Research

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Original Investigation

Subtyping Attention-Deficit/Hyperactivity Disorder Using Temperament Dimensions Toward Biologically Based Nosologic Criteria

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IMPORTANCE Psychiatric nosology is limited by behavioral and biological heterogeneity within existing disorder categories. The imprecise nature of current nosologic distinctions limits both mechanistic understanding and clinical prediction. We demonstrate an approach consistent with the National Institute of Mental Health Research Domain Criteria initiative to identify superior, neurobiologically valid subgroups with better predictive capacity than existing psychiatric categories for childhood attention-deficit/hyperactivity disorder (ADHD).

OBJECTIVE To refine subtyping of childhood ADHD by using biologically based behavioral dimensions (ie, temperament), novel classification algorithms, and multiple external validators.

DESIGN, SETTING, AND PARTICIPANTS A total of 437 clinically well-characterized, community-recruited children, with and without ADHD, participated in an ongoing longitudinal study. Baseline data were used to classify children into subgroups based on temperament dimensions and examine external validators including physiological and magnetic resonance imaging measures. One-year longitudinal follow-up data are reported for a subgroup of the ADHD sample to address stability and clinical prediction.

MAIN OUTCOMES AND MEASURES Parent/guardian ratings of children on a measure of temperament were used as input features in novel community detection analyses to identify subgroups within the sample. Groups were validated using 3 widely accepted external validators: peripheral physiological characteristics (cardiac measures of respiratory sinus arrhythmia and pre-ejection period), central nervous system functioning (via resting-state functional connectivity magnetic resonance imaging), and clinical outcomes (at 1-year longitudinal follow-up).

RESULTS The community detection algorithm suggested 3 novel types of ADHD, labeled as mild (normative emotion regulation), surgent (extreme levels of positive approach-motivation), and irritable (extreme levels of negative emotionality, anger, and poor soothability). Types were independent of existing clinical demarcations including DSM-5 presentations or symptom severity. These types showed stability over time and were distinguished by unique patterns of cardiac physiological response, resting-state functional brain connectivity, and clinical outcomes 1 year later.

CONCLUSIONS AND RELEVANCE Results suggest that a biologically informed temperament-based typology, developed with a discovery-based community detection algorithm, provides a superior description of heterogeneity in the ADHD population than does any current clinical nosologic criteria. This demonstration sets the stage for more aggressive attempts at a tractable, biologically based nosology.

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Psychiatric nosology remains exclusively syndromic, depending on clusters of signs and symptoms rather than biologically based measures. This dependence introduces fundamentally confounding factors limiting better understanding of mental illness.1–4 For these reasons, the National Institute of Mental Health, under the Research Domain Criteria (RDoC) initiative,2 has emphasized broad neurobiologically based dimensions (e.g., positive/negative valence, cognitive control) to refine existing nosologic criteria. The long-term goal for this initiative, and the field in general, is to improve neurobiological validity, clinical prediction, and treatment matching.2 Although it is clear that eventually nosologic criteria will need to be revised, a tractable approach to advance the current classification system is not agreed upon. For example, no study of alternative nosologic criteria has demonstrated both biological validity and clinical prediction within the same sample.

We address this problem for the case of attention-deficit/hyperactivity disorder (ADHD). Like other psychiatric categories, ADHD is suspected of identifying children with diverse etiologies5,6 but DSM-IV subtypes (and thus DSM-5 presentations) fail to elucidate clear differences in pathophysiology or clinical course, in part because of their own instability over time.5,7–9 To better parse heterogeneity some experts have advised looking beyond existing symptom lists toward phenotypic measures that can be represented dimensionally and have well-theorized relationships with neurobiological systems,2,10–12 which is the core of the RDoC approach. At the same time, phenotype measures that retain clinical applicability are desirable. Attention-deficit/hyperactivity disorder is a good starting point for achieving RDoC aims because children with the disorder can be characterized in terms of several features that are best represented as dimensions and have well-theorized relationships to biological systems.

