

Predicting the clinical outcome of stimulant medication in pediatric attention-deficit/hyperactivity disorder: data from quantitative electroencephalography, event-related potentials, and a go/no-go test

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Background: We searched for predictors of the clinical outcome of stimulant medication in pediatric attention-deficit/hyperactivity disorder (ADHD), emphasizing variables from quantitative electroencephalography, event-related potentials (ERPs), and behavioral data from a visual go/no-go test.

Methods: Nineteen-channel electroencephalography (EEG) was recorded during the resting state in eyes-open and eyes-closed conditions and during performance of the cued go/no-go task in 98 medication-naïve ADHD patients aged 7–17 years and in 90 controls with the same age and sex distribution as the patients. For patients, the recording was followed by a systematic trial on stimulant medication lasting at least 4 weeks. Based on data from rating scales and interviews, two psychologists who were blind to the electrophysiological results independently rated the patients as responders (REs) (N=74) or non-responders (non-REs) (N=24). Using a logistic regression model, comparisons were made between REs and non-REs on the EEG spectra, ERPs (cue P3, contingent negative variation, and P3 no-go of the ERP waves and independent components [ICs] extracted from these waves), reaction time, reaction time variability, number of commission and omission errors, intelligence quotient, age, sex, ADHD subtype, and comorbidities.

Results: The two groups differed significantly on eight of the variables, with effect sizes (Cohen's *d*) ranging from 0.49 to 0.76. In the multivariate logistic regression analysis, only three of these variables were significantly associated with clinical outcome. The amplitude of the IC cue P3, which has a parietal–occipital distribution, was normal in REs but significantly smaller in non-REs, whereas the centrally distributed IC P3 no-go early was smaller in REs than in non-REs and controls. In addition, the REs had more power in the EEG theta band. A quartile-based index was calculated using these three variables. The group with the lowest scores comprised only 36% REs; response rates in the three other groups were 83%, 86%, and 89%.

Conclusion: The clinical outcome of stimulant medication was best predicted by electrophysiological parameters. The brain dysfunctions of the REs appear to be primarily associated with prefrontal lobe hypoactivation. The non-REs were deviant from the controls in parietal–occipital functions.

Keywords: ADHD, stimulants, predictions, clinical outcome, QEEG, ERP, go/no-go test

Introduction

Attention-deficit/hyperactivity disorder (ADHD)^{1,2} has a prevalence of approximately 3%–6% in school-aged children, relatively consistent across class, culture, and race.^{3,4}

According to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV)² (and DSM-5⁵), the combined subtype (ADHD-C) is characterized by six or more symptoms of hyperactivity/impulsivity and six or more symptoms of inattention. The predominantly inattentive subtype (ADHD-I) requires six or more symptoms of inattention only, and the hyperactive/impulsive subtype (ADHD-H) requires six or more symptoms of hyperactivity/impulsivity. In the DSM-5, this subtyping is kept, although it is pointed out that a change of subtype throughout the lifespan of the disorder is not uncommon. Symptoms have to be present in more than one setting, start in childhood, and should not be better explained by other psychiatric conditions. In the DSM-5, ADHD has been moved from the category of disruptive behavior disorders to neurodevelopmental disorders. Comorbid conditions, such as behavioral disorders, anxiety, and learning disabilities, are seen in the majority of cases.⁶ Although ADHD is considered a brain-based disorder, no neuropsychological or neurophysiological test results are necessary to make the diagnosis.

Psychosocial interventions are commonly supplemented by psychostimulants like methylphenidate (MPH), dextroamphetamine (DEX), and the nonstimulant atomoxetine (ATX). Therapeutic effects and side effects of psychostimulants are described in several studies.^{7–13} MPH has shown a therapeutic response in approximately 70% of patients.¹⁴ A shift to DEX or ATX for non-responders (non-REs) increases therapeutic effects to 80%.⁴ Therapeutic response to MPH may vary from patient to patient. Numerous studies have generally implicated the fronto-subcortical networks of the brain as a prime candidate for the source of the underlying dysfunction, including hypofunctioning dopamine and norepinephrine systems.¹⁵ The influence of genetic factors is well documented.^{4,16}

Behavior ratings from parents and teachers are generally used as outcome measures. Because these scales are vulnerable to placebo and source effects, the inclusion of such objective measures as continuous performance tests (CPTs) has been recommended by several authors.¹⁷ There is no consensus on what constitutes a meaningful clinical response. Improvement of at least 0.5 standard deviations (SDs) on an ADHD rating scale or at least a 25% reduction in raw scores is often used. Doses for optimal cognitive improvement seem to be lower than for behavioral improvement.¹⁸ Sangal and Sangal¹⁹ argue that a suboptimal clinical response is too often accepted. If response is defined more strictly, allowing for a return to normal, the usual quoted 70% response will drop to 40%. The authors also argue that the reduction in symptom

raw scores should be at least 50%, in order to control for placebo effects.

