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Influence of a Latrophilin 3 (*LPHN3*) risk haplotype on event-related potential measures of cognitive response control in attention-deficit hyperactivity disorder (ADHD)

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Abstract

Current research strategies have made great efforts to further elucidate the complex genetic architecture of attention-deficit hyperactivity disorder (ADHD). The present study examined the impact of an *LPHN3* haplotype that has recently been associated with ADHD (Arcos-Burgos et al., 2010) on neural activity in a visual Go-NoGo task. Two hundred sixteen adult ADHD patients completed a Continuous Performance Test (CPT) while the ongoing EEG was simultaneously recorded. Results showed that patients carrying two copies of the *LPHN3* risk haplotype (*n*=114) made more omission errors and had a more anterior Go-centroid of the P300 than patients carrying at least one *LPHN3* non-risk haplotype (*n*=102). Accordingly, the NoGo-Anteriorization (NGA; topographical ERP difference of the Go- and NoGo-condition), a neurophysiological marker of prefrontal functioning, was reduced in the *LPHN3* high risk group. However, in the NoGo-condition itself no marked differences attributable to the *LPHN3* haplotype could be found. Our findings indicate that, within a sample of ADHD patients, the *LPHN3* gene impacts behavioral and neurophysiological measures of cognitive response control. The results of our study further strengthen the concept of an *LPHN3* risk haplotype for ADHD and support the usefulness of the endophenotype approach in psychiatric and psychological research.

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Keywords

Latrophilin 3 (LPHN3); Attention-deficit hyperactivity disorder (ADHD); Prefrontal cortex; Go-NoGo; Imaging genetics

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common psychiatric childhood disorder that frequently persists into adulthood (Barkley, 1998) and is accompanied by a wealth of socio-economic problems (Kessler et al., 2006). Core symptoms comprise inattention, hyperactivity and impulsivity, and comorbid conditions are common (Biederman, 2005; Polanczyk et al., 2007; Skounti et al., 2007). While most children display all symptoms, subtypes emphasizing inattention or hyperactivity-impulsivity have been defined (Saß et al., 2003). Overall, ADHD puts children at higher risk for prospective disadvantage (Mannuzza et al., 1993) and places a substantial economic burden on patients, families, and society (Birnbaum et al., 2005; Matza et al., 2005).

One well-elaborated neuropsychological model assumes ADHD to be based on a core deficit in behavioral inhibition (Barkley, 1997, 1998; Döpfner and Lehmkuhl, 2006), subsequently affecting related executive functions. More recent concepts stress the importance of other response control aspects in pathogenesis, particularly higher-order controlled motor (dys-) functioning as well as deficient attentional control and mental flexibility (Slaats-Willemse, 2003). In his dual-pathway model, Sonuga-Barke (2003) proposed—in addition to the mentioned inhibition deficit (executive circuit)—a second mechanism potentially underlying ADHD symptoms in at least part of the patients, which is associated with an increased delay aversion and related to reward circuitry dysfunction (motivational subtype). Currently a triple-pathway model is under debate (with additional temporal processing deficits), which, however, still needs to be empirically replicated (Sonuga-Barke et al., 2010). The concept of ADHD-related deficits in response inhibition, motor control, and general executive processes (i.e. the executive circuit according to Sonuga-Barke) has been supported by numerous neuropsychological studies (e.g., Barkley et al., 1992; Borger and van der Meere, 2000; Hanisch et al., 2006; Losier et al., 1996; Martel et al., 2007; Nigg, 1999; Uebel et al., 2010). Accordingly, brain imaging studies found reduced activity in prefrontal areas during performance of response inhibition/higher order motor control paradigms (Rubia et al., 1999; Rubia et al., 2005) and other executive processes (Bush et al., 1999; Schweitzer et al., 2000).

There is evidence for substantial genetic influences on the etiology and pathogenesis of ADHD (Biederman, 2005; Faraone and Doyle, 2000; Faraone et al., 2005; Franke et al., 2012; Gizer et al., 2009; Martin et al., 2002). Especially variations in genes of the dopaminergic, but also the noradrenergic and the serotonergic system have been examined in association and linkage studies. Potential candidate genes include the dopamine transporter (DAT) gene, the dopamine receptor D4 (DRD4) gene, the dopamine β hydroxylase (DBH) gene, and the serotonin transporter (5-HTT) gene. Despite the high heritability of ADHD shown in twin studies (Faraone and Doyle, 2000; Levy et al., 1997), results from molecular genetic studies indicate a complex genetic architecture with many

