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Toward a Revised Nosology for ADHD Heterogeneity

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Abstract

ADHD is among the many syndromes in the psychiatric nosology for which etiological signal and clinical prediction are weak. Reducing phenotypic and mechanistic heterogeneity should be useful to arrive at stronger etiological and clinical prediction signals. We highlight key conceptual and methodological issues, highlighting the role of dimensional features aligned with RDoC and cognitive, personality, and temperament theory as well as neurobiology. We describe several avenues of work in this area, utilizing different statistical, computational, and machine learning approaches to resolve heterogeneity in ADHD. We offer methodological and conceptual recommendations. Methodologically, we propose that an integrated approach utilizing theory and advanced computational logic to address targeted questions, with consideration of developmental context, can render the heterogeneity problem tractable for ADHD. Conceptually, we conclude that the field is on the cusp of justifying an emotionally dysregulated sub-profile in ADHD that may be useful for clinical prediction and treatment testing. Cognitive profiles, while more nascent, may be useful for clinical prediction and treatment assignment in different ways depending on developmental stage. Targeting these psychological profiles for neurobiological and etiological study to capture different pathophysiological routes remains a near-term opportunity. Subtypes are likely to be multifactorial, cut across multiple dimensions, and be dependent for their ultimate selection on the research or clinical outcomes of interest. In this context parallel profiles based on cognition, emotion, and specific neural signatures appear to be on the horizon, each with

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somewhat different utilities. Efforts to integrate such cross-cutting profiles within a conceptual dysregulation framework are well underway.

Keywords

ADHD; heterogeneity; subtypes; Emotion; cognition; machine learning

Introduction

ADHD exhibits complex yet clinically relevant and unresolved heterogeneity (1, 2). It ranges widely in severity with the mild end almost indistinguishable from typical childhood behavior. Comorbidity is common, outcomes and treatment response are hard to predict, and etiological studies suggest multiple routes to the disorder. ADHD has no universal biological correlate. Because outcomes are unpredictable and often severe, understanding different profiles and pathways to account for outcomes and mechanisms is urgently important. ADHD thus exemplifies many of the issues about within-syndrome heterogeneity that challenge etiological research in the DSM at large (3). Heterogeneity requires better resolution for identifying stronger mechanistic signals (4). We recap critical conceptual contexts then selectively review avenues of potential progress in ADHD.

Conceptual background

The DSM is reflects a deep tradition, but is not the only psychopathology framework available. A long-standing empirical tradition in child psychopathology seeks data-driven, empirical solutions to organize psychopathology via consideration of behavioral or problem *dimensions*. This body of work, over hundreds of studies, began to be developed well before the DSM-III was published in 1980 (5). That tradition identifies two correlated domains of psychopathology (externalizing and internalizing). Structured hierarchically under these domains are less than a dozen non-orthogonal problem dimensions (6). These can be utilized to form an array of profile solutions corresponding to clinical phenomenon of interest (e.g., dysregulation (7)), although the feature set will be primarily descriptive and likely insufficient for questions related to processes or mechanisms. Whereas it is encouraging that the empirical dimensions map to a certain extent onto the DSM, results are not isomorphic with regard to heterogeneity. For example, ADHD is a single dimension in some dimensional psychopathology models, but is bi-dimensional (based on factor analytic studies) in DSM. Hybrid dimensional and categorical models of the nosology, such as the HiTop proposal, (8) are now gaining traction. These typically classified ADHD, or at least hyperactivity-impulsivity, under behavior or impulse disorders due to its strong correlation with oppositional, conduct, and aggressive behaviors (inattention sometimes “loads” equally with mood or anxiety conditions). Yet often overlooked in large multi-disorder correlational studies are ADHD’s equally compelling correlations with neurodevelopmental problems such as learning disabilities, intellectual development, motor development, and autism spectrum disorder. These are influential in developmental theory of ADHD (9). Thus, consideration both of this empirical tradition and of a developmental perspective are advisable for capturing ADHD heterogeneity (10).

Second, other approaches beyond the "clinical problem" domain are important to recall. For over a century, psychologists have sought to link personality and temperament traits "inward" to biology and "outward" to psychopathology. Online Supplement part E provides background on that tradition and an explanation of personality and temperament traits (for review see (11)). Higher order traits are similar in children and adults. For example, the classic three-to-five higher order traits in adult personality include *extraversion/surgency*, *neuroticism*, and *conscientiousness/constraint* (12). One child temperament model (13) highlights (a) *surgency* with sub-features of activity level and positive-affect, similar to *extraversion*; (b) *negative affectivity*, meaning prone to fearfulness, worry, and anger, similar to *neuroticism*; and (c) *effortful control*, the ability to over-ride an immediate impulse, similar to *conscientiousness* or *constraint*. Personality traits in adults are, of course, more elaborated and differentiated than in children. Progression of traits and their integration from infant-to-toddler-to-child-to-adolescent-to-adult remains a critical area for developmental science (13) and for ADHD. However, this developmental understanding is increasingly promising, bolstered by updated theories about neurobiology (14) (for more background, see (11, 13, 15, 16) and Online Supplement Part E). Psychopathology is hypothesized to relate to particular trait configurations (11, 13).

A modern incarnation of this logic is the RDoC proposal from NIMH (17, 18). It does not directly address heterogeneity or the idea of multiple mechanisms in an existing disorder. However, its logic can facilitate work in this area just as the personality-temperament traditions have done. RDoC proposes to link dimensions of psychological functioning such as negative emotional valence, working memory, and other transdiagnostic features, with neurobiological systems, and then to psychopathology, to advance knowledge about psychopathology. It thus equally elevates psychological and neural phenomena, and highlights dimensional measures.

