Data-Driven Analysis of Simultaneous EEG/fMRI Reveals Neurophysiological Phenotypes of Impulse Control

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Abstract: Response inhibition is the ability to suppress inadequate but prepotent or ongoing response tendencies. A fronto-striatal network is involved in these processes. Between-subject differences in the intra-individual variability have been suggested to constitute a key to pathological processes underlying impulse control disorders. Single-trial EEG/fMRI analysis allows to increase sensitivity for inter-individual differences by incorporating intra-individual variability. Thirty-eight healthy subjects performed a visual Go/Nogo task during simultaneous EEG/fMRI. Of 38 healthy subjects, 21 subjects reliably showed Nogo-related ICs (Nogo-IC-positive) while 17 subjects (Nogo-IC-negative) did not. Comparing both groups revealed differences on various levels: On trait level, Nogo-IC-negative subjects scored higher on questionnaires regarding attention deficit/hyperactivity disorder; on a behavioral level, they displayed slower response times (RT) and higher intra-individual RT variability while both groups did not differ in their inhibitory performance. On the neurophysiological level, Nogo-IC-negative subjects showed a hyperactivation of left inferior frontal cortex/insula and left putamen as well as significantly reduced P3 amplitudes. Thus, a data-driven approach for IC classification and the resulting presence or absence of early Nogo-specific ICs as criterion for group selection revealed group differences at behavioral and neurophysiological levels. This may indicate electrophysiological phenotypes characterized by inter-individual variations of neural and behavioral correlates of impulse control. We demonstrated that the inter-individual difference in an electrophysiological correlate of response inhibition is correlated with distinct, potentially compensatory neural activity. This may

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suggest the existence of electrophysiologically dissociable phenotypes of behavioral and neural motor response inhibition with the Nogo-IC-positive phenotype possibly providing protection against impulsivity-related dysfunction. *Hum Brain Mapp* 37:3114–3136, 2016. © 2016 Wiley Periodicals, Inc.

Key words: electrophysiological phenotypes; inter-individual differences; simultaneous EEG/fMRI; Go/Nogo; response inhibition; independent component analysis (ICA)

INTRODUCTION

Response inhibition is one component of impulse control [Aron, 2011; Simmonds et al., 2008; Stahl et al., 2014; Swick et al., 2011]. It refers to the ability to suppress inadequate but inadvertently activated prepotent or ongoing response tendencies [Barkley, 1997; Miyake, 2000; Stahl et al., 2014; Swick et al., 2011]. Go/Nogo tasks are frequently used to assess neural processes related to the inhibition of a prepotent motor response. Previous functional magnetic resonance imaging (fMRI) studies showed that response inhibition is associated with activations in cortical and subcortical structures [Aron, 2011; Chambers et al., 2009]. These include the inferior frontal gyrus (IFG), the (pre-)supplementary motor area (pre-SMA, SMA), as well as the inferior parietal lobe and insular cortex [Aron et al., 2003; Chikazoe et al., 2009; Konishi et al., 1998; Sebastian et al., 2013b; Sharp et al., 2010; Swick et al., 2011]. Subcortically, the subthalamic nucleus (STN) and the basal ganglia, especially putamen and caudate nucleus, are of particular importance [Aron, 2003; Jahfari et al., 2011].

In the electroencephalography (EEG) literature, Go/Nogo tasks have been used to study the electrophysiological correlates of response inhibition [Huster et al., 2013]. Comparisons between Nogo and Go conditions revealed robust task-dependent event-related potential (ERP) differences, mainly concerning the N2/P3 complex. This is a pronounced negative deflection (N2) followed by a late positive deflection (P3) over fronto-central electrodes which are both elicited by Nogo stimuli [Bokura et al., 2001; Falkenstein et al., 1999; Jodo and Kayama, 1992; Kopp et al., 1996; Ruchow et al., 2008b]. Taking advantage of the fMRI's high spatial resolution and the EEG's high temporal resolution, combined analysis of simultaneous EEG and fMRI data has also been used to disentangle neural responses related to different aspects or stages of information processing during response inhibition [Baumeister et al., 2014; Huster et al., 2011; Karch et al., 2014; Lavalley et al., 2014; Mulert et al., 2008; Schmäser et al., 2014]. Although these studies provided inhomogeneous results, they demonstrated that trial-by-trial coupling of inhibition-related EEG features with fMRI blood-oxygen-level dependent (BOLD) signal can help to disentangle different stages of neural processing during response inhibition. EEG data allow the analysis of trial-to-trial neural variability. Based on that, it allows also for detailed inter-individual difference analysis. This information can be

used to classify neurocognitive differences in inter-individual neural variability. Nevertheless, to the best of our knowledge, up to now there exist no combined EEG/fMRI studies that used this neural variability information for subgroup classification. One data-driven approach to detect and use this neural variability information is analysis by independent component analysis (ICA). This has been shown in a previous publication of our own group [Schmäser et al., 2014]. Importantly, using an approach sensitive to inter-individual differences allows for subgroup classification and hence to identify and characterize the neural correlates of inter-individual differences in response inhibition in healthy subjects. This in turn may provide important information for our understanding of deficits in response inhibition in heterogeneous psychiatric disorders such as attention deficit/hyperactivity disorder (ADHD) or borderline personality disorder (BPD).

The degree and effectiveness of inhibition in response inhibition paradigms varies not only between patient and healthy control groups but also across individuals in a group of healthy subjects. Thus, it seems reasonable to assume that such inter-individual differences constitute valuable information. The relationship between the personality trait of impulsivity and the neural underpinnings of inhibitory control has been investigated by several neuroimaging [Asahi et al., 2004; Brown et al., 2015; Collins et al., 2012; Horn et al., 2003] and electrophysiological studies [Kam et al., 2012; Ruchow et al., 2008b; Russo et al., 2008; Shen et al., 2014]. Some studies found negative correlations between high impulsive personality traits as assessed by the Barratt Impulsiveness Scale (BIS-11, [Patton et al., 1995]) and reduced neural activity in prefrontal areas [Asahi et al., 2004] and significantly reduced P3 amplitudes [Kam et al., 2012; Russo et al., 2008; Shen et al., 2014]. Other studies found an association between reduced prefrontal activity and higher risk tendency but not with higher BIS scores [Brown et al., 2015]. In contrast, several studies reported positive correlations between different impulsivity measures and enhanced neural activity in right prefrontal areas and left temporal gyrus [Horn et al., 2003], overall enhanced neural activity in Go condition [Collins et al., 2012], as well as significantly enhanced P3 amplitudes in high impulsive subjects [Kóbor et al., 2014]. Using reaction time variability as a task-related measure of impulsivity instead of self-rated questionnaires, Ruchow et al. [2008b] demonstrated that non-clinical high impulsive subjects compared to low impulsive subjects had

significantly reduced Nogo-P3 amplitudes but no differences in Nogo-N2. Thus, although these studies provided a mixed picture, they indicate that inter-individual differences in impulsivity traits of healthy subjects may influence the related neural activity which in turn may affect the results of group comparisons in clinical studies.

As measures from self-reported questionnaires and behavioral tasks are only weakly correlated [Cyders and Coskunpinar, 2011; Jacob et al., 2010; Reynolds et al., 2006; Stahl et al., 2014], subgroup classification based on task-related measures could provide more reliable results. Thus, to obtain an internally driven measure of individual differences we used Nogo-related independent components (ICs) as derived from the simultaneously acquired EEG for group selection. Electrophysiological ICs reliably associated with early processes of response inhibition were automatically classified for each subject [Schmüser et al., 2014]. Early processes of response inhibition means inhibition-related electrophysiological activity that are occurring within a time-window starting after visual processing and object recognition [Johnson and Olshausen, 2003] and ending before the subject's mean Go response time. This is a latency range in which the inhibition process most likely takes place. Subgroups were based on the existence or absence of such early Nogo-related ICs. This enabled us to test whether inter-individual differences in neural and behavioral correlates of responses inhibition may be driven by intra-individual variability in a data-driven way. These potential phenotypic groups within healthy subjects were further characterized and compared using behavioral, neuropsychiatric, unimodal ERP, and fMRI measures, as well as single-trial ERP/fMRI correlations.

METHODS AND EXPERIMENTAL DESIGN

Subjects

Thirty-eight healthy subjects (15 males; mean age: 37.34 ± 16.0) were included in this analysis. Subjects were recruited from a larger sample [Sebastian et al., 2013a] on the basis of good overall data quality for EEG and fMRI. All subjects were right-handed [Oldfield, 1971] and had normal or corrected-to-normal vision. Structural Clinical Interview for DSM-IV Axis I and II Disorders (SCID-I/II) was used (SCID I: [First et al., 1997]; German version: [Wittchen et al., 1997]; SCID II: [First et al., 1996]; German version: [Fydrich et al., 1997]) to exclude subjects with a lifetime history of axis I or axis II disorders. The study was approved by the Ethics Committee of the University of Freiburg Medical School and all subjects gave their informed consent prior to MRI scanning. Each subject received a financial compensation of €55.

Questionnaires

As this study was part of a larger study on response inhibition in healthy controls in comparison to psychiatric

diseases, besides of questionnaires typically used to assess self-rated impulsive personality traits as the Barratt Impulsiveness Scale-11 (BIS-11; [Patton et al., 1995]), the Sensation Seeking Scale (SSS-V; [Beauducel et al., 2003]), and the UPPS Impulsive Behavior Scale [Whiteside and Lynam, 2001], all subjects were asked to complete the German validated forms of the Wender Utah Rating Scale (WURS-k; childhood ADHD symptoms [Retz-Junginger et al., 2003]) and the Conners' Adult ADHD Rating Scale (CAARS-S:L; [Christiansen et al., 2011, 2012]) as well as an clinical assessment of the frequency and severity of manifestations of BPD (BPDSI = Borderline Personality Disorder Severity Index [Arntz et al., 2003]; German version: [Freese and Kröger, 1999]), and the clinical assessment (MADRS = Montgomery Asberg Depression Scale [Montgomery and Asberg, 1979]; German version: [Neumann and Schulte, 1988]) and self-rating scales (BDI = Beck Depression Inventory [Hautzinger et al., 1995]) of current depressive mood.

