Integrative neuroscience approach to predict ADHD stimulant response

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Despite high rates of prescription, little is known about the long-term consequences of stimulant medication therapy for attention-deficit hyperactivity disorder (ADHD) sufferers. Historically, the clinical use of stimulants for ADHD has been based on trial and error before optimal therapy is reached. Concurrently, scientific research on the mechanism of action of stimulants has influenced neurobiological models of ADHD, but has not always informed their prescription. Whilst the two main stimulant types (methylphenidate and dexamphetamine) have numerous similarities, they also differ (slightly) in mechanism and possibly individual response. A further issue relates to differences in cost and availability compounded by the expectation for stimulants to be effective in ameliorating a broad spectrum of ADHD-related symptoms. Thus, there is an increasing need for treating clinicians to prescribe not only the most effective drug, but also the most appropriate dose with the associated release mechanism and schedule for each ADHD patient presented. In this regard, the field is witnessing an emergence of the personalized medicine approach to ADHD, in which treatment decisions are tailored to each individual. This shift requires a new approach to research into treatment response prediction. Given the heterogeneity of ADHD, a profile of information may be required to capture the most sensitive predictors of treatment response in individuals. These profiles will also benefit from the integration of data from clinical rating scales with more direct measures of cognition and brain function. In conclusion, there is a need to establish a more robust normative framework as the baseline for treatment, as well as diagnostic decisions, and as discussed, the growth of integrated neuroscience databases will be important in this regard.

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Overview of attention-deficit hyperactivity disorder

Attention-deficit hyperactivity disorder (ADHD) is a common, developmental disorder, involving inappropriate and disruptive levels of inattention and/or hyperactivity with impulsivity. ADHD is typically identified in the younger childhood years with symptoms often persisting throughout adulthood [1]. Males are more likely to be diagnosed with ADHD. Comorbidities are frequent with ADHD diagnoses and can be broadly classified into three categories of learning, externalizing and internalizing disorders.

ADHD pathophysiology

ADHD is considered the most common neurodevelopmental or child psychiatric disorder [2–4] with severe consequences in social, vocational, academic, individual and family settings, often resulting in a financial burden [5,6]. Diagnosis of ADHD is currently founded on a classical triad of symptoms: inattention, hyperactivity and impulsivity [7], but remains extremely heterogeneous with the classical symptoms varying in severity. The American Psychiatric Association [8] stated that gross hyperactivity and excessive motor activity is typical in younger ADHD

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individuals, apparently dissipating as adolescence and adulthood is reached. It is generally accepted that hyperactivity transforms into feelings of restlessness with increasing age or experience, whereas inattention and impulsivity tend to endure [9].

Decades of research using neuropsychological, genetics, pharmacological and neuroimaging techniques have generally implicated the fronto–subcortical networks of the brain as a prime candidate for the source of the underlying dysfunction in ADHD [10]. Biederman and Spencer provide a definition of the term fronto–subcortical as a behavioral or cognitive dysfunction that appears frontal but may be influenced by subcortical projections [11]. The fronto–subcortical systems that control attention and motor behavior are rich in catecholamines, which have been implicated in ADHD via mechanism-of-action research of stimulants.

The traditional neurobiological paradigm considers that ADHD is mediated by decreased dopaminergic functioning [12]. According to Sagvolden and Sergeant, the life-long nature of ADHD is an irreversible consequence of hypofunctioning dopamine (DA) systems [13]. More broadly, the dysregulation and interplay of the catecholamines, DA and norepinerphrine (NE), is implicated in the etiology of ADHD [5,14].

ADHD prevalence

Recent US and other National estimates indicate that the prevalence of ADHD ranges from 2 to 16% of people aged 6–17 years, with some of the lowest levels seen in Britain [15–30]. These figures are beyond the potentially conservative 3–5% estimate based on the Diagnostic & Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria [31,32]. Variation in prevalence studies is primarily due to the differences between clinically referred or epidemiological samples. Differences in estimates are often due to the choice of informant, methods of sampling and data collection and the diagnostic definition [12]. Basic information about how the prevalence of ADHD varies by race/ethnicity, sex, age and socioeconomic status remains poorly described [33].