RDoC, trait theory, and dimensional measures of psychopathology all offer a critically useful perspective that warrants integration to solve the heterogeneity problem in ADHD. Yet the challenges cannot be overlooked: (a) Dimensions require conversion into decision algorithms or cut points for clinical decision making; this is tractable if we retain clarity about goals (e.g., clinical versus biological discovery). (b) The structure of relations among the dimensions is missed in studying a single dimension (as RDoC can lead to), sacrificing potentially essential information about trait combinations in clinical syndromes. Configural trait models can address this. (c) A one-to-one correspondence of neurobiological or psychological function to psychopathology is unlikely (15, 19, 20).

Third, it is crucial to recognize the importance of integrating data driven and conceptual efforts and assumptions. Alone, mathematical methods cannot "reveal" nature's true categorical structure in a multidimensional space (21, 22). Nearly unlimited ways are available to divide a multivariate sample. Assumptions, beliefs, theory, and goals are necessary in order to choose how to do so and to interpret results. See Online Supplement Part A and Part B and Figures S1 and S2 for more explanation, including the role of sample size. In short, if we fail to recognize the critical role of our beliefs, assumptions, and goals, we may be misled by a given data "solution" or may misapply our conclusions to clinical situations or populations for which they are inappropriate. Therefore, we highlight the value

of an integrated approach to data-driven studies in which conceptual models, assumptions, and goals are explicitly (rather than implicitly) combined with data-driven approaches. This logic is summarized in Figure 1 (also see Online Supplement Part B).

This review highlights approaches using measures of the child's psychology and neurobiology (e.g., cognition, emotion, brain imaging). Space does not permit consideration of equally important literatures on environmental/contextual variation, genetic variation, pharmacogenomics, and G × E interaction (23–27) in ADHD (for additional review see (28, 29)).

ADHD heterogeneity using DSM ADHD symptoms

The DSM provides three well known subtypes/presentations. An older conceptual or clinical idea is that there is a sub-population associated with ADHD that is inattentive (and maybe impulsive) but *hypo*active. Introduced in DSM-III (APA, 1980), and formalized in DSM-IV, the concept has now shifted more heavily to the concept of sluggish-cognitive tempo (30)—which may represent a group only partially overlapping with ADHD.

A substantial literature has sought to improve on the DSM presentations via revised clustering of the 18 DSM symptoms—typically using latent class/profile analysis (a type of maximum likelihood analysis). This approach identifies classes of ADHD roughly corresponding to DSM inattentive and combined presentations, but further divided by the severity within those domains (e.g., mild inattentive, severe inattentive), and these results tend to replicate reasonably well (31, 32). However, individual profiles change over development in a manner that exceeds expectations from normative behavioral change, at least when rating scales are relied on for assessment (10, 32). For example, hyperactivity normatively declines during late childhood and adolescence, suggesting that we could expect a child's ADHD presentation to develop from combined to inattentive. Yet the opposite frequently occurs as well. Overall, it is not clear that these solutions improve on existing utilization of symptom severity in regard to clinical evaluation or for mapping neurobiology (33, 34).

A potentially promising approach uses item response theory (35) or versions of a *bifactor model* to account for shared and distinct underlying dimensions within ADHD symptoms. The bifactor model is beginning to replicate, albeit with developmental variation. This model appears to improve the account of ADHD heterogeneity in relation to comorbidity and clinical prediction (36–38). (For a criticism of the bifactor approach, see (39)).

Another approach applies *network modeling* (40, 41) to interrogate symptom structure (see online Supplement Part C for explanation and contrast with bifactor model). Rather than assume a latent disorder or trait causes observed symptoms of psychopathology, it assumes that the confluence of symptoms *is* the disorder (40). In other words, symptoms lead to one another and accumulate until the syndrome is in place. A network is made up of *nodes* and *edges*. Nodes are the features of interest (e.g., symptoms of ADHD). Edges are the relations among them (e.g., correlations) (40, 41). In the case of ADHD, the network approach appears to enable further traction related to developmental change and population specificity

of syndrome structure and heterogeneity. Martel et al (42) reported that symptoms differentiated with age, but a small core set of symptoms drove the others. Somewhat similar findings were reported by Silk et al (43). This approach may help identify unique pathways to syndrome emergence via one symptom leading to another set of symptoms (44), perhaps in different ways for different subgroups. Such insights if confirmed could open avenues for more targeted intervention.

Overall, contemporary approaches to refining symptom structure are poised to bring useful improvements in characterizing ADHD heterogeneity that are relevant to clinical assessment within the DSM context. They have not been much used to relate symptoms to cognitive, affective, or neural mechanisms, but this work is on the horizon.

ADHD heterogeneity via broader dimensional feature set: cognition and temperament

Even more promising may be approaches using neurobiologically and psychometrically informed dimensional measures of psychological or biological functioning. This approach relates to RDoC, goes outside of the DSM symptom lists, and can emphasize cognitive or emotional domains as well as neurobiological measures.

Cognitive heterogeneity in ADHD.

A key set of conceptual proposals for ADHD mechanism has involved neuropsychological or cognitive differentiation within ADHD, via different kinds of attentional breakdowns. This approach dates back half a century. It has included a long-standing interest in frontal lobe-related executive functions, reward or reinforcement, and arousal systems (45, 46). Barkley (46–48) sought to integrate multiple neuropsychological and cognitive domains related to ADHD, emphasizing response inhibition and temporal information processing. In the 1980s and 1990s, Sergeant, van der Meere, and colleagues advocated an energetic state perspective in which *arousal* or else *activation* is a key moderator of performance (49–51). Long standing ideas about reinforcement or reward-based mechanisms in ADHD have remained of interest (52–56), motivated by sophisticated neurobiological theories (57–60) and treatment utility (61). Sonuga Barke (62) introduced the idea of a dual-pathway to ADHD that might integrate different accounts. Multi-pathway approaches have been further articulated to attempt to integrate the picture, building on the idea that only some children have a problem with a given function (such as executive functioning) while others have a different dysfunction. Table 1 summarizes many of these ideas.