How are novel types to be empirically identified and validated? Clustering algorithms can be expected to yield varying results depending on the algorithm used and features selected as input13 and therefore are, in themselves, exploratory;4 the main question concerns whether clusters are clinically useful. Our key considerations were (1) input features, (2) choice of clustering method, and (3) multiple external validators.

Phenotypic Features
For the features, we used a well-accepted, low-cost, parent-rated measure of child temperament. Temperament traits can be described as a set of biologically based behavioral and emotional tendencies. Although not the only approach available, these traits extend beyond single-disorder clinical symptoms to expand coverage of negative and positive emotion systems, as well as attentional capacities.15–17 These in turn are directly related to the RDoC domains of negative valence systems, positive valence systems/approach motivation, and cognitive control, respectively. These traits also are related to, although not identical with, personality traits in adults and are assessed relatively easily via parent-report questionnaires, which can be easily translated into clinical applications. Temperament traits also have distinct neurobiological correlates with a substantial amount of literature on humans and animals.

Clustered methods:
In the present report we follow up on earlier work10 that used a clustering method known as community detection, which stems from the mathematical discipline of graph theory.30

Methods
Participants and Diagnostic Procedures
Data are reported for 437 children between the ages of 7 and 11 years: 190 individuals (46.3% male) served as the control group, and 247 (71.6% male) were in the ADHD group. Participants were drawn from the Oregon ADHD Program, a child cohort for which the community-based recruitment and enrollment procedures and multi-informant assessment procedures for ADHD diagnosis are published elsewhere31–33 and described in the eAppendix in the Supplement. Sample characteristics for background on the ADHD and control groups are presented in eTable 1 in the Supplement. Ethics approval was obtained from the institutional review board at Oregon Health and Science University. A parent or legal guardian provided written informed consent, and children provided written assent. Participants received financial compensation.

Temperament Ratings
A parent or legal guardian completed the widely used Temperament in Middle Childhood Questionnaire (TMCD).34 Items form 16 subscales and 3 higher-order factors that are hypothesized to be influenced by underlying neurobehavioral sys-
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Community Detection Analyses
Community detection is an optimization clustering method. As used here, a matrix of child-by-child correlations was created based on the 16 TMCQ subscales, standardized to the sample mean and SD. Community detection was applied to the child matrix using Rubin and Sporns' weight-conserving modularity algorithm. This algorithm starts with each node (ie, child) being the sole member of a community and iteratively produces partitions whose conjunction produces the largest increase in the quality index (Q) until Q reaches a maximum. In our case, Q is a weighted combination of the modularity for positive relationships (Q⁺) and negative relationships (Q⁻) introduced by Rubin and Sporns. We provide the formal definition in the eAppendix in the Supplement. Conceptually, Q represents the overall segregation between identified communities, with higher values indicating stronger separation of communities. This and other modularity algorithms are not deterministic, and thus can yield slightly different solutions on different runs. To generate a single, stable depiction of structure, final group assignments for each child were based on the modal group assignment across 10 runs of the modularity algorithm. A secondary validation method (variation of information algorithm) was also used to evaluate internal validity (group robustness to chance data variation).

External Validation
Physiological Recording
Physiological response data were available for 178 children with ADHD and 128 control children. Temperament traits are conceptually related to positive and negative emotion domains; therefore, recording was completed during an emotion induction and suppression task with positive and negative emotion conditions, as well as during an emotionally neutral baseline condition, exactly as described in prior publications. Respiratory sinus arrhythmia (RSA), a measure of heart rate variability strongly influenced by parasympathetic regulation and hypothesized to be related to emotion regulation, was derived from the electrocardiogram signal (MindWare Heart Rate Variability software, version 2.6) and was quantified as the high-frequency component (>0.15 Hz) of the R-R peak time series (time between R spikes in the electrocardiogram in 60-second epochs). Standard methods for artifact detection were followed as published in prior work and are also provided in the eAppendix in the Supplement.