genes of small effect mediating the genetic vulnerability (Faraone et al., 2005). Linkage analyses found markers at diverse loci on different chromosomes (Arcos-Burgos et al., 2004) that are related to the diagnosis of ADHD. Recently, common variants of the Latrophilin 3 (*LPHN3*) gene located on chromosome 4 were found to increase the susceptibility for ADHD in several populations (Arcos-Burgos et al., 2010). LPHN3, the most brain-specific latrophilin (Ichtchenko et al., 1998; Sugita et al., 1998), is a member of the LPHN subfamily of G-protein coupled receptors (GPCRs). LPHN3 mRNA showed significant expression in human amygdala, caudate nucleus, cerebellum, and cerebral cortex, and individuals carrying the *LPHN3* susceptibility haplotype exhibited a significantly decreased NAA/Cr ratio[2] in the left lateral and medial thalamus as well as the right striatum (Arcos-Burgos et al., 2010). As *LPHN3* is particularly expressed in mesolimbic regions of the brain that have been implicated in ADHD (Krain and Castellanos, 2006), a functional relation with ADHD symptomatology is quite plausible. Recently, Domene et al. (2011) could show that the susceptibility haplotype was not associated with significant coding region changes or canonical splice site alterations, which indicates non-coding variations to be likely contributors for ADHD.

Genetic approaches are hampered as the relation of specific genes and discrete disorders is often not as close as twin studies suggest. The endophenotype concept (cf. Almasy and Blangero, 2001; for more recent conceptual considerations see also Kendler and Neale, 2010) aims at identifying markers that are more directly connected to the underlying psychopathology than the clinical diagnoses themselves, and therefore much “closer” to etiological factors (e.g., genes, environment). Besides measuring psychological constructs (Zobel and Maier, 2004), assessing brain function is one means of characterizing such endophenotypes (Ehlis et al., 2007; Hariri et al., 2002; Hariri and Weinberger, 2003). By combining neuroimaging with genetic analyses, associations of genetic variants (e.g., single nucleotid polymorphisms; SNPs) with measures of brain function can be examined. The first imaging genetic study described an effect of the 5-HTT genotype on the topography of event-related potentials during a response inhibition task (Fallgatter et al., 1999). Hence, it is possible to measure gene-related differences in neural activity that are not necessarily apparent on a behavioral level (Bookheimer et al., 2000; Dresler et al., 2010; Egan et al., 2001; Ehlis et al., 2007).

Among the different endophenotypes that have been proposed for ADHD, dysfunctions in response inhibition as well as in attentional control and motor control processes play a particularly important role (Slaats-Willemse, 2003). A cognitive paradigm that comprises all of these functions is the Continuous Performance Test (CPT; Rosvold et al., 1956), a Go–NoGo task that requires both the execution and the inhibition of primed motor responses. The CPT can easily be applied and has been used several times to study behavioral inhibition and related neurophysiological markers in ADHD (e.g., Dhar et al., 2010; Losier et al., 1996; Spronk et al., 2008). For this paradigm, a reliable electrophysiological marker presumably capturing prefrontal functioning, the so-called NoGo-Anteriorization (NGA), has been identified and established (Fallgatter et al., 1997, 2002b; Fallgatter and Strik,

[2]Ratio of N-acetylaspartate to creatine (assessed via proton magnetic resonance spectroscopy), which provides an index of neuronal number or viability.

1999). In line with conventional P300 single electrode data, indicating increased P300 amplitudes over fronto-central electrode positions under inhibitory (NoGo) conditions, the NGA quantitatively describes the amount of anteriorization of the positive brain electrical field during the inhibition (NoGo-condition) relative to the execution (Go-condition) of a primed motor response and has been suggested as a topographical ERP marker of cognitive response control (see, e.g., Fallgatter et al., 1997). Neuroanatomically, the phenomenon of the NGA seems to reflect an increased activation of prefrontal areas during motor inhibition (Fallgatter et al., 2002b). The NGA, as well as the underlying Go- and NoGo-centroids, were shown to have an excellent short- (Fallgatter et al., 2001) and long-term test-retest reliability (Fallgatter et al., 2002a). Adult ADHD patients were characterized by reduced NGA values (Fallgatter et al., 2005), indicating that this parameter might be an adequate endophenotypic marker for prefrontal dysfunction during processes of response control in ADHD. Moreover, an impact of dopaminergic (Dresler et al., 2010; Ehlis et al., 2007), glutamatergic (Fallgatter et al., 2006) and serotonergic (Baehne et al., 2009) genetic polymorphisms on the NGA has been shown, indicating that the NGA constitutes a suitable functional parameter for imaging genetic studies.

In the present study, we examined if variants of the *LPHN3* gene are associated with altered neural activity, i.e. differences in the NGA, in adult ADHD patients. Because of the expression of *LPHN3* in ADHD relevant brain regions, and because of the prominent executive/inhibitory dysfunctions associated with the disorder, we hypothesize an influence of *LPHN3* on this measure of prefrontal functioning in an adult ADHD sample. Although there is a plethora of findings on ERP parameters in ADHD assessing various cognitive processes (e.g. Doehnert et al., in press; Marzinzik et al., 2012), we focus on a specific response execution/response inhibition parameter that has proven to be well-suited for our purpose.