We attempted to evaluate these ideas by integrating theory and method (Figure 1) (63). We administered a broad range of measures of executive function, arousal, reaction time, and other functions selected to reflect commonly studied domains in ADHD. After this conceptual feature selection, we turned to a data-driven approach. We introduced the use of a clustering method from graph theory called community detection (64) (see Online Supplement, Part D for explanation) to identify profiles in ADHD (63). Internal validation provided strong evidence of >0 clusters or profiles. The resulting profiles suggested a subgroup with top-down or executive function problems (65), as well as an additional

subgroup with bottom up (e.g., signal detection response) weakness (66). Notably, similar profiles were seen in both ADHD and typically developing populations (63). Such nested context may be necessary to isolate deficits specific to ADHD. This work partially reproduced in an independent sample (67). That effort yielded a result consistent with the same principles: more than 0 but fewer than 5 profiles justified by internal validation, and distinctions along conceptually top-down versus bottom-up functions. However, the specific profiles differed.

Vaidya and colleagues (68) examined executive functions as assessed via rating scales in children with ADHD, autism, and typically developing controls. First, they used community detection to propose profiles and applied a support-vector-machine algorithm to predict group membership in a confirmation sample. Then, they sought biological validation with task-based functional MRI in a subset of the youth. Although the measurement method was quite different (ratings versus laboratory tests), results provided again support multiple cognitive profiles in ADHD (also see (62, 66, 69–71)). That study illustrates the potential and importance in combining discovery and validation and the potential for clinical prediction.

Longitudinal studies evaluating whether cognitive development modulates ADHD outcome are emerging as another view of heterogeneity. For example, a cohort of preschoolers with hyperactivity followed by Halperin and colleagues yielded several contributions. In one finding (72) of 214 preschoolers followed over time, ADHD childhood status varied in relation to whether hyperactive preschoolers were impaired focally in neuropsychological measures of attention/executive function or globally in a range of neuropsychological abilities. In a related finding (73), cognitive control was related to inattention symptoms, but stimulus-driven processes related to hyperactivity over time. In an older sample from childhood into early adolescence followed by our group (74), working memory change was associated with symptom recovery over time, while response inhibition and reward processing changes were not. (But see (75) for a discrepant set of findings).

Overall, these various findings illustrate that adding neurobiologically informed measures of cognition can generate novel insights into heterogeneity. Findings are broadly but not specifically reproducible, in that studies consistently find useful cognitive sub-profiles in ADHD but not necessarily the same sub-profiles across studies. They also confirm clinical observation for an initial argument of at least one executive dysfunction subgroup in ADHD (65). Several interpretive challenges remain, however, regarding generalizability, reproducibility, and specific feature selection and external validation relevant to a given goal (for more discussion see (76).

Further progress may be possible using computational decompositions of cognitive performance. For example, we have used signal detection theory and diffusion models to isolate cognitive processes related to ascending noradrenergic systems (77, 78). The results, combined with use of latent variable modeling to increase measurement reliability, have helped clarify and amplify the locus of genetic effects in ADHD via cognition— i.e., polygenic effects on ADHD proceed via working memory and arousal, but not other cognitive functions (79). In another study, these computational phenotypes helped isolate

shared and unique cognitive features for the disorders that inform neurobiological study (80).

Emotional and trait heterogeneity in ADHD.

Another long-standing conceptual focus concerns emotional and/or anger dysregulation as an important feature and source of heterogeneity in ADHD (81). This relates to a proposal by Barkley and colleagues (82) and others, and a related proposal using a different conceptual framework by Nigg and colleagues (11, 83) and others that ADHD reflects variation in etiological pathways across temperament or emotion regulation systems (see below). Several groups have worked on ADHD in relation to temperament. For example, Halperin and colleagues (84) have effectively pursued the hypothesis that negative emotionality and anger dysregulation influences development of ADHD via disruption of executive functioning, from preschool into the early school years. In a 9 year prospective sample, Miller and colleagues reported links between infant temperament and childhood ADHD that were moderated by sex and parenting style, suggesting subtyping via contextual moderation and temperament (85, 86). Auerbach and colleagues have also linked early temperament to subsequent ADHD with potential contextual and genetic moderation (87, 88). Sullivan and colleagues also noted potential early markers of ADHD risk (89).

Formal mathematical efforts to discover emotion-related sub-profiles were slower to emerge, however. Therefore, drawing upon related developmental theory about ADHD (83, 87) we evaluated trait ratings (online Supplement Part E). We stress that using trait ratings is only one approach to the much broader domain of emotion regulation (see (90)). In initial, relatively constrained linear models, traits were strongly correlated with ADHD but not isomorphic with it, suggesting traits brought new, useful information (91, 92).

Subsequently, we applied the Rothbart et al. perspective (13) (Online Supplement Part E) to feature selection. We identified three reproducible profiles in ADHD samples (which did not appear in a non-ADHD sample) (a) normative temperament ratings (and by implication, normative emotional regulation), (b) high surgency, extraversion, or sensation seeking, (c) high anger and other negative affect (93–98). (See Online Supplement Part #E for details of the measure and profiles). These profiles converge with the developmental proposal by Nigg and colleagues (83).The identification of a group with high negative affect converges with growing evidence of the importance of irritability and emotional lability in ADHD (99–101). Figure 2 illustrates that these profiles were quite stable over a 1 year period and moderately stable over two years; they were somewhat more stable than DSM profiles that rely on ratings data. Figure 3 illustrates these groups' proportional breakdown in relation to corresponding DSM-5 profiles, showing that these are not isomorphic but that traits introduce new information.