The cardiac pre-ejection period (PEP) was derived from electrocardiogram and impedance cardiography in 60-second epochs (MindWare, version 2.6). It was calculated as the time interval in milliseconds from the onset of the Q-wave to the B-point of the derived impedance signal (dZ/dt) using published methods. Pre-ejection period reactivity is a generally agreed upon measure of sympathetic influence on the heart; the interpretation of tonic PEP is more complex.

Neural Functioning
Resting-state functional connectivity magnetic resonance imaging (MRI) data (420-600 seconds) are reported for 39 children with ADHD and 15 typically developing children. Participants were scanned using a 3.0-T scanner (Magnetom Trio Tim system; Siemens Healthcare) with a 12-channel head-coil using previously published methods.

Functional images were processed to reduce artifacts and connectivity was processed following published methods reproduced in the eAppendix in the Supplement. Motion, a known confound in functional MRI studies, was corrected and quantified several ways (details provided in the eAppendix in the Supplement).

As noted above, one major candidate for neural involvement in temperament is the amygdala, so it was chosen as our single seed region for this demonstration analysis. Left and right amygdala regions of interest were obtained for participants using FMRIB’s Integrated Registration and Segmentation Tool, distributed with the FMRIB Software Library. The regions of interest were created in the Montreal Neurological Institute atlas space and then converted to Talairach atlas space. All subsequent operations were performed on the Talairach atlas-transformed regions of interest.

For all participants, the resting blood oxygen level-dependent time series for each region of interest was correlated with all other voxels in the brain, generating voxelwise functional connectivity maps. We performed 2-sample, 2-tailed t tests on all potential connections (Fisher transformed r values) between community-defined subgroups (assuming unequal variance; \(P < .05\)), as well as between each community-defined subgroup and controls. One-sample tests were run for within-group connectivity maps. To account for multiple comparisons, thresholding based on Monte Carlo simulation was implemented. To obtain multiple comparisons–corrected voxel clusters (\(P < .05\)), a threshold of 53 contiguous voxels with a z value greater than 2.25 was used.

Longitudinal Follow-up
One-year longitudinal follow-up data on clinical features and TMCQ ratings are reported for 101 children with ADHD. The longitudinal study is ongoing, and the sample of 101 children is 98% of those due for follow-up at the time of data analysis.

Results
Community Detection Analyses
Subgrouping was done in a multistep fashion using community detection. At the first step, including all 437 children in the sample, community detection identified 3 profiles of children (Q = 0.55) with sizes of 192, 181, and 64. Profile 1 included 82% of the control children and 13% of the ADHD children. Profiles 2 and 3 combined included 87% of the ADHD children and 18% of the non-ADHD control children. Separation of the ADHD and non-ADHD samples was not attributable to sample differences in age or sex (see the eAppendix in the Supplement). We concluded that our initial clustering
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Figure 1. Spring-Embedded Visualization of Temperament Groups

Graphical representation of the community detection results in the attention-deficit/hyperactivity disorder (ADHD) sample, which shows many strong correlations among individuals in the same temperament type and fewer between-type connections. Nodes represent individuals in each temperament group and connecting edges indicate correlations between individuals. Blue indicates the mild; red, surgent; and green, irritable types of ADHD. Correlations are thresholded at .50 for purposes of visual representation.

Analysis recovered a primarily control profile and 2 ADHD profiles. Thus, at the second step, the analysis was conducted on the ADHD and control samples separately with the aim of better characterizing variation within those 2 populations. Results from the control participants revealed weakly divided, marginal subgroups and therefore were not subjected to further validation (see the eAppendix in the Supplement).