2. Materials and methods

2.1. Participants

Two hundred sixteen adult in- and outpatients of the Department of Psychiatry, Psychosomatics and Psychotherapy of the University of Wuerzburg participated in the study, all fulfilling the diagnostic criteria for ADHD (according to DSM-IV). Patients gave their written informed consent after complete description of the study. Exclusion criteria were age below 18 and above 60 years, current medication with methylphenidate[3] or other psychotropic compounds, as well as severe somatic or neurological disorders. Patients were stratified according to their *LPHN3* genotype and grouped into patients with either two copies of the Latrophilin risk haplotype (“high risk group”, *n*=114) or a maximum of one copy of the risk haplotype (heterozygous genotype [*n*=85] or homozygous non-risk haplotype carriers [*n*=17]; “low risk group”, *n*=102; cf. Arcos-Burgos et al., 2010). Sample

[3]Methylphenidate (MPH) acts as an indirect dopamine agonist with a putative site of action within the prefrontal cortex (cf., Berridge et al., 2006; Spencer et al., 2012; Vaidya et al., 1998). As previous genetic findings could show an impact of dopaminergic risk alleles on the NGA and CPT-related neurophysiology (Dresler et al., 2010; Heinzel et al., in press) and the prefrontal cortex is strongly involved in the phenomenon of the NGA (Fallgatter et al., 2002b), we chose to exclude patients treated with MPH to avoid confounding effects of this medication. Also, the strong link of LPHN3 to dopaminergic pathways (see above) contributed to our decision to exclude this potential confound from our analyses.

characteristics are given in Table 1. These two groups were comparable in age, gender distribution, distribution of handedness, mean WURS-*k* score (German short version of the Wender Utah Rating Scale; Retz-Junginger et al., 2002)[4] and mean verbal IQ estimated according to the MWT-B, a measure of crystallized intelligence[5]. 64 patients of the whole sample belonged to the inattentive subtype of ADHD, 13 to the hyperactive-impulsive subtype and 139 to the combined subtype. Subtype composition did not significantly differ between genotype groups. All patients were of Caucasian origin. Regarding psychiatric comorbidities, 45 out of the 216 ADHD patients (20.8) had a comorbidity with another axis I disorder as assessed via the Structured Clinical Interview for the DSM-IV (SCID-I). Details regarding comorbidities and medication can be found in Table 1.

The study was reviewed and approved by the Ethics Committee of the University of Wuerzburg, and the procedures involved were in accordance with the latest version of the Declaration of Helsinki.

2.2. *LPHN3* genotyping

For *LPHN3* genotyping, we selected four single nucleotide polymorphisms (SNPs) defining the ADHD-associated at-risk haplotype in the study by Arcos-Burgos and associates (Arcos-Burgos et al., 2010): rs2305339, rs734644, rs1397547, and rs1397548. DNA was extracted from venous blood using a routine de-salting method. SNPs were genotyped according to the manufacturer's instructions by using the Sequenom MassArray system (Sequenom, San Diego, CA) coupled to a Bruker Autoflex mass spectrometer (Bruker Daltonics, Bremen, Germany). PCR was performed using iPlex chemistry along the manufacturer's recommendations as found in the MassArray iPlex standard operation procedure. Primer sequences can be obtained on request. All genotyped SNPs were in Hardy–Weinberg equilibrium. Subsequent to genotyping, individual haplotypes were constructed using the famhap software package (Becker and Knapp, 2004; Herold and Becker, 2009). Likelihood weight was above 0.96 in every case (means, 0.997). rs2305339—rs734644—rs1397547—rs1397548 AGCC was defined as the ADHD-risk haplotype H1, whereas all other haplotypes were grouped together and designated as No-H1. Individuals carrying two H1 copies were considered as a *LPHN3* high risk group, while all other subjects were grouped together forming the *LPHN3* low risk group.

2.3. Electrophysiological investigation

Patients performed an OX-version of the Continuous Performance Test (Rosvold et al., 1956) during registration of the ongoing EEG. The measurement took place in a dimly lit, sound-attenuated and electrically shielded room. Letters were presented sequentially on a computer screen (viewing distance: 80 cm) in pseudo-randomized order. The stimuli were approximately 30 mm high and 20 mm wide, resulting in a visual angle of 2.15° vertically and 1.43° horizontally. Patients were instructed to press a response button only when the letter O was directly followed by the letter X. Speed and accuracy were emphasized equally

[4]The WURS-*k* assesses the severity of earlier childhood ADHD symptoms by investigating adults retrospectively. The WURS-*k* score thus reflects severity of childhood ADHD symptoms for each participant. For a total of 7 patients no WURS-*k* score was available due to single items missing.