External validation with regard to both biological signal and clinical outcome was supportive. The emotionally dysregulated groups had higher genetic loadings for ADHD liability (102), distinct EEG profiles in (103), and in preliminary evidence distinct functional connectivity on MRI. Most important for our purposes, reasonably consistent evidence indicates that these profiles predict clinical outcomes over a 1–3 year period better than symptom severity, baseline comorbidity, impairment, ADHD subtypes, or ADHD symptom

profiles and that they predict over and above other clinical information (93–95, 98). Children in the irritable profile were more than twice as likely as other groups to have onset of additional psychiatric disorder one year later.

Thus, approaches using emotion and temperament appear poised to converge on a useful reframing of heterogeneity that may relate to developmental outcome as well as particular aspects of neurobiology.

Starting with neurobiological dimensions instead of behavior to address ADHD

Until this point, we highlighted use of an expanded feature of either cognition or ratings of temperament to characterize heterogeneity in ADHD, in low-dimensional data sets. A further set of RDoC-compatible dimensions arise from direct measures of neurobiology that have strong empirical or theoretical links to psychological, mental, or behavioral constructs (but see (20) for cautions).

EEG subtypes within ADHD.

Within ADHD, electroencephalogram (EEG) features have received longstanding attention, mostly on frequency patterns in the resting state EEG. Early studies converged on two ADHD profiles characterized by relatively greater frontal activity in (a) slow (particularly theta) versus fast (particularly beta) frequency bands, interpreted as reflecting cortical *under*-arousal (104), and (b) a small but consistent group with relatively high beta activity initially interpreted as a cortical *hyper*-arousal profile (105). Although intriguing, this proposal lacked a theoretical interpretation, after the arousal-based interpretation of these frequency patterns was challenged, and clinical or concurrent validation was lacking (106).

In the largest and most carefully done EEG heterogeneity study of ADHD to date, Loo et al. (107) addressed clinical validation empirically in children with ADHD (n=620) and without ADHD (n=121). They identified five distinct EEG sub-profiles each with an elevation in one of the traditionally measured EEG frequency bands (e.g., high delta, high theta, etc.). Children with and without ADHD were distributed across all five profiles, raising again the possibility of nested variation similar to some cognitive profiling studies, including ours (108–112). The EEG-based groups differed in age, mandating more examination of developmental trends and potential population admixture. Profiles appeared psychologically meaningful: a group with elevations at lower frequency bands exhibited cognitive impairment, whereas those with elevations in higher frequencies (alpha, beta) exhibited emotional dysregulation. Loo et al.'s findings may converge with our own recent work suggesting EEG-measured alpha power distinguishes subgroups with ADHD with varying degree of negative emotionality (103).

Overall, EEG-based profiles hold promise, but the literature to date underscores both (a) the interpretive challenges associated with lack of strong theory, and (b) the utility of identifying the goal, such as clinical validation. Feature selection has also been limited; whether use of more high-dimensional EEG input features will be productive remains untested.

MRI subtypes within ADHD.

In a major review in 2012, Willcutt et al (10) noted that at that time there were minimal contemporary MRI studies of the ADHD DSM profiles. Now, several studies have attacked this *classification* problem, productively using machine learning methods (109, 113–116). More work in this area will be useful evaluating alternative sub-profiling schemes (see recent discussion in (29)). We focus here, however, on the *clustering* problem--on efforts to discover new and more informative neurobiological 'types' of ADHD. Recent reviews have highlighted the diversity of brain imaging findings associated with ADHD (117), underscoring the need for clarification of heterogeneity.

Efforts at an integrated conception have considered variation in the involvement of parallel frontal-subcortical-thalamic loops (118, 119), or the relative importance of top-down or bottom-up signaling (120). While many of these ideas are focused on function, heterogeneity can be adjudicated via studies of brain structure as well. For example, variation in rate of development of cortical thickness may be important to ADHD outcome (15, 121–123). Consideration of widespread intrinsic functional networks allows for hypotheses related to differential disruption or cross talk among these networks (124). Although it is early days in this area for ADHD, several groups have worked in this direction in recent years with initial encouraging results (125). However, outcomes depend on levels of analysis and feature set.

For example, we (126) identified ADHD sub-populations based on a targeted analysis of variation in nucleus accumbens activity (NA). NA resting state functional connectivity corresponded to reward processing deficits--but only in a discrete subset of participants with ADHD. This finding helps amplifying the search for mechanisms in that subgroup. However, how these participants clustered using this feature set is very specific and does not take into account the rest of the brain's organization. An overall picture of heterogeneity requires pairing this solution with alternatives using a different classification logic.

Therefore, we identified and validated a different set of sub-groups based on specified individual network phenomenon utilizing a novel clustering method called *GIMME* (127). Here, we classified individuals with ADHD into groups with distinct network phenomenon based on higher order brain systems (e.g., fronto-parietal, cingulo-opercular). We validated these findings via simulation. We expect this finding to be useful in searches for mechanistic linkage to neurodevelopmental, genetic, or environmental influences.

These latter two findings taken together underscore that *there exists more than one valid solution depending on the approach and features used*. There is simply more than one "right" answer. The importance of a given *valid* division depends on the question or outcome of interest (e.g., diagnosis, prognosis, treatment outcome, biological signal, etiology, etc.). (See online supplement Part B and Figures S1, S2 for details of possible methodological solutions such as the functional random forest (128)).

In short, the literature specific to characterizing heterogeneity in ADHD based on MRI is maturing at a rapid pace. What is clear is that unique patterns in brain physiology exist in individuals with ADHD. The task now is determine their best use, identify the best

formulation for a given goal, and to maximize this information to improve long term outcomes.

Conceptual Contexts Revisited

Dysregulation as an organizing framework for many findings.

