminal 2003 paper that may have revived the field of intrinsic functional connectivity (54). Among Menon's numerous contributions, the most enduring may be his role in identifying the salience network as a key intermediate partner of the default mode network and the frontal parietal cognitive control network (78, 79). In a prescient review presenting his triple network model of psychopathology (78), Menon laid out “a parsimonious account that may explain various clinical symptoms as a function of enhanced, reduced, or otherwise altered salience detection.” This derives from the observation, masterfully compiled in that authoritative overview, that the anterior insula, a key salience network node, is crucial for network

switching among the default mode network and frontoparietal network in a broad range of tasks and clinical conditions (78).

In his group's most recent contribution, Menon and colleagues implement technical and statistical innovations such as ultrafast temporal resolution fMRI (490 ms) and a novel Bayesian switching dynamic system unsupervised learning algorithm (80) to identify dynamic brain states, and drift-diffusion modeling of simple choice response time-series data obtained in 29 children with ADHD and 23 healthy comparison participants (culled from 90 scanned and 107 recruited children). Building on the triple-network focus, the authors examined regions of interest within the default mode network, salience network, and frontoparietal network obtained from an independent study. The Bayesian algorithm detected four brain states; their temporal properties and behavioral correlates were examined. Two of the states were associated with enhanced or worse (more variable) behavioral performance. The former state was also associated with faster and more accurate responding and exhibited stronger coupling between salience network and frontoparietal network regions of interest. The other state predicted worse inattention scores and differentiated children with ADHD from comparison participants. The overall approach is consonant with RDoC, even if diagnostic categories were used during recruitment. Still, the proof of this pudding will be in replication. Will ultrafast scanning turn out to be essential? If so, that will take years. If not, there are myriad data sources, from ABCD to the Healthy Brain Network (81), in which analyses of dynamic states could be conducted in relation to performance measures such as response time. Given the energy and vitality of the field (82, 83), such attempts may already be under way.

As I warned, I have presented a biased and selective perspective. I have neglected important lines of work, from the ingenious efforts of Philip Shaw (84), the fruitful partnership of Damien Fair and Joel Nigg addressing heterogeneity (27, 85–87), the foundational work of Katya Rubia on developing real-time fMRI biofeedback to influence brain networks (88, 89), admirable consortia such as NeuroIMAGE (90, 91) and the International Multicenter Persistent ADHD Collaboration (ImpACT) (92), a longitudinal study of default mode network development by Yong He (93), the rigorous contributions by Susan Shur-Fen Gau (94–96), Luis Rohde and colleagues (97, 98), and the indefatigable Edmund Sonuga-Barke (77), the astonishingly productive Steve Faraone (5, 38), and on and on. Beyond brain imaging, there are too many interesting developments in ADHD research to catalog succinctly. They can all be summarized by the words of Jerry Fodor with which this essay opened. We will continue to pull each other up by our bootstraps, while we celebrate and critique our remotely plausible theories. As always, they will benefit from technical advances, permitting greater precision as we identify brain networks without needing to blur and distort them to analyze them in a common space. At the other end of spatial resolution, high-throughput ultra-low-field-strength anatomic imaging is about to become a reality (99), with functional imaging at the point of care now on the horizon. These

and the continued adoption of large-scale open data-sharing efforts (100) will provide the next generation of interdisciplinary scientists with the bases to build the royal road of physiological understanding of brain function and dysfunction in the context of lifelong development.

## AUTHOR AND ARTICLE INFORMATION

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