The literature on electroencephalography (EEG) and event-related potentials (ERPs) in ADHD is extensive. Some studies relate to biomarkers or endophenotypes, searching for objective characteristics in EEGs and ERPs that may be helpful in a differential diagnosis. Others focus on changes in EEGs and ERPs resulting from treatment, particularly medication and neurofeedback. Using a quantitative EEG (QEEG), many studies find excess power in the theta band (4–7 Hz) and/or an increased theta:beta ratio (ie, 4–7:13–21 Hz) in ADHD, in agreement with theories of cortical hypoactivation.²⁰ More recent studies have found, however, that the excessive theta:beta ratio characterizes only a subgroup of ADHD. We recently found this pattern in 26% of pediatric ADHD patients, compared with 2.5% in healthy controls.^{20–22} In addition to excess theta, other EEG-based subtypes of ADHD have been reported: excess beta, excess alpha, low alpha peak frequency, and hypercoherence.^{20,23–28}

Several researchers have examined changes in EEG parameters resulting from stimulant medication and EEG predictors of clinical response. Most – but not all of them – report that stimulants induce changes toward normalization, like reduction in theta and, to some extent, increases in beta frontally.^{29–40} Power in the alpha and low beta band seems to increase in patients and controls.^{41,42} In a review of the clinical utility of EEG in ADHD, it was concluded that good responders (REs) to stimulants have an excess of slow wave activity (theta), and that stimulant medication results in increased beta, reduced theta, and improvements in deviant ERP measures.²⁹ One study reported that stimulants increased beta in medication REs and reduced beta in non-REs.⁴³ The beta excess found in the beta subtype of ADHD does not reflect hyperactivation, because it was reduced by stimulants.⁴⁴ In a study comparing children with ADHD and controls, significant deviances in ERP components N1, P2, and N2 were not present after administration of MPH to the patients.⁴⁵ Hermens et al¹⁵ classified ADHD patients as REs or non-REs on the basis of behavioral measures in an oddball task and a working memory task. ERPs were also extracted from these tasks. Correct classifications based on ERPs were reported for 85%–90% of the cases. In a study using an oddball paradigm, it was found that the ratio of right fronto-central to parietal P300 ERP component predicted robust clinical response to stimulants.⁴⁶ Recent reviews of the literature on EEG in ADHD provide further details.^{20,22,27}

ERPs are electrophysiological expressions of information processes that appear as curves with characteristic peaks and troughs when the background EEG has been cancelled out. ERPs are characterized by latencies in milliseconds (ms), amplitudes in microvolt (μV), and topography. ERP waves are associated with underlying stages of sensory-related and action-related information flow in various cortical areas. Deviances in ADHD have been reported for several ERP components. The P3b wave (peaking 300–500 ms after stimulus presentation) can be found in paradigms like oddball and go/no-go in which action is involved.⁴⁷ The amplitude of the component is said to reflect the allocation of attention resources, and latency reflects classification speed.⁴⁸ Cue P3 with a parietal/occipital location occurs as a response to target-relevant information.^{49,50} The contingent negative variation (CNV) is a low potential evoked in cued paradigms (go/no-go, signal stop) when an individual prepares for action.^{51–53} ERP waves are regarded as the sum of multiple sources generated in different locations and associated with different neural processes.⁵⁴ In a recent study,⁵⁵ we describe how these multiple sources comprising the ERP waves can be decomposed into reliable independent components (ICs) with different functional meanings.^{55,56}

Many studies have reported P3 waves (go and no-go) to be deviant in ADHD.^{49,50,57–60} In a recent longitudinal study,⁶¹ CNV was found to be the only ERP component with significantly smaller amplitude in ADHD patients of all ages, compared with controls. There was no evidence of normalization with increasing age.⁵⁰ A number of studies have examined changes in P3, CNV, and other ERP components resulting from stimulant medication.^{62–66} The most consistent finding is an increase of amplitude in P3 components. Interestingly, one study found an increase in P3 amplitude when correct responses were rewarded.⁶⁷ The CNV can be seen as a dopaminergic biomarker, as the amplitude of this component was shown to increase following an intake of stimulant medication in a group of healthy young adults.^{68,69} Kratz et al⁷⁰ report that MPH administered to a group of children with ADHD resulted in reduced reaction time variability accompanied by an increase in CNV.

Predicting clinical responses to stimulants is complicated for several reasons. Some attention-enhancing effects of stimulants have been reported even for control subjects,^{69,71} although smaller than those seen in ADHD medication REs. As mentioned, there is no consensus about the definition of an adequate medication response or the measures that should be included. When informants evaluate effects, the presence of side effects may influence their opinion. We recently found

a significant negative correlation of -0.38 between clinical effects and side effects.⁷² Hale et al¹⁸ found that patients with adequate baseline performances on tests for “cool” and “hot” executive function did not show robust clinical effects of stimulants. Children with ADHD-I may respond more poorly to stimulants than do children with ADHD-C, and comorbidities related to anxiety and autism spectrum disorders may increase the risk of a poor response.^{18,73,74}

Based on the ADHD literature, we hypothesized that good REs to stimulant treatment – compared with non-REs – belong to the ADHD-C subtype; are characterized by a lack of comorbid anxiety, learning, and autism spectrum disorders; and have more impaired behavioral results on the go/no-go test. We also hypothesized that REs, compared with non-REs, would not have excess beta, would have more power in the theta band, a higher alpha peak frequency, and smaller amplitudes in ERPs – all of which have been found in several studies to be deviant in ADHD (cue P3, CNV, P3 no-go) compared with non-REs.

