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Single-subject prediction of response inhibition behavior by event-related potentials

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Abstract

Much research has been devoted to investigating response inhibition and the neuronal processes constituting this essential cognitive faculty. However, the nexus between cognitive sub-processes, behavior and electrophysiological processes remains associative in nature. We therefore investigated whether neurophysiological correlates of inhibition sub-processes merely correlate with behavioral performance or actually provide information expedient to the prediction of behavior on a single-subject level. Tackling this question, we used different data-driven classification approaches in a sample of n=262 healthy young subjects who completed a standard Go/Nogo task while an EEG was recorded. Based on median-split response inhibition performance, subjects were classified as “accurate/slow” and “less accurate/fast”. Even though these behavioral group differences were associated with significant amplitude variations in classical electrophysiological correlates of response inhibition (i.e. N2 and P3), they were not predictive for group membership on a single-subject level. Instead, amplitude differences in the Go-P2 originating in the precuneus (BA7) were shown to predict group membership on a single-subject level with up to 64% accuracy. These findings strongly suggest that the behavioral outcome of response inhibition greatly depends on the amount of cognitive resources allocated to early stages of stimulus-response activation during responding. This suggests that research should focus more on early processing steps during responding when trying to understand the origin of inter-individual differences in response inhibition processes.

Keywords

EEG, response inhibition, machine learning, single subject prediction
Introduction

The ability to inhibit one's own responses is central to action control and indispensable for self-regulation as well as an important prerequisite to higher-order executive functions and cognitive flexibility (19). Poor or dysfunctional response inhibition may profoundly interfere with everyday life requirements and has been shown to be prevalent in a variety of neurological and psychiatric diseases (2, 4, 6, 10, 16, 32). On the behavioral level, different paradigms and parameters are used to measure response inhibition performance and abilities (19, 65). While the rate of false alarms (i.e. the failed inhibition of the Go response in Nogo trials) is the main measure of inhibition in Go/Nogo tasks, Stop-signal-tasks estimate the stop signal reaction time (SSRT) which is thought to reflect a “race” between largely independent go and stop processes (19, 65). Mostly based on these two kinds of inhibition paradigms, the functional neuroanatomical architecture and neuronal processes underlying the ability to inhibit prepotent responses have been subject to intense research in cognitive neuroscience (3, 4). In this context, electroencephalographical (EEG) techniques have long been applied to elucidate the neuronal mechanisms underlying this important executive control function (13, 23, 34, 35, 49, 63). Using EEG techniques, it has been suggested that there are at least two distinct neurophysiological sub-processes which contribute to successful response inhibition: It has repeatedly been demonstrated that a frontal-midline N2 event-related potential (ERP) reflects pre-motor processes like conflict monitoring or updating of the response program, while a P3 ERP reflects evaluative processing of the successful outcome of inhibition (6, 8, 11, 24, 34, 45, 52), or possibly of the inhibition process itself (68).

However, the relationship between the behavioral outcome of response inhibition and the neurophysiological responses reflecting underlying cognitive processes is still largely associative in nature. Importantly, this associative nexus does not imply that it is possible to
predict behavior from electrophysiological data. It is still elusive whether electrophysiological correlates of response inhibition allow for the prediction of the behavioral outcome of response inhibition on a single-subject level. In the current study, we hence examine the single-subject predictability of the behavioral outcome of response inhibition based on electrophysiological response inhibition substrates using data-driven classification approaches. In this context, it needs to be stressed that we do not confine our analyses to ERP data within the time frames of the N2 and P3 components. Instead, we examine different time frames over the entire post-stimulus period. One of the main reasons for this is that response times are typically quite low in Go/Nogo tasks (often no more than 300 – 350 ms in healthy young subjects, e.g. 10, 32, 54, 57). While the N2 might often still fall within this range, the P3 component usually peaks after the average response time. When rating performance based on hit rates and false alarm rates, whatever cognitive process allows to predict performance should occur before any response is given (i.e. before the mean response time). In this context, some results suggest that early stages of either stimulus-response-activation (29) and/or resource allocation processes, as reflected in a P2 component (12, 14, 57, 61), may also be important for response inhibition processes (12, 28, 57). Others have suggested that the P2 reflects higher order perceptual processing in terms of relevant stimulus features, which are enhanced while irrelevant ones are suppressed at the same time (18). This is all the more relevant in the current context, considering that successful inhibition has been suggested to rely on the adjustment of attentional settings to optimize stimulus detection and evaluation (22, 31, 66). Given all this, we expect that an above-average allocation of resources as reflected by the P2 component should be one of the features allowing for the prediction of the behavioral outcome of response inhibition (as operationalized by group membership in this study).
Summing up our hypotheses, we expect the “classical” components (i.e. N2 and P3) to correlate with inhibition performance but deem earlier components such as the P2 to be similarly suitable to predict behavioral performance / group membership. We will therefore take two complementary approaches: In order to provide results that can be compared to previous publications in the field, the P2, N2, and P3 component will be analyzed by quantifying ERPs at mid-frontal electrodes and using a regression analysis approach in order to explain behavior by (Nogo)-N2 and (Nogo)-P3 components. Furthermore, we will additionally take a machine-learning approach to identify potential predictors of behavioral performance / group membership performance among earlier, inhibition-related ERP components. Both of these approaches will be complemented with source localization techniques (sLORETA) in order to determine the brain regions that can be used to predict inhibition performance. In order to be able to predict group membership based on behavioral measures of response inhibition, we will investigate n =262 healthy young subjects that are subdivided into two groups based on a median split of the false alarm rate. Subsequently, the nexus between groups, behavioral data (accuracy and RTs), classical ERPs (i.e. P2, N2 and P3) and different predictors identified by means of machine leaning (see methods section) will be compared.