Group selection

Based on an automated independent component (IC)-classification procedure (cf. Data analysis, section IC classification) the initial group of 38 subjects was split into two subgroups: Nogo-IC-positive (in short: IC+; $N = 21$; 7 males; mean age: 35.0 ± 14.6) and Nogo-IC-negative (in short: IC-; $N = 17$; 8 males; mean age: 40.24 ± 17.6). Subgroups were defined on electrophysiological level using the existence or absence of specific ICs related to Nogo processing at an early latency located prior to the individual's mean Go response time (RT) as group separator.

Experimental Paradigm

A visual Go/Nogo-task was performed during simultaneous EEG/fMRI data acquisition. On the center of the screen, with visual angle of 3.5° vertically and 5.3° horizontally, a stream of in total 300 consonant letters was presented serially. Each consonant was shown for 500 milliseconds followed by a black screen for the next 500 milliseconds. The consonants covered all consonants of the alphabet and were presented in a pseudo-randomized manner, with the restriction that the Nogo stimulus (=X) is presented with a mean probability of 29% and each Nogo stimulus is followed by at least one go stimulus (=one of the remaining consonants). During task performance, the subjects were instructed to respond by pressing a mouse button with the right index finger to every go stimulus and to withhold this response in case of the Nogo stimulus. In total, every subject completed two runs each consisting of 300 stimuli. To familiarize subjects with the task, every subject received a brief training session on the task outside the scanner room prior to the scanning session. The paradigm was programmed using the software "Presentation" (Neurobehavioral Systems, Version 11.1 <http://www.neurobs.com/>). Visual stimuli were projected on a screen at the head end

of the scanner bore and viewed with the aid of a mirror mounted on the head coils.

Data Acquisition

Data acquisition was performed at the University Hospital of Freiburg (Department of Radiology). For simultaneous EEG/fMRI data acquisition, fMRI and EEG data recordings were initiated manually while visual presentation was initiated by a trigger code sent from the MR scanner to the presentation host. To allow for gradient artifact correction, the EEG-amplifier hardware clock was synchronized with the timing of gradient switching during fMRI measurements (SyncBox, Brain Products, Gilching, Germany). Furthermore, the onsets of echo-planar image (EPI) scans and visual stimulation as well as the subject's response were registered on a trigger channel of the EEG acquisition system.

fMRI/MRI

MRI data was collected on a Magnetom 3 T tim-TRIO scanner (Siemens Medical Systems, Erlangen) using a 12-channel head coil for signal reception. To limit head motion within the coil and thus reduce motion-related artifacts, the subject's head was stabilized by means of foam padding. Ear plugs and headphones were used to reduce acoustical stress of the subject due to the scanner noise. For functional BOLD imaging, T2*-weighted echo planar imaging (EPI) volumes were acquired with repetition time (TR) = 2,250 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 92 mm, voxel size = 3 mm × 3 mm × 3 mm, and 36 interleaved slices. In each scanning session, movement and distortion correction were performed automatically by applying fully automated PACE (Prospective Acquisition Correction) motion correction [Thesen et al., 2000] and distortion correction based on point spread function mapping [Zaitsev et al., 2004]. A total of 157 complete brain volumes were acquired for each run. Subsequent to simultaneous EEG/fMRI data acquisition, the EEG cap was removed. This allowed for acquisition of high resolution 3D MRI data for anatomical references by using a 3D magnetization prepared, rapid acquisition gradient echo (MPRAGE) sequence with TR = 2,200 ms, TE = 4.11 ms, flip angle = 12°, FOV = 256 mm, voxel size = 1 mm × 1 mm × 1 mm.

EEG

Simultaneously with fMRI data acquisition, continuous EEG data was recorded using a 64-channel EEG-system consisting of two 32-channel MR compatible EEG-amplifiers (BrainAmp MR plus; Brain Products) powered by a MR-compatible rechargeable battery pack (Power-Pack, Brain Products). To reduce potential scanner artifacts caused by wires moving inside the magnetic fields, the EEG system was placed inside the scanner bore directly behind the head coil to keep cabling short. The 64-channel easycap EEG-recording caps (Falk Minow Services,

Herrsching, Germany) compatible with 56 cm or 58 cm head size were used. A total of 62 sintered Ag/AgCl ring electrodes were placed within these elastic EEG-recording caps according to an extended international 10-20 system [Klem et al., 1999]. FCz served as reference electrode and AFFz as ground during recording. An additional electrode was placed below the subjects left eye to better monitor vertical eye movements and eye blinks (EOG). To facilitate ballistocardiogram (BCG) artifact correction, another electrode was placed beneath the subject's left scapula in order to monitor the electrocardiogram (ECG). Electrode-skin contact impedances were maintained below 10 kΩ. The recorded analog EEG signal from the 64-channels was filtered between DC and 1 kHz. To obtain a good sampling of the scanner artifacts, the analog EEG signal was digitized with a sampling frequency of 5 kHz. To facilitate the subtraction of the gradient artifact the EEG sampling was driven by the clock board of the MR scanner (Sync-Box, Brain Products). The digitized EEG signal was transmitted via fiber optic cables to the EEG acquisition host placed outside the scanner room. The Brain Vision Recorder software (Brain Products) running on the EEG acquisition host was used to acquire, store, and display EEG recordings online.

Data Preprocessing

fMRI preprocessing

fMRI data preprocessing was performed using SPM5 (Wellcome Trust Centre for Neuroimaging at UCL, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software/spm5>) running under Matlab 7.7.0 (The MathWorks Inc., Natick, MA; <http://www.mathworks.com>). Prior to data analysis, images were screened for motion artifacts as caused by excessive head motion (>2 mm). Functional images were manually reoriented to the T1-template of SPM. The first five volumes of each run were then discarded to allow for equilibrium effects. The remaining functional images of both runs were realigned to the first functional image of the first run using a six degrees-of-freedom rigid body transformation and then co-registered to the individual anatomical T1 image. This T1 image was then spatially normalized to the reference system of the Montreal Neurological Institute's (MNI) reference brain using linear and nonlinear transformation. Using the resultant normalizing parameters the functional images were spatially normalized to the standard MNI space, this allows for comparing functional images from different individuals. Finally, all functional images were smoothed by applying a 3D isotropic Gaussian kernel with 8 mm full-width at half maximum, FWHM.

EEG preprocessing

Continuous raw EEG data was processed offline using AvgQ ([Feige, 1999]; Freiburg, Germany; <https://github>).

com/berndf/avg_q). This is an open source multichannel EEG/MEG data processor that is driven by Python scripts. Gradient artifact correction was performed by the template subtraction method by Allen et al. [2000]. Gradient artifact correction was facilitated by high EEG sampling rates (5 kHz) together with a synchronization of EEG-amplifier hardware clock and the timing of gradient switching during fMRI measurements so that further lowpass filtering was not needed [Mullinger et al., 2008]. Nevertheless, in a second step following the gradient artifact correction we used bandpass filtering (0.2–48 Hz) to remove potential residual gradient artifacts as these artifacts may occur by very small variations in timing in the high frequency domain as well as to remove slow drifts in the EEG signal in addition. Subsequently, the data was down-sampled to 100 Hz. Using the extended infomax algorithm (ICA, [Lee et al., 1999]) an unmixing matrix was estimated for the artifact-cleaned EEG data of each subject and run separately. BCG and EOG artifact correction was performed by detecting and excluding BCG- and EOG-related ICs: First, EEG averages related to heart beats and eye blinks were computed by detecting single heart beats and EOG blinks. Heartbeat detection was done by convolution with a time-domain ECG template. Similarly, EOG artifact detection and correction was performed on the BCG artifact corrected EEG data. Artifact-free EEG was obtained by back-projecting all ICs except those loading on ECG and EOG. The BCG/EOG artifact corrected back-projected EEG was then re-referenced to the average of TP9 and TP10 and segmented into epochs of 1,200 ms, with the 200 ms pre-stimulus interval being used for baseline correction. Epochs belonging to the same event type—correct Go, correct Nogo, omission of Go trials, and commission errors in Nogo trials—were averaged, resulting in four different event-related averages. ERPs of the same event type were averaged over the entire group.

Single-trial EEG/fMRI data preprocessing

Based on visual inspection these grand averages, F4 and Cz were selected for further single-trial EEG/fMRI analysis, as the Nogo-N2/-P3 effects were most pronounced in the grand average at these electrode sites. Subsequently, the latency ranges which covered best the task-related N2 effect at F4 and P3 effect at Cz on the group level were chosen. For the single trial ERP analysis, we quantified the N2 and P3 ERP components at the same latency ranges as it was used for unimodal ERP statistic. N2 was measured from electrode F4 while P3 was quantified at electrode Cz where the most pronounced Nogo-N2/-P3 effects across all subjects were expected. Visual inspection of grand averages as well as statistical comparisons based on an omnibus ANOVA (calculated separately on the amplitude values of N2 and P3 extracted from the nine electrode sites used for unimodal ERP analysis) confirmed that Nogo amplitudes were significantly different from Go amplitudes in the grand averages at these electrode sites. How-

ever, while the largest Nogo-Go differences at the N2 latency was clearly allocated to F4, at the P3 latency Nogo-Go differences were present at all electrode sites (cf. Supporting Information Table 1). Thus, we decided to quantify P3 at a fronto-central electrode site in accordance with most EEG literature [Baumeister et al., 2014; Huster et al., 2013; Karch et al., 2014; Wessel and Aron, 2015]. This is also in compliance with findings from neuroimaging and some electrophysiological studies which suggest to expect a lateral right inferior prefrontal cortical source for the inhibition-related N2 component in contrast to a more central cortical source for the P3 component [Aron, 2007; Aron and Poldrack, 2006; Bokura et al., 2001; Fisher et al., 2011; Lavric et al., 2004; Sebastian et al., 2013b,].

Thus, for the N2-regressor, the mean amplitude was extracted for each subject from F4 at a time window starting 240 ms after stimulus onset and ending 350 ms after stimulus onset. For the later P3-regressor, the mean amplitude was extracted from Cz at a time window starting 350 ms after stimulus onset and ending 580 ms after stimulus. In the end, this resulted in two vectors of single-trial ERP amplitude vectors for each subject. While amplitude values are available for each trial ($f = 1$ Hz), not every trial was sampled by fMRI data acquisition ($f = 1/2.25$ Hz). Thus to compensate for these deviant sampling frequencies, each ERP amplitude vector was first interpolated over time by using a cubic smoothing spline function and then re-sampled at the time points of fMRI data acquisition. This down-sampled time course was then normalized to inter-quartile range ($IQR = 1$) and convolved with a canonical hemodynamic response function.