Methods

Participants

Ninety-eight consecutive clinical cases aged 7–17 years diagnosed with ADHD were included in the study, along with 90 controls drawn from the HBi normative database (<http://www.hbimed.com>), with the same age and sex distributions, mean ages, SDs, and maximum and minimum ages. The controls were typically developing children without psychiatric, neurological, developmental, or learning disorders. The test equipment (QEEG, go/no-go task) was identical for patients and controls. The HBi database for cases aged 7–17 years contains 300 subjects. After positive screening for ADHD by the GP, the school psychology service, or the local child psychiatry outpatient clinic, the 98 patients were referred to our study with the neuropsychiatric team in the county of Østfold, Norway, for further diagnostic assessment and treatment. They were all diagnosed with either ADHD-C or ADHD-I. The majority had comorbid diagnoses (Table 1). All diagnostic conclusions were in accordance with the DSM-IV and based on clinical interviews with parents (Kiddie Schedule for Affective Disorders and Schizophrenia or Development and Well-Being Assessment);^{75,76} developmental and medical histories; rating scales from parents, teachers, and, in some cases, self-reports; and intelligence testing (the Wechsler Intelligence Scale for Children III/IV or the abbreviated form, the Wechsler Adult Intelligence Scale). These data were supplemented with neuropsychological assessment, reports from the school psychology service and GP, and, in some

Table 1 Demographics of the ADHD sample by sex

	Male (N=66)	Female (N=32)	Difference
Age, years (SD)	11.5 (2.4)	12.8 (3.0)	P=0.04
ADHD-C (combined subtype)	43 (65%)	15 (47%)	NS
ADHD-I (inattentive subtype)	23 (35%)	17 (53%)	NS
Total IQ	93 (15)	90 (13)	NS
Behavior problems (ODD-CD)	23 (35%)	11 (34%)	NS
Emotional problems	26 (26%)	13 (41%)	NS
Learning disorders ^a	36 (55%)	16 (50%)	NS
Autism spectrum disorders	9 (14%)	3 (9%)	NS
Other disorders ^b	7 (11%)	4 (13%)	NS

Notes: ^aGeneral learner disorder (IQ <80, special education in several school subjects) and specific learning disorder (IQ >80, dyslexia, dyscalculia); ^bTourette's syndrome, reactive attachment disorder.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; IQ, intelligence quotient; NS, not significant; ODD-CD, oppositional defiant disorder-conduct disorder; SD, standard deviation.

cases, more informal meetings with parents and teachers. In most cases, the parent and teacher forms of both Conners' Rating Scale – Revised (CRS-R),⁷⁷ and the Behavior Rating Inventory of Executive Function (BRIEF)⁷⁸ were administered. Reports from the schools and the school psychology service included information regarding social functioning, behavior, learning disorders, and the need for special education. Learning disorders represented a mixed group of general learning disabilities (an intelligence quotient [IQ] below 80 with significant learning problems in several school subjects requiring special education) or specific learning disabilities (including dyslexia and dyscalculia with an IQ above 80). Another category, “other disorders,” included Tourette's

syndrome and reactive attachment disorder. Diagnostic conclusions were discussed in the team, which comprised two specialists in neuropsychology, a pediatrician, and a specialist in school psychology. The project was approved by the Regional Committee for Medical Research Ethics.

After diagnostic conclusions were drawn, all 98 patients were offered a systematic trial on stimulant medication lasting at least 4 weeks. All testing used in predictions was carried out before onset of medication. The standard procedure consisted of the administration of single tablets of MPH during the trial period, titrated from 5 mg × 1 per day up to a maximum of 20 mg × 3 per day – lower if side effects occurred or if significant clinical effects were observed on lower doses. Seven of the patients, who were also participating in another study, underwent a similar procedure on DEX, based on test results in that study. (A χ^2 test showed no difference in clinical effects for the two medications [$P=0.64$]).

Parents and teachers completed daily ratings of ADHD symptoms before the trial period started and during the 4-week period. Children aged over 9 years were asked to complete daily self-ratings. Some of the parents and teachers filled in four-point ratings consisting of the 18 ADHD symptoms in the DSM-IV. In other cases, abbreviated forms were used, asking for comparisons with the period before onset of medication (better, as usual, or worse). Similarly, the children were asked to evaluate their attention, behavior, and feelings as better, worse, or the same, comparing with the period before onset of medication. The parents were invited to contact us with any questions they might have