[5]For a total of 7 patients no IQ data were available.

during explanation of the test. A short training session was performed to ensure correct understanding of the instructions. The complete stimulus set consisted of 400 letters (114 letters O=primer condition, 57 X following an O=Go-condition, 57 other letters following an O=NoGo-condition, and 172 letters not following an O=distractors) with a stimulus-onset asynchrony (SOA) of 1850 ms and a stimulus presentation time of 200 ms. The whole CPT procedure lasted about 15 min.

The current version of the CPT allows for an examination of Go and NoGo processes at the same time (both of which also contribute to the calculation of the NGA; see above). Since the P300 is particularly sensitive to stimulus probability, both conditions can be directly compared only with an equal probability of Go and NoGo trials. In order to provoke response preparation and thereby motor inhibition in NoGo trials, we—therefore—chose not to manipulate the Go:NoGo ratio (which would be one way to ensure heightened inhibitory control in NoGo trials, if for example an 80:20 ratio of Go:NoGo trials was chosen), instead including a primer ("cued CPT") which preceded both Go and NoGo trials thus provoking response preparation in either case. That way, prepared motor responses had to be suppressed in the NoGo condition, hopefully involving about the same amount of inhibitory control that would also have been provoked by unequal stimulus probabilities (e.g. Eimer, 1993). Beyond that, as we were not only interested in inhibition processes but also in general cognitive and motor control, respectively, an equal probability of Go and NoGo trials seemed the most suited.

During performance of the task, the EEG was recorded from 21 scalp electrodes placed according to the International 10/20-System (Jasper, 1958). Three additional electrodes were attached at the outer canthi of both eyes and below the right eye for registration of eye movements. The technical equipment consisted of a 32-channel DC-amplifier and the recording software Vision Recorder (Brain Products, Munich, Germany). The hardware filter was set to a bandpass from 0.1–100 Hz; A/D rate was 1000 Hz. The recording reference was placed between Fz and Cz, the ground electrode between Fpz and Fz. All electrode impedances were kept below 5 k.

2.4. Data analysis

Electrophysiological data were processed using the Vision Analyzer software (Brain Products, Munich, Germany). As a first step, data were filtered offline with a bandpass from 0.1 to 70 Hz and re-referenced to an average reference. They were corrected for ocular artifacts using the standard algorithm implemented in the software (Gratton and Coles, 1989). After a computerized artifact rejection (only amplitudes <70V were allowed in all EEG-channels within 100 ms before and 700 ms after stimulus presentation), the artifact-free epochs after correct responses were segmented and individually averaged to one Go- and one NoGo- event-related potential (ERP). For the NoGo-ERP, the time point of the most positive peak at electrode position Cz within a P300 time-window (277-434 ms) (Fallgatter et al., 1997) was used to calculate the two-dimensional topography by means of the centroid method (Lehmann, 1987), whereas the respective peak at electrode position Pz was used for the Go-condition. The location of each individual centroid on an anterior-posterior axis was determined by numbers from 1 (level of electrode position Fpz) to 5 (level of Oz) as

illustrated in Figure 1 (locations somewhere in between two electrode positions were expressed by respective decimal numbers). Smaller values of centroid-locations indicate a more anterior localization. For a more detailed description of the centroid-method, please confer the work of Lehmann (Lehmann, 1987) and our previous publications (e.g., Fallgatter et al., 1997). The individual NoGo-Anteriorization (NGA) was calculated as the difference between the Go- and NoGo-centroid on the anterior-posterior axis.

2.5. Statistical analysis

All statistical analyses were performed with the software SPSS for Windows (version 14.0). For the P300 centroids, a 2 × 2 analysis of variance (ANOVA) was conducted, comprising the between subject factor “genotype” and the within-subject factor “CPT condition” (Go vs. NoGo). Post-hoc analyses were calculated by means of two-tailed t-tests for independent samples for between-group comparisons of the Go- and NoGo-centroid as well as the NGA. T-tests were also used to compare mean Go reaction times between the two genotype groups. Equality of variances was tested by means of Levene's test and corrections for unequality were performed when necessary. Since none of the CPT error data (number of commission errors after NoGo stimuli; commission errors after primers or distractors; number of omission errors) was normally distributed according to Kolmogorov– Smirnov's *Z*-statistic (all *p*-values <0.001), Mann–Whitney *U*-tests were used for between-group comparisons of these variables. The significance level was set to $p<0.05$. We derived our hypotheses for the risk haplotype from the recently published literature and intended to test these in a first study on the functional impact of the LPHN3 risk haplotype on specific parameters of brain function in ADHD. For this first, exploratory analysis we think that our methodological approach of foregoing a strict correction for multiple testing is warranted.