Methods

Sample

A sample of n =262 healthy subjects between 18 and 30 years of age (mean age 23.9 SD = 3.06) was recruited for the study. 114 of the subjects were females. None of the participants enrolled in the study reported a history of neurological or mental illness. The study was approved by the Ethics committee of the Ruhr-Universität Bochum, Germany. The study was...
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conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent and received 10 € reimbursement or course credits for their participation.

**Task**

We used a standard Go/Nogo task, which has frequently been used by our group to assess response inhibition performance (11, 48, 50). Each trial started with the 200 ms presentation of either the German word “DRÜCK” or “STOPP” (translating to “PRESS” and “STOP”) in the center of a 17” screen. Subjects were required to respond with their right index finger on a custom-made button as fast as possible whenever the Go stimulus (“DRÜCK”) was presented. Upon presentation of the Nogo stimulus (“STOPP”), the subjects were required to withhold their Go response. 70% of all trials were Go trials and subjects were instructed to respond as fast as possible, resulting in a relatively high rate of false alarms (i.e. a lower rate of correct Nogo trials). Each trial was terminated by the participant’s first response (correct responses in Go trials or false alarms in Nogo trials) or ended after 2200 ms had elapsed (missed Go responses or correct inhibition in Nogo trials). The inter-trial interval (ITI) was jittered between 1000 and 1300 ms. In total, the paradigm comprised 450 trials.

**EEG recording and analysis**

The EEG was recorded from 64 Ag/AgCl electrodes using the extended 10/20 system against a reference electrode placed at electrode FCz. The sampling rate was 1 kHz. Electrode impedances were kept below 5 kΩ. After recording, the data were down-sampled to 256 Hz. Off-line, the EEG was digitally filtered using IIR band-width filters at 0.5 and 20 Hz (each with a slope of 48dB/oct). Then, the data were visually inspected and gross artifacts were manually removed from the EEG. Horizontal and vertical eye-movements as well as pulse
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Artifacts were removed using an independent component analysis (ICA) (infomax algorithm). After reconstructing the rectified EEG from the remaining components, electrode FCz was topographically interpolated. The EEG was then segmented into epochs of 800 ms length starting 200 ms prior to the target stimulus onset, which was set to zero. Due to the large number of data files that underwent manual and semiautomatic correction, an automatic artifact rejection procedure was applied to eliminate any artifacts that might have survived the prior corrections. A value difference above 200 μV in a 100 ms interval as well as an activity below 0.5 μV in a 200 ms period were used as rejection criteria. Next, a current source density (CSD) transformation (46) (order of splines m = 4, maximum degree of the Legendre polynomials n = 10, precision of $2.72^{-7}$) was applied to re-reference the data. Due to this, the resulting CSD values are given in μV/m². A baseline correction was applied in the time range from -200 ms to 0 ms (i.e. prior to target onset) before the segments were separately averaged for Go and Nogo trials with correct responses on a single subject level. The average number of epochs included in the data analysis was 285 ± 13 for Go trials and 115 ± 10 for Nogo trials. For the classical time-domain analysis of the ERP components, the Nogo-P2 was quantified by extracting the mean amplitude in the time interval from 175 to 180 ms. The Nogo-N2 was quantified by extracting the mean amplitude of the time interval from 250 to 310 ms. The Nogo-P3 was quantified by extracting the mean amplitude of the time interval from 350 to 440 ms. For the correctly answered Go trials, amplitudes of the Go-P2, Go-N2, and Go-P3 were measured in the corresponding time intervals of the individual averages. Due to quantifying the peak amplitudes by using mean amplitude values and due to the fact that no change in peak latencies could be visually detected in the mean averages of the groups, we refrained from determining peak latency values. The electrodes used for ERP classification were chosen based on scalp topographies of the averaged event-related potentials in Go and
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Nogo trials across the entire sample (refer Figure 1).