Table 2 Demographics in responder (RE) and nonresponder (non-RE) groups

	REs (N=74)	Non-REs (N=24)	Difference
Age, years (SD)	11.6 (2.7)	12.7 (2.7)	NS
Sex (male: N=66, female: N=32)	Male: 47 (71%) Female: 26 (81%)	Male: 19 (29%) Female: 6 (19%)	NS
Total IQ	94 (14)	87 (15)	NS
ADHD subtype (ADHD-C: N=58, ADHD-I: N=40)	ADHD-C: 43 (74%) ADHD-I: 30 (75%)	ADHD-C: 15 (26%) ADHD-I: 10 (25%)	NS
Behavior problems (ODD-CD) (ODD-CD: N=34)	ODD: 26 (77%) No ODD: 47 (73%)	ODD: 8 (23%) No ODD: 17 (27%)	NS
Emotional problems (Em: N=30)	Em: 23 (77%) No Em: 50 (74%)	Em: 7 (23%) No Em: 18 (26%)	NS
Learning disorders (LDs: N=53) ^a	LD: 38 (71%) No LD: 35 (78%)	LD: 15 (29%) No LD: 10 (22%)	NS
Autism spectrum disorders (ASD: N=12)	ASD: 7 (58%) No ASD: 66 (77%)	ASD: 5 (42%) No ASD: 20 (23%)	NS
Other disorders (TS, RAD, etc: N=11)	“Other:” 5 (45%) No “other:” 68 (78%)	“Other:” 6 (55%) No “other:” 19 (22%)	P=0.05

Note: ^aGeneral LD (IQ <80, special education in several school subjects) and specific LD (IQ >80, dyslexia, dyscalculia).

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-C, combined subtype; ADHD-I, inattentive subtype; IQ, intelligence quotient; NS, not significant; ODD-CD, oppositional defiant disorder-conduct disorder; SD, standard deviation; TS, Tourette's syndrome; RAD, reactive attachment disorder.

during this period, and after 4 weeks we arranged a meeting with those involved. Parents, teachers, and the majority of patients aged over 12 years accepted the invitation. Parents, teachers, and children were asked informally to tell us about the last 4 weeks. Was there anything new, anything positive, or anything negative to report? Did they perceive that the medication had produced any changes? What were the effects of increased doses? We also asked them to describe any side effects compared with the weeks before medication started. The rating scales were examined, and a conclusion was usually drawn about further medication. This decision was followed by telephone contacts and meetings, as needed, before the case was referred back to the outpatient clinic.

The forms used to evaluate therapeutic effects and side effects were not the same in all cases, and some key information conveyed in meetings and phone calls did not show up in the rating scales. We therefore used the following method to evaluate clinical effects. In accordance with clinical routines, all the information acquired from meetings, phone calls, rating scales, and testing was registered in the patient journals. This information, which did not include data from QEEG/ERP testing, was independently evaluated by the first author and a psychologist from the team. The following criteria regarding clinical effects were used. We started with a 2–1–0 scale (2= significant positive changes; 1= moderate positive changes, or seen only at school or at home; 0= small/insignificant or negative clinical changes). The team's two psychologists also rated the effects on a 1–0 basis, splitting the "mid-group" into REs and non-REs, which resulted in a "responder" classification for most patients. Agreement on the 2–1–0 scale was 80% before discussions and higher on the 1–0 scale that was used in the statistical analyses. The parents gave written consent for their children to participate, and the children were informed.

Assessment of QEEG and ERP

All assessments were completed before onset of medication tryout. The time interval was between 2 weeks and 5 weeks, with very few exceptions, and no difference between the RE and non-RE groups. EEGs were recorded using a Mitsar 201 (Mitsar Co, Ltd, Saint Petersburg, Russia) (<http://www.mitsar-medical.com>), a PC-controlled, 19-channel electroencephalographic system. The input signals referenced to the linked ears were filtered between 0.5 Hz and 50 Hz and digitized at a sampling rate of 250 Hz. Impedance was kept below 5 kOhm for all electrodes. An

electrode cap with tin electrodes based on the International 10–20 system (Electro-cap International, Eaton, OH, USA) was used. Quantitative data were obtained from WinEEG software (Mitsar Co, Ltd) common reference montage prior to data processing.⁷⁹ Eye-blink artifacts were corrected by zeroing the activation curves of individual independent component analysis components corresponding to eye blinks.⁸⁰ In addition, epochs of the filtered electroencephalogram with excessive amplitude ($>100 \mu\text{V}$) and/or presented with excessively fast ($>35 \mu\text{V}$ in 20–35 Hz band) and slow ($>50 \mu\text{V}$ in 0–1 Hz band) frequency activities were automatically marked and excluded from further analysis. Finally, the EEG was manually inspected to verify artifact removal. All 98 patients and 90 controls were tested in eyes-closed, eyes-open, and task conditions in the cued go/no-go task comprising 400 pairs of pictures and lasting 20 minutes. The pictures were presented for 100 ms. In each pair the interstimulus interval was 1,000 ms. The time interval between pairs was 1,800 ms. The instruction was to press the button only when the two pictures in a pair were animals (A-A: go) – not "animal-plant" (A-P: no-go), "plant-human," or "plant-plant" (100 pairs of pictures in each category). ERPs were recorded during a visual continuous performance task (VCPT). See Mueller et al⁷⁹ for a more detailed description of the task. Correct responses had to occur within a time window from 200 ms to 1,000 ms after stimulus presentation.