The various psychological mechanisms involved in ADHD and the theories put forward about them can be schematized within a model of self-regulation (15). One widely used conceptual framework in this vein is the triarchic model, depicted in the Online Supplement (Part F, Figure S5). (Such models require partially collapsing the artificial distinction between cognition and emotion). If ADHD broadly captures a population of individuals with varying kinds of dysregulatory problems (and risk for serious dysregulation-related complications), such an integrated conception helps organize where the most tractable paths for differentiation may lie for a given goal. Considering this model and the findings highlighted herein, we can postulate:

- **a.** The clinical features that comprises the ADHD syndrome for a given individual manifest through *a subset* of particular breakdowns within self-regulation;
- **b.** The specific breakdowns vary between groups individuals, and
- **c.** Differentiating these may enable identification of neurobiological correlates and prediction of different clinical pathways within the ADHD population.

While different solutions will be useful in different ways, we highlight two exemplar applications of the general self-regulation model based on this review.

Cognitive profiles as useful in different ways at different developmental stages.

It appears that appropriate feature selection and validation may differentiate ADHD sub-groups characterized by (a) disruption of relatively late-stage “top down” cognitive operations (working memory) versus (b) relatively early-stage “bottom up” operations (reward temporal discounting, arousal state). Such cognitive profiles need more work, and may not map on to the temperament profiles. With regard to utility, the identification of a subgroup of youth with ADHD characterized by executive dysfunction may suggest interventions related to that weakness—adapted to developmental stage. For example, a body of work has argued that preschool intervention to help children with weak executive functioning may enhance academic outcome (129, 130). Such intervention may also secondarily support emotion regulation. In adolescence, variation in trajectory of working memory development may inform clinical persistence or desistence (131). Additionally, a subgroup with a low arousal profile may require a different approach (or may be particularly responsive to a particular medication class). These hypotheses could be tested.

Temperament profiles as useful for clinical prediction in childhood.

Support is quite promising for evaluating emotionally dysregulated ADHD sub-profiles, at least in pre-adolescent children. These profiles, varying in positive or negative valence dysregulation but possibly anchored by anger-dysregulation are promising with regard to (a) accessing developmental science of temperament, (b) detecting a stronger biological signal,

and (c) enhancing clinical prediction. Such an approach thus warrants consideration in the nosology. However, this perspective also has limitations. It may not detect distinct etiological signals, or it may only be useful for predicting some clinical outcomes and not others. Developmental stage may be particularly important. The temperament profiles may be most useful in outlining early developmental sequences and childhood functioning and outcome. Figure 4 illustrates a set of hypotheses for follow up study.

A developmental story may be possible.

We can speculatively propose the following in regard to possible developmental and clinical heterogeneity. In early life, ADHD can emerge through breakdowns in the regulation of approach signaling (Surgent/exuberant) or negative emotion regulation (irritability, anger, negative affectivity). These profiles may be modulated by a recursive process in early life by which extreme negative emotionality disrupts top down control and this in turn leads to further emotional dysregulation. When compensatory mechanisms are insufficient, such processes emanate in emergence of ADHD in an emotionally dysregulated profile or profiles (14, 74, 78, 83, 131–133). In adolescence, distinct cognitive profiles re-emerge that both reflect continuation or potential recovery of ADHD with or without an emotional dysregulation profile (74, 78, 131). Further empirical integration remains a priority.

Next Steps and Conclusion

Next Steps.

Key next steps are several. In the context of the current review, we suggest five of the most central questions, taking into account the *purpose* of a given heterogeneity proposal or clustering solution.

1. In neurobiological work (e.g., EEG, MRI, physiology), what is the most useful level of analysis for identifying clinically-actionable predictors or mechanisms that differentiate children for particular clinical or other goals? Here network cross-talk, functional versus structural features, degree of data reduction, and other considerations require specification in regard to utility or other goal.
2. In psychological work, do working memory (in the control domain) and arousal (in the energetic state domain) capture distinct features of heterogeneity related to clinical prediction or are they overlapping?
3. Relatedly, do these psychological profiles serve as useful targets for neurobiological study, enhancing understanding of pathways mechanistically?
4. Are temperament, cognitive, or neural profiles useful in detecting differential etiological sources, particularly those that may be modifiable?
5. Are temperament, cognitive, or neural subtypes useful in determining specific differential treatment response? We proposed hypotheses for both temperament and cognitive profiles. EEG or functional MRI profiles could be targetable by refined neurofeedback approaches or transcranial neural stimulation technologies.

Conclusion.

Resolving heterogeneity in ADHD requires at least three considerations. First, identifying the goals and using theory to explicitly guide analytic decision making is essential to the many valid solutions in complex multifactorial space. Second, ADHD-related cognitive and emotional features should be considered in both (a) incentive context (positive and negative valence) and (b) developmental context. Third, and crucially, work in this area still has relatively rarely considered psychosocial variations that may modulate subtypes, such as social adversity (134, 135).

These considerations, in conjunction with theory and dimensional feature sets outside of the DSM symptom list, can make the problem of heterogeneity tractable. It can lead to improvements in clinical characterization and detection of neurobiology. It therefore begins to be possible to foresee integrating an RDoC framework with developmental theory and with DSM syndromes to work toward a functional or mechanistic nosology.

We offer a cautionary yet optimistic concluding note. Most ADHD subtyping work to date has addressed relatively small data sets varying in their depth of clinical characterization. It has not engaged large data sets very often. Sample size is an important concern with regard to appropriate model selection, reproducibility, and sufficient representation of full population variation to isolate heterogeneity. Larger samples are now increasingly available —for example, the Adolescent Brain Cognitive Development (ABCD) study of over 11,000 children over a 10 year period (136–139). While ABCD and other data sets like it cannot avoid some lack of depth in ADHD sub-phenotyping, they can be very helpful in identifying heterogeneity in clinical change and in brain and other neurobiological profile. Findings from such large data sets then can be ‘yoked’ with smaller, but more deeply phenotyped samples to address various issues in discovery and validation.