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Nogo trials across the entire sample (refer Figure 1). Insert Figure 1 about here

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For the P2, this yielded electrodes O2 and O1. For the (No)Go-N2, this yielded electrodes FCz and Cz, while the (No)Go-P3 was quantified at electrodes FC1 and C1. (refer map in Figure 1). This choice of electrodes was validated using a statistical procedure previously described by Mückschel et al. (39). For the standard (non-data-driven) ERP analysis, parametric statistics were used. To compare behavioral performance on Go and Nogo trials, independent samples t-tests were used. The ERP data were analyzed using mixed effects ANOVAs using “condition” (Go vs. Nogo) and “electrode” as within-subject factors and “performance group” (accurate/slow vs. less accurate/fast) as a between-subject factor. Greenhouse-Geisser correction was applied and performance post-hoc tests were Bonferroni-corrected whenever necessary. Separate ANOVAs were conducted for the P2, N2, and P3 components.

Data-driven ERP analysis

The average event-related potential on Go and Nogo trials across the entire sample (n = 262) is shown in Figure 1. Our machine learning approach was performed in four separate stages of analysis: data preparation, feature selection, classifier selection, and validation. The bulk of this analysis was done in Matlab (Mathworks, USA) with help from the open-source packages Weka (data mining software in Java, available online at http://www.cs.waikato.ac.nz/ml/weka/), LibSVM (support vector machine library, available online at http://www.csie.ntu.edu.tw/~cjlin/libsvm/) and bolasso.m (bootstrap-enhanced least
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absolute shrinkage operator, available online at http://code.google.com). The goal of this analysis was to predict group membership in the Go/ Nogo task, as based on the false alarm rate, from electrophysiological data on a single-subject level. As described above, participants were grouped based on a median split involving the Nogo condition). Irrespective of group membership, the whole sample was then randomly split into two groups to obtain a training set (2/3; n = 173) for hypothesis formation and another, albeit smaller validation set (1/3; n = 89) for validation and discrimination, in order to minimize the chance of over-fit.

In the first stage (data preparation), ERP data were reduced in dimensionality, which is basically done to assure that the number of machine learning features does not exceed the number of participants, which would produce trivial classifiers. For this purpose, we first calculated topographical difference strength maps, i.e. bootstrapped scalp current source density differences between high and low performers averaged across all conditions. Based on these difference strength maps, we selected the following electrodes for further analyses: midline electrodes Fz, FCz, Cz, CPz, Pz, and Oz; as well as lateral parieto-occipital electrodes P1, P2, P3, P4, PO7, PO8, PO9, PO10, O1, and O2. Next, ERPs were divided into different time bins that were specifically tailored to represent several ERPs reflecting perceptual and attentional processing (i.e., P1, N1, P2) as well as inhibition-related processes (N2 and P3) in the Go and Nogo conditions. These bins were (I) 75-120 ms, (II) 90-135 ms, (III) 145-210 ms, (IV) 250-310 ms, (V) 350-440 ms, and (VI) 390-450 ms. The bins were set on the basis of the waveform at electrode FCz (refer Figure 1), because this electrode was located at the center of the topographies in the Nogo-N2 (time bin IV) and Nogo-P3 (time bin V). As can be seen in Figure 1, two time bins in the P3 range (i.e. V and VI) overlap. These two time bins were chosen for the P3-time window as the peaks of the P3 differed in their latency between Nogo and Go trials (i.e. the P3 peaked later in Go than in Nogo trials). For the other time bins, there
we only used one time window for each ERP as there were no differences in the latencies between the Go and Nogo conditions. Finally, ERP features were entered into machine learning analysis on the basis of selected electrodes (N=16), time bins (N=6), and experimental conditions (N=2).

In the second stage (feature selection), 50 Monte Carlo simulations were performed using 2 equally sized random splits of the training set to cross-validate features with significant differences among the two conditions, using a two-sided Kolmogorov-Smirnov (KS) test with a p<.05. For each Monte Carlo simulation, a different subset of features was selected. Within each simulation, features were further tested for significance of difference within test data in order of training set discrimination strength. Figure 2 shows the mean accuracy of linear threshold classification (simplest classifier) based on each individual feature.

Of note, different feature selection processes are viable for dimension reduction, such as advanced principal component analyses (20), recursive feature elimination (15), or strong feature identification (55). We chose to use the KS test to identify strong features, as this method is firmly established and has been shown to provide robust classification results in our previous studies (42, 55).

In the third stage of the analysis (classifier selection), we explored a hypothesis space which was the product of all combinations of predictive features (from the 3 listed above), and all the classifiers to be tested. The order in which these hypotheses were validated on (unseen) test data was based on the correlation between features and their estimated individual
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predictive ability (using a simple threshold classifier is the fundamental assumption of the Kolmogorov-Smirnoff test), based on the correlation-scaled conditional information. Suppose we have a series of predictors $x_1, x_2, \ldots, x_n$ of relevance to a binary variable $y$ and these predictors have a correlation structure $P$ with individual elements $\rho_{i,j}$. The basic concept is to prefer combinations of uncorrelated individual predictors to those who may be redundant. For this, we calculate the individual predicted accuracy for every single predictor using a simple classifier (a binary threshold or range) $r(x_i)$ which for a single predictor is simply the value obtained on the training set. Then we define an intermediate utility function $m$:

\[ m = \text{Insert Equation 1 and 2 about here} \]

And based on that, the recursively defined predicted accuracy function:

\[ \text{Insert equations 2 and 3 about here} \]

Where $H$ is the Shannon entropy of a binary channel with accuracy $r$, $H^{-1+}$ is the inverse of this function taken at the upper (of two) roots, and $|\rho_{1,n-1,n}| = \min_{j=1,n-1} |\rho_{jn}|$.