The ERPs for each individual are based on averaging the trials of the respective task conditions after artifact correction. ERPs based on fewer than 20 trials may not be valid. This was true for one person in each group. The mean number of trials (and SDs) for REs and non-REs in go and no-go conditions were REs go: 60 (23), no-go: 66 (21); and non-REs go: 70 (19), no-go: 70 (22) ($P=0.054$). Although the number of trials was lower in REs compared with non-REs, the number of valid trials was still high in both groups, and the group means were not influenced by the difference.

Variables in the model

Differences between the two groups before medication were checked on 13 continuous and ten categorical/dichotomous variables.

Demographic variables: sex, age, IQ

- Diagnostic variables: subtype of ADHD (ADHD-C or ADHD-I); comorbidity (behavior problems [oppositional defiant disorder–conduct disorder], emotional problems [anxiety/depression], learning disorders, and autism spectrum disorders).

- Behavioral variables from the go/no-go test: omission errors, commission errors, reaction time, and reaction time variability.
- Variables from EEG spectra: grand average spectra curves in the task condition for the RE and non-RE groups were computed in WinEEG. Subtracting the non-RE curve from the RE curve highlights possible significant differences in spectra between the groups. This information was used as a guideline for exporting individual data to the SPSS statistical program (IBM Corporation, Armonk, NY, USA) for further analysis. The mean theta sums at sites P3, P4, Pz, T5, T6, T3, and T4 were exported.

In addition, each patient was individually compared with the HBI database and classified as deviant or not deviant in the theta, alpha, and beta bands. For a person to be judged as deviant, the statistical deviance had to be seen in at least two of the three conditions eyes closed, eyes opened, or go/no-go task, and the pattern had to be confirmed in relative power. Statistical significance was set at 0.05. Alpha peak frequency, defined as the frequency with maximal reduction in alpha power from the eyes-closed to the eyes-open condition, was included in the analysis because it has been reported to be lower in non-REs.³¹

ERP variables

ERPs in the cued go/no-go task were selected on the basis of the literature on ADHD showing that cue P3, CNV, and P3 no-go are particularly sensitive to ADHD.^{49,57,59} The selected ERP waves were decomposed into ICs, as described in our earlier studies.^{55,56,81} In the present study, the spatial filters for extracting ICs from the individual ERPs were based on 102 controls, as we describe in detail in Brunner et al.⁵⁵ The amplitudes of these ICs were exported to SPSS for further analysis. The amplitude of the back-projected IC cue P3 was measured at Pz as peak amplitude in the 220–400 ms time window after presentation of the first stimulus. The amplitude of the back-projected IC CNV late was measured at Cz as averaged amplitude in time interval 900–1,100 ms after the first stimulus presentation. The amplitude of the back-projected IC P3 no-go early was measured at Cz as peak amplitude in the 250–470 ms time window after presentation of the second stimulus.

Statistical methods

Logistic regression was used to identify factors associated with clinical effects of stimulant medication. In step 1, all 23 variables were checked for significant differences between the groups based on *t*-tests (13 continuous variables) and χ^2 tests

(ten categorical variables). A correlation was run on all the variables. Because we found no correlations >0.70 or <-0.70 , no variables were excluded from the model. Significant variables in step 1 were used in logistic regression, applying forward variable selection (Wald). Statistical analyses were performed in SPSS Vol 18 (<http://www.spss.com>), and the significance level was set at 5%.

Results

Demographics of REs and non-REs are shown in Table 2. An overview of the positive medication effects reported for the group of 74 medication REs at least 4 weeks after the onset of medication tryout is shown in Table 3. The eight categories (emotion, social, attention, executive function, impulsivity, hyperactivity, alert, other) are partly overlapping.

Eight of the 13 continuous variables and two of the ten categorical variables that were checked were significantly different in the RE and non-RE groups. The categorical variables that were significantly different in the RE and non-RE groups were excess theta ($P=0.011$) (the RE group had significantly more power in the theta band) and excess alpha ($P=0.038$) (the non-RE group had significantly more posterior alpha). The significant continuous variables are shown in Table 4. There was no significant difference between the two groups in five of the continuous variables (age, verbal IQ, total IQ, commission errors, and alpha peak frequency) and four of the categorical variables (sex, subtype of ADHD, comorbid disorders [behavioral, emotional, learning, autism spectrum]) and two of the deviances in spectra (excess beta, excess mu). The categorical variables that were significantly different in the RE and non-RE groups were excess theta ($P=0.011$) (the RE group had significantly more power in the theta band) and excess alpha ($P=0.038$) (the non-RE group had significantly more posterior alpha).