The prevalence of ADHD in adults is estimated at 2–7% [34], although there are claims that there have been no definitive epidemiological studies of adult ADHD prevalence [35]. It is assumed that 30–50% of children continue to manifest ADHD in adulthood [12,36,37]. One of the distinguishing features of adult ADHD is the increased rate of self-diagnosis [36,38]. There is a general consensus that ADHD occurs primarily in male children. In various populations, male-to-female ratios range from 9:1 to 2:1 [39–41], with the ratio of males to females being approximately 4:1 for all three subtypes of the DSM-IV [42]. Worldwide, this ratio has been found to vary dramatically, for example, 11:1 males to females in Thailand [16], compared with a UK estimate of 12:1 [30].

Stimulant treatment of ADHD

While stimulants have served as the mainstay of ADHD treatment, reviewing the literature reveals a number of important limitations. Fundamentally, there is a need for a more integrated approach to identifying sensitive markers of treatment response in ADHD (differentiated from normals), at both the group and individual level. In other words, the use of stimulant medication in ADHD will only advance when more research is directed at personalized medicine (tailoring medication to individuals). It is well known that, at the group level, individuals with ADHD generally respond well to stimulants; however, predicting who will respond in a specific way is far from clear.

Stimulant use & efficacy in ADHD

The majority of medicated ADHD individuals are treated with stimulants, with nonstimulants being the second line of treatment [43]. The efficacy of stimulant medications in ADHD treatment has provided support for models of ADHD and a possible explanation for their paradoxical effect, since hyperactivity, which is considered to be secondary to pathological hypoarousal, is alleviated by stimulants [44,45]. In ADHD, the core symptoms of hyperactivity, inattention and impulsivity have all been demonstrated to respond to treatment with stimulant medications [12]. However, there is evidence that normal children treated with stimulants also demonstrate similar improvements in behavior [46]. This is counterintuitive to notions of a unique medicinal effect on individuals with an ADHD diagnosis [47]. An exception to this is a study by Vaidya and colleagues who found that, while on stimulants, the ADHD group displayed increased subcortical activation, while the control group displayed reduced activation and both groups were found to demonstrate improved performance with increased frontal activation [48].

It has been estimated that 70–90% of ADHD patients treated with stimulant medication demonstrated a positive response [30,49,50]. However, a positive response is in terms of improving attention and behavior, which is also observed in normal children or individuals with other disorders [50]. Furthermore, despite the apparently high levels of positive response, there is a significant subset of ADHD individuals who do not respond favorably and experience negative side effects [49]. Generally, stimulants are considered safe and efficacious with a long history of use for ADHD treatment [51,52].

Using strict diagnostic criteria, it has been estimated that approximately 13% of children diagnosed with ADHD are prescribed stimulants [53,54], which is much less than estimates from community samples [55]. From another perspective, it is claimed that nine out of ten children/adolescents diagnosed with ADHD will be prescribed stimulant medication at some stage [56]. In the USA, stimulant prescriptions increased by 250% between 1990 and 1995 [56,57], with over 10 million prescriptions in 1996 alone [58]. Such an escalation in stimulant use has been attributed to numerous factors, including lengthened treatment duration; the inclusion of ADHD with comorbidities (such as learning and conduct disorders); increasingly more inattentive subtypes (possibly as a consequence of), and increased recognition of ADHD in adolescents, adults and females [59].

Research into the short-term efficacy of stimulants in treating ADHD, has been described as the largest body of treatment literature across childhood-onset psychiatric disorders [50]. There are four types of stimulants available to treat ADHD: methylphenidate, dextroamphetamine, mixed-salts amphetamine and pemoline. A detailed description of each of these stimulants is beyond the scope of this review; however, there are several comprehensive reviews of these, and other ADHD-related medications [50,60,61]. This review will primarily address methylphenidate and dextroamphetamine (and, to a lesser degree, amphetamine); however pemoline will not be covered because of paucity of research and decreased use owing to potential complications with liver function [50].

Thus, the two primary stimulant medications used to treat ADHD are methylphenidate and dextroamphetamine. There is little argument that methylphenidate is the most widely used and best studied of the stimulants. Methylphenidate has been shown to be more effective in reducing motor hyperactivity and has fewer side effects than dextroamphetamine; however, dextroamphetamine is longer lasting and typically less expensive [51,52,62]. Algorithms, entailing factors such as high efficacy, good safety record and the sheer prevalence of scientific investigation, have singled out methylphenidate as the general first-choice stimulant medication for ADHD treatment [63]. However, it is often recognized that not all individuals respond to methylphenidate or dextroamphetamine, and clinicians are required to proceed with trial and error to assess which drug is more effective (and has fewer side effects) for each individual.