The order of evaluation of multi-dimensional hypotheses (i.e. with more than 1 predictor combined) is then done in order of decreasing $r$.

The applied classifiers are common classification algorithms used in machine learning practice and include linear and quadratic discriminants (LDA/ QDA and their diagonal variants), support vector machines (SVM with radial basis, linear, polynomial, sigmoid, and multi-layer perceptron kernels), naïve Bayes; k-nearest neighbors with Euclidean and cosine distance measures, and Mahalanobis with different types of regularization of the covariance matrix.
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estimator (no regularization, pseudo-inverse, probabilistic reasoning model, BOLASSO, and robust regression).

In the fourth and final step (validation), hypotheses are evaluated (best-to-worst) on the validation subset, i.e. 1/3 remaining from the original split, which until this step has not played a part in any fitting or optimization. Hypotheses that resulted in tested over-fit according to a 2-sided binomial test were discarded.

Results

Behavioral data

For the descriptive statistics, the mean and standard error of the mean (SEM) are given. The mean rate of false alarms in the entire sample was 11.7 % (0.5). Mean reaction times (RTs) in Go trials were 349 ms (2.1) and 289 ms (3.9) in erroneous Nogo trials. As expected, RTs were faster for false alarms (erroneous reactions on Nogo trials) than in Go trials (t_{257} = 18.02; p < .001). A comparison of common behavioral measures across groups is given in Table I.

As the high and low performance groups were based on the rate of false alarms, the rate of false alarms necessarily differed between groups (t_{260} = 14.92; p < .001). However, all other behavioral measures also differed between groups (all p ≤ .011, see table I). Of note, the RT data shows that on both Go and Nogo trials, participants showing high false alarm rates show speeded responding as compared to participants showing a lower false alarm rate. This shows that there is a speed-accuracy trade-off (SAT) between the groups. Therefore the groups were termed as “accurate/slow” and “less accurate/fast”.
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308 Standard analysis of ERP data

309 Figure 3A shows the ERPs on Go and Nogo trials for electrodes Cz, FC1 and FCz.

310 Insert Figure 3 about here

311

Concerning the N2 data, the results showed significant main effects of “condition”, “electrode”, and “group” as well as a significant interaction of “condition x group”. The main effect of “condition” (F(1,260) = 32.93; p < .001; η^2 = .112) showed that the N2 was larger in Nogo (-11.62 µV/m^2 ± 0.5) than in Go trials (-9.1 µV/m^2 ± 0.5). The main effect of “electrode” (F(1,260) = 10.90; p = .001; η^2 = .040) was based on a higher N2 amplitude at electrode FCz (-11.86 µV/m^2 ± 0.6), compared to Cz (-8.84 µV/m^2 ± 0.7). The main effect of “group” (F(1,260) = 7.86; p = .005; η^2 = .029) relied on a larger N2 amplitude in the low performance (-11.73 µV/m^2 ± 0.7) than in high performance group (-8.97 µV/m^2 ± 0.6).

321 Importantly, there was an interaction of “condition x group” (F(1,260) = 4.30; p = .025; η^2 = .019). Post-hoc t-tests showed that there was a significant N2 difference between groups in Nogo trials (low performers: -13.40 µV/m^2 ± 0.6; high performers: -9.84 µV/m^2 ± 0.7; t260 = -3.12; p = .002), but not in Go trials (high performers: -8.10 µV/m^2 ± 1.1; low performers: -10.06 µV/m^2 ± 1.4; t260 = -1.13; p > .2). All other interaction effects were not significant (all F < 0.16; p > .6).

327 For the P3 data, there were main effects of “condition” and “electrode” as well as an interaction of “condition x electrode”. The main effect of “condition” (F(1,260) = 758.75; p < .001; η^2 = .745) showed that the P3 at frontal electrode sites was larger in Nogo (19.86 µV/m^2 ± 0.8) than in Go trials (4.57 µV/m^2 ± 0.6). The main effect of "electrode" (F(1,260) = 38.36;...
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\( p < .001; \eta^2 = .129 \) indicated that the P3 was larger at electrode C1 (13.78 µV/m² ± 0.8) than at FC1 (10.65 µV/m² ± 0.6). The interaction of "electrode x condition" (F(1,260) = 82.69; \( p < .001; \eta^2 = .241 \)) was based on a larger amplitude difference between Go and Nogo trials at electrode FC1 (18.06 µV/m² ± 0.6) than at electrode C1 (12.53 µV/m² ± 0.7), as shown by post hoc testing (t_{261} = 9.11; \( p < .001 \)). There was no main effect of "group" and there were also no interactions with this factor (all F < 1.6; \( p > .2 \)).