Community detection using the 247 children with ADHD identified 3 profiles (referred to herein as types) as the modal solution with type 1 including 64 (25.9%); type 2, 85 (34.4%); and type 3, 98 (39.7%) children based on modal type assignments. The quality quotient suggested strong separation of the groups (Q = 0.50). Variation of information algorithm analyses indicated that the types were robust to modest random perturbations in the data (see the eFigure in the Supplement). Types reproduced with similar quality scores after a random split replication of the ADHD population (Q = 0.46 and Q = 0.50).

Clinically, type 1 children were more impulsive and inattentive (all P < .01) than controls, as well as less affiliative (all P < .05), but otherwise did not differ significantly from controls on any temperament domain. Type 1 children had milder impulsivity, inhibition, and attentional dyscontrol compared with the other 2 ADHD types (all P < .001). We labeled type 1 as mild ADHD. Type 2 children had more severe impulsivity compared with type 1 children, and also demonstrated less shyness and more assertiveness/dominance, high-intensity pleasure seeking, and activity level than either of the other 2 types or the controls (all P < .001); we labeled this type surgent ADHD. Type 3 children, in addition to greater impulsivity and attentional dyscontrol than those categorized as having the mild type of ADHD, also had more negative emotionality than the other 2 types or the controls (all P < .001). This included higher levels of anger, discomfort, fear, and sadness, and lower levels of soothability (all P < .001), suggesting that this is a group of children prone to anger, tantrums, and irritable behavior as described in recent literature. Type 3 was thus labeled irritable ADHD. Figure 1 provides a spring-embedding graph for depiction of the degree of group separation in terms of the distance between the participants. Figure 2 depicts the profile for each group on the 16 temperament scales.

The DSM-5–based presentations of ADHD were split across the types suggesting the temperament types did not reduce to DSM presentations. Additional clinical and demographic description can be found in eTable 2 in the Supplement.

External Validity I: Peripheral Physiology

Physiological measurements of peripheral nervous system response were recorded for 63 mild, 61 surgent, and 64 irritable children with ADHD and 128 controls. Group differences were examined in 2(valence: positive/negative) × 2(condition: induction/suppression) × 4(group) repeated-measures analyses of variance with sex covaried. The analysis of variance matrix was decomposed following procedures recommended by Keppel with embedded correction for type I error using a Fisherian decomposition strategy and a least significant difference test for simple comparisons.

Pre-Ejection Period

There were baseline differences in PEP between groups (F2,304 = 2.73; P = .044; η2 = 0.03). Post hoc tests indicated that the surgent group had significantly shorter PEP values than did typically developing children or the other ADHD types. Similarly, tonic PEP scores in each of the 4 emotion task conditions were compared. Only the group main effect was significant (F2,304 = 3.95; P = .009; η2 = 0.04). Post hoc tests again confirmed that the surgent type had shorter PEP values than did the typically developing controls, the irritable ADHD type, and the mild ADHD type. None of the groups showed significant change in PEP from baseline to task (i.e., PEP reactivity scores did not differ significantly from zero; all P > .05), and there were no significant main or interaction effects when PEP reactivity scores were examined for the emotion task (all P > .05). These results are summarized in Figure 3 and in eTable 3 in the Supplement.

Respiratory Sinus Arrhythmia

The RSA change from baseline to task was assessed, with positive scores (increases) interpreted as increased parasympathetic activity and negative scores (decreases) as reduced parasympathetic activity. A main effect of group (F2,304 = 3.97; P = .047; η2 = 0.01) was qualified by a 3-way interaction of valence × condition × group (F2,304 = 4.09; P = .018; η2 = 0.05). The follow-up simple comparisons revealed that the irritable type group had a smaller increase in RSA compared with the con-
trol and mild type groups during the 2 negative emotion conditions (all $P < .05$).