Three of the significant variables were amplitudes of ERP components: IC CNV late, IC no-go early, and IC cue P3 (Table 4). The RE group had significantly more power in the theta band, whereas the non-RE group had more posterior alpha. The finding of excess theta in the RE group (task condition) was confirmed when the means of theta values at all 19 sites were compared: RE: $9.4 \mu V^2$ (2.6), non-RE: $7.3 \mu V^2$ (1.6), $P=0.007$, effect size; Cohen's $d=0.92$. Comparing grand average spectra in the RE and non-RE groups, we found that the amplitude of the mean alpha peaks at sites O1 and O2 were $1.86 \mu V^2$ for REs and $2.50 \mu V^2$ for non-REs (controls: $1.63 \mu V^2$), supporting the alpha finding based on categorical classifications. We also found that the RE group had a significantly slower reaction

Table 3 Positive effects of medication reported for responders^a

Category	Number of positive reports
Emotion	26 (33%)
Increased emotional stability, reduced irritability, better mood	
Social function	16 (22%)
Improved social interaction, reduced peer conflicts	
Attention	59 (80%)
Improved attention and vigilance, better academic function, better at homework, more focused	
Executive function	21 (28%)
Increased initiative, less dependent on others, better routines, better at completing tasks	
Impulsivity	11 (15%)
Reduction of impulsive acts	
Hyperactivity	26 (35%)
Reduced overactivity and restlessness	
Alert	6 (8%)
More awake, engaged, increased effort	
Other	10 (14%)
Reduced fatigue, fewer tics	

Note: ^aThe number and percentage of positive patient reports in each category are shown.

time and significantly higher reaction time variability in the VCPT than did the non-RE group.

Logistic regression, forward variable selection (Wald), was performed to assess the impact of the ten significant variables on clinical effects of stimulant medication. Three of the variables were statistically significant in the multivariate logistic regression model (IC cue P3, IC no-go early, and excess theta in EEG spectra; individually scored, compared with age norms). Results for IC cue P3 and IC no-go early are shown in Figures 1 and 2. The figures also include the results of the 90 controls from the HBi database, with the same age and sex distributions as the patients. IC cue P3, which has

a parietal/occipital distribution, was close to normal in the RE group but significantly lower in amplitude in the non-RE group. The opposite was true for IC P3 no-go early, which has a frontal distribution; the amplitude of the component was lower in the RE group, whereas the non-RE group was close to normal controls. These two continuous IC ERP variables were transformed into quartiles. For both variables, low scores (after inversion of IC P3 no-go early) were associated with a lack of clinical response. The 25% of children with the lowest scores on the scale were given a score of 1, the next 25% group a score of 2, and so on. The scores for the categorical variable “excess theta” were 1 (normal) or 3 (significantly deviant from norms). These scores were summed for each patient, resulting in scores from 3 to 11. This 9-point scale was later transformed to an approximation of a quartile scale (the number of patients in each group: quartile 1=22, quartile 2=18, quartile 3=21, quartile 4=35 [missing data for one RE and one non-RE]). As Figure 3 shows, there were only 36% REs in quartile 1, compared with 83%, 86%, and 89% REs in quartiles 2, 3, and 4, respectively.

Comparisons with controls

The two ERP components that differed significantly between the RE and non-RE groups were also computed for the 90 controls. As Figures 1 and 2 show, the RE group was close to normal on the IC cue P3 variable, whereas the non-RE group had a much smaller component. On IC P3 no-go early, controls had the strongest component, 9.01 μ V compared with 4.30 μ V for the RE group. The amplitude for the non-RE group was 6.38 μ V.

Compared with the 90 controls, the reaction time of the RE group was close to normal (420 ms vs 450 ms in controls; non-RE =381 ms). Regarding reaction time variability,

Table 4 Independent samples t-tests showing continuous variables with significant differences between the responder (RE) group and the nonresponder (non-RE) group^a

Variable	Mean (SD) RE group	Mean (SD) non-RE group	P-value	t	df	Effect size Cohen's d
Theta sum 7 sites (μ V ²)	69 (45)	48 (28)	0.034	-2.15	96	0.49
Omission errors	18.4 (15)	11.4 (10)	0.013	-2.56	61.5	0.49
Reaction time (ms)	420 (77)	381 (70)	0.028	-2.23	96	0.52
Reaction time variability	16.3 (4.8)	12.8 (3.9)	0.002	-3.23	96	0.75
IC ERP CNV late amplitude	-0.936 μ V (1.4)	-0.715 μ V (1.1)	0.010	-2.61	96	0.58
IC ERP cue P3 amplitude	5.62 μ V (2.9)	3.56 μ V (1.9)	<0.001	-4.05	61.3	0.76
IC ERP P3 no-go early amplitude	6.82 μ V (4.5)	10.26 μ V (5.5)	0.002	3.13	94	-0.72
Performance IQ	96 (17)	87 (17)	0.031	-2.17	96	0.53

Notes: ^aIC CNV late, mean power at site Cz in time interval 900–1,100 ms after stimulus 1 when this stimulus was a target. IC ERP cue P3, peak amplitude at site Pz after stimulus 1 in time interval 220–400 ms when this stimulus was a target. IC ERP P3 no-go early, peak amplitude at site Cz after stimulus 2 in time interval 250–470 ms when this stimulus was not a target.

Abbreviations: CNV, contingent negative variation; df, degrees of freedom; ERP, event-related potential; IC, independent component; IQ, intelligence quotient; SD, standard deviation; RE, responder; non-RE, non-responder.