Regression analyses were calculated to investigate how variance in the behavioral performance (i.e. rate of false alarms) is explained by the Nogo-N2 and Nogo-P3 amplitudes and whether there are differences between the performance groups. The rate of false alarms was used as the dependent variable while group, as well as Nogo-N2 and Nogo-P3, served as predictors within the same model. The 'inclusion' (enter) method was used. The regression model yielded a significant result (F(3,261) = 73.81; \( p < .001 \)). Only the factor group significantly contributed to the regression model (\( \beta = -.679; t = -14.77; p < .001 \)). This is however trivial because the groups were built upon a median split on the false alarm rate data. Neither the Nogo-N2 amplitude, nor the Nogo-P3 amplitude were significant predictors in the regression model (all \( \beta < -.054; t < -1.16; p > .2 \)).

sLORETA analyses were calculated to contrast the Go with the Nogo condition in the entire sample in the N2 and P3 time ranges. The results are shown in Figure 3B. For the N2 time range, the analysis revealed stronger activity in Nogo trials in the left and right middle frontal gyrus (Brodman Area (BA) 9), left and right medial frontal gyrus (BA9, BA6), cingulate gyrus (BA24) and the left and right precentral gyrus (BA6). For the P3 time range, the sLORETA analysis revealed stronger activity in Nogo trials in the anterior cingulate cortex (ACC) (BA23, BA24), para-central lobe (BA6), and the middle frontal gyrus (BA9).
Because the interaction of "condition x group" had revealed differences between performance groups on Nogo trials in the N2 time range, we also contrasted the Nogo-N2 in the low performance group to the Nogo-N2 in the high performance group. This was however not done for the Nogo-P3 because there was no difference between performance groups. The sLORETA analysis suggests that activation differences between the groups were due to activation differences in the ACC (BA24, BA23) in the Nogo-N2 time window with low performers displaying a larger activation than high performers (refer Figure 3C).

Aside from the analysis of these classical response inhibition-related ERPs (i.e. (No)Go-N2 and (No)Go-P3) we also analyzed the P2, which could be of importance as some studies suggest that early stages of either stimulus-response-activation (29) and/or resource allocation processes, as reflected in a P2 component (12, 14, 57, 61), may also be important for response inhibition processes (12, 28, 57). The P2 was maximal at electrode Oz and O2, as validated using statistical techniques (refer methods section). For the P2 at these electrodes, the mixed effects ANOVA only revealed a main effect "electrode" (F(1,260) = 12.19; p = .001; η² = .045). All other main or interaction effects were not significant (all F < 0.96; p > .3).

Single-subject classification (data-driven analysis)

The top hypotheses derived by machine learning are shown in Table II, in terms of classification accuracy of both the training and (independent) test set. The first hypothesized estimate is the top row, and has a 64% test accuracy rate (P < .07) on hitherto untested data (i.e. the validation set). Being evaluated independently of subsequently ranked hypotheses, this result is not dependent on any multiple comparison correction, and stands alone. Note that the predicted (training) and validated (test) accuracies are not only
within the margin of error, but are very similar, which is particularly convincing and strongly argues against over-fitting the mathematical model to the data. Subsequent hypotheses would not retain their nominal p values (shown) after multiple comparison correction and thus primarily serve as comparative algorithmic models. Of note, chosen features were identified by virtually all algorithms. The features most consistently selected were: Go P2 ERP 250-310 ms at electrode PO9 (feature 1) (Figure 4 top), Nogo P2 ERP 145-210 ms at electrode O1 (feature 2) (Figure 4 middle), and Nogo P3 ERP 350-440 ms at electrode PO7 (feature 3) (Figure 4 bottom). Figure 4 shows the ERPs at the respective electrode sites, time bins and conditions. It is important to note that in the employed EEG electrode setup, electrodes PO9/PO10 are not edge electrodes, as electrode P11 and P12 were evident in this setup. This is important since CSD transformations can introduce distortions of activity at edge electrodes, which may compromise the reliability of data.

Comparing the “accurate/slow” to the “less accurate/fast” group on these extracted features using independent samples t-tests revealed that for feature 1, there was a significant difference between the “accurate/slow” (5.3 ± 1.4) and the “less accurate/fast” group (0.16 ± 1.4) ($t_{260} = -2.57; p = .005$). For feature 2 and feature 3, there was no significant difference between the two performance groups (all $t < -1.16; p > .2$). This pattern of results highlights the non-trivial nature of machine learning analysis that allows to identify even those ERP features which are not significantly different on a group level if there is no explicit procedure to eliminate them (i.e. feature selection) as to increase inference specificity while controlling the (potentially combinatorially large) number of hypotheses such selection implies. This result also depends
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on the choice of statistical test used in the preselection of predictors, which either rely on
differences of distribution (such as the Kolmogorov-Smirnoff test used during our feature
selection approach) or on more narrowly defined and commonly used differences of mean
values and their standard deviation (such as the t-test).