The surgent type group differed from the other 3 groups during the negative suppression condition ($P = .04; \eta^2 = 0.04$) because they showed no significant change in RSA in this condition from baseline. In the positive emotion conditions, the surgent group also differed significantly from the other ADHD types and non-ADHD controls ($P = .01; \eta^2 = 0.05$). Where other ADHD types and typically developing children demonstrated increased RSA, the surgent group had decreased RSA ($P = .01; \eta^2 = 0.05$), consistent with withdrawal of parasympathetic activity (see Figure 2 and eTable 3 in the Supplement).

Thus, data suggest that children with the surgent and irritable types of ADHD have distinct peripheral physiological profiles compared with each other and with typically developing children. Children with the mild type, in contrast, showed a physiological profile similar to that of typically developing children.

**External Validity II: Neural Connectivity**

We examined functional connectivity of the amygdala for 18 mild, 11 surgent, and 10 irritable type children with ADHD and 15 controls. Findings related to each group were distributed throughout the cortex. We highlight a few of these differences here and they are reported fully in the Table and shown in Figure 4.

The irritable type group displayed weaker connectivity (in the form of reduced negative relationships) from the amygdala to the anterior insula relative to all other groups (including non-ADHD controls) and weaker connectivity to the posterior cingulate (a key hub in the default network).
Table. ROI Table for Between-Group Comparisons

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<th>ROI Comparison</th>
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(continued)
relative to typically developing and surgent type children. The mild type showed the reduced connectivity profile of the posterior cingulate/precuneus vs the typically developing and surgent type groups. The surgent type evidenced increased connectivity from the amygdala to the cingulate/precuneus compared with the mild and irritable type groups, but was similar relative to control population. All groups had differential patterns of connectivity to unique dorsolateral prefrontal cortex regions compared with at least one other group (Table). Overall, each ADHD type had a distinct pattern of central nervous system connectivity.

**External Validity III: Longitudinal Stability and Clinical Outcome**

Community detection was repeated using time 2 data. Again, the modal solution suggested 3 ADHD profiles (Q = 0.51), which could be characterized as mild (n = 18), surgent (n = 42), and irritable (n = 41).

Multinomial logistic regression indicated that temperament types were more stable than expected by chance (χ² = 71.84; P < .001). In both the surgent and irritable types, more than 70% of the children were assigned to the same type at follow-up. In contrast, the mild type often changed profile: at the time 2 evaluation, 43.6% of the children remained in the mild type, 41.0% were assigned to the surgent type, and 15.4% were assigned to the irritable type (see the Video for depiction of stability of types over time).

With regard to clinical outcomes, children in the irritable type at time 1 were more likely than those in the other 2 ADHD types to develop a new comorbid disorder over the course of longitudinal follow-up (χ² = 10.11; P = .006), with more than double the rates of onset compared with either of the other types or the non-ADHD control participants (11.1%, 18.2%, 11.1%, and 39.5% in controls, mild type, surgent type, and irritable type, respectively). This prediction was superior to other nosologic designations at baseline that may be related to prognosis: neither DSM-5 presentations nor groups based on the presence or absence of oppositional defiant disorder symptoms (ie, 0 symptoms vs 1+ symptoms) differed in their rates of new comorbid disorder onsets at time 2 (χ² = 0.68; P = .41 and χ² = 2.54, P = .11, respectively).

Furthermore, when temperament types, DSM-5 presentations, and oppositional defiant disorder symptom status were entered into a logistic regression model, the temperament types were the best predictor of comorbidity onsets (P = .019; odds ratio, 2.46). Neither the presence of time 1 oppositional deficit disorder symptoms (P = .56) nor ADHD DSM-5 presentation (P = .11) uniquely predicted new onsets at time 2. Future work can examine other clinical designations that were less common in the sample.

