

Distinct neuropsychological subgroups in typically developing youth inform heterogeneity in children with ADHD

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Research and clinical investigations in psychiatry largely rely on the de facto assumption that the diagnostic categories identified in the *Diagnostic and Statistical Manual (DSM)* represent homogeneous syndromes. However, the mechanistic heterogeneity that potentially underlies the existing classification scheme might limit discovery of etiology for most developmental psychiatric disorders. Another, perhaps less palpable, reality may also be interfering with progress—heterogeneity in typically developing populations. In this report we attempt to clarify neuropsychological heterogeneity in a large dataset of typically developing youth and youth with attention deficit/hyperactivity disorder (ADHD), using graph theory and community detection. We sought to determine whether data-driven neuropsychological subtypes could be discerned in children with and without the disorder. Because individual classification is the sine qua non for eventual clinical translation, we also apply support vector machine-based multivariate pattern analysis to identify how well ADHD status in individual children can be identified as defined by the community detection delineated subtypes. The analysis yielded several unique, but similar subtypes across both populations. Just as importantly, comparing typically developing children with ADHD children within each of these distinct subgroups increased diagnostic accuracy. Two important principles were identified that have the potential to advance our understanding of typical development and developmental neuropsychiatric disorders. The first tenet suggests that typically developing children can be classified into distinct neuropsychological subgroups with high precision. The second tenet proposes that some of the heterogeneity in individuals with ADHD might be “nested” in this normal variation.

psychiatric disorders | research domain criteria | cognition | modularity | executive functions

In psychiatry, research and clinical investigation largely relies on the de facto assumption that the diagnostic categories identified in the *Diagnostic and Statistical Manual* of mental disorders (DSM-IV) represent etiologically homogeneous syndromes. However, there is considerable evidence that suggests the DSM does not necessarily describe homogenous conditions, but rather reflects the end result of multiple unique independent mechanistic pathways within a given disorder (1, 2). The mechanistic heterogeneity that potentially underlies the existing classification scheme might be limiting our ability to clarify etiology and identify novel therapeutics for several psychiatric illnesses (3).

A salient example, and our focus here, is attention deficit/hyperactivity disorder (ADHD). It is one of the earliest onset, most common, and costly neurodevelopmental disorders in child psychiatry (4, 5). Until recently, causal models of ADHD, as with other mental disorders, proposed a single core dysfunction (6). Investigators typically compare a group of children with ADHD defined by core symptoms (i.e., DSM) to a group of control children without the disorder. Statistical group differences based on psychometrics, functional brain imaging, or genetics are then used to inform models of the disorder.

This assumption of homogeneity in the case of ADHD has been questioned in numerous theoretical papers (7–13). For example, Nigg et al. (13) showed that several neuropsychological measures central to ADHD had substantial distributional overlap between ADHD and control samples. The data suggested that only a small minority of subjects with the disorder could be considered clinically “affected” on the basis of any one measure (13). Similar findings have been noted elsewhere (14, 15). In other words, whereas numerous unique neuropsychological measures have been proposed as related to ADHD, perhaps each of them applies to only a subset of those subjects with the disorder.

Although the role of heterogeneity in clinical populations has caught the collective attention of funding agencies (16) and the scientific community (8, 13, 15, 17), another, perhaps less palpable, reality may also be interfering with progress in understanding psychiatric illnesses—heterogeneity in typical populations. In the same way that investigators are often bound by the “cognitive box” (1) of the DSM when examining atypical development, they are also generally obliged to conduct their analysis as if typically developing comparison populations represent a monolithic group. Although consensus remains elusive on defining specific personality or cognitive “types” (18, 19), substantial evidence has accrued that individual differences in successful adaptive psychological styles are central to human development, functioning, social cohesion, and health outcomes (20–23). It may be that identifying a mechanism associated with a mental disorder requires comparing individuals to well-adjusted persons with the same cognitive style or profile.

Although it is easy to propose conceptually that there must be distinct subgroups within mental disorders (or typical populations), empirically demonstrating such subgroups is not straightforward. In the case of ADHD, emphasis has been on latent class analysis using symptom profiles (24), personality traits (25), and developmental trajectories of symptoms (26). These approaches are promising but appear to have mainly tended to identify severity classes rather than distinct categories (27). Efforts to identify types using neurocognitive measures—in theory, related to pathophysiological mechanisms—are still in the beginning stages. A key goal of this work is to identify procedures that are not prone to simply identifying severity groupings.