We further investigated feature 1 (Figure 4 top) that likely reflects processes related to
P2 amplitude variation. To examine this feature variation between the “accurate/slow” and the
“less accurate/fast” group on a systems level, we ran an sLORETA analysis, contrasting the
“accurate/slow” and the “less accurate/fast” group. This was done for the time point showing
the most positive amplitude value of the P2 in the “accurate/slow” group, i.e. at 297 ms. The
results show that group-dependent performance differences were due to activation differences
in the precuneus (BA7) (refer Figure 4 top). Note that the result was identical when using the
whole bin in the sLORETA analysis).

Discussion

In the current study, we examined the predictability of behavioral performance by
electrophysiological substrates of response inhibition processes using data-driven pattern
recognition approaches. While electrophysiological data are widely used to study response
inhibition processes, it has remained unclear whether it is possible to predict response
inhibition performance (accuracy) on the basis of electrophysiological response inhibition
indices on a single-subject level. For this purpose, we median-split a sample of 262
participants into an “accurate/slow” and a “less accurate/fast” group. Our data analyses
suggest that the prediction of group membership is indeed possible, but not on the basis of the
electrophysiological correlates that are usually associated with response inhibition processes
(i.e. the Nogo-N2 and Nogo-P3).
The standard analysis of response inhibition ERP-correlates using parametric tests revealed the usual and expected effects including higher N2 and P3 amplitudes on Nogo than on Go trials. The Nogo-N2, but not the Nogo-P3 was differentially modulated across groups, being smaller in “accurate/slow” than in the “less accurate/fast” group. It therefore seems that especially pre-motor processes like conflict monitoring or updating of the response program (23, 34, 44) distinguish between groups, while this is not the case for processes that either reflect evaluative processing of the successful outcome of the inhibition or the inhibition process itself (34). Given that requirements of the paradigm were rather simple, it however seems logical that response evaluation processes differed less between groups. Further supporting the importance of reduced pre-motor inhibition in the “less accurate/fast” group, we found that this group shows faster responding than in the “accurate/slow” group. It is possible that compared to “accurate/slow” group, the “less accurate/fast” group seems to experience an enhanced conflict between responding and non-responding when confronted with Nogo stimuli, which is reflected in the enhanced Nogo-N2. Source localization analyses revealed that in the N2 time window, areas in the left and right middle frontal gyrus (BA9), left and right medial frontal gyrus (BA9, BA6), cingulate gyrus (BA24) and the left and right pre-central gyrus (BA6) were more activated in Nogo than Go trials (38, 67). In the context of our task, the heightened activation in BA6 most likely reflects the conflict to inhibit motor response plans while activity in the dIPFC (BA9) might reflect pre-movement associated cognitive control processes (21, 47, 53, 62). The heightened activity in the ACC (BA24) most likely depicts aspects of voluntary response inhibition and conflict monitoring (9, 27, 32, 53, 67). In the P3 time window, the sLORETA analysis revealed that areas encompassing the anterior cingulate cortex (ACC) (BA23, BA24), para-central lobe (BA6), and the middle frontal gyrus (BA9) were more activated in Nogo than in Go trials (25, 26, 38, 67).
finding that the P3 peak was largest over electrodes left from the midline might be explained by the response modality: Even though stimuli were centrally presented, all participants had been explicitly instructed to only use their right hand for responses, which might explain inhibition of motor plans in contralateral left premotor areas / the left SMA (i.e. BA 6). Furthermore, it has previously been shown that important aspects of response evaluation may be shifted towards the hemisphere which is in charge of generating and sending the motor command of required responses (58, 60). In sum, the areas showing N2 and P3 differences between Go and Nogo trials have frequently been reported as elements of a response inhibition network (4, 38, 64, 67) and electrophysiological studies using source localization approaches also report sources of the Nogo-N2 and Nogo-P3 in the brain regions identified in this study (1, 1, 30, 36). While these results clearly show that neurophysiological processes reflected by the Nogo-N2 and Nogo-P3 are associated with response inhibition processes, a regression analysis taking performance group into account showed that response inhibition performance could not be inferred on the basis of Nogo-N2 and Nogo-P3 amplitude modulations in the entire cohort. This suggests that performance was unrelated to modulations in components that are commonly suggested to reflect pre-motor processes like conflict monitoring/ updating of the response program (Nogo-N2), or evaluative processing of the successful outcome of the inhibition, or the inhibition process itself (Nogo-P3) (1, 6, 8, 11, 24, 30, 36, 43, 45, 52; for review: 34). However, several other studies found correlations between performance and neurophysiological indices (7, 8, 51, 54). One possible explanation might be that in many EEG studies, the sample sizes are rather small, with often no more than 15-25 subjects per group. In such setups, it cannot be ruled out that some of the observed differences are due to special sample characteristics (54).
Our data-driven analysis offers an alternative approach to predict group membership on the single-subject level. Furthermore, none of the employed algorithms showed an effect for classical response inhibition correlates, even though time windows used for ERP quantification were adjusted to Nogo-N2 and Nogo-P3 peaks. Instead, the data-driven analysis revealed that a small set of features that includes amplitude modulations in the P2 time range of Go trials predicted group membership on a single-subject level with up to 64% accuracy, i.e. well above chance. Yet, both the electrode sites and time window of the P2 differed from the topography-based ones used in the standard ERP analysis. Given that healthy subjects usually display rather small inter-individual differences in such a simple task and that the severe impairments caused by schizophrenia have been demonstrated to account for approximately 75% of the inter-individual neurophysiological variance (as compared to controls) in similar tasks (40–42), the current results are in line with these rates of variance explanation. Even though there are some claims that the P2 largely reflects sensory processing (5), the P2 ERP has been suggested to reflect either stimulus-response-activation (29) and/or resource allocation processes (12, 14, 57, 61), which have already been shown to be important for response inhibition (12, 57). Especially on Go trials, the P2 amplitude was larger in the “accurate/slow” group, than the “less accurate/fast” group, suggesting that the “accurate/slow” group shows enhanced resource allocation processes on Go trials. Given that Go trials were the most frequent trials in the task, we infer that stronger resource allocation processes, as reflected by the P2 component, are one of the main reasons for being rather accurate but slow. Such resource allocation processes may reflect the degree of top-down guided attention and the cognitive “effort” that the participants invest in performing the task. One possible explanation for the enhanced Go-P2 amplitude in the “accurate/slow” group would be that an increase in top-down attentional processes counteracts the formation of the
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automated response tendency induced by the large proportion of Go trials in the task. Following this logic, automatic response tendencies should be less intense in subjects belonging to the “accurate/slow” group. Alternatively, one could assume that automated response tendencies always form in a similar fashion, but are subject to varying degrees of top-down cognitive control as reflected by the P2 amplitude. In this case, automatic response tendencies should be more or less similar for everyone, but subjects being more accurate but slow may exert more top-down control to modify this tendency. In line with this interpretation, the sLORETA analysis suggests that activation differences in the precuneus (BA7) are related to the predictive P2-feature. The precuneus has been demonstrated to be involved in the orientation, allocation and shifting of attention, as well as in conscious information processing (17, 37), thus supporting the claim that the observed P2 differences might reflect the top-down allocation of cognitive resources to (Go) stimulus processing. Our findings hence suggest that in the context of inhibition, one of the most predictive features for belonging to an “accurate/slow” group, or a “less accurate/fast” group is the parietal allocation of (attentional) resources to the more frequent Go response as reflected by the Go-P2 component. Against this background, it would be logical to assume that the amount of attention allocated to regular responses modulates the automatization of responding, which should be reflected by the difficulty to inhibit prepotent response tendencies. Yet, aside from the Go-P2, there were also two time periods / ERP features in Nogo trials that also contributed to the prediction of performance. As can be seen in Figure 4, these features fall in time frames preceding or following the P2 time window, suggesting that these processes may also be related to processes of resource allocation. It may be speculated that these reflect the speed with which resource allocation processes can be switched on and off. While 3 of our 4 top models included NoGo 145-210 ms as a predictor in the feature set, we however chose to
focus our discussion on the best model. The main reasons for this is that this model stands out due to the best classification accuracy in the test sample, best lower boundary of the 95% CI, and significant p when testing the final accuracy against a random distribution. Moreover, NoGo 145-210 ms does not seem to be a genuine component, but a process directly preceding the P2 component (compare to figure 4, middle row).