2.6. sLORETA source localization analyses

Source localization of between-group differences in topographical ERP data was carried out using standardized low resolution brain electromagnetic tomography (sLORETA) (Fuchs et al., 2002; Jurcak et al., 2007; Pascual-Marqui, 2002). sLORETA is a weighted minimum norm inverse solution for EEG/MEG data used to compute statistical maps from scalp potentials indicating the location of underlying neural sources with small error. Briefly, sLORETA calculates the standardized current density at 6239 Gy matter voxels in the cortex, ACC and hippocampus of the MNI-reference brain under the assumption that neighboring voxels should have a maximally similar electrical activity. The inverse solution was computed separately per condition and subject. In order to detect sources for between-group differences, comparison of *LPHN3* groups was conducted for each voxel using the non-parametric method implemented in the software, performing randomization (5000 permutations) and correcting for multiple comparisons (Pascual-Marqui, 2002). Specifically, voxel-based sLORETA images were compared between genotype groups for the time-point of the mean Go latency of the P300 across the whole study sample (350 ms; low-risk group, $n = 102$: 344±49 ms; high-risk group, $n=114$: 353±41 ms). Log of ratio of averages was used and considered with a 5 level of significance.

3. Results

3.1. Behavioral data

The two genotype groups did not differ significantly regarding their mean reaction times to Go-stimuli (low risk group: 511.44±117.58 ms vs. high risk group: 490.52±115.34 ms; t_{214}=1.32, p=0.19). Mann-Whitney U-tests also indicated a similar number of commission errors after NoGo stimuli and after primers/distractors (U= 5647.0 and 5408.5, respectively; Z= −0.61 and −0.94; p>0.35), however, patients with a high risk genotype made significantly more omission errors than patients of the low risk group (U=4796.0, Z= −2.29, p=0.02). Reaction time variability was comparable between the two genotype groups (t_{214}=0.169, p=0.866).

3.2. ERP data

The grand average ERPs and mean centroids of both genotype groups are shown in Figure 1, along with a schematic illustration of the quantification of the NGA as the geometrical distance between the Go- and NoGo-centroid. The 2 × 2 ANOVA for the centroids revealed a significant main effect “CPT condition” ($F_{1, 214}$=471.10, p<0.001) as well as a significant interaction “CPTcondition × genotype” ($F_{1, 214}$ = 3.96, p<0.05). No significant main effect “genotype” occurred ($F_{1, 214}$=2.08, p=0.15). Post-hoc analyses revealed that the two genotype groups did not differ significantly regarding their NoGo-centroids (high risk group: 3.03±0.40 vs. low risk group: 3.04±0.41; t_{214}=0.15, p=0.88), however, patients of the high risk group displayed Go-centroids that were located significantly more anterior (3.62±0.43) than Go-centroids of the low risk group (3.75±0.39; t_{214} = 2.26, p = 0.025). This topographical ERP finding was accompanied by a statistical trend for reduced activation within the left middle frontal gyrus (BA 10; MNI coordinates according to sLORETA software: −40, 45, 25; p=0.1) in *LPHN3* high risk carriers (see Figure 2)[6]. The differential impact of *LPHN3* genotype on Go- and NoGo-centroids resulted in a significantly reduced mean NGA in patients of the high risk (0.59±0.46) as compared to the low risk group (0.71±0.42; t_{214}=1.99; p<0.05). The main effect “CPT condition” indicated that NoGo-centroids were located significantly more anterior than Go-centroids across the whole sample of ADHD patients (mean Go-centroid: 3.68±0.42; mean NoGo-centroid: 3.03±0.40), which reflects the well known finding of the NoGo-Anteriorization (NGA). Neither the NGA nor the centroids were significantly correlated with WURS-*k* scores (−0.05<r<0.06; p>0.4). P300 latencies for Go- and NoGo-trials did not differ significantly between the haplotype groups (t_{214}<1.53, p>0.13). The electrophysiological data did not correlate with the behavioral data. Results remained virtually unchanged, when patients with a current tricyclic medication were excluded from the analysis. Adjusting the analyses for effects of age and sex did not change the results.

We split the sample into three separate groups (0 [n = 17] vs. 1 [n = 85] vs. 2 risk haplotypes [n=114]) and checked in an additional analysis whether there were any gene-dose effects.

[6]Due to the left-lateralized finding, we repeated the analysis for right-handers only, in order to exclude the possibility of a confounding influence of patients ' handedness. This analysis confirmed the reported finding with overall stronger effects (minimal p=0.042) and a significant impact of LPHN3 genotype on left-frontal structures (BA 10 and 46; left middle frontal gyrus as well as left inferior and superior frontal gyrus).

For the omission errors there was a significant linear trend ($F_{1, 213} = 5.244$, $p=0.023$); however, this effect was mainly driven by the group with 2 risk haplotypes, i.e. the groups with 0 and 1 risk haplotype did not substantially differ (see Figure 3). The same was found for the NGA (see Figure 3). The linear trend test revealed a marginally significant effect ($F_{1, 213} = 3.336$, $p=0.069$), but this was also due to the group with 2 risk haplotypes without differences between the other two groups. This analysis of the gene-dosage model suggests a recessive rather than an additive effect of LPHN3.