Data Analysis

IC classification

IC classification was performed as described in detail elsewhere [Schmüser et al., 2014] and will be described shortly in the following. First, EEG data preprocessing was performed as described in the section “Data preprocessing.” Then, instead of back-projecting all ICs except for those loading on ECG and EOG, for the automated classification of Nogo-related ICs we used all 64 ICs simply excluding those ICs representing BCG/EOG artifacts. The continuous IC time courses of each subject were first segmented into epochs of 1,200 ms length with 200 ms pre-stimulus time and 1,000 ms post-stimulus time. All epochs were baseline corrected using the 200 ms pre-stimulus interval. Subsequently, epochs belonging to the same event type were averaged, resulting in event-related averages for correct Go, correct Nogo, omission of Go trials, and commission errors in Nogo trial. Within the process of averaging, the pointwise mean as well as the pointwise variance information for each time point was collected. These values were used to compute pointwise t tests on each IC time course and event type.

Comparing the averaged IC time courses against baseline by using one-sample *t*-tests yielded that part of the data reliably different from baseline at a specific time point. Second, comparing the Nogo and Go conditions by means of a two-sample *t*-test for independent groups allowed for assessing the latency ranges in which the IC is characterized by significantly larger in amplitude for Nogo than Go trials. The resultant pointwise *t* values were transformed into Z scores. Z score differences between Nogo- and Go-related IC averages were used to determine IC reliably associated with the Nogo condition. On the basis of 300 trials per block with maximally 90 Nogo trials, a Z score value corresponding to a two-sided *P*-value of 0.01 (two-sample *t*-test with *df* = 89), with the degree of freedom been chosen conservatively from the condition with the smaller number of epochs, i.e. the Nogo condition was chosen. Thus, only ICs with absolute Z score differences as obtained by the two-sample *t*-test comparing Nogo and Go conditions crossing this predefined threshold of $Z = 0.275$ were classified as sufficiently reliable Nogo-related.

From those preliminary Nogo-related ICs only those were finally classified as Nogo-related (i.e., related to early processes of response inhibition) if the latency of significant Nogo-related activation (i.e., above Z score threshold) was falling into a time windows located prior to the individual's mean Go response time. Importantly, these time windows were defined for each subject individually by taking the stimulus onset and the individual's median correct Go response time (RT) as points of reference. Thereafter, subgroups were defined using the existence or absence of those Nogo-related ICs as group separator. This resulted in two subgroups: Nogo-IC-positive (in short: IC+; *N* = 21; 7 males; mean age: 35.0 ± 14.6) and Nogo-IC-negative (in short: IC−; *N* = 17; 8 males; mean age: 40.24 ± 17.6).

Statistical analysis of behavioral data

To assess group differences on behavioral level, measures of interest were mean response time on correct Go trials (RT), percentage of commission errors on Nogo trials, and omission errors on Go trials. To assess intra-individual RT variability the coefficient of variability (CoV) was computed by dividing the standard deviation of RT by the mean RT [Stuss, 2003]. Statistical analyses, i.e. two-tailed *t*-tests were performed using the statistical computing software “R” (<http://cran.r-project.org/>).

Unimodal fMRI data analysis

Statistical analysis of fMRI data was performed using SPM8 running under Matlab 7.7.0. For each subject the first-level GLM consisted of two onset regressors which corresponded to the correct and incorrect Nogo conditions. As the frequent Go stimuli were presented in a frequency that is beyond the fMRI's temporal resolution, the Go

stimuli were not modeled by onset regressors but instead used as active baseline [Sebastian et al., 2012, 2013a,b]. Using Go as active baseline allows comparing Nogo vs. Go (=active baseline) implicitly. The time courses of regressors and functional data were then run through a high-pass filter (128 s cut-off) in order to remove artifacts resulting from low-frequency temporal variations.

For statistical analyses, beta images corresponding to the correct Nogo vs. Go contrast were subjected to a two-sample *t*-test for independent groups comparing IC+ subjects against IC− subjects. Task-related brain activation as well as differential brain activation between groups (IC+ vs. IC−) was initially examined with a whole brain analysis. This allows to assess global brain activations irrespective of *a priori* defined regions of interest. For whole brain analysis, multiple comparisons correction of the statistical maps was based on cluster-extent based thresholding [Friston et al., 1994; Woo et al., 2014] using a primary voxel-level threshold of $P < 0.001$ and an minimum cluster-extend level of $k = 10$ continuous voxels. This yielded a cluster-level corrected significance of $P < 0.05$ (family-wise error = FWE correction for multiple comparisons). We chose a minimum cluster-extend level of 10 continuous voxels to avoid false positives by small but high peak voxel activity.

In addition to this whole brain analysis, we performed small volume correction in *a priori* predefined ROIs in order to test specifically for brain activity in areas associated with response inhibition [Aron, 2007; Aron and Poldrack, 2006; Sebastian et al., 2013b]. In this context, voxel-wise test of significance was performed using the small volume correction toolbox within SPM8 which allows accounting for the multiple comparison problem within the selected ROI. Peak-wise significance was assessed by using a height threshold of $P < 0.05$ (FWE corrected) after using a primary voxel-level threshold of $P < 0.05$ and no minimum cluster-extend level. The following ROIs were defined based on atlas-based masks: pars opercularis of the lateral inferior frontal cortex; pre-supplementary motor area (pre-SMA; derived from the SMA region with $y > 0$); caudate nucleus; putamen and pallidum, STN (10 mm³ box at MNI coordinates $-/+10, -15, -5$), inferior parietal lobule and superior parietal lobule [Sebastian et al., 2013b].

Data presentations in all figures are uncorrected for the purpose of visualization only, which is stated in each figure legend. Figures displaying results of within-group analyses are thresholded at $P < 0.001$ (unc.) and $k = 10$ voxels. Figures displaying results of between-group analyses are thresholded at $P < 0.005$ (unc.) and $k = 10$ voxels.

Unimodal ERP analysis

Due to the overall low error rate, ERPs corresponding to incorrect behavioral responses—i.e., omissions of Go trials and commissions of Nogo trials—were statistically not analyzable and therefore discarded from further analyses. For evaluation of Go and Nogo-related effects, N2 and P3

amplitudes were measured as the mean amplitude in the time windows 240–350 ms (N2), and 350–580 ms (P3) after stimulus onset. The latency ranges were chosen to cover best the task-related N2 and P3 effects at the selected electrode sites as determined based on visual inspection of the grand-averaged waveforms across all subjects. Following Ruchow et al. [2008a] ERP values were extracted from a 3 by 3 electrode array: frontal-left (F3), frontal-midline (Fz), frontal-right (F4), central-left (C3), central-midline (Cz), central-right (C4), parietal-left (P3), parietal-midline (Pz), and parietal-right (P4). Amplitudes and latencies of N2 and P3 were subjected to separate repeated measure analysis of variance (ANOVA) including within-subject factors condition (correct go; correct Nogo), anteriorization (frontal: F3, Fz, F4; central: C3, Cz, C4; parietal: P3, Pz, P4), and laterality (left: F3, C3, P3; midline: Fz, Cz, Pz; right: F4, C4, P4) and between-subject factor group (IC+ subjects vs. IC– subjects). In case of nonsphericity as indicated by a significant Mauchly test, the corrected *P*-values and ϵ -values (Greenhouse-Geisser epsilon correction) are reported. As the study was focused on group differences in Go and Nogo-related effects, only significant main effects as well as significant two-way interactions effects including group as factor were further assessed with post hoc *t*-tests by means of Tukey multiple comparisons of means with 95% family-wise confidence level. All three-way significant effects involving the factor group were analyzed post hoc by applying second ANOVA models and post hoc *t*-tests. Statistical analysis was performed using the packages “stats” [R Core Team, 2014] and “ez” [Lawrence, 2015] from the open-source statistical computing software “R” (<http://CRAN.R-project.org/>).

Single-trial EEG/fMRI analysis

Statistical analysis of fMRI data was performed using SPM8 (Wellcome Trust Centre for Neuroimaging at UCL, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software/spm8>) running under Matlab 7.7.0 (The MathWorks Inc., Natick, MA; <http://www.mathworks.com>). For each subject and run different GLMs were fitted for each ERP-regressor separately to the fMRI data. Besides the three onset regressors Go, Nogo, and errors, the design matrix of each GLM contained one ERP-regressor derived from N2 at F4 or P3 at Cz ERPs. To remove artifacts resulting from low frequency temporal variations, the time courses of regressors and functional data were run through a high-pass filter with a 128 s cut-off. For each subject and time window (i.e., ERP component N2 or P3) the two contrast images belonging to the first and the second run of the task were averaged prior to group analysis resulting in one contrast image per subject and ERP component, i.e. N2 and P3.

Single trial correlations of fMRI BOLD responses with electrophysiological regressors derived from N2 and P3 ERP single-trial amplitude values were tested for group-specific significance using paired *t*-test for each group

independently. For statistical analyses group-specific activation pattern, beta images corresponding to the single trial correlations of fMRI BOLD responses with electrophysiological regressors derived from N2 and P3 ERP single-trial amplitude values were subjected to paired *t*-test for each group independently. To test for group differences, a full factorial repeated measures model with N2 and P3 as within-subject factor and group (IC+ vs. IC–) as between-subject factor was used. As this study aimed at testing for functional group differences in neural activity related to different phases of response inhibition and not in the effects exclusively driven by the electrophysiological regressors, the full factorial model was fitted with ERP-regressors not orthogonalized with respect to classical onset regressors (Go, Nogo, Errors).