Overall, the future is bright. The problem of creating a neurobiologically and clinically superior nosology to reduce ADHD heterogeneity is becoming tractable. We are hopeful that a better clinical characterization and the corresponding neurophysiology of ADHD is coming on to the horizon and will facilitate clinical prediction and etiological mapping efforts. We anticipate parallel efforts across the nosology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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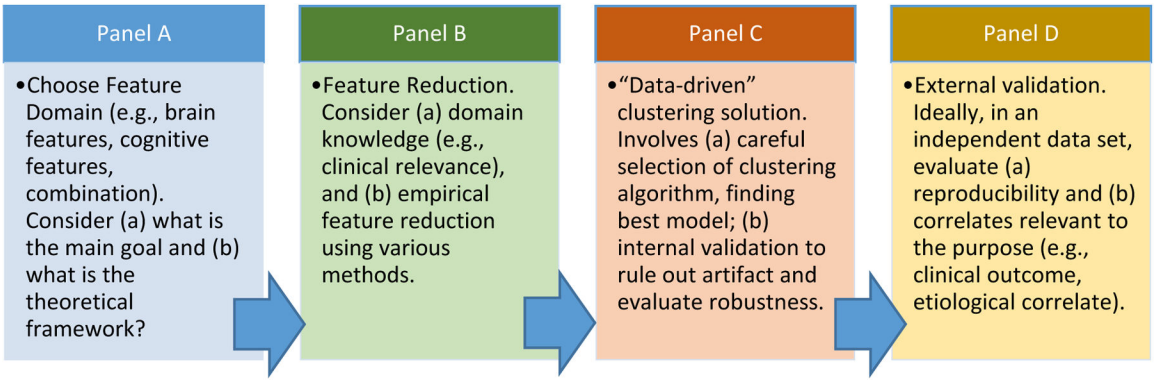

Figure 1: Recommended Workflow for examining heterogeneity in ADHD and similar conditions

Schematic or conceptual workflow guiding our view of how data-driven and machine learning approaches are best utilized in psychopathology research. The problem of heterogeneity appears tractable using approaches that include (a) careful feature selection based on both theoretical and empirical considerations, (b) exploration and novel discovery that targets specific questions of interest, followed by (c) internal or statistical validation (various robustness indexes, simulation studies), and (d) external validation in independent datasets. For example, external validation might include further exploration of clinical utility (e.g., predictive accuracy differential) or enhanced etiological signal. Because the research space is multi-level (one can study physiology, psychology, behavior) and multi-dimensional, and because the intended purpose can vary (clinical prediction, discovery of etiology, etc.), different clustering solutions will be valid and correct in different research contexts. The role of conceptual purpose, theory, and assumptions about the nature of the phenomenon should be explicit. Then, feature domain can be chosen. Feature reduction can then proceed with the end goal in mind, as in the functional random forest (128) described in the Online Supplement (part B). Then, the clustering solution can be explored using unsupervised (discovery-based) approaches. Internal and external validation then follow. Internal validation evaluates the likelihood of artifact in the data, and external validation evaluates the usefulness of the solution. Different solutions can be pitted against one another competitively to determine which is most useful for a goal. The approach can assume a non-zero number of groups within statistical and machine-learning contexts, with a specific, hypothesis driven, targeted set of features (21). Doing so strengthens feature selection, goal identification, and interpretation of solutions to answer targeted questions.