4. Discussion

In the present EEG study we investigated if *LPHN3*, a haplotype presumably conveying susceptibility for ADHD (Arcos-Burgos et al., 2004), is associated with a neural marker of cognitive response control that has been found to be aberrant in adult ADHD patients (the so-called “NoGo-Anteriorization” or NGA; Fallgatter et al., 2005). To this end, we compared two groups of adult ADHD patients, one being homozygous for the risk haplotype (high risk group) and the other one carrying at least one copy of the non-risk haplotype (low risk group), regarding their behavioral and ERP responses during a primed Go-NoGo task (Continuous Performance Test, CPT) which has been shown to represent a suitable paradigm for endophenotype research in ADHD (Uebel et al., 2010). In previous CPT studies with control populations, the general behavioral and ERP findings can be summarized as follows (Fallgatter et al., 2004, 2005; Baehne et al., 2009; Dresler et al., 2010): Controls show an increased frontalization of the brain electrical (P300) field during NoGo trials (as indexed by the topographical ERP parameter of the NGA) as compared to childhood and adult ADHD populations. They also generally make less omission and commission errors, show reduced reaction times and also a significantly reduced reaction time variability. NoGo-related ACC function has been shown to be reduced in ADHD patients compared to controls.

In line with our hypotheses, we found a significant impact of *LPHN3* haplotype on ERPs evoked by the CPT, with a significantly reduced NGA in the high risk group of patients. Remarkably, this effect was solely carried by differences in the Go-centroid (brain electrical distribution of the P300 during Go-trials), which showed a significantly more anterior location in the high risk as compared to the low risk group, with a tendency for reduced activation within the middle frontal gyrus (BA 10) according to sLORETA source localization. The NoGo-centroid however, which has primarily been associated with processes of inhibitory control, was very similar for both groups of patients. These findings are in remarkable accordance with the results of Fallgatter et al. (2005), who found a significantly reduced mean NGA in adult patients with a probable childhood ADHD that was mainly attributable to a significantly more anterior location of the Go-centroid in patients as compared to healthy and psychiatric controls. In line with our electrophysiological findings, analyses of the behavioral data showed that patients of the high risk *LPHN3* group made more omission errors (i.e. no response to a Go-stimulus) than patients of the low risk group, whereas reaction times and commission errors (i.e. button presses following NoGo, primer, or distractor stimuli) were comparable for both haplotypes. Behavioral data, therefore, confirmed abnormalities in the high risk group of ADHD patients during the execution of primed motor responses, without indicating a specific influence of

LPHN3 on processes of inhibitory control. Given the attentional nature of many ADHD symptoms, it should also be considered that differences in omission errors may indicate differences in inattention between genotype groups without being specifically related to processes of response or motor control.

Taken together, these findings show that a functional haplotype recently associated with the diagnosis of ADHD (Arcos-Burgos et al., 2010) is also related to basic neural activity and processes of cognitive response control (and possibly attention in general) in these patients. The haplotype group more susceptible for ADHD (the high risk group) showed an altered pattern of neural activation, as well as behavioral deficits, during the execution of prepared motor responses. Since impaired processes of attentional and motor control have been proposed to be specifically related to (the genetic vulnerability for) ADHD (compare Slaats-Willemse, 2003), this finding nicely links a putative genetic risk factor (*LPHN3* risk haplotype) to an endophenotypic marker of the disease. Since both haplotype groups were comparable with respect to various possible confounds, including the distribution of ADHD subtype diagnoses (see Section 2), the above described differences cannot simply be explained by differences in any of the registered confounding factors.

The underlying neurobiological mechanisms of *LPHN3* and its endogenous function in vertebrates are far from being understood. Currently, it is discussed if *LPHN3* mutations may impact the development of synaptic circuits: fibronectin leucine-rich repeat transmembrane (FLRT) proteins have been found to act as endogenous LPHN3 ligands and in-vitro findings indicate an involvement of the FLRT3–LPHN3 complex in glutamatergic synapse development (O'Sullivan et al., 2012). Such developmental pathways may alter general task-dependent circuit activity by modifying glutamatergic-GABAergic balance in subcortical and cortical brain areas. A possible relationship of FLRT3 copy number variations with ADHD (Lionel et al., 2011) hints at a putative mechanism mediating the development of ADHD symptoms. As LPHN3 is expressed in brain structures belonging to the nigrostriatal, the mesolimbic, and the mesocortical dopaminergic systems (Martinez et al., 2011), interaction with prefrontal cortex activity is quite likely and may explain differences in the investigated neurophysiological marker. However, these preliminary findings—without further support from in-vitro and in-vivo studies—have yet to be considered with caution.