Clinical practice guidelines for ADHD, with an emphasis on stimulant medication treatment, have recently been published by both the American Academy of Pediatrics [64] and the American Academy of Child and Adolescent Psychiatry [34,50]. These guidelines are clinically oriented and are designed to aid clinicians in the diagnosis and treatment of ADHD. They suggest that an individual with an ADHD diagnosis may respond (with a great level of reliability) to either methylphenidate or dextroamphetamine, and that both are efficacious in alleviating core symptoms. That is, if clinicians adhere to the recommended therapeutic ranges for each stimulant, there tends to be improvements in both behavioral and cognitive measures with increasing dose [34]. More specifically, stimulants have been shown to facilitate improvements for ADHD in a range of cognitive measures, including attention [65], working memory [66], executive functions [67] and recognition memory [68]. These improvements are typically generalized (at the group level) and exclusive, that is, since these tests are separate, improvements in one cognitive measure over and above another cannot be examined.

However, these general effects of stimulants are not without some criticisms. Sunohara and colleagues reported clinical evidence of some children becoming over focused, cognitively constricted and introverted when treated with stimulants [69]. Furthermore, because stimulants may have the effect of increasing attention and concentration in patients without ADHD, and because not all patients with ADHD improve with such therapy, the patient's response cannot be used to confirm or exclude the diagnosis of ADHD [36]. The findings that individuals without ADHD respond in similar ways, suggests that the stimulants do not target a specific neurobiological deficit in ADHD, but rather exert compensatory effects [61]. In a review of the neuropsychopharmacological mechanisms of stimulants, Solanto describes methylphenidate and dextroamphetamine as indirect catecholamine agonists that facilitate the action of both DA and NE [61]. Both are maximally effective in alleviating ADHD symptoms because of the effects they exert on both neurotransmitters, as opposed to one or the other.

Can stimulants account for the heterogeneity of ADHD?

The interaction of increased stimulant use and the heterogeneity of ADHD is driving more scientific research into the efficacy of such treatment in ADHD. What remains unclear in the field is which are the most important factors affecting the decisions to appropriately deal with each individual case. The authors propose that three of the most important factors in the treatment of ADHD, currently, are adequately determining and quantifying:

- The response to the stimulants
- The scope of individual variation
- Reliable prediction techniques of stimulant response

Clearly, these three factors affect each other and there is the need for a consensus on an appropriate determination of stimulant response, which allows for the heterogeneity of ADHD (individual symptomatology), to facilitate reliable prediction techniques. This review aims to highlight that, with developing technologies in ADHD research (such as, imaging and genetics), coupled with an increased demand on efficient treatment strategies, the natural progression of the stimulant-prediction approach is to encompass a broad range of integrated measures on the one individual. That is, an appropriate means to account for the heterogeneity of ADHD.

At the ADHD group level, it is well established that stimulant medications alleviate ADHD symptoms; however, for an individual, each of the symptoms may not normalize [34] or there may be large variations between individual responses [70,71] or symptoms may be exacerbated by stimulants [72]. Group studies may also cloud individual differences between stimulant types [73], since most studies of this kind treat all ADHD individuals with the same medication and weight adjustments [50]. Predicting an individual's response, to stimulants may be more difficult than predicting a groups response [74]. Furthermore, more immediate stimulant intervention may be less relevant to mild ADHD cases compared with severe impulsive, aggressive and noncompliant cases [34]. Individual symptomatology do not necessarily indicate which stimulant (type, dose or release mechanism) is best for a given situation [62]. Hence, there is a belief that multiple outcome measures, across settings, are essential to evaluating treatment response [34,75]. Additionally, comprehensive and regular follow-up evaluation of symptoms is important [50]. Since a clinician's initial choice of stimulant

type, dose and release mechanism is fundamentally an area of uncertainty; there are calls for more information relating optimal stimulant response to demographic and clinical information, with the overall aim to tailor treatment regimens for specific aspects of ADHD, as opposed to the whole complex [75].