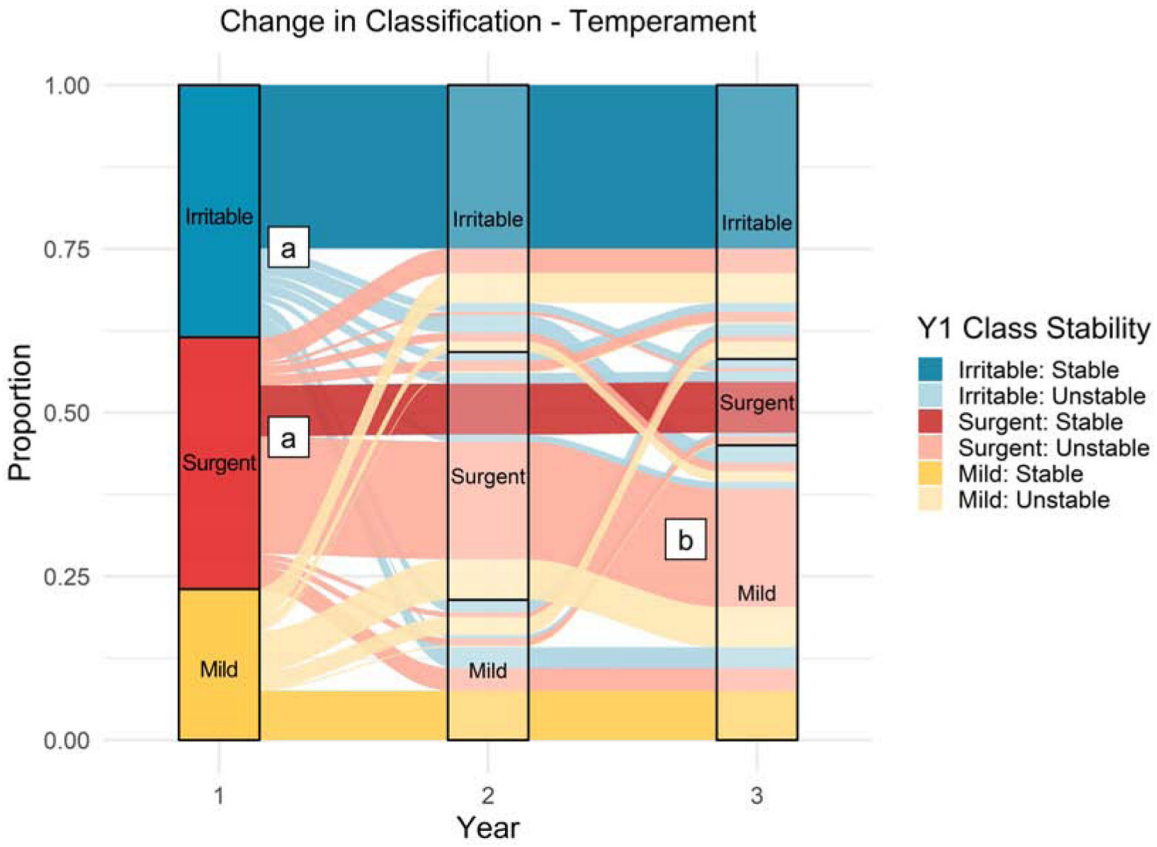

Figure 2: Alluvial plot illustrating stability of temperament heterogeneity in ADHD.

This plot represents just under 400 children with ADHD at 3 times points (see (93, 94)). Time point 1 ages are 7–11, time point 2 are 8–12, and time point 3 are 9–13. The plot illustrates the proportion of children in each initial profile (by different colors), and then where they go at the next time point (by shading of the colors). Tracing the flows, the chart shows several points. (a) The Irritable and Surgent profile are highly stable over a 1 year follow (note the dark and light blue and the dark and light red from year 1 to year 2). However, (b) over a 2 year period, many of the Surgent profile convert to a mild profile, and a subgroup of the irritable, while remaining dysregulated, convert to a Surgent profile. The mild profile can become Surgent (usually, only temporarily, as show in the pale yellow path from mild to Surgent to mild) or Irritable (and then remain there, note steep pale yellow path up to and remaining at irritable). To summarize, only a small fraction of Irritable children transition to the emotionally-regulated group. In addition, once a child transitions to the Irritable group from Mild or Surgent, they often remain there at least in this age range. In contrast, the Surgent and mild groups are less stable, with significant transitions between these two groups across years, as well as some transitions into the Irritable group. We hypothesize that anger dysregulation may inform impairment in both dysregulated profiles.

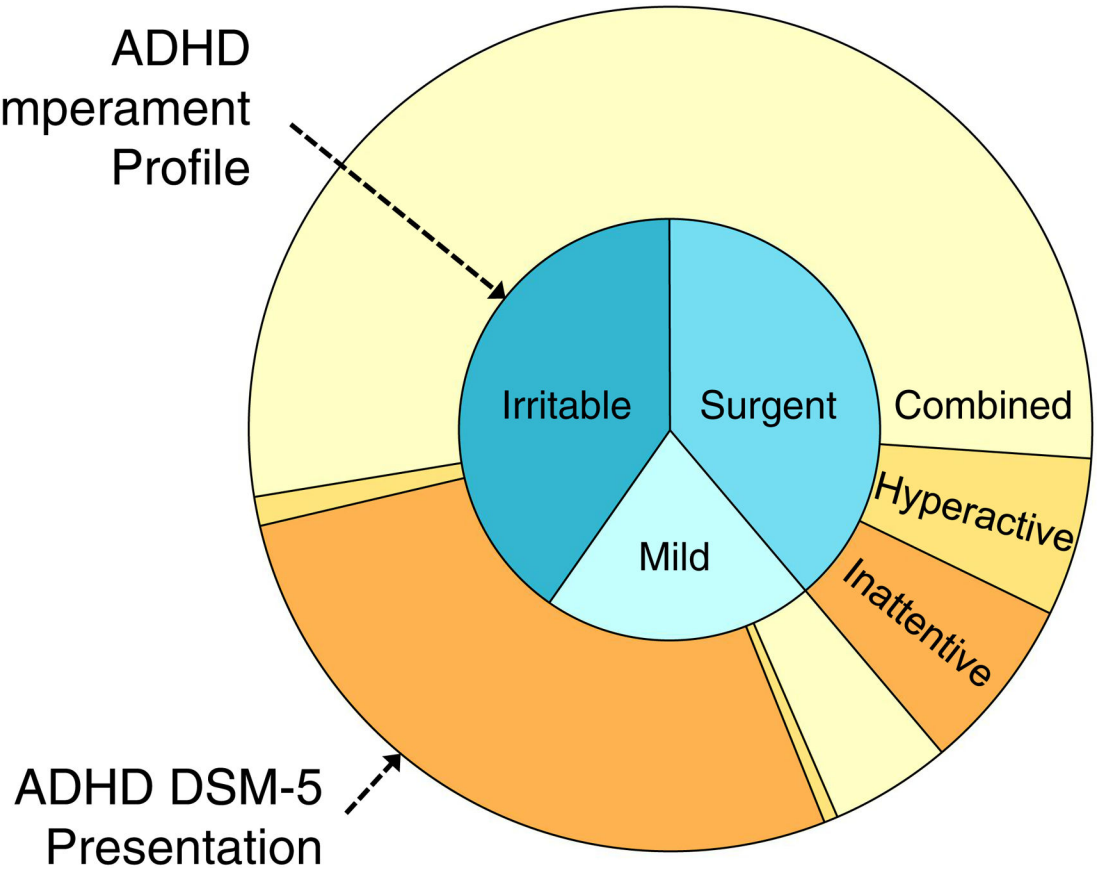

Figure 3: DSM-5 presentations and proposed emotion regulation profiles are not the same.
Sunburst plot showing the relation among DSM baseline presentations and temperament-based baseline profiles. The inner (blue) ring shows the proportion of children in the ADHD sample in each temperament profile at baseline (ages 7–11). The outer (yellow) ring shows for the same children their DSM-5 assigned clinical profile at the same point in time. The mapping thus shows that the ADHD-combined type (pale yellow) is evenly divided between Surgent and Irritable profiles, but that all are in a dysregulated group. The Inattentive DSM profile (gold) is divided between irritable, Surgent, and mild profiles, exemplifying heterogeneity. The small number of hyperactive profile children are exclusively in the mild profile of temperament, underscoring the likelihood that this group may less severe of a group than the combined type with which it is often associated. Data from (93).