**Discussion**

In the present study, we demonstrated an approach to revising psychiatric nosologic criteria that (1) goes beyond clinical symptoms, in this case choosing temperament measures that are closely related to RDoC domains; (2) uses a novel, discovery-based clustering algorithm; (3) demonstrates external validation concurrently using peripheral and central physiology; and (4) shows superior clinical prediction vs existing clinical categories related to ADHD or ADHD with comorbidity. The results of the study suggest that revising the nosologic criteria in the case of ADHD is tractable and will be biologically meaningful. The present results add to prior research on schizophrenia, suggesting that the use of biologically influenced indicators, optimization-based clustering techniques, and comparison of groups on external validators is an informative approach for understanding heterogeneity in psychiatric disorders.

We identified 3 distinct types of ADHD based on temperament profiles: (1) a mild type characterized only by deficits in core ADHD symptom domains; (2) a surgent type characterized by high levels of positive approach–motivated behaviors and activity level, shorter PEP, parasympathetic withdrawal in response to positive emotions, and atypical amygdala connectivity to medial frontal areas; and (3) an irritable type characterized by high levels of negative emotionality, weak parasympathetic response to negative emotional stimuli, reduced amygdala-insula connectivity, and a doubling of risk for onset of new behavioral or emotional disorders.

Crucially, we considered multiple validators, choosing a subset from the classic validators suggested by Robins and Guze and Cantwell including biological correlates and clinical course. We found promising results suggesting that these types outperform the existing nosologic criteria of ADHD. In the pres-
Figure 4. Resting-State Functional Connectivity Data Magnetic Resonance Imaging Conjunction Maps

A Mild type

B Surgent type

C Irritable type

Amygdala connectivity maps for each temperament type were directly compared with the 2 other types and a matched control population. Results from each of these comparisons are provided in the Table. The figure is a conjunction map for the comparisons. For each comparison (eg, mild vs surgent, mild vs irritable), a voxel was coded as either 0 (not significantly different between groups) or 1 (significantly different between groups). Maps were summed such that voxels that never differ between groups have a value of $No. = 0.0$ and voxels that differ in all comparisons for that group have a value of $No. = 3.0$. A, Mild type differed from other types in areas in the posterior cingulate/precuneus (black arrow). B, As with the mild type, the surgent type showed areas in the posterior cingulate and precuneus (black arrow) where it was distinct from at least 2 other groups. C, The irritable type was distinct from the mild, surgent, and control populations in the anterior insula (black arrows)—a region important for emotional regulation and task level control. No. indicates the number of comparisons in which the voxel significantly differed between groups. The colors range from 0.0 (never different) to 3.0 (different in all comparisons).

In the present study, the surgent and irritable types survived every test of validation, including distinct physiology and functional connectivity, stability over time, and better clinical prediction than DSM presentations or the most common comorbid grouping, op-
psychiatric disorders at the 1 year follow-up as an index of clinical deterioration. The new categories provided improved prediction vs existing clinical indicators.

With regard to implications for ADHD, these findings are broadly consistent with, but suggest some modifications to, prior theory of ADHD temperament variation that inspired this work,66,67 while being mostly consistent with and building on previous work68 exploring temperament subgroups in ADHD in a different sample. Although the subgroups found in the present study were largely stable over time, future work will need to address issues related to family history, genetics, replicability in other samples, and treatment response.57,58

In addition, despite well-described limitations of parent-report measures,69 the results that we have reported suggest that parent-reported temperament characteristics (at least as measured in the present study) may be related to important individual differences in underlying physiology, suggesting some validity and clinical applicability for these measures. Temperament traits have been investigated70 in many other disorders, and further exploration of temperament types in other DSM-defined disorders may be informative for understanding shared and unique risk profiles and revising psychiatric nosologic criteria. Similarly, detailed comparison and integration of results obtained using alternative clustering algorithms or based on different input features will be important.

Conclusions

Overall, progress toward neurobiologically based nosologic criteria, as envisioned in the National Institute of Mental Health RDoC Initiative,2 is tractable. In the illustration provided in the present study, temperament profiles in children with ADHD can be related to meaningful differences in both the central and peripheral nervous systems and the longitudinal course, setting the stage for improving nosology.

REFERENCES