One approach, which may prove fruitful toward this goal, emanates from graph theory. Graph theory is a mathematical discipline about the study of networks, in which networks are

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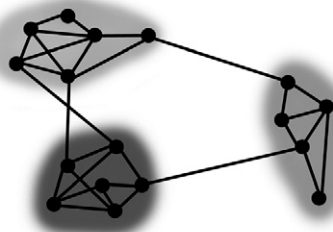


Fig. 1. Graph theory and community detection. Displayed is a depiction of a network, where nodes (solid circles) are connected by edges (solid lines). In this paper nodes are participants and edges are correlations between participants' neuropsychological scores. Community detection algorithms (29) can be applied to graph structures to identify clusters of nodes (shaded clouds) that share many edges within clusters relative to between clusters.

simply sets of nodes or vertices joined in pairs by lines or edges (Fig. 1). Graph theory has been used to examine the organization of a number of relationships within systems (28). Importantly, many systems have well-defined internal structures and can be described or demarcated with graph theoretical analyses (28, 29). One area that has received considerable attention is the detection of **community structure** in networks. Community structure refers to the appearance of densely connected groups of nodes, with only sparse connections between the groups (Fig. 1) (29). The focus of this report is whether groups of children that share similar empirical neuropsychological features segregate to form specific data-driven phenotypic subtypes.

Because individual classification is the *sine qua non* for eventual translation to clinical use, we followed our community detection analysis with an investigation using support vector machine (SVM)-based multivariate pattern analysis (MVPA) (30, 31) to identify how well individual children can be identified as defined by the community detection delineated subtypes. SVMs are supervised classification algorithms rooted in statistical learning theory, capable of recognizing patterns for the purposes of categorization. Typically SVMs examine a set of training data for which each data point (e.g., person) has been assigned to a unique category with several defining features. On the basis of patterns among the features within each category, the training algorithm then builds a model capable of assigning new data points (e.g., individuals) into these specific categories. Here we use SVM-based MVPA to determine whether there is sufficient information in the neuropsychological scores to predict whether any individual can be accurately classified into a particular neuropsychological subgroup or profile defined by the community detection procedure. We also use the approach to determine whether ADHD status can be more accurately assigned after considering **the community-based profiles**.

Results

Feature Reduction Supported a ~~Seven-Factor Model~~ of Cognitive Abilities. For the current investigation we apply community detection to a well-characterized dataset of 498 children who include both typically developing control youth (TDC) ($n = 213$) and youth with ADHD ($n = 285$) (Table S1). From these youth, some 20 neuropsychological measures were obtained that were intended to cover a wide domain of cognitive functions variously theorized to be involved in ADHD (Table S2 and Fig. 2).

Our approach was to use a broad set of neuropsychological variables relevant to ADHD, while avoiding use of an excessive number of redundant indicators in our analysis. We therefore conducted a rational feature reduction using confirmatory factor analysis (CFA), according to the conceptual model that had guided our work (Fig. 2 and refs. 32 and 33). All measures were transformed such that higher scores were indicative of worse

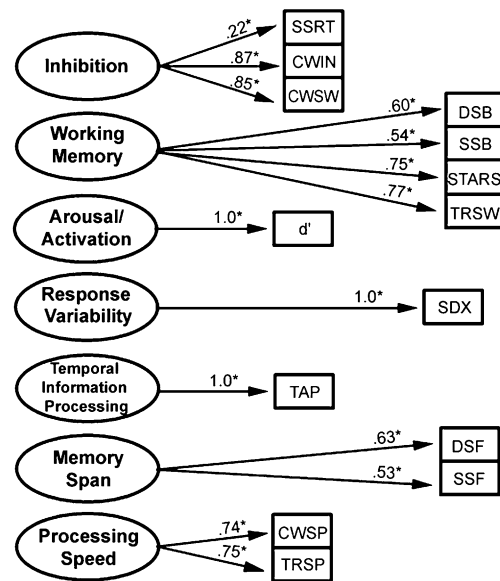


Fig. 2. Data reduction for neuropsychological measures. Confirmatory factor analysis (CFA) was used to conduct rational reduction of the measures listed in Table S2. Shown is our conceptual model that depicts how we hypothesized that our measured variables relate to seven latent factors. It also displays the factor loadings for the seven-factor model. For ease of presentation, the figure does not display error terms, cross loadings, or correlations among latent factors. CWIN, color word inhibition; CWSP, color word speed; CWSW, color word switching; d' , D-prime; DSB, digit span backward; DSF, digit span forward; SDX, response variability; SSB, spatial span backward; SSF, spatial span forward; SSRT, stop signal reaction time; STARS, stars task; TAP, tapping task (temporal information processing task); TRSP, trails number and letter naming speed average; TRSW, trails-making task switching.

performance (e.g., slower speed or worse accuracy). Fig. 2 portrays our primary model with the empirical factor loadings (SI Text). Because we were sensitive to the possibility of equivalent models, we also tested several competing models that conformed in varying degrees to our theorized reasons for choosing these measures. Fit of all models was evaluated using several indexes, including the χ^2 -value, the comparative fit index (CFI), the Tucker Lewis index (TLI), and the root mean-square error of approximation (RMSEA) (SI Text).