Predicting stimulant response in ADHD

Predicting stimulant response in ADHD is particularly difficult without a universally accepted (gold-standard) change-with-response criteria [50]. More recently, there has been a shift to using objective measures such as the continuous performance test (CPT) [76,77], but these tests have received criticism of high levels of false-negative and -positive error [50]. Guidelines have suggested that the definition of positive response is dependent on the trade-off between target symptom improvement with the severity of side effects [34]. For Barkley, the distinction between responders and nonresponders is quite simple, those that improve versus those that remain unchanged or worsen [72]. Prediction profiling may be useful, since the pattern of results may not only guide the clinician as to which stimulant (or not) to prescribe, but could also serve to monitor the progress (or not) of the selected medication. Facilitation of optimal therapy and efficient treatment is the motive behind predicting which medication an individual will respond to.

An earlier review of the neurobiology of ADHD suggested that no neurological, physiological or psychophysiological measures are reliable predictors of stimulant response [78]. However, as efforts to consolidate reliable predictors persist, it has been argued that a thorough evaluation of the predictive power of a measurable medication response should be based on a comprehensive model, which accounts for, and integrates:

- The biological systems targeted
- Relationships between these systems and clinical outcomes
- The functional relationships among outcome measures [79]

It therefore remains conceivable that the integration of measures (objective and subjective) is the key to unraveling the complexities of predicting a response to medication in a condition as heterogeneous as ADHD.

Integrative approach to predicting treatment response

To the authors' knowledge, only two major reviews to date have considered the prediction of response to stimulants in ADHD, one dating back to 1976 (a review of 36 studies [72]) and an extension of this review, spanning 59 studies, by Gray and Kagan in 2000. Notably, the latter review lamented that, collectively, research into predicting stimulant response in ADHD is remarkably inconsistent and that case-by-case stimulant prediction is not possible, with a lack of generalization from group-study findings [74].

Barkley's review of variables employed across numerous studies to assess the effects of stimulants, particularly with respect to responders versus nonresponders set out to identify whether such measures demonstrated predictive utility [72]. Barkley discussed the impact of the following categories of predictor variables:

- Psychophysiological
- Neurological
- Familial
- Demographic/sociological
- Diagnostic category
- Subjective rating scales
- Psychological
- Profile types

The overarching conclusion of this review was that the most consistent predictors of a positive response to stimulants were measures of attention span and psychophysiological correlates of attentional processes. The remaining predictors, whilst informative, were inconsistent and collectively flawed. Barkley highlighted these relationships by referring to the profiling studies by Conners [80,81]. Conners' factor analysis of a substantial number of behavioral (rating scales), psychological, and psychophysiological measures revealed that profiles containing measures of inattentiveness and physiological correlates were the best predictors of stimulant response. These studies appear to be the earliest forms of integrated profiles (see below) for stimulant prediction.

In Gray and Kagan's review, they expanded on Barkley's work by reviewing the pertinent literature from 1976 to 1998, with refinements in their approach owing to advances in genetics, psychopharmacology and cognitive neurosciences [74]. Furthermore, they limited the review to reports only on methylphenidate and not other stimulants. Gray and Kagan build on stimulant-prediction criteria formulated by Taylor [74] of:

- Blindness and placebo control
- Reliable outcome measures
- Drug compliance
- Flexible individually defined dosage
- Prospective design to eliminate experimenter bias, by adding four other criteria
- Research-based (more conservative) diagnostic criteria
- Avoid collinear predictors of IQ
- Age and validation of predictors in new samples

Both the Barkley and Gray and Kagan reviews highlight the following shortcomings in the stimulant-prediction approach:

- Differences in ADHD classification or diagnosis across (clinical and research-oriented) studies;
- Response definition – including the constructs used to define response (e.g., responders vs nonresponders, good vs poor and variable vs consistent) and the different variables employed to gauge response.

Gray and Kagan concluded that across stimulant studies, ADHD individuals who were older, with less severe symptoms, but with comorbid anxiety were less likely to respond well [74]. Measures of inhibitory control and catecholamine metabolites demonstrated weak predictive association, other measures, such

as aggression, sex, race, body weight, socioeconomic status and IQ above 45, demonstrated little or no association with response. Gray and Kagan discussed that, since single variables demonstrated little predictive utility (with even the strongest predictors failing to replicate), multivariate approaches might be more informative and reliable. That is, since single-variable approaches are apparently exhausted, previous profiling attempts should be revisited [80,81].