Similar to the group unimodal fMRI analysis, whole brain analysis was used to examine global brain activations irrespective of *a priori* defined regions of interest. Whole brain results were corrected at the cluster level using a height threshold of $P < 0.05$ (FWE corrected) using a primary voxel-level threshold of $P < 0.001$ and a minimum cluster-extend level of $k = 10$ continuous voxels. Additionally, small-volume correction was performed for *a priori* defined regions of interest (ROIs) located in brain areas associated with response inhibition [Aron, 2007; Aron and Poldrack, 2006; Sebastian et al., 2013b]. Thus small volume correction was used for the same predefined ROIs as described in the section of unimodal fMRI group analysis and assessed for peak-wise significance by using a height threshold of $P_{FWE} < 0.05$ based on a primary voxel-level threshold of $P < 0.05$ and no minimum cluster-extend level. Data presentations in all figures are uncorrected for the purpose of visualization only, which is stated in each figure legend. Figures displaying results of within-group analyses are thresholded at $P < 0.001$ (unc.) and $k = 10$ voxels. Figures displaying results of between-group analyses are thresholded at $P < 0.005$ (unc.) and $k = 10$ voxels.

RESULTS

Demographics, Psychometrics, and Task Performance

Both groups did not differ significantly with respect to age, gender, and verbal intelligence as measured by the German vocabulary test MWT-B (Mehrfachwortschatztest Version B; [Lehrl, 1995] (Table I). The Nogo-IC positive (IC+) group was characterized by a shorter Go-RT, lower coefficient of variance (=CoV) i.e. intra-individual variability of Go-RT as well as by reduced error rates (commission error and omission error). However, group differences were only statistically significant regarding the CoV rate of Go-RT and reached trend level for the omission error rate (Table I). As depicted in Table II, group differences were significant or reached a trend level of significance on the subscales of questionnaires on self-rated impulsive

TABLE I. Group comparison of demographic and performance data in Nogo-IC positive (IC+) and Nogo-IC negative (IC-) subjects

	IC+		IC-		Group comp.	
	Mean	SD	Mean	SD	t	P
Demographic						
Age	35.00	14.6	40.24	17.6	1.00	n.s.
MWT-B	30.71	3.5	30.76	3.8	0.00	n.s.
Gender	7/21		8/17			
Performance						
RT [ms]	408.24	45.2	431.24	66.0	1.62	n.s.
Commission errors [%]	10.19	8.2	12.19	10.0	0.46	n.s.
Omission errors [%]	0.19	0.3	1.21	2.5	3.56	.067
CoV	0.195	0.04	0.224	0.05	4.16	.049

Demographic data regarding age in years and intelligence as measured with MWT-B (sum score). Behavioral data regarding mean reaction time (RT) on Go trials in milliseconds (ms), coefficient of variability of RTs (CoV), mean % omission errors of Go trials and mean % of commission errors of Nogo trials. CoV is estimated by dividing SD of RT by mean RT. Percentage error is estimated by dividing the number of incorrect trials (Go for omission error and Nogo for commission error) by the total number of each trial type. Gender (male/N) = ratio of number of males and sample size. SD = standard deviation. N.S. = not significant ($P > 0.1$).

personality traits (BIS-11 and SSS-V) and on the questionnaires used for clinical ratings regarding ADHD symptoms in childhood (WURS-k) and adulthood (CAARS:S-L). The Nogo-IC negative (IC-) group was characterized by enhanced ratings on the subscales assessing motor impulsivity and hyperactivity (BIS-11 subscales: Motor impulsiveness and Non-planning impulsiveness; CAARS:S-L subscales: Hyperactivity/restlessness, Impulsivity/emotional lability, and DSM-IV hyperactive-impulsive symptoms) but also by higher rating on the boredom/sensation seeking domain (SSS-V subscales: Experience seeking, and Boredom susceptibility) and enhanced ratings on retrospective and current ADHD symptoms (CAARS:S-L: "DSM-IV ADHD symptoms total" and WURS-k).

Unimodal fMRI Analysis

Task related activation

Task-related activation (Table III) in Nogo-IC positive (IC+) and Nogo-IC negative (IC-) group are shown in Figure 1, rows A and B. Side-by-side comparison revealed overlapping but also different regions of task-related activation in both groups. However, in the IC- group the activated network appeared to be extended. Significant task-related activation was found in both groups in frontal areas including SMA/pre-SMA, a cluster stretching from

left precentral gyrus to left superior and middle frontal gyrus, and in bilateral posterior medial frontal cortex. Further congruent cortical activity was found in right middle temporal gyrus, right superior parietal lobule, and left middle occipital gyrus. Subcortically, both groups displayed task-related activity in a cluster in left putamen, which was in IC- subjects extended to the p. opercularis of left posterior IFG. In IC- subjects only, significant task-related cortical activation was found in bilateral posterior IFG (p. opercularis)/insula, a cluster enclosing right superior/middle temporal gyrus and right supramarginal gyrus, and clusters in left inferior and superior parietal lobule. Subcortically, IC- subjects also displayed significant task-related activity in right caudate nucleus, right pallidum, and right putamen extended to right posterior IFG (p. opercularis)/insula.

Between group comparisons as revealed by t-tests for independent samples

Between group comparison (Table IV, Fig. 1 row C) of the contrast "correct Nogo-Go" revealed significantly more activation in posterior IFG (pars opercularis)/insula (significant in left IFG and on trend level in right IFG) and left putamen/insula in IC- subjects compared to IC+ subjects at the predefined threshold of $P < 0.05$ (FWE corrected).

Unimodal ERP Analysis

Grand averages at two selected electrode sites and series of topographical maps plotted from 50 to 800 ms post-stimulus of Nogo and Go related ERPs are shown in Figure 2. Results of repeated measures ANOVA on amplitudes and latencies of N2 and P3 as extracted from nine electrode sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) with within subject factors anteriorization (F = frontal, C = central, P = parietal), lateralization (3 = left side, z = midline, 4 = right side), and task condition (Go, Nogo) are presented in Table V.

N2 amplitude and latency

Significant main effects of condition but not of group was found for N2 amplitudes and latencies indicated that across both groups and all electrode sites, the N2 peaked later (Nogo-Go = 2.28 ms, $P = 0.001$) and with larger amplitudes (Nogo-Go = 1.08 μV , $P < 0.001$) in Nogo compared to Go condition ($F_{amp}(1,36) = 19.96$, $P < 0.001$ and $F_{lat}(1,36) = 5.76$, $P = 0.022$). Additionally, a significant main effect of anteriorization ($F(1.29,46.30) = 18.10$, $P < 0.001$) indicated that across all groups and task conditions, the N2 amplitude was significantly more pronounced, i.e. showed the strongest negativity at frontal (1.20 μV) and central (1.81 μV) as compared to parietal (3.23 μV) electrode sites (frontal-parietal = -2.04 μV , $P < 0.001$; central-parietal = -1.43 μV , $P < 0.001$). There was no significant interaction effect involving the factor group.

TABLE II. Group comparison of psychometric data in Nogo-IC positive (IC+) and Nogo-IC negative (IC-) subjects

	IC+		IC-		Group comp.	
	Mean	SD	Mean	SD	<i>t</i>	<i>P</i>
BIS-11						
Attentional impulsiveness	13.24	3.0	13.75	1.8	0.35	n.s.
Motor impulsiveness	20.19	3.0	22.75	4.9	3.87	.057
Non-planning impulsiveness	21.14	3.9	23.50	3.8	3.39	.074
UPPS						
Premeditation	22.57	4.0	23.56	4.4	0.51	n.s.
Urgency	37.90	4.0	37.50	4.6	0.08	n.s.
Sensation seeking	28.38	6.2	26.88	6.4	0.52	n.s.
Perseverance	16.33	3.6	16.63	3.6	0.06	n.s.
SSS-V						
Thrill and adventure seeking	6.24	2.6	6.56	2.7	0.13	n.s.
Disinhibition	2.81	2.1	3.69	2.1	1.63	n.s.
Experience seeking	5.86	1.8	7.19	1.9	4.65	.038
Boredom susceptibility	1.57	1.2	3.56	2.2	12.47	.001
CAARS:S-L						
Inattention/memory problems	42.00	6.5	45.06	5.6	2.33	n.s.
Hyperactivity/restlessness	42.14	5.7	46.41	7.6	3.97	.054
Impulsivity/emotional lability	40.10	4.8	42.94	5.0	3.13	.085
Problems with self-concept	41.67	3.8	43.35	3.3	2.06	n.s.
DSM-IV inattentive symptoms	40.86	7.5	45.12	7.7	2.98	.093
DSM-IV hyperactive-impulsive symptoms	37.19	4.7	42.06	9.5	4.27	.046
DSM-IV ADHD symptoms total	37.43	6.4	43.12	8.7	5.43	.026
ADHD index	39.48	6.2	42.82	7.3	2.35	n.s.
WURS-k						
WURS	7.21	5.0	11.44	8.9	3.15	.085
BPDSI						
BPDSI	0.66	0.7	0.68	0.6	0.00	n.s.
BDI						
BDI	1.22	1.9	1.88	3.6	0.46	n.s.
MADRS						
MADRS	0.15	0.5	0.41	1.0	1.07	n.s.

Neuropsychological data with self-ratings regarding impulsivity (BIS-11 = Barratt Impulsiveness Scale; UPPS = UPPS Impulsive Behavior Scale; SSS-V = Sensation Seeking Scale), clinical ratings regarding childhood ADHD symptoms (WURS-k = Wender Utah Rating Scale, [total score]) and current ADHD symptoms (CAARS-S:L = Conners' Adult ADHD Rating Scale, [t-value]), clinical assessment of the frequency and severity of manifestations of BPD (BPDSI = Borderline Personality Disorder Severity Index), and the clinical rating (MADRS = Montgomery Asberg Depression Scale) and self-rating (BDI = Beck Depression Inventory) of current depressive mood. SD = standard deviation. Gender (male/N) = ratio of number of males and sample size. ADHD = attention deficit/hyperactivity disorder. BPD = borderline personality disorder. N.S. = not significant ($P > 0.1$).