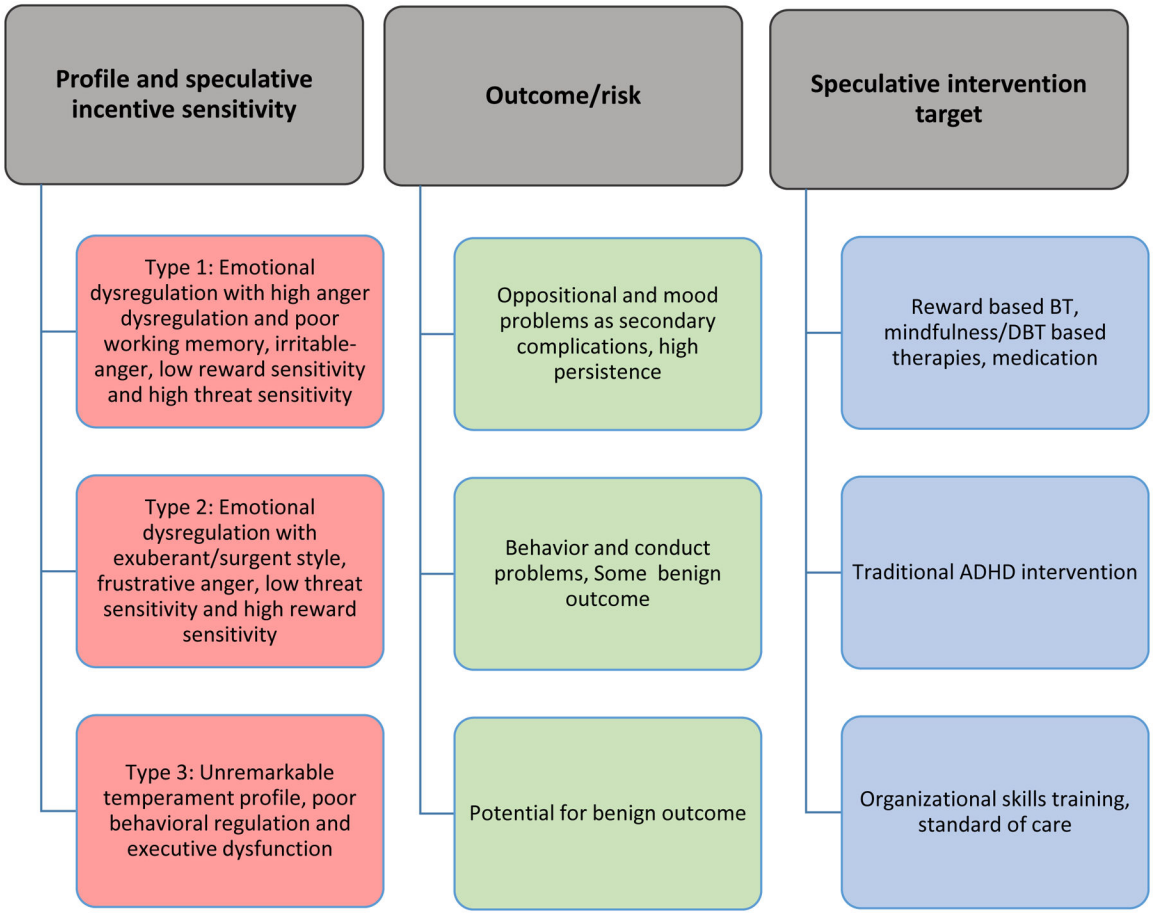

Figure 4:
Potential ADHD heterogeneity related to clinical outcome and treatment

Table 1:
A selection of proposals for addressing ADHD mechanistic heterogeneity.

The table includes illustrative conceptual and empirical citations for reference. As it shows, the proposals though many, fall into a few basic themes related to clinical symptom profiles, cognition/executive function, motivation/reward function, emotional regulation/temperament, and neurobiological proposals involving clues from MRI, EEG, and other methods. Cognitive proposals are the most numerous, emphasizing functions such as working memory, processing speed, inhibition, timing, reward discounting, and delay aversion. Etiological proposals are numerous; one is included one here as an exemplar.

Perspective	General proposal for heterogeneity	Example papers
Clinical	Sluggish cognitive tempo	(30, 140–142)
Clinical	Non-hyperactive/hypoactive	DSM-III
Clinical	Predominantly hyp, inat, comb	DSM-IV
Neurobiological-cognition	Executive dysfunction subtype	(65)
Neurobiological-cognition	inhibition, working memory, time processing	(69, 143)
Neurobiological-cognition	EF, time processing	(69, 70, 143)
Neurobiological-motivation	EF vs delay aversion	(62, 71)
Neurobiological-motivation	EF, Reward response/discounting	(59, 60, 66, 144)
Emotion-regulation/temperament	Callous-unemotional	(145)
Emotion-regulation/temperament	Emotional dysregulation	(82, 146)
Emotion-regulation/temperament	Irritability	(81, 94)
Emotion-regulation/temperament	Surgent, Negative affect, cog control	(83)
Neurobiology	Differential cortical-subcortical engagement	(69, 143)
Neurobiology	Differential rates of neurodevelopment	(131)
Etiological	Perinatal exposure vs genetic or GxE	(147)