Results for the feature reduction for the neuropsychological measures showed that a one-factor model fit inadequately [$\chi^2(70) = 386.2$, CFI = 0.87, TLI = 0.84, RMSEA = 0.09], justifying our effort to create a multiconstruct model. Fit was satisfactory and comparable for the best-fitting five-, six-, and seven-factor models as follows: five-factor $\chi^2(63) = 103.4$, CFI = 0.98, TLI = 0.97, RMSEA = 0.036; six-factor $\chi^2(58) = 95.1$, CFI = 0.98, TLI = 0.98, RMSEA = 0.035; and seven-factor $\chi^2(52) = 89.9$, CFI = 0.98, TLI = 0.97, RMSEA = 0.038. For our main analysis we present results for the seven-factor model because we viewed it as conceptually the most differentiated description of the abilities tested, the most consistent with our conceptual framework, and equivalent in fit to the other models. However, we conducted the modularity analysis using the best-fitting six- and five-factor solutions as well to see whether community assignments were conceptually similar with these slightly different indicators, and indeed they were (Fig. S1).

Comparing the Full ADHD and TDC Cohorts Replicated Previous Findings. The second stage of our analysis began with a traditional comparison between the ADHD and TDC cohorts. This analysis was followed by our SVM pattern classifier to determine how well the neuropsychological scores can inform individual distinctions between ADHD and TDC.

Atypical Neuropsychological Measures Are Unique on the Basis of Profile and ADHD Classification Improves Within Profiles. Considering the unique nature of the subclassifications, we next returned to our group comparisons between ADHD and TDC. However, instead of comparing all ADHD with all TDC, we now compared ADHD and TDC neuropsychological scores within their specific assigned neuropsychological “type” or group. The results are presented in Fig. 3 and Table S3. Whereas the ANOVA in six of the seven factors showed a main effect of diagnosis, the post hoc comparisons showed that not all subgroups had the same atypical neuropsychological scores.

Among ADHD subgroups, atypical inhibitory control, speed, and working memory were each found in three groups. Atypical arousal and span were each identified in two groups. Atypical response variability and temporal information priming were each found in four groups. Interestingly, the ADHD classification improved or remained the same for all but one of the groups, relative to the initial All ADHD vs. All TDC analysis. Group 4A had the maximal improvement at 84.1% classification of ADHD vs. TCD youth (83.3% sensitivity and 84.6% specificity). The remaining groups were as follows: group 1, 68% total, 49.2% sensitivity, 80.4% specificity; group 2A, 68.5%, 83.7%, 51.2%; group 2B, 64.7%, 80.4%, 44.2%; group 3, 73.6%, 88.73%, 46.2%; group 4A, 84.1%, 83.3%, 84.6%; and group 4B, 61.9%, 37%, 76.9%.

Discussion

Trait Variation in the Typically Developing Population Informs Heterogeneity in ADHD. In this report we used graph theoretical tools to clarify a portion of the heterogeneity that exists within ADHD and typically developing control populations. Two important principles were identified that have the potential to advance our understanding of typical development and developmental neuropsychiatric disorders. The first tenet suggests that, on the basis of neuropsychological performance, typically developing children can be classified into distinct subgroups with high precision. The second tenet proposes that the heterogeneity in individuals with ADHD appears to be “nested” in this normal variation. As illustrated by our single subject classification procedures, comparing typically developing children with ADHD children within each of these distinct subgroups increases diagnostic accuracy (i.e., ADHD vs. non-ADHD classification) on the basis of the neuropsychological

measures. This work highlights that illumination of such subgroups could potentially have significant practical importance for understanding the nature of typical development and identifying the etiologic underpinnings of complex disorders such as ADHD.

What Is the Role of Behavioral Variation in the Typically Developing Population and How Might It Arise? For years evolutionary psychologists have argued that human behavior (and that of other animal species) is under the same selective pressures as the physical traits so elegantly described by Darwin (34). Indeed, Darwin himself predicted this likeness to be the case at the end of his work *On the Origin of Species*, noting “In the distant future I see open fields for far more important researches. Psychology will be based on a new foundation, that of the necessary acquirement of each mental power and capacity by gradation” (Darwin, 1859) (ref. 19, p. 399). As such, there are evolutionary arguments to be made with regard to how neuropsychological diversity might arise in the population.