P3 amplitude and latency

Significant main effects of condition but not of group on P3 amplitude and latency showed that across both groups and all electrode sites, the P3 peaked later (Nogo-Go = 7.23 ms, $P < 0.001$) and with larger amplitudes (Nogo-Go = 3.39 μV , $P < 0.001$) in Nogo compared to Go condition ($F_{\text{amp}}(1,36) = 136.26$, $P < 0.001$ and $F_{\text{lat}}(1,36) = 8.40$, $P = 0.006$). Furthermore, a significant main effect of anteriorization on P3 amplitudes ($F(1.34, 48.09) = 8.44$, $P = 0.003$) and P3 latencies ($F(1.48, 53.11) = 7.30$, $p = 0.004$) indicated that across both groups and task conditions, the P3 amplitude was significantly more pronounced at central (3.61 μV) and parietal (3.71 μV) as compared to frontal (2.57 μV) electrode sites (frontal-

central = -1.04 μV , $P < 0.001$; frontal-parietal = -1.14 μV , $P < 0.001$), and peaked significantly earlier at parietal electrodes (451.63 ms) compared to frontal (456.98 ms) electrode sites (frontal-parietal = 5.35 ms, $P = 0.005$). There was a significant interaction effect between group and task condition of P3 amplitude values ($F(1,36) = 8.33$, $P = 0.007$). Post hoc analysis of the interaction effect revealed significantly higher amplitudes in Nogo condition compared to Go condition in both groups (IC+: Nogo-Go = 4.14 μV , $P < 0.001$; IC-: Nogo-Go = 2.46 μV , $P < 0.001$) as well as significantly higher Nogo-P3 amplitudes in IC+ subjects compared to IC- subjects (Nogo_{IC+}-Nogo_{IC-} = .29 μV , $P < 0.001$) and higher Nogo-P3 amplitudes in both groups compared to Go-P3 amplitudes in the other group (Nogo_{IC+}-Go_{IC-} = 4.74 μV ,

TABLE III. Task-related activity in Nogo-IC positive (IC+) and Nogo-IC negative (IC-) subjects

Region	IC+						IC-					
	<i>k</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>Z</i>	<i>K</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>
Frontal												
R IFG (p. Opercularis)							94*	0.018*	3.81	39	15	12
L IFG (p. Opercularis)							76*	0.027*	3.61	-39	9	12
pre-SMA	259*	<0.001*	4.80	-6	3	57	235*	<0.001*	4.95	6	3	63
IC+: L/R Post.-medial frontal/IC-: L/R Post.-medial frontal; R Mid./Sup. Frontal G.; R Precentral G.; L MCC	285	<0.001	5.46	6	0	66	502	<0.001	5.27	6	0	63
IC+: L Precentral G.; L Sup. Frontal G.; L Mid. Frontal G./IC-: L Precentral G.; L Mid. Frontal G.	78	0.008	4.24	-42	-3	51	138	<0.001	4.85	-42	-3	48
Subcortical												
R Caudate Nucleus							119*	0.009*	3.92	21	21	3
R Putamen; R IFG (p. Opercularis)							121	0.001	4.06	21	18	3
R Putamen							182*	0.010*	3.90	24	15	0
IC+: L Putamen												
IC-: L Putamen; L IFG (p. Opercularis)	87*	0.029*	3.56	-24	9	6	112	0.001	5.02	-24	9	6
R Pallidum							13*	0.034*	2.99	21	0	6
Temporal												
R Sup. Temporal G.; R Mid. Temporal G.; R SupraMarginal G.							342	<0.001	4.55	51	-36	9
IC+: R Mid. Temporal G.; R Sup. Occipital G.; R Mid. Occipital G./IC-: R Mid. Temporal G.; R Mid. Occipital G.; R Cuneus	107	0.002	5.27	48	-72	0	274	<0.001	5.69	48	-72	0
Parietal												
L Inf. Parietal Lob.							110*	0.042*	3.69	-27	-51	54
L Sup. Parietal Lob.; L Inf. Parietal Lob.							50	0.047	3.96	-21	-60	51
R Sup. Parietal Lob.	111*	0.012*	3.86	33	-63	54	151*	0.006*	4.01	21	-63	57
Occipital												
L Mid. Occipital G.	61	0.023	4.79	-24	-87	6	224	<0.001	5.59	-42	-78	0

The region in which the cluster's local maximum is located in Montreal Neurological Institute (MNI) coordinates (*x*, *y*, *z*) for the contrast "correct Nogo-Go" with associated *z*-score ($P_{FWE} < 0.05$, cluster level corrected; * small volume corrected, $P_{FWE} < 0.05$) and cluster extend in number of voxels (*k*).

R = right, L = left, IFG = inferior frontal gyrus, ACC = anterior cingulate cortex, MCC = middle cingulate cortex, Sup = superior, Mid = Middle, Inf = Inferior, Post = Posterior, G = Gyrus, Lob. = Lobule.

$P < 0.001$; $\text{Nogo}_{IC-} - \text{Go}_{IC+} = 1.85 \mu\text{V}$, $P < 0.001$). There was no further significant interaction effect involving the factor group.

N2/P3-ERP Single-Trial EEG/fMRI Analysis

Group specific correlations with ERP-regressors as revealed by within-group paired *t*-tests

Single-trial fluctuations of electrophysiological activity as derived from the latency ranges N2 (240–350 ms post-

stimulus) at F4 site and P3 (350–580 ms post-stimulus) at Cz site correlated positively with several cortical and subcortical regions in both groups (Tables VI and VII; Supporting Information Fig. 1).

Single-trial correlations with ERP-regressors revealed widespread activity in cortical and subcortical regions, especially at the N2 latency range in IC+ subjects. Correlations exclusively with the N2 regressor were found in IC+ subjects in bilateral frontal areas (including left posterior IFG/insula, anterior cingulate cortex (ACC), bilateral dorsolateral, and ventrolateral prefrontal cortices), bilateral

A) Unimodal fMRI: Task-related activity in Nogo-IC-positive subjects ($p < .001$) **B) Unimodal fMRI: Task-related activity in Nogo-IC-negative subjects ($p < .001$)** **C) Unimodal fMRI: Between group differences: Nogo-IC-negative > Nogo-IC-positive ($p < .005$)** **Figure 1.**

Activation maps displaying task-related activity during “successful inhibition–correct Go” as assessed by unimodal fMRI analysis. **A:** Task-related activity in Nogo-IC-positive subjects. **B:** Task-related activity in Nogo-IC-negative subjects. **C:** Results of between group differences (Nogo-IC-negative > Nogo-IC-positive). Images of task-related activity are displayed at $P < 0.001$

(unc.) and $k = 10$ for display purposes. Images of between group comparisons are displayed at $P < 0.005$ (unc.) and $k = 10$ for display purposes. The color bar indicates t -scores (0–11.2380). IFG: inferior frontal gyrus. Pre-SMA: presupplementary motor area. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

putamen, bilateral temporal, and parietal areas (Table VI), while in IC– subjects (Table VII) positive correlations exclusively with the N2 regressor were found in left temporal gyrus and right parietal lobule. Significant positive correlations with both ERP-regressors were found in both groups in pre-SMA, and left caudate nucleus. Additionally, in IC– subjects both ERP-regressors correlated positively with left medial frontal cortex, bilateral ACC, and left middle temporal gyrus, while in IC+ subjects further

correlations with both ERP-regressors were found in right basal ganglia (putamen and caudate nucleus), right posterior IFG (p. opercularis)/insula, and bilateral parietal lobule.

Furthermore, correlations with the P3 but not the N2 ERP-regressor were found in IC+ subjects in right IFG (p. triangularis and p. opercularis), bilateral posterior-medial frontal cortex, left middle cingulate cortex (MCC) as well as left temporal and parietal areas, and bilateral middle

TABLE IV. Between group comparison of task-related activity in Nogo-IC positive (IC+) subjects compared to Nogo-IC negative (IC-) subjects

Region	IC+ vs. IC−						IC− vs. IC+					
	<i>k</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>Z</i>	<i>k</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>
Frontal												
L IFG (p. Opercularis)							42*	0.049*	3.41	−39	6	15
Subcortical												
L Putamen/Insula							80*	0.024*	3.62	−33	−3	−6

The region in which the cluster's local maximum is located in Montreal Neurological Institute (MNI) coordinates (*x*, *y*, *z*) for the contrast "correct Nogo-Go" with associated z-score ($P_{\text{FWE}} < 0.05$, cluster level corrected; * Small volume corrected, $P_{\text{FWE}} < 0.05$) and cluster extend in number of voxels (*k*).

R = right, L = left, IFG = inferior frontal gyrus.

occipital areas. While the strength of positive correlations is decreasing from N2- to P3-associated neural activity in IC+ subjects, more positive correlations with P3 compared to the N2 regressor was found in IC- subjects. This included frontal areas such as bilateral posterior IFG (p. opercularis)/insula, bilateral superior medial gyrus and a cluster enclosing left superior frontal/medial gyrus, right middle orbital gyrus and ACC as well as temporal areas (left hippocampus, left parahippocampus and right fusiform gyrus), left parietal areas enclosing precuneus, lingual gyrus and inferior occipital gyrus, as well as bilateral occipital gyrus. Subcortically, the P3 but not the N2 regressor correlated positively with the fMRI BOLD signal in right caudate nucleus and bilateral putamen in IC- subjects.

Between group comparisons as revealed by full factorial design

Group comparison of full factorial single-trial correlations with N2/P3 ERP-regressors also revealed significant group differences at the N2 and P3 latency (Table VIII, Fig. 3). In IC+ subjects compared to IC- subjects, the N2 regressor correlated significantly stronger with right pre-SMA while the P3 regressor correlated significantly stronger with fMRI BOLD signal in right posterior IFG (p. opercularis)/insula. The inverse comparison (IC- > IC+) revealed no significant differences at the N2-latency and significantly stronger correlations of P3 regressor with the fMRI BOLD signal in a cluster located in pregenual ACC/ left superior medial gyrus.

DISCUSSION

In a group of 38 subjects, 21 subjects (Nogo-IC-positive, in short: IC+) were characterized by the existence of ICs related to Nogo in a latency range located prior to the individuals mean Go RT whereas 17 subjects (Nogo-IC-negative, in short: IC-) were characterized by the absence of such early Nogo-related ICs. Although groups did not differ with respect to demographic characteristics, group comparisons revealed important differences on psychomet-

ric, behavioral, and neurophysiological levels. This suggests the existence of electrophysiologically dissociable phenotypes of behavioral and neural motor response inhibition.