In our study, several limitations need to be considered. First, the statistical effects—though existent—are rather small ($p<0.05$), indicating small haplotype effects on behavioral and neurophysiological measures of cognitive response control in ADHD. Thus, results may also represent false positive errors. However, as we had explicit hypotheses derived from recent literature regarding the direction of effects, and genetic effects were not expected to be large, we deem our results meaningful in a way that they add to the existing knowledge about the complex genetic influences in psychiatric disorders such as ADHD. The convergence of an association on a categorical level (Arcos-Burgos et al., 2010) and our support for an association on an endophenotypic supports a contribution of LPHN3 to ADHD pathogenesis. Second, about 20 of the investigated sample had psychiatric comorbidities that might have affected the present findings, even if these comorbidities are commonly associated with ADHD (Jacob et al., 2007). However, since comorbidity

distribution across genotype groups was rather even and ADHD was always the primary diagnosis, we consider our sample to be representative for the ADHD population. Third, a control sample stratified for the respective haplotype is missing in our analyses. Therefore, our results—though hypothesis-driven—have to be considered preliminary and explorative. Nonetheless, an endophenotypic effect of the same *LPHN3* haplotype previously associated with ADHD (Arcos-Burgos et al., 2010) further supports the assumed involvement of *LPHN3* in ADHD pathogenesis. Fourth, although we investigated a rather large sample for an imaging genetic study, it is relatively small as compared to genetic association studies which may prevent detecting genetic influences that—as single genes—actually only share a small proportion on the overall large hereditary influences in genetically complex disorders such as ADHD. Fifth, the sLORETA results have to be considered with caution as the (limited) number of electrodes prevents a more precise localization, which might have been most critical for localizing deeper structures such as the hippocampus or ACC. Adding to that, effects we detected were rather weak on a statistical level. Therefore, the sLORETA analysis should be considered preliminary. What increases our confidence in the findings is the fact that a prefrontal structure plausibly involved in processes of cognitive response control (the middle frontal gyrus) was detected as the source of our topographical ERP findings and that the results of the source localization were exactly replicated (with increased statistical significance) in a subgroup of patients including only right-handers (with several neighboring voxels showing the same effect).

Recently, theoretical and conceptual aspects of the endophenotype concept have been considered in the scientific community stressing the importance of differentiating between mediational (i.e. the endophenotype mediates the relation from gene to disorder) and liability-index models (i.e. the endophenotype is risk-indicating and may only be an epiphenomenon) and of considering bidirectional relationships of endophenotype and disorder (Kendler and Neale, 2010). Beyond that, relationships may be more complex with endophenotypes also reflecting environmental influences, and some genetic influences may only affect the endophenotype while others only affect the clinical symptoms. This indicates that with our investigation we can only cover a part of the gene-disorder-relationship, and additional prospective studies using multivariate analyses are needed to further elucidate the complex aetiopathology of mental disorders. As genetic influences may change over the life course (Dresler et al., 2010; Franke et al., 2010), it also has to be mentioned that our results only apply to adult ADHD patients as there is no data available for children.

To our best knowledge, our study is the first to show an influence of the *LPHN3* susceptibility haplotype on behavioral and neurophysiological responses of adult ADHD patients in an executive function task. The results of our study further strengthen the concept of an *LPHN3* risk haplotype for ADHD, and seem to implicate that motor control processes might be a basic cognitive mechanism mediating a respective genetic influence on overt behavior (symptomatology). The significant (behavioral and neurophysiological) differences between both haplotype groups *within* a clinical group of ADHD patients might furthermore indicate that the *LPHN3* risk haplotype is related to a specific subtype of the disorder, going beyond the subtypes defined by DSM-IV. Since the *LPHN3* risk haplotype is associated with a significantly decreased NAA/Cr ratio in brain regions also associated with ADHD

pathology (see introduction, Arcos-Burgos et al., 2010; Krain and Castellanos, 2006), we propose that a pathologically altered function (i.e. neuronal loss or damage) in these brain regions underlies the impact of *LPHN3* on cognitive response control and, thereby, ADHD symptomatology. In summary, our findings support a link between *LPHN3* and behavioral and neurophysiological measures of cognitive response control in ADHD patients, and once again emphasize the usefulness of the endophenotype approach in psychiatric and psychological research to elucidate putative etiological pathways.

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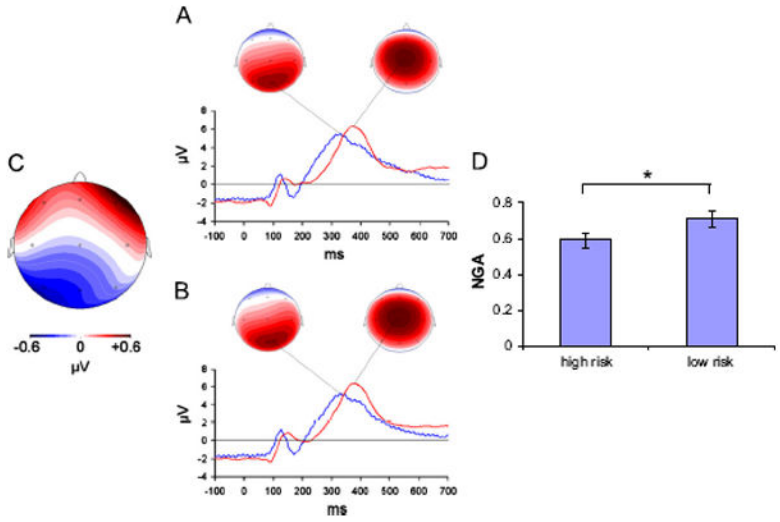

Figure 1.