Approximately 22% of the studies reviewed by Gray and Kagan specifically addressed stimulant prediction in ADHD samples. The predictor variables employed across the studies were varied: rating scales, demographics, IQ, cognitive tests, psychophysiological and biological. Thus, a consistency in measures across studies is lacking, despite about half of these studies employing subjective predictors with objective response criteria. The remaining studies were combinations of objective and subjective predictors and response criteria.

The current review, will focus only on recent key studies that have specifically addressed stimulant prediction in ADHD, since the most recent review of this topic [74]. The purpose is to build on the overall findings from the two aforementioned reviews and hypothesize the future of this approach. Aside from the early profiling attempts by Conners very little research into predicting stimulant response has integrated data across domains and instead there is a body of research with separate accounts of stimulant prediction within domains [80,81]. The following sections are summaries of research that primarily employ subjective (typically rating scales) versus objective (performance or psychophysiological measures) predictor variables. In addition to variations in predictor and response criterion variables, there are substantial differences in drug administration and design across these studies [82]. Key features of the studies summarized below are listed in TABLE 1.

Subjective predictor variables

Studies that employ subjective predictor variables are typically based on clinical ratings (by parent, teacher and/or clinician). These studies also include demographic variables, that are not technically subjective, such as age and gender, but which are included in this summary.

In a large study of 336 ADHD children, neurological status (presence of a disorder), inattention and hyperactivity (rated by parent or teacher) were found to predict a good stimulant response [82]. Analysis of how well predictor variables classified responders versus nonresponders (based on Conners rating scales and clinical judgement) demonstrated a 76% sensitivity and 59% specificity. Another study found that increased hyperactivity and inattention at school (in addition to low age) and low levels of internalizing symptoms at home, predicted stimulant response with 71% sensitivity and 71% specificity in 36 ADHD males aged 7–11 years [83].

After examining whether inattention and/or hyperactivity predicted methylphenidate response in 60 ADHD children, Denney and Rapport redefined their model of stimulant treatment response and investigated how observed academic efficiency (proportion of classroom work completed) could predict response [79]. They found no reliable prediction of inattention or hyperactivity measures (unlike previous studies that prompted the initial model); however, the strongest (with the broadest impact [84]) predictor was academic performance. They reported that 98% of children who demonstrated significant improvement in academic performance were the strongest responders (indexed by teacher-rating scales), with only 11% of those who did not demonstrate significant improvement being nonresponders.

Essentially these studies have demonstrated some consistent levels of sensitivity using subjective predictors (and not necessarily demographic factors). However, efforts to target biological systems are limited and there remain few attempts to examine functional relationships between systems and outcome measures. There is a lack of studies integrating subjective with objective predictor variables. Furthermore, there may be a problem of circularity, with subjective predictors of equally subjective measures employed to define response.

Objective predictor variables

Studies employing objective predictor variables are typically based on cognitive laboratory testing (performance of the individual) and, to a lessor extent, psychophysiological variables. These studies also include behavioral and demographic variables; however, for the purpose of a summary, they have been categorized based on their inclusion of objective tests.

After earlier calls to further explore the predictive potential of electroencephalography (EEG) [85], Chabot and colleagues performed an investigation using EEG (as the biological correlates of response) to specifically predict stimulant response in 130 ADHD subjects aged 6–16 years [86]. The study revealed that those who showed a positive treatment response (measured behaviorally) had significantly higher initial scores on Conners (inattention, hyperactivity, memory problems and peer interaction) than those who demonstrated negative treatment response. Those with a negative treatment response also showed a greater EEG abnormality. Chabot and colleagues discriminated groups using two clinical and two EEG variables and were able to correctly classify 83% of responders versus 88% of nonresponders [86]. They concluded that a discriminant function, based upon a combination of neuropsychological and psychophysiological predictor variables can prove useful in determining stimulant response in ADHD.

Stimulant-response prediction has also been undertaken using event-related potentials (ERPs) in 20 ADHD children aged 6–12 years [87]. The topographical ratio of auditory P300 amplitude predicted robust response (defined as a 60% reduction in baseline symptoms by parent rating), with a positive predictive value of 0.67 and a negative predictive value of 0.73. In contrast to other studies using subjective/clinical predictors only, robust versus nonrobust responders did not differ in baseline attention or hyperactivity ratings. Sangal

Table 1. Key studies since 1998 (post Gray and Kagan, review [2000]) that have specifically assessed stimulant–response prediction in ADHD.