Psychometric and behavioral characteristics of IC- subjects indicate an impulsive personality trait that is to some degree comparable to adult ADHD. Findings of higher scores on subscales addressing motor impulsivity/hyperactivity and impulsive/non-planning characteristics as well as ADHD traits in IC- subjects but not on any other questionnaires complete the picture of a group of healthy subjects that is characterized by a more impulsive personality trait. In line with this, the IC- group was behaviorally also characterized by significant higher intra-individual variability (CoV) of Go reaction time (RT) and a trend toward higher omission error rates. This is strikingly similar to comparisons of adult ADHD patients with healthy control subjects, with increased intra-individual RT variability being hypothesized as a candidate for an intermediate endophenotypic trait of ADHD (e.g. [Albrecht et al., 2013; Carmona et al., 2012; Epstein et al., 2011; Feige et al., 2013; Klein et al., 2006; Sebastian et al., 2012; Vaurio et al., 2009]; for review see [Tamm et al., 2012]).

In unimodal fMRI analysis, both groups displayed significant activations in typical regions of response inhibition network, though to different extents. These regions were the medial prefrontal areas (SMA/pre-SMA, posterior-medial gyrus, and precentral gyrus), left basal ganglia (putamen), and tempo-parietal regions (middle/superior temporal gyri and right superior parietal lobule). In the IC+ group significant activations were restricted to these regions, while the IC- group showed a more distributed network with additional significant clusters of activation in bilateral posterior IFG (p. opercularis)/insula and right basal ganglia (caudate nucleus, putamen, and pallidum). These group differences were further supported by significant between-group differences (IC- > IC+) in left IFG and left putamen/insula in region of interest analysis, suggesting that IC- subjects might have additionally recruited these regions to successfully solve the Go/Nogo

A) Nogo-related potentials in Nogo-IC-positive (IC+) and Nogo-IC-negative (IC-) subjects

A.1) Grand averages at F4

A.2) Grand averages at Cz

A.3) Topographies (200 – 600 ms) in IC+ subjects

A.4) Topographies (200–600ms) in IC- subjects

B) Go-related potentials in Nogo-IC-positive (IC+) and Nogo-IC-negative (IC-) subjects

B.1) Grand averages at F4

B.2) Grand averages at Cz

B.3) Topographies (200 – 600 ms) in IC+ subjects

B.4) Topographies (200 – 600 ms) in IC- subjects

Figure 2.

task. Thus, together with the differences in RT and error rates, these results suggest that both groups used a neural response inhibition network differing mainly in activation extent which may be due to increased behavioral (here increased CoV) and thus neural variance in responses. Increased extent in activation in IC− subjects could then be necessary compensatory activity to maintain a comparable level of inhibitory control compared to IC+ subjects. As others also found additional or potentially overactive recruitment of neural resources in more impulsive subjects compared to less impulsive subjects [Chester and DeWall, 2014; Collins et al., 2012; Horn et al., 2003], our finding of increased extent in activation of left IFG and left putamen/insula regions in higher impulsive (=IC−) subjects may hint as well to an overactive [Chester and DeWall, 2014] or compensatory [Collins et al., 2012] neural activity in left hemispheric fronto-striatal regions while less impulsive subjects (=IC+) have access to an effective impulse control network that is well orchestrated and thus requires less neural sources.

In accordance with this assumption, single-trial correlations with N2/P3 regressors revealed stronger activations in response inhibition and attention network in the low impulsive group. In contrast to this, the high impulsive group was characterized by enhanced activity in the more affective, pregenual ACC possibly indicating overactivity or compensatory activity in IC− subjects. The activation pattern revealed by single-trial correlation with N2/P3 ERP-regressors in IC+ subjects resembled a mixture of networks related to response inhibition and the ventral attention system, which is in line with the notion that in addition to inhibitory control mechanisms the Go/Nogo task might also trigger processes related to response selection and selective attention [Mostofsky and Simmonds, 2008; Stahl et al., 2014]. In contrast to this the activation pattern in the IC− group seems to be a mixture of inhibitory control and medial prefrontal evaluative and limbic system. Medial prefrontal activity in higher impulsive subjects during inhibitory control paradigms have been linked to an interaction of motivational aspects and cognitive processing [Horn et al., 2003]. When comparing results of single-trial ERP/fMRI data analysis in both groups, two

essential regions of inhibitory control were significantly stronger correlated with N2 (pre-SMA) and P3 (right posterior IFG/insula) regressors in IC+ subjects, whereas in IC− subjects the P3 regressor was significantly stronger correlated with the left pregenual ACC/superior medial gyrus a region associated with several processes such as emotion regulation, working memory, attention, and response selection [Bush et al., 2000; Criaud and Boulenger, 2013; Drevets et al., 2008; Simmonds et al., 2007]. This might indicate a central role of the more affective, pregenual ACC in higher impulsive subjects, although it not clear whether this activity is an overactivity or compensatory activity [Chester and DeWall, 2014; Collins et al., 2012] leading either to an interference or maintenance, respectively, of an appropriate level of synchronized neural activity in regions necessary for inhibitory control.

Results of the ERP analysis also supports this finding of an overall intact inhibitory control network in high impulsive subjects, but also the assumption of a less effective network functioning as indicated by a robust main effect of group as well as a significant interaction between group and task condition on the dependent variable P3 amplitude. Although within-group post hoc comparisons of Nogo-P3 and Go-P3 amplitudes revealed significantly higher Nogo amplitudes in both groups, this difference was more pronounced in IC+ subjects relative to IC− subjects (as IC+ subjects were characterized by significantly higher Nogo-P3 amplitudes but not Go-P3 amplitudes). Results of the ERP analysis also supports this finding of an overall intact inhibitory control network in high impulsive subjects, but also the assumption of a less effective network functioning in these subjects. Within-group post hoc comparisons of Nogo-P3 and Go-P3 amplitudes revealed significantly higher Nogo amplitudes in both groups, potentially indicating an overall intact inhibitory control network in both groups. However, post-hoc analyses of the robust main effect of group as well as a significant interaction between group and task condition revealed that this difference was more pronounced in IC+ subjects relative to IC− subjects, as IC+ subjects were characterized by significantly higher Nogo-P3 amplitudes

Figure 2.

Nogo (A) and Go (B) related grand mean event-related potentials (ERP) and topographic map series from 200 to 600 ms after stimulus onset, averaged from stimulus onsets in 21 Nogo-IC-positive subjects (IC+, blue) and 17 Nogo-IC-negative subjects (IC−, green). (A.1 and A.2) show the time courses of Nogo related ERPs at right-frontal electrode (A.1, F4) and at central electrode (A.2, Cz). (A.3 and A.4) show series of topographical maps related to Nogo condition in Nogo-IC-positive subjects (A.3) and Nogo-IC-negative subjects (A.4), plotted every 50 ms from 200 ms to 600 ms after stimulus onset. (B.1 and B.2) show the time courses of Go related ERPs at right-frontal electrode (B.1, F4) and at central electrode (B.2, Cz). (B.3 and B.4) show

series of topographical maps related to Nogo condition in Nogo-IC-positive subjects (B.3) and Nogo-IC-negative subjects (B.4), plotted every 50 ms from 200 ms to 600 ms after stimulus onset. In A.1, A.2, B.1, and B.2: Mean (solid lines) and 95% confidence interval (C.I., shaded areas) of Nogo-IC-positive (IC+, blue) and Nogo-IC-negative (IC−, green) related waveforms; the black lines indicate the N2 latency at 240–350 ms after stimulus onset and P3 latency at 350–580 ms after stimulus onset. In A.3, A.4, B.3, and B.4: Black lines demark the zero line; black dots demark the positions of 62 scalp-electrodes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE V. Results of repeated measures analysis of variance (ANOVA) separate amplitudes and latencies of N2 and P3 ERPs in Nogo-IC-positive subjects and Nogo-IC-negative subjects

Effect	N2 Amplitude				N2 Latency			
	DF	MT	F	P	DF	MT	F	P
Group	1, 36	—	1.10	n.s.	1, 36	—	0.04	n.s.
Condition	1, 36	—	19.96	<.001	1, 36	—	5.76	.022
Ant.	1.29, 46.30	*	18.10	<.001	1.57, 56.63	*	2.81	.081
Laterality	1.44, 51.73	*	0.81	n.s.	1.66, 59.74	*	0.20	n.s.
Group:Condition	1, 36	—	0.06	n.s.	1, 36	—	0.64	n.s.
Group:Ant.	1.29, 46.30	*	0.58	n.s.	1.57, 56.63	*	0.23	n.s.
Group:Laterality	1.44, 51.73	*	2.56	n.s.	1.66, 59.74	*	0.80	n.s.
Condition:Ant.	1.22, 43.85	*	10.96	.001	1.61, 57.98	*	1.04	n.s.
Condition:Laterality	1.33, 47.89	*	0.59	n.s.	2, 72	—	1.87	n.s.
Ant.:Laterality	4, 144	—	4.12	.003	3.24, 116.55	*	2.51	.058
Group:Condition:Ant.	1.22, 43.85	*	0.11	n.s.	1.61, 57.98	*	0.52	n.s.
Group:Condition:Laterality	1.33, 47.89	*	0.08	n.s.	2, 72	—	0.90	n.s.
Group:Ant.:Laterality	4, 144	—	1.03	n.s.	3.24, 116.55	*	0.79	n.s.
Condition:Ant.:Laterality	3.22, 115.91	*	6.77	<.001	4, 144	—	2.14	.079
Group:Condition:Ant.:Laterality	3.22, 115.91	*	0.78	n.s.	4, 144	—	0.86	n.s.