Grand average curves for the CPT Go (blue; Pz) and NoGo condition (red; Cz) in patients with no copy (*n*=17) or one copy (*n*=85) of the *LPHN3* risk haplotype (low risk group; A) vs. patients homozygous for the risk haplotype (*n*=114; high risk group; B). Maps above the curves display the brain electrical field at the time-point of the P300 peak at Pz (Go condition; left map of a pair) and Cz (NoGo condition; right map of a pair), respectively. The difference map for the comparison of the two haplotype groups with respect to the Go-centroid (high minus low risk group) is depicted in the left part of the figure (C). Right panel depicts the main result of a reduced NoGo-Anteriorization in LPHN3 high risk carriers (vertical bars represent the standard error of the mean) (D). (For interpretation of references to color in this figure legend, the reader is referred to the web version of this article.)

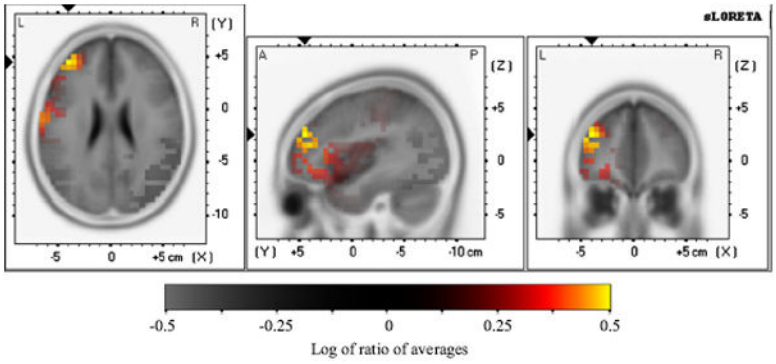

Figure 2.

Source localization of the difference in P300 data between genotype groups for the Go conditions of the CPT; sLORETA image displays the maximum difference, which was found in Brodman Area 10 (middle frontal gyrus) where patients of the *LPHN3* low risk group (n=102) tended to exhibited stronger activation values than patients of the high risk group (n=114; p=0.1).

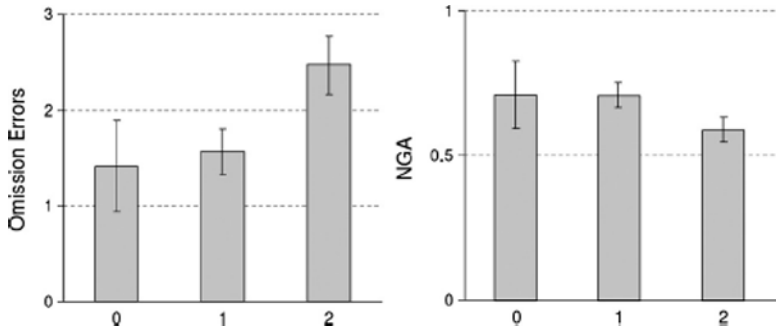

Figure 3.

Analysis of potential gene-dose effects for omission errors (left panel) and the NGA (right panel).

Table 1

Sample characteristics.

	High-risk (*n*=114)	Low-risk (*n*=102)	Statistics
Age	34.85±10.43	34.92±9.36	t_{214}=0.052, *p*=0.96
Male/female	58/56	52/50	χ^2=0.99, *p*=0.55
Right-/left-handed	105/9	95/7	χ^2 = 0.77, *p* = 0.49
WURS-*k* score	34.69±14.27	36.00±13.39	t_{207}=0.68, *p*=0.50
verbal IQ	112.08±13.23	110.65±13.21	t_{207}=0.78, *p*=0.43
Subgroup composition (combined/inattentive/hyperactive-impulsive)	74/34/6	65/30/7	χ^2=0.24, *p*=0.89
Comorbidities	22	23	χ^2=0.35, *p*=0.56
Alcohol dependence	3	3	
Depressive episode	9	5	
Agoraphobia	1	2	
Social phobia	4	4	
Panic disorder	0	1	
Generalized anxiety disorder	2	2	
Obsessive-compulsive disorder	1	3	
Hypochondriac disorder	0	1	
Bulimia	2	2	
Medication			
SSRI	6	9	
Tricyclic antidepressants	3	2	
Benzodiazepines	0	2	

For a total of 7 patients no WURS-*k* score was available due to single items missing. For a total of 7 patients no IQ data were available.