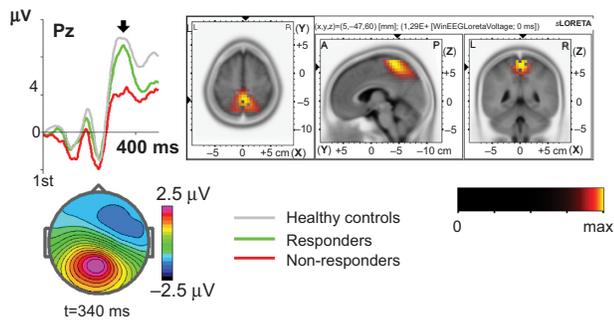


Figure 1 The independent component cue P3 is decreased in non-responders (non-REs).

Notes: Left the independent component for the group of REs (green) and non-REs (red) in comparison with the group of healthy controls (grey). X-axis – time after the onset of the first stimulus in ms. Y-axis – amplitude of the component back-projected and measured at site Pz. Right: the standardized low-resolution brain electromagnetic tomography (sLORETA) image of the cortical generators of the component. The scale is shown below. Bottom: the map of the difference; REs minus non-REs. The scale is shown on the right.

Abbreviation: t, time.

both clinical groups had higher scores than controls had, the non-RE group being closest to the controls (RE =16.3, non-RE =12.8, controls =11.7).

Discussion

From 23 parameters describing demographic and diagnostic factors, IQ, behavioral parameters in the go/no-go task, EEG spectra, and ERP parameters, three parameters contributed independently to the prediction of clinical response to stimulant medication. They were all associated with brain electrophysiology; two were amplitudes of ERP components and one was the power of EEG spectra in the theta band. As confirmed in this study, excess power in the theta band is typical for a relatively large subgroup of ADHD^{20–22} and a predictor of clinical response to stimulants.^{32,40,42,43,82} The amplitude of IC cue P3 was smaller among non-REs than among REs. The REs did not differ from controls on this

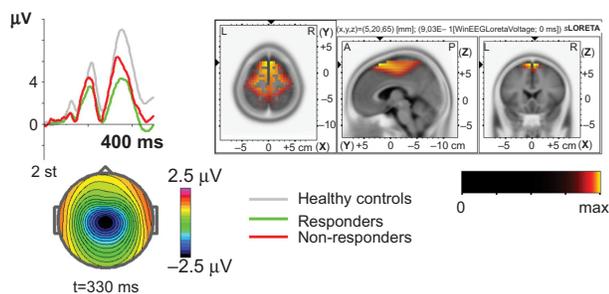


Figure 2 The independent component no-go early is decreased in the responder (RE) group. Left: the independent component for the group of REs (green) and non-REs (red) in comparison with the group of healthy controls (grey). X-axis – time after the onset of the second stimulus in ms. Y-axis – amplitude of the component back-projected and measured at Cz. Right: the standardized low-resolution brain electromagnetic tomography (sLORETA) image of the cortical generators of the component. The scale is shown below. Bottom: the map of the difference REs minus non-REs. The scale is shown on the right.

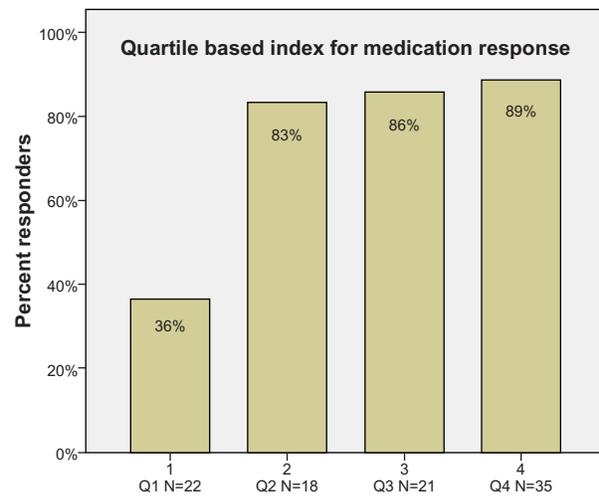


Figure 3 Based on scores combining the three significant variables, patients were placed in four (quartile [Q]) groups. Only 36% in the first group were responders. In quartile groups 2, 3, and 4, 83%, 86%, and 89% were responders.

variable. The cue P3 wave has a parietal distribution and appears to reflect processes of orienting to relevant information.^{49,50,83} The decrease of the cue P3 wave in ADHD was reported in a previous study.⁴⁹ In our study, decreased IC cue P3 was present primarily in the non-RE group. If we consider the distribution of receptors for major mediator systems, the parietal orienting network is primarily innervated by noradrenergic pathways.^{84,85} On the basis of these data, we can speculate that the non-RE group may respond to ATX as an inhibitor of noradrenalin receptors, which has been reported in another study.⁴ An opposite pattern was shown for the amplitude of IC P3 no-go early in our study. It was smaller in the RE group than in the non-RE group. In several previous studies, the amplitude of the P3 no-go wave was shown to decrease in the ADHD population.⁵⁹ IC P3 no-go early is part of the P3 no-go wave, and our results seem to be in agreement with that previous research. According to sLORETA (standardized low-resolution brain electromagnetic tomography, <http://www.uzh.ch/keyinst/loreata.htm>), this component is generated in the supplementary motor area of the prefrontal cortex,⁵⁶ an area that receives high-density inputs for the dopaminergic system.⁸⁶ We therefore suggest that members of the RE group are demonstrating frontal lobe dysfunction and are responsive to medication directed to the dopaminergic system.