Effect	P3 Amplitude				P3 Latency			
	DF	MT	F	P	DF	MT	F	P
Group	1, 36	—	7.44	.010	1, 36	—	0.83	n.s.
Condition	1, 36	—	136.26	<.001	1, 36	—	8.40	.006
Ant.	1.34, 48.09	*	8.44	.003	1.48, 53.11	*	7.30	.004
Laterality	1.43, 51.56	*	1.62	n.s.	1.48, 53.36	*	0.02	n.s.
Group:Condition	1, 36	—	8.33	.007	1, 36	—	1.36	n.s.
Group:Ant.	1.34, 48.09	*	0.09	n.s.	1.48, 53.11	*	1.91	n.s.
Group:Laterality	1.43, 51.56	*	2.15	n.s.	1.48, 53.36	*	0.73	n.s.
Condition:Ant.	1.15, 41.52	*	1.52	n.s.	1.50, 54.06	*	9.77	.001
Condition:Laterality	1.57, 56.53	*	8.68	.001	1.36, 49.12	*	0.57	n.s.
Ant.:Laterality	2.91, 104.74	*	2.99	.036	3.05, 109.79	*	1.03	n.s.
Group:Condition:Ant.	1.15, 41.52	*	0.76	n.s.	1.50, 54.06	*	0.12	n.s.
Group:Condition:Laterality	1.57, 56.53	*	1.16	n.s.	1.36, 49.12	*	1.63	n.s.
Group:Ant.:Laterality	2.91, 104.74	*	0.16	n.s.	3.05, 109.79	*	1.06	n.s.
Condition:Ant.:Laterality	4, 144	—	3.33	.012	4, 144	—	0.53	n.s.
Group:Condition:Ant.:Laterality	4, 144	—	1.43	n.s.	4, 144	—	0.99	n.s.

Main and interaction effects of separate repeated measures analysis of variance (ANOVA) on N2 amplitudes and latency values and P3 amplitudes and latency values with within-subject factors condition (correct Go; correct Nogo), anteriorization (frontal: F3, Fz, F4; central: C3, Cz, C4; parietal: P3, Pz, P4) and laterality (left: F3, C3, P3; midline: Fz, Cz, Pz; right: F4, C4, P4) and between-subject factor group. In case of sphericity as indicated by a significant Mauchly test (MT=) the corrected *P*-values and DF-values (Greenhouse-Geisser epsilon correction) are reported. MT= Mauchly Test, *= significant Mauchly Test. N.S. = not significant ($P > 0.1$).

Ant.= Anteriorization, N2 = 240–350 ms after stimulus onset, P3 = 350–580 ms after stimulus onset.

but not Go-P3 amplitudes. Furthermore, reduced Nogo-P3 amplitudes in the high impulsive group, i.e. IC– subjects is also consistent with findings from other ERP studies who demonstrated significantly reduced Nogo-P3 amplitudes but no differences in Nogo-N2 amplitudes in non-clinical high impulsive subjects compared to low impulsive subjects [Kam et al., 2012; Ruchow et al., 2008b; Russo et al., 2008; Shen et al., 2014]. Moreover, this is also strikingly similar to the finding of significantly reduced Nogo-P3 amplitudes in psychiatric diseases such as ADHD [Fisher et al., 2011; Helenius et al., 2011; Prox et al., 2007; Wiersma et al., 2006; Woltering et al., 2013]. This

may point toward that shared differences in Nogo-related neural processing in ADHD and IC– subjects potentially are related to the enhanced higher impulsivity trait in these groups compared to IC+ subjects. Thus these data-driven identified electrophysiological phenotypes point toward important inter-individual differences in inhibitory control.

Although reduced Nogo-P3 amplitudes in IC– subjects seem to indicate disturbed or altered neural processing during response inhibition, it is important to see this finding in the context of the ongoing debate on which neuro-cognitive subprocesses of response inhibition are reflected

TABLE VI. Correlations of fMRI BOLD signal with ERP-regressors at N2 and P3 latency in Nogo-IC-positive subjects

Region	N2 regressor						P3 regressor					
	<i>K</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>k</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>
Frontal												
L Sup. Frontal G.	41	0.018	4.79	−18	63	21						
R Mid. Frontal G.; R Sup. Frontal G.	42	0.016	4.87	33	57	27						
R Sup. Medial G.	32	0.049	3.95	9	51	24						
Pre-SMA	351*	<0.001*	5.08	0	9	54	197*	0.004*	4.38	−3	6	51
L IFG (p. Opercularis)	115*	<0.001*	4.73	−33	6	27						
R IFG (p. Opercularis)	253*	0.001*	4.55	42	6	24	123*	0.003*	4.32	45	9	27
R IFG (p. Triangularis); R IFG (p. Opercularis)							311	<0.001	5.09	21	−30	30
L post-medial frontal; R post-medial frontal							54	0.005	4.47	51	−63	−9
L Insula L.; L Putamen; L ACC	201	<0.001	4.93	−9	24	3						
Cingulum												
R ACC	667*	0.008*	4.28	9	30	27						
R MCC; R/L Mid. Frontal G.; R IFG (p. Triangularis); L IFG (p. Opercularis); L post-medial frontal	1581	<0.001	5.19	9	15	30						
L MCC							36	0.031	4.26	63	−27	15
Subcortical												
L Caudate Nucleus	34*	0.003*	4.21	−12	24	3						
R Putamen; R Insula L.; R Pallidum	32	0.049	4.04	33	6	0						
R Putamen	128*	0.008*	4.04	33	6	0	94*	0.005*	4.16	27	−12	3
R Caudate Nucleus	48*	0.009*	3.99	18	3	18	9*	0.029*	3.69	18	−15	21
L Caudate Nucleus	95*	<0.001*	4.86	−21	−24	21	54*	<0.001*	5.66	−21	−21	24
L STN	7*	0.032*	3.02	−12	−12	−9						
Temporal												
L Sup. Temporal G.; L Mid. Temporal G.	40	0.020	4.35	−54	−24	9						
R Sup. Temporal G.; R Postcentral G.; R SupraMarginal G.	133	<0.001	4.64	63	−27	15						
L Fusiform G.; L Hippocampus	59	0.003	4.49	−30	−39	−15						
R Mid. Temporal G.; R Inf. Temporal G.	104	<0.001	4.47	48	−42	−3						
L Mid. Temporal G.	32	0.049	4.24	−60	−54	0						
R Inf. Temporal G.							123	<0.001	4.72	57	27	18
R Sup. Temporal G.							80	<0.001	4.38	−3	6	51
Parietal												
L Inf. Parietal L.	383*	<0.001*	5.39	−45	−33	39	395*	<0.001*	5.35	−45	−33	39
R Inf. Parietal L.	173*	0.048*	3.63	27	−57	54						
L Sup. Parietal L.	283*	0.001*	4.68	−21	−63	42	235*	<0.001*	5.39	−21	−63	42
R Sup. Parietal L.	130*	0.003*	4.26	15	−72	51	153*	<0.001*	4.78	27	−60	57
L Sup. Parietal L.; L Inf. Parietal L.; L SupraMarginal G.							154	<0.001	6.28	−15	−24	30
Occipital												
L Calcarine G.; L Postcentral G.; L Inf. Parietal L.; R Precuneus;	1975	<0.001	6.44	−15	−81	9						

TABLE VI. (continued).

Region	N2 regressor						P3 regressor					
	<i>K</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>k</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>
L Sup./Mid. Occipital G.; R Linual G. R Mid./Sup. Occipital G.; R Sup. Parietal L.; R Cuneus; R Mid. Tempo- ral G. L Mid./Sup. Occipital G.; R Linual G.; R Cuneus; R Calcarine G.; L Mid. Temporal G.							38	0.025	5.26	−6	27	0
							373	<0.001	5.39	−21	−63	42

The region in which the cluster's local maximum is located in Montreal Neurological Institute (MNI) coordinates (*x*, *y*, *z*) for N2 (240–350 ms after stimulus onset at F4 electrode site) and P3 (350 – 580 ms after stimulus onset at Cz electrode site) with associated *z*-score ($P_{\text{FWE}} < 0.05$, cluster level corrected; * Small volume corrected, $P_{\text{FWE}} < 0.05$) and cluster extend in number of voxels (*k*).

R = right, L = left, IFG = inferior frontal gyrus, ACC = anterior cingulate cortex, MCC = middle cingulate cortex, pre-SMA = pre-supplemental motor area, Sup = superior, Mid = Middle, Inf = Inferior, G = Gyrus, Post. = Posterior, L = Lobule.

in the N2 and P3 components. Thus, despite that the N2/P3 complex has been associated with the inhibitory process there is evidence that N2/P3 may reflect separable aspects of response inhibition, attentional processes, and/or conflict and performance monitoring rather than response inhibition only [Huster et al., 2013]. As the Nogo-N2 is typically observed in a latency range clearly located prior to the individual Go response, it has been suggested to reflect early pre-motor processes either directly related to response inhibition [Beste et al., 2010; Falkenstein et al., 1999; Jodo and Kayama, 1992; Lavric et al., 2004] or related to cognitive processes such as conflict monitoring or action updating potentially [Donkers and van Boxtel, 2004; Huster et al., 2013; Nieuwenhuis et al., 2004]. Regarding P3, it has also been argued that the P3 peaks too late to reflect inhibitory processes [Dimoska et al., 2003; Huster et al., 2013; Naito and Matsumura, 1994] so that it has been claimed that P3 may reflect rather evaluative processes such as stimulus or performance evaluation after response inhibition proper [Friedman et al., 2001; Huster et al., 2013; Liotti et al., 2005; Schmajuk et al., 2006; Wu and Zhou, 2009], while others suggested that the Nogo-P3 reflects the process of response inhibition itself [Beste et al., 2010; Falkenstein et al., 1999; Huster et al., 2013; Huster et al., 2014; Wessel and Aron, 2015].

The results of the current study add multiple multimodal evidence to this discussion. On one hand, our unimodal ERP results of reduced Nogo-P3 amplitudes in the high impulsive group (i.e., IC−) but no group differences in N2 amplitudes may support the notion that Nogo-P3 may reflect motor response inhibition rather Nogo-N2 since this seem to be unaffected in high impulsive subjects. This is also in line with findings from other ERP studies who demonstrated significantly reduced Nogo-P3 amplitudes but no differences in Nogo-N2 amplitudes in non-

clinical high impulsive subjects compared to low impulsive subjects [Kam et al., 2012; Ruchow et al., 2008b; Russo et al., 2008; Shen et al., 2014]. However, if we use the multimodal information (i.e., ERP correlated fMRI) we do see pronounced response inhibition network differences speaking to the point of N2 group differences beyond insignificant unimodal ERP amplitude differences. Significant pre-SMA difference between IC+ and IC− (Fig. 3A) implies differences already at an early stage of processing in response inhibition proper. This is supported by the single-trial correlation with the N2 component revealing a neural network clearly related to response inhibition in IC+ subjects but not in IC− subjects (Supporting Information Fig. 1). Regarding P3, our finding of stronger posterior IFG in IC+ subjects (Fig. 3B) may point at P3 being also involved in response inhibition itself. However, data of our recent study dissecting response inhibition proper from its attentional components [Sebastian et al., 2016] show that this very region as an attentional area possibly monitoring the response inhibition process. Our of greater ACC activity in lower performing IC− subjects (Fig. 3C) related P3 may actually speak to the role of P3 in performance evaluation (error monitoring).