In summary, the study shows that it is possible to predict on a single-subject level by means of event-related potentials whether subjects belong to an “accurate/slow” or “less accurate/fast” response inhibition group. While 'classical' neurophysiological correlates of response inhibition were clearly modulated by response inhibition performance, they were not suitable to predict group membership on a single-subject level. Instead, resource allocation processes associated with the function of the precuneus (BA7) seem to determine response inhibition performance and allow the prediction of group membership on a single-subject level. The results call for a change in the way we investigate inhibition-related neurophysiological data: Even though the Nogo-N2 and Nogo-P3 reflect cognitive processes involved in response inhibition, they may simply occur too late in the processing cascade to provide us with information useful for making predictions about behavioral performance. This information is however provided by the Go-P2 component which occurs earlier and most likely reflects resource allocation and / or the attentional control exerted during stimulus-response activation. Consequentially, research should take more heed of early processing steps when investigating or drawing inferences about the neural mechanisms mediating inhibitory control in order to receive a complete picture of all cognitive sub-processes relevant to response inhibition.
Acknowledgements

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Disclosures

There are no conflicts of interest.

References


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Figure legends

Figure 1
This illustration shows the mean potentials for \( n = 262 \) on Nogo (blue) and Go trials (brown) at electrode FCz including scalp topography maps. In the scalp topography plots, red colours denote positivity, blue colours negativity. The grey shadings show the different time bins used for data extraction for standard ERP analysis and the data-driven analysis to predict performance on a single-subject level. Note that the time bins V and VI overlap.