Study	ADHD sample	Design	Predictor variables	Responder definition	Key predictors of response	Note	Ref.
Thomson Varley, (1998)	278 M:58 F 3–16 years	Double-blind placebo-controlled	Demographics, parents and teacher ratings	Rating scales and clinical judgement	Neurological status, inattention, hyperactivity	Reported poor predictive associations	[82]
Zeiner *et al.*, (1999)	36 M 7–11 years	Double-blind placebo-controlled crossover	Parents and teacher ratings	Parent and teacher ratings	Hyperactivity, inattention, age, internalizing symptoms	Used neuropsychological test, but did not use for prediction	[83]
Denney Rapport, (1999)	60 M:10 F 6–11 years	Double-blind placebo-controlled crossover	Observation of academic efficiency	Teacher rating	Academic performance	Inattention/hyperactivity prediction model not supported	[79]
Chabot *et al.*, (1999)	98 M:32 F 6–16 years	Open-label	Clinical ratings and EEG	Clinical rating	θ/β EEG	MPH or DEX treatment determined by cognitive testing	[81]
Sangal and Sangal, (2004)	12 M:8 F 6–12 years	Single-blind	ERP	Parent rating	P300 ratio	Follow-up study with nonstimulant	[87]
Gordon *et al.*, (2005)	31 M:10 F 11–17 years	Open-label	Demographic, behavioral, cognitive and psychophysiological	Overall cognitive performance	Self-esteem, memory, ERP	Responder groups also compared in clinical and parent ratings	[90]
Hermens *et al.*, (2005)	40 M:10 F 9–18 years	Open-label	Psychophysiological	Performance in two attention tasks	EEG, ERP	Responder groups also compared in clinical and parent ratings	[91]

Studies demonstrated variations in subjective and objective predictor and response-criterion (responder definition) variables.
ADHD: Attention-deficit hyperactivity disorder; DEX: Dexamphetamine; EEG: Electroencephalography; ERP: Event-related potentials; F: Female; M: Male; MPH: Methylphenidate.

and Sangal have followed up on this approach to ADHD medication prediction investigating the nonstimulant, atomoxetine [88]. The consistency in methodology has helped to pinpoint whether a stimulant or nonstimulant is more suitable to a given individual.

While the exact relationship between psychophysiology (EEG/ERP) measures and biological systems targeted by stimulant medications is yet to be resolved, these findings suggest that the integration of cognitive (performance), psychophysiological and behavioral (clinical) data may provide valuable insights into response prediction. The studies summarized above have attempted to combine objective (cognitive performance or psychophysiological) with subjective (clinical ratings) measures and are demonstrating comparable discrimination between responder groups. However, there is a lack of consistency (primarily owing to a limited number of studies and variations in the types of measures) and despite the promise of integration, the attempts to profile responders from nonresponders is no more advanced than those provided by Conners over 30 years ago [81,89]. Recent exceptions are described below [90,91].

Integrative approach to stimulant prediction in ADHD

The integration of multiple measures to profile ADHD and predict stimulant medication response has recently been carried by Hermens and colleagues [90,91]. These studies highlight how the attempt to profile and predict response is facilitated by a large standardized and multidimensional Brain Resource International Database (BRID) [90,92,93]. These studies investigated the utility of an integrative approach, in which cognitive and psychophysiological measures are combined, to predict treatment response in ADHD. They provide a unique contribution to the field by examining biological systems (indexed by psychophysiology and cognitive performance) with clinical outcomes (behavioral indices) and the functional relationships between these measures (statistical associations).

After presenting data on a normalization technique (to account for age and gender effects), which allows for direct comparison between ADHD and normal subjects, Gordon and colleagues present a profile of EEG/ERP and autonomic measures that provide a means to accurately predict treatment response in 41 ADHD individuals (11–17 years) [90]. Responders and nonresponders were separated on the basis of an overall cognitive

performance. That is, different scores from a cognitive test battery before and after stimulant treatment were computed to give an overall response score. The two groups were then classified by a stepwise discriminant function analysis with 20 demographic, behavioral, psychometric and psychophysiological predictors. The resultant discriminant function demonstrated 90% sensitivity and 91% specificity. The analysis revealed increased self-esteem, decreased long-term memory recall and two ERP abnormalities (decreased right frontal N200 amplitude to targets and delayed right posterior P200 to targets) before treatment best predicted a good response to stimulants. *Post hoc* analysis revealed that responders also showed decreased inattention, hyperactivity/impulsivity and global scores measured by Conners rating scales (parents).