Since the specificity of N2 (and P3) for inhibition associated neurocognitive processes is still not clear group selection here was deliberately data-driven based on the existence of specific IC with significantly Nogo- vs. Go-related activity occurring within a latency range located clearly before the subject's typical Go response time. Thus in line with the ongoing debate on the functional association of N2 with response inhibition it could be argued that, N2 indeed reflects other cognitive processes but not response inhibition or, at least, not response inhibition only. Since single-trial correlation with the N2 component revealed a neural network clearly related to response

TABLE VII. Correlations of fMRI BOLD signal with ERP-regressors at N2 and P3 latency in Nogo-IC negative subjects

Region	N2 regressor						P3 regressor					
	<i>k</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>Z</i>	<i>k</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>
Frontal												
L/R Sup. Medial G.							97	<0.001	4.84	0	51	39
L Mid. Frontal G.; L Sup. Frontal G.	65	0.001	4.27	−9	42	3	41	0.016	4.39	−24	51	15
L Sup. Frontal G.; L Sup. Medial G.; L ACC; R Mid Orbital G.							209	<0.001	4.96	−15	45	−6
Pre-SMA	25*	0.028*	3.86	−12	18	63	176*	0.001*	4.57	−6	15	63
R IFG (p. Opercularis)							39*	0.025*	3.82	45	15	0
L IFG (p. Opercularis)							134*	0.007*	3.99	−57	6	9
Cingulum												
R ACC	38	0.022	4.05	21	36	9	58	0.003	4.34	3	27	18
L ACC	353*	0.008*	4.27	−9	42	3	376*	<0.001*	4.96	−15	45	−6
L ACC	70	0.001	4.95	−21	24	3						
Subcortical												
L Caudate Nucleus	154*	0.025*	3.73	−12	18	−6	97*	0.002*	4.34	−18	9	18
R Caudate Nucleus							67*	0.002*	4.33	21	6	21
R Putamen							73*	0.028*	3.72	24	3	9
L Putamen							53*	0.012*	3.91	−24	3	−9
Temporal												
L Hippocampus							127	<0.001	4.59	−24	−15	−6
L Parahippocampal G.							37	0.025	4.34	−18	−36	−12
L Medial Temporal Pole; L Mid. Temporal G.	52	0.005	4.85	−45	9	−33						
L Mid. Temporal G.	104	<0.001	4.70	−57	−51	9	65	0.001	4.92	−57	−51	9
R Fusiform G.							64	0.001	4.90	30	−63	0
Parietal												
R Precuneus; R PCC;	36	0.028	4.01	21	−42	0						
R Linual G.												
L Precuneus; L Linual G.;							294	<0.001	5.10	−30	−69	21
L Inf. Occipital G.												
Occipital												
L/R Calcarine G.; L Cuneus							47	0.008	4.37	−3	−72	15
R Cuneus; R Sup. Occipital G.							69	0.001	4.83	21	−90	9

The region in which the cluster's local maximum is located in Montreal Neurological Institute (MNI) coordinates (*x*, *y*, *z*) for N2 (240–350 ms after stimulus onset at F4 electrode site) and P3 (350–580 ms after stimulus onset at Cz electrode site) with associated *z*-score ($P_{\text{FWE}} < 0.05$, cluster level corrected; * small volume corrected, $P_{\text{FWE}} < 0.05$) and cluster extend in number of voxels (*k*).

R = right, L = left, IFG = inferior frontal gyrus, ACC = anterior cingulate cortex, MCC = middle cingulate cortex, pre-SMA = pre-supplemental motor area, Sup = superior, Mid = Middle, Inf = Inferior, G = Gyrus, L = Lobule.

inhibition in IC+ subjects but not in IC− subjects, it could also be argued that Nogo-N2 reflects an early stage of response inhibition which is less effectively activated in high impulsive subjects.

There is an alternative interpretation of the current results coming with a motor control rather than inhibitory control view of the neurocognitive processes underlying Go/Nogo paradigms. The observed group differences reflect important differences in the Go rather than stopping behavior. Indeed as already implied in our own component analysis of the response inhibition tasks especially the Go/Nogo task entails both response selection (selecting go vs. stopping behavior) as well as response inhibi-

tion (withholding a prepotent action) components [Stahl et al., 2014]. Since response selection and monitoring is often associated with neural activity in the pre-SMA and the ACC, respectively, our current finding could point toward a behavioral and neural difference in response selection rather than response inhibition proper. This will also fit our finding of prominent differences in P3 rather than N2 ERP amplitudes. In this view our finding of neural-based behavioral differences (IC+ vs. IC−) can be interpreted as a primary go selection, hence “motor” control finding. Interestingly, in adult ADHD behavioral differences are found mainly in CoV and omission error rates but not on the commission error rates, supporting this view

A) Multimodal fMRI (N2 regressor): Nogo-IC-positive > Nogo-IC-negative ($p < .005$) **B) Multimodal fMRI (P3 regressor): Nogo-IC-positive > Nogo-IC-negative ($p < .005$)** **C) Multimodal fMRI (P3 regressor): Nogo-IC-negative > Nogo-IC-positive ($p < .005$)** **Figure 3.**

Activation maps displaying the results of comparing effects of positive correlations with N2/P3 regressors in Nogo-IC-positive and in Nogo-IC-negative subjects. **A:** Stronger correlations with N2 single-trial amplitude values (from F4 at 280–340 ms) in Nogo-IC-positive subjects relative to Nogo-IC-negative. **B:** Stronger correlations with P3 single-trial amplitude values (from Cz at 350–580 ms) in Nogo-IC-positive subjects relative to Nogo-IC-negative. **C:** Stronger correlations with N2 single-trial amplitude values (from F4 at 280–340 ms) in Nogo-IC-negative subjects relative to Nogo-IC-positive. Please note that the

threshold for visualization is set at $P < 0.005$ ($k = 10$) level uncorrected for multiple comparisons for the purpose of presentation only. This may lead to the depiction of clusters that does not reach corrected significance levels, e.g. IFG/IFJ activity in (A) is in difference to (B) just not significant for multiple comparisons. The color bar indicates t -scores (0–11.2380). ACC: anterior cingulate cortex. IFG: inferior frontal gyrus. IFJ: inferior frontal junction. Pre-SMA: presupplementary motor area. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

from a disease model [Fisher et al., 2011; Helenius et al., 2011; Prox et al., 2007; Wiersema et al., 2006; Woltering et al., 2013]. On the neural level this view is supported by our finding that IC+ more than IC- show pre-SMA activity (response selection) related to N2. In addition, we find IFG activity for IC+ more than IC- during both phases of

response inhibition (N2 and P3; see Fig. 3; significant in P3). Interestingly, this particular subregion of the IFG, which is the inferior frontal junction, has been shown to handle primarily attentional information during response inhibition [Sebastian et al., 2016]. Hence activity in this region during both phases of response inhibition may

TABLE VIII. Between group comparisons of correlations of fMRI BOLD signal with ERP-regressors at N2 and P3 latency in Nogo-IC-positive subjects compared to Nogo-IC-negative subjects

Region	N2 regressor						P3 regressor					
	<i>k</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>Y</i>	<i>Z</i>	<i>k</i>	<i>P</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>Z</i>
A. Nogo-IC-positive > Nogo-IC-negative												
Frontal												
Pre-SMA	193*	0.035*	3.72	3	9	51	65*	0.028*	3.70	42	9	27
R IFG (p. Opercularis)												
B. Nogo-IC-negative > Nogo-IC-positive												
Frontal												
L Sup. Medial G.;							61	0.015	4.01	−6	57	9
L pregenual ACC												

The region in which the cluster's local maximum is located in Montreal Neurological Institute (MNI) coordinates (*x*, *y*, *z*) for N2 (240–350 ms after stimulus onset at F4 electrode site) and P3 (350–580 ms after stimulus onset at Cz electrode site) with associated *z*-score ($P_{\text{FWE}} < 0.05$, cluster level corrected; * small volume corrected, $P_{\text{FWE}} < 0.05$) and cluster extend in number of voxels (*k*).

R = right, L = left, ACC = anterior cingulate cortex, pre-SMA = pre-supplemental motor area, IFG = inferior frontal gyrus, Sup = superior; G = Gyrus.

represent enhanced attentional monitoring of response inhibition in IC+ subjects. Lastly, pregenual ACC overactivity in IC− compared to IC+ subjects could mean greater error monitoring in subjects with lesser “motor” (behavioral) control. However, this attractive alternative interpretation of our findings is challenged by the fact that our basic, data-driven neural contrast identifies neural activity which is greater during Nogo, hence response inhibition proper (stopping/withholding an action), than during Go (motor behavior/control). However, if there is a difference on the neurocognitive level between what we call motor control on the one hand and response inhibition/inhibitory control on the other hand might rather be a semantic than a biological question.

In conclusion, our data suggests the existence of electrophysiologically dissociable phenotypes of behavioral and neural motor response inhibition. Group comparisons performed on behavioral data revealed significantly higher intra-individual variability of Go RT and enhanced omission errors in IC− subjects. In line with this, results of unimodal fMRI analysis revealed differently recruited neural networks with additional activation of left IFG/insula and left putamen in IC− subjects. This may indicate that subjects with lower trait impulsivity have access to a more effective impulse control network. Thus, the recruitment of only few key areas of inhibitory control in fMRI may be the result of an effective and well-orchestrated (as indicated by higher P3 amplitudes) network performance. Alternatively, additional activations may be the cause of higher intra-individual variability in performance and more impulsive traits. Therefore, the presence or absence of identifiable Nogo-related ICs may represent different neurophysiological phenotypes of response inhibition. Although we cannot unambiguously distinguish between different mechanisms in terms of state (short-term strategy

adaptation) vs. trait (static individual neurobiologically determined differences), the behavioral data together with psychological data support a trait hypothesis of different neurophysiological phenotypes of response inhibition.

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