Figure 2
This illustration of the feature selection process shows the mean accuracy of linear threshold classification based on each individual feature, trained on training sets and evaluated on corresponding test sets (y-axis) vs. the median p value of the Kolmogorov-Smirnoff test, calculated on the same test set sample for pre- and post-selected features. As can be seen, the most frequent pre- and post- features are also those that discriminate on test splits (the features pre- and post- selected in more than 50% of the trials are marked in red), they are among the ones promising highest discrimination accuracy. Also shown is the 95% confidence interval of accuracy for random classifier for the same test set size based on the binomial distribution.

Figure 3
(A) Event-related potentials on Go and Nogo trials shown for the entire sample (black) as well as the high (green) and low performance group (red). The scalp topography plots show the Nogo-N2 and the Nogo-P3 for the high and low performance groups. In the scalp topography plots, red colours denote positivity, blue colours negativity. (B) Results from the sLORETA
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analysis contrasting Go against Nogo trials (Nogo > Go) in the entire sample for the (Nogo)-N2-time window (left) and the (Nogo)-P3-time window (right). (C) Results from the sLORETA analysis of Nogo trials between the high and low performers in the N2-time window (accurate/slow < less accurate/fast).

Figure 4

Event-related potentials shown for the different features that best predicted task performance on a single-subject level. The entire sample (black) as well as the high (green) and low performance group (red) are shown. At the top of the figure, the extracted feature shows the P2 on Go trials. The sLORETA analysis contrasting the amplitude of the P2 on Go trials between high and low performers (accurate/slow < less accurate/fast) revealed a source in the precuneus (BA7). The other ERP plots (middle and bottom) show the two other extracted features. In all figure parts, the grey shading shows the time bins that best predicted performance on a single-subject level. The scalp topography plot is also shown for these time bins. In the scalp topography plots, red colours show positivity, blue colours negativity. The right of the figure shows the scatterplots for the extracted feature as a function of the false alarm rate. Black dots denote the “accurate/slow” group and grey dots the “less accurate/fast” group.
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Equations

1. \( m(x_i, \phi, P) = 1 - H(r(x_i)) \)

2. \( m(x_1, x_2, P) = m(x_1, \phi, P) - (1 - |\rho_{12}|) m(x_2, \phi, P) \)

3. \( r(x_1, x_2, P) = 1 - H^{-1}(1 - m(x_1, x_2, P)) \)

4. \( r(x_{1..n-1}, x_n, P) = r(r(x_{1..n-2}, x_{n-1}, P), x_n, P) \)
Table I

Even though the performance groups were based on differences in false alarms (FA) rates, all common behavioral measures differed between groups.

<table>
<thead>
<tr>
<th>Measure</th>
<th>FA rate</th>
<th>Omission rate</th>
<th>GO RTs</th>
<th>FA RTs</th>
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<tbody>
<tr>
<td>Entire sample</td>
<td>11.70 % ± .53</td>
<td>1.12 % ± .06</td>
<td>349 ms ± 2</td>
<td>289 ms ± 4</td>
</tr>
<tr>
<td>Accurate/slow</td>
<td>5.26 % ± .22</td>
<td>.97 % ± .08</td>
<td>360 ms ± 3</td>
<td>305 ms ± 7</td>
</tr>
<tr>
<td>Less accurate/fast</td>
<td>18.05 % ± .65</td>
<td>1.27 % ± .09</td>
<td>339 ms ± 3</td>
<td>276 ms ± 3</td>
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<tr>
<td>Group difference</td>
<td>p &lt; .001</td>
<td>p = .011</td>
<td>p &lt; .001</td>
<td>p = .002</td>
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</table>
Table II

Each algorithm is tested on a combination of selected event-related potential features and provides classification accuracies for the training set (2/3) and the test set (1/3). The final accuracy of the test set is complemented by a 95% confidence interval. The p value denotes the probability of the final accuracy of the test set being erroneously different from a random p. Abbreviations: SVM, support vector machine; MAHA, Mahalanobis distance classifier; lin, linear; pinv, pseudo-inverse; prm, probabilistic reasoning model.

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Accuracy training</th>
<th>Accuracy test</th>
<th>95% CI test</th>
<th>p</th>
<th>Features</th>
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<tr>
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<td>0.56</td>
<td>0.64</td>
<td>0.571-0.709</td>
<td>0.0048</td>
<td>PO7_Nogo_350-440ms</td>
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<td>PO9_Go_250-310ms</td>
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<td>MAHA pinv</td>
<td>0.57</td>
<td>0.63</td>
<td>0.546-0.714</td>
<td>0.0089</td>
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<td>PO9_Go_250-310ms</td>
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<td></td>
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<td>O1_Nogo_145-210ms</td>
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<tr>
<td>MAHA prm</td>
<td>0.55</td>
<td>0.60</td>
<td>0.571-0.629</td>
<td>0.043</td>
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<td>O1_Nogo_145-210ms</td>
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<tr>
<td>SVM lin</td>
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<td>0.60</td>
<td>0.532-0.668</td>
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