Drawing on this integrative approach, Hermens and colleagues employed two cognitive (attention) tests to define responder versus nonresponder groups [91]. Pretreatment psychophysiological measures were employed as predictors of stimulant medication response. Two discriminant analyses (based on each response criterion) revealed that specific (those with a functional relationships to each attention test) resting EEG and task-related ERP profiles were associated with stimulant response. With the selective attention (oddball) response criterion, there was 85% sensitivity and 95% specificity. Similarly, the working memory/sustained attention (CPT) response criterion revealed 80% sensitivity and 90% specificity. Importantly, there was consistency, with posterior fast-wave EEG (β) and right frontal ERP to distractor stimuli (P300) found to predict response in both analyses. *Post hoc* analysis, revealed that before treatment, responders (in both criterion conditions) had significantly higher scores on the 'restless-impulsive'; 'global index total' and 'DSM-IV total' subscales from the Conners rating scales (parents) and pediatrician-rated 'hyperactivity-impulsivity' symptomatology, which is consistent with previous studies.

The aforementioned studies employed an integrative approach to the prediction of stimulant response in ADHD to examine distinct predictive profiles of ADHD that are characteristic of favorable response to stimulant treatment. To the authors knowledge these studies are the most comprehensive attempts to integrate a range of measures for the purpose of predicting ADHD stimulant response since Conners' studies over 30 years ago. While there appears to be a consistency of predictor variables (and clinical patterns of responders) this approach requires further replication and direct examination of the functional relationships between predictors and outcome measures (e.g., psychophysiological markers and clinical ratings).

Conclusion

Despite two major reviews on predicting stimulant response in ADHD there have been few attempts to assess potential 'profiles' characteristic of ADHD individuals who respond to stimulant treatment since the work of Conners over 30 years ago. To our knowledge, only two recent studies have revisited this approach and generated integrated prediction profiles of ADHD stimulant response [90,91]. It is hoped that with the advances in neuroimaging and genetics techniques more integrated and reliable profiles of ADHD stimulant (and other medication) response will emerge. To date there are good levels of consistency in clinically based scales, however, the incorporation of objective predictors, tapping into cognitive, psychophysiological, demographic and genetic domains is warranted. Certain levels of standardization in both response criterion and predictor variables need to be achieved for this approach to develop further, that is, for more accurate levels of comparison across studies.

Expert commentary & five-year view

Recommendation for future ADHD stimulant prediction research

In the next 5 years, ongoing assessment of predicting stimulant (and nonstimulant) medication response in ADHD will benefit from the incorporation of the following:

- A standardization of predictor and response criterion variables
- Analysis of integrated prediction profiles
- A personalized medicine perspective and
- Resources from large standardized databases

The following sections briefly discuss each of these areas of interest.

Standardization of predictor & criterion variables

Despite a number of existing studies dedicated to predicting stimulant response in ADHD, the relationships between predictor and response criterion variables have generally been subtle [82]. There is also considerable methodological variation between studies in both predictor and response-criterion variables employed. The present review has focused primarily on the variety of predictor variables employed; however, response criterion variables have also been varied (subjective clinical rating measures vs objective cognitive measures). The lack of any gold-standard stimulant-response prediction protocol is problematic in light of the frequency with which individuals are prescribed stimulant medications to treat ADHD (often for considerable lengths of time). The choice of optimal stimulant (or nonstimulant) type, dose and release mechanism should be governed by data-driven analysis and not other factors, such as cost (which will often have an influence).