Excess theta in the central–frontal electrodes has been found in many studies on ADHD.^{20,22} In the Introduction section of this paper, we refer to studies showing that ADHD patients with this EEG pattern respond favorably to stimulant medication. Our data support these studies. In our group of REs, however, the excess of theta was more widely distrib-

uted, including in the posterior regions of the cortex. Our non-RE group showed more posterior alpha activity than the RE group did. The posterior alpha is considered as an idling rhythm because it increases in the eyes-closed condition.⁸⁷ Posterior brain regions in the non-RE group may be idling to a greater extent than is seen in the RE group and in controls, corresponding to the reduced amplitude of IC cue P3 in non-REs. In addition, we found that the non-RE group had a significantly lower performance IQ than the RE group (Table 4). Reduced-IC cue P3 and reduced-performance IQ correlated significantly ($r=0.22$), but the correlation with verbal IQ was not significant (0.09). Taken together, these data suggest that the non-RE group is characterized by a parietal/posterior dysfunction.

Our hypotheses regarding theta and ERPs were confirmed. We did not find a relationship between alpha peak frequency and medication effects, however, as reported by Arns et al,³¹ who found that ADHD patients with low alpha peak frequencies, mimicking excess theta, showed suboptimal medication responses. Our study and the Arns et al³¹ study both found a relationship between excess posterior alpha and nonresponse to stimulants, however. The subgroup of ADHD patients with excess power in the beta band has been seen as cortically hyperaroused and not expected to be stimulant REs. This view was not supported in a study by Clarke et al⁴⁴ reporting positive medication response for this subgroup. In a recent study, the same authors concluded that the beta subtype of ADHD is not hyperaroused.⁸⁸ The data from our study agree with the findings of Clarke et al.

We hypothesized that comorbid learning disabilities, anxiety disorders, and autism/Asperger's syndrome predict nonresponse. These hypotheses were not confirmed. In our previous study on side effects,⁷² comorbid learning disabilities and anxiety (measured by indexes in ERP) increased the risk of adverse effects. It may be that the widely accepted notion that comorbidity reduces medication effects is partly related to side effects.

We also predicted that patients with the most deviant behavioral results in VCPT would turn out to be REs. This was found to be the case for omission errors and reaction time variability, and confirms research showing that such deviances are common in ADHD and improve with medication.²⁰ It is also a reasonable hypothesis that patients with the most pronounced difficulties have the most to gain from treatment. In a previous study,⁷² we found that a fast reaction time was associated with side effects. In this study we found the same association with non-RE. Both findings are in accordance with studies showing that choice reaction time is associated with frontal lobe function.⁸⁹

Limitations

Based on all available information from rating scales and interviews, medication effects were independently evaluated by two psychologists, one of them being the first author. Although he was blind to all data involved in predictions, it can be claimed that a key author who is responsible for interpretations of data should not be involved in such subjective decisions. A scale with scores of 2–1–0 was later converted into a 1–0 scale (see Methods section). An outcome measure that included a rating scale of ADHD symptoms might have resulted in more details. On the other hand, the key question in the clinic is whether or not there is an effect. We report effects on optimal dose after 4 weeks. We have no data relating effects to dose. Although this could be seen as a limitation, we would argue that our procedures are close to clinical reality. The sample size ($N=98$) in this study is relatively low for a logistic regression analysis with many parameters, and some key predictors found to be nonsignificant might have been significant with a larger sample size.

Clinical implications

A large number of children and adolescents with ADHD worldwide are treated with stimulants. About 20%–30% are non-REs, requiring close follow-up, careful titration, changes in medication, or reliance on other treatment options. Knowing who is at risk for nonresponse before the onset of treatment is clinically relevant. To draw the line between REs and non-REs can be difficult, as some attention-enhancing effects of stimulant medication are seen even in non-ADHD controls. In other cases, positive effects can be overshadowed by comorbid problems. Access to data predicting the probability of clinical response can be useful in such cases. As new medications for ADHD are developed, the question of “what works for whom” will be even more compelling. We argue that the non-RE group, characterized by parietal and not primarily frontal dysfunctions, may constitute a meaningful subgroup for research. Combining the results of this study with our findings on side effects⁷² will increase the clinical utility of the methods described.

Conclusion

Three variables in this study contributed significantly to the prediction of clinical effects of stimulant medication in pediatric ADHD: power in the QEEG theta band (excessive in REs in comparison with norms); ERP component IC cue P3, reflecting processing of target relevant information (normal in REs); and ERP component IC P3 no-go early related to inhibition of motor response (lower in REs). According to

sLORETA, the IC P3 no-go early component was localized in the supplementary motor cortex (BA 6), and the IC cue P3 component was localized in the parietal cortex (BA 5). It should be stressed here that we did not find that excess beta, a low alpha peak frequency, or comorbid diagnoses predicted the negative outcome that has been reported in previous studies. We argue that the brain deviances of REs are related to dopaminergic frontal systems, whereas the deviances of non-REs are related to temporal/parietal systems that are not considered dopaminergic.

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Disclosure

The authors report no conflicts of interest in this work.

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