The modeling literature related to adaptive complex social systems also provides significant evidence that suggests psychological heterogeneity is an important means by which to improve the robustness of the collective when faced with shifting environmental demands (35). It is a key feature in the stability of complex social systems and thus has likely been an important attribute of our evolving species.

With respect to our findings it should be noted that at times heritable diversity might form along a continuous dimension (i.e., unimodal distribution), whereas at others times it may form as multiple discrete strategies (i.e., multimodal distributions) (21, 36–38). In the latter proposal, average fitness would be about equal across the normal range of any given behavioral strategy, but individuals of different strategies might vary in the way they achieve fitness. Rapid and sizeable changes in environmental demands across time may have served as the driving force toward multiple “peaks” with regard to neurocognitive strategies or profiles in typical populations (21, 36), as found here.

For example, in the cognitive neuroscience literature some have recently argued that the single-nucleotide polymorphism (val158-met) of the catechol O-methyltransferase (COMT) gene, which codes for an enzyme that degrades dopamine in prefrontal cortex, may relate to evolutionary trade-offs between efficient executive functioning (met) and improved emotional regulation (val) (21,

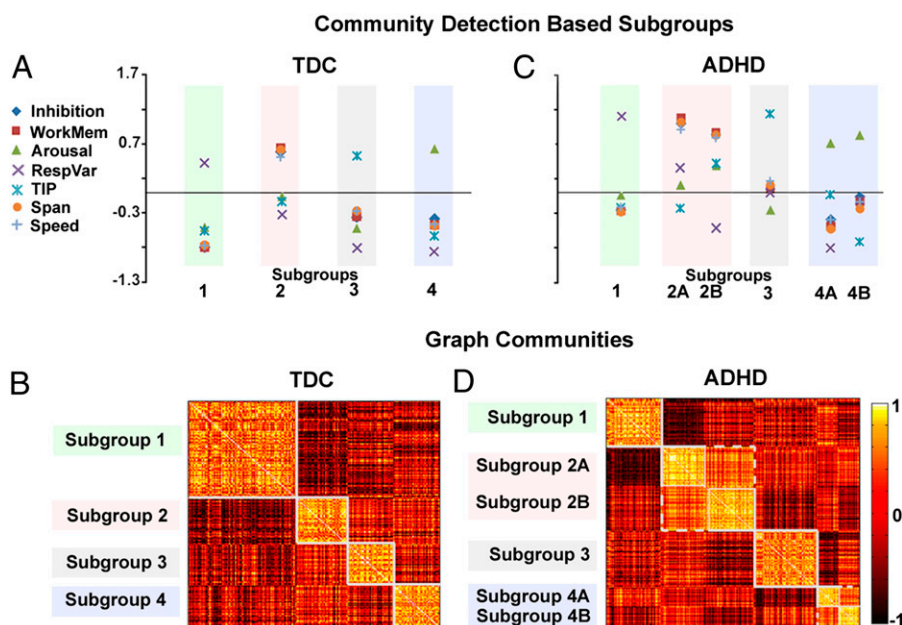


Fig. 4. Community detection identified subgroups. (A) After applying the community detection procedure to the typically developing cohort, four unique subgroups (i.e., cognitive profiles) emerge (y axis = z score). The community structure is depicted by correlation matrices shown in B. These correlation matrices represent a 213×213 matrix (for TDC) and 285×285 matrix (for ADHD). On the grid, darker colors reveal lower or negative correlations between subjects, and lighter colors reveal positive correlations between subjects. Identified communities are outlined in white. (C) Independently applying the community detection algorithm to the ADHD cohort shows similar findings to those in A. The difference between the two appears to be split in subgroup 2 and subgroup 4. The correlation matrices of the ADHD cohort are presented in D.

applied a weight-conserving modularity algorithm not dependent on threshold selection (50). Both additional procedures yielded largely consistent results (Fig. S2 and SI Text). The strength of the modularity assignments was based on the quality index (Q), VOI (29, 51), and simulations created by iteratively repeating our analyses after randomizing the factor scores across participants (SI Text and Figs. S2 and S3). All of the preceding calculations were performed in MATLAB (Mathworks), using scripts generously provided by Olaf Sporns, Mikail Rubinov, and other collaborators (52) (Indiana University, Bloomington, IN).

Support Vector Machine-Based Multivariate Pattern Analysis. For the SVM-based MVPA we use Spider (<http://people.kyb.tuebingen.mpg.de/spider/main.html>), an object-orientated environment for machine learning in MATLAB. Full details of this procedure are provided in SI Text.

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