Clearly, the field would benefit from a standardization of both predictor and response criterion measures to facilitate replication and reliable prediction profiles of ADHD stimulant response. It is arguable that both variables types should be represented by both subjective (clinical) and objective (cognitive) measures. Whilst clinical rating scales such as Conners, and sustained attention tasks (e.g., CPT), have been established (separately) in the field as commonly used diagnostic aids in ADHD assessment, their use in determining response to stimulants requires integration and standardization. Once this is established, there is also a need to determine a standardized (and appropriate) degree of response to medication, which currently varies across studies. Terms such as responder versus nonresponder or robust versus nonrobust still

cloud the field and make comparisons across studies difficult. The standardization of predictor variables is also critical for cross-study comparison (and replication), a good starting point would be some consensus on the methodology used to determine which predictors should be used in discriminant analyses, according to strict entry criteria.

Integrated prediction profiles

This review has previously alluded to the potential wealth of information generated by the use of multidimensional and integrated measures to gauge response-prediction profiles in ADHD. The use of single predictor variables has received skepticism and criticism, motivating the use of integrated measures across domains. Relatively little has been done since Conners' profiling work 30 years ago, but with emerging advances in neuroimaging, genetics and databasing (to name a few) it seems an appropriate time to endorse the use of (statistically and theoretically driven) integrated measures. That is, the integration of measures across established domains (clinical, demographic, cognitive and psychophysiological) and then the incorporation of emerging predictor variable categories (e.g., genetics). There is still plenty of scope in this field for the suggestions of Denney and Rapport to be fully realized [79]. That is, thorough investigations of the relationships between underlying biological systems and clinical outcomes to determine the functional relationships among response criterion and predictor variables. The use of integrated prediction profiling has the potential to generate more efficient and expansive functional relationships between such variables.

Personalized medicine

The next few years of stimulant (or alterative medication) response in ADHD may benefit from taking a 'personalized medicine' approach [90]. Possibly as a result of integrated prediction profiling, standardization of measures and large referential databases, a personalized approach should only broaden our understanding of the heterogeneity of ADHD. That is, the field has discovered many general aspects of stimulant response in ADHD as measured at the group level, however, there is an increasing need for individually tailored levels of analysis, to provide clinicians with more informative profiles.

As a consequence of adopting personalized medicine approaches the field will be more adequately equipped to generate predictive profiles for subgroups of ADHD, such as subtypes and comorbid conditions, which could be further refined by considering the impact of both experience (such as role of early stressors) and genetic profiles. There should be a reciprocal approach to the interpretation of group- and individual-level findings, which will only broaden our understanding of ADHD and produce more reliable predictors of stimulant response.

Large standardized database support

Johnstone and colleagues recently called for statistical-driven analysis backed by a broad clinical database to identify clusters of medication responsive individuals [94]. This is now being realized with the advent of large normative international databases that offer predictive profiles of ADHD response to treatment [90,91]. Efforts to standardize response criterion and predictor variables, to integrate prediction profiles and assess a personalized medicine perspective would all benefit from the reverential nature of a large international standardized and multidimensional database.

The efficiencies of the internet permit access to centralized resources and large international databases that facilitate integrated and personalized medication prediction. From office-based ADHD treatment clinics information can be collected and transmitted to a centralized database facility for scoring, analysis and comparison with the normative database. Then returned to the clinician in the form of a clinical profile or personalized report to assist with diagnostic and treatment decisions. An increasing number of clinicians are making use of such a system by implementing computerized cognitive test batteries and web-based questionnaires in their private rooms. Traditionally, the collection of psychophysiological or imaging data has been restricted to separate research centers. However, recently the integrated and standardized protocols (from single databases) has permitted clinicians to refer patients to centralized testing facilities for additional profiling of more comprehensive and complex measures using the same report format and integrated data. With the growing size of clinical databases this is leading to the generation of standardized prediction profiles. Further collaboration between large ADHD treatment clinics and research centers (with physiological and imaging equipment) will facilitate the refinement of the measures required for reliable predictor variables. In other words, such work will lead to the development of practical and efficient tools to aid treatment prediction in office-based clinics (e.g., integrated computerized cognitive testing with specialized compact psychophysiological recording).

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Key issues

- Historically, treatment of attention-deficit hyperactivity disorder (ADHD) with stimulants has been based on trial and error before optimal therapy is reached.
- There is an increasing need for treating clinicians to prescribe the most effective drug with a personalized medicine approach to ADHD.
- Stimulant prediction protocols in ADHD are limited without universally accepted response criteria.
- More recently, there has been a shift from using subjective to objective predictor variables.
- The future of stimulant-response prediction may benefit from standardization and profiling with reference to integrated measures from neuroscience databases.

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