Behavioral/Cognitive

Unexpected Events Induce Motor Slowing via a Brain Mechanism for Action-Stopping with Global Suppressive Effects

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When an unexpected event occurs in everyday life (e.g., a car honking), one experiences a slowing down of ongoing action (e.g., of walking into the street). Motor slowing following unexpected events is a ubiquitous phenomenon, both in laboratory experiments as well as such everyday situations, yet the underlying mechanism is unknown. We hypothesized that unexpected events recruit the same inhibition network in the brain as does complete cancellation of an action (i.e., action-stopping). Using electroencephalography and independent component analysis in humans, we show that a brain signature of successful outright action-stopping also exhibits activity following unexpected events, and more so in blocks with greater motor slowing. Further, using transcranial magnetic stimulation to measure corticospinal excitability, we show that an unexpected event has a global motor suppressive effect, just like outright action-stopping. Thus, unexpected events recruit a common mechanism with outright action-stopping, moreover with global suppressive effects. These findings imply that we can now leverage the considerable extant knowledge of the neural architecture and functional properties of the stopping system to better understand the processing of unexpected events, including perhaps how they induce distraction via global suppression.

Introduction

Slowing down ongoing behavior after unexpected events could buy time for the cognitive system to assess whether an ongoing action is still appropriate given a changed set of circumstances. In the laboratory, motor slowing following unexpected events is a ubiquitous finding. It occurs after unexpected perceptual events (hereafter referred to as "novels"; Barcelo et al., 2006; Parmentier et al., 2008; Vachon et al., 2012), action errors (Rabbitt, 1966; Laming, 1979; Debener et al., 2005; Jentzsch and Dudschig, 2009; Eichele et al., 2010; King et al., 2010; Logan and Crump, 2010), unexpected action effects (Gentsch et al., 2009; Wessel et al., 2012), and reward prediction errors (Cavanagh et al., 2010). Given the pervasiveness of such motor slowing, there is considerable interest in the underlying mechanism(s) (Marco-Pallarés et al., 2008; Notebaert et al., 2009; Danielmeier and Ullsperger, 2011; Parmentier et al., 2011). Here we test whether unexpected events recruit a brain network that underlies the rapid outright stopping of action.

Rapidly stopping a response recruits a brain network comprising prefrontal and basal ganglia regions (Mars et al., 2009; Neubert et al., 2010; Forstmann et al., 2012; for review, see Chambers et al., 2009; Chikazoe, 2010; Ridderinkhof et al., 2011). In human scalp-electroencephalography (EEG), activity of this network is reflected in medial frontal delta-band (Nigbur et al., 2011; Schmiedt-Fehr and Basar-Eroglu, 2011) and theta-band activity (Yamanaka and Yamamoto, 2010; for review, see Huster et al., 2013), as well as the N2/p300-ERP (Kok et al., 2004; Ramautar et al., 2006).

To test the potential role of this network in motoric slowing after novels, we used a verbal reaction-time (RT) task (hereafter the "novelty task") in which novel sounds induce RT-slowing (cf. Parmentier et al., 2008, 2011). We measured EEG during a stop-signal task (SST) and the novelty task. Focusing on the stop-signal data, we used independent component analysis (ICA; Jutten and Herault, 1991) to separate the scalp-EEG signal into statistically independent components (IC; Onton et al., 2006). For each subject, we localized a frontocentral IC with increased activity for successful versus failed stopping. Then, for the novelty task, we tested whether the same ICs had increased activity following novels, and whether the level of activity related to the level of novelty-induced slowing (this IC-based method has been previously used to demonstrate that identical EEG signatures are active on seemingly different psychological events; Gentsch et al., 2009; Roger et al., 2010; Wessel et al., 2012).

Finally, if slowing after novels is explained by the same system underlying outright stopping, novels should induce global motor suppression, just as outright stopping does (Badry et al., 2009; Cai et al., 2012; Majid et al., 2012; Wessel et al., 2013). As for those studies of outright stopping, we used transcranial magnetic stimulation (TMS) to measure corticospinal excitability (CSE) of the

Received Aug. 12, 2013; revised Sept. 22, 2013; accepted Oct. 15, 2013.

Author contributions: J.R.W. and A.R.A. designed research; J.R.W. performed research; J.R.W. contributed unpublished reagents/analytic tools; J.R.W. analyzed data; J.R.W. and A.R.A. wrote the paper.

This study was funded by National Institutes of Health Grant DA026452 and the Kavli Foundation. We thank Julie Schmuttermair for help with behavioral data collection, Michael Berkebile for help with EEG data collection, Jordan A. Comins for providing the auditory stimulus material, and Fabrice Parmentier for helpful advice.

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DOI:10.1523/JNEUROSCI.3456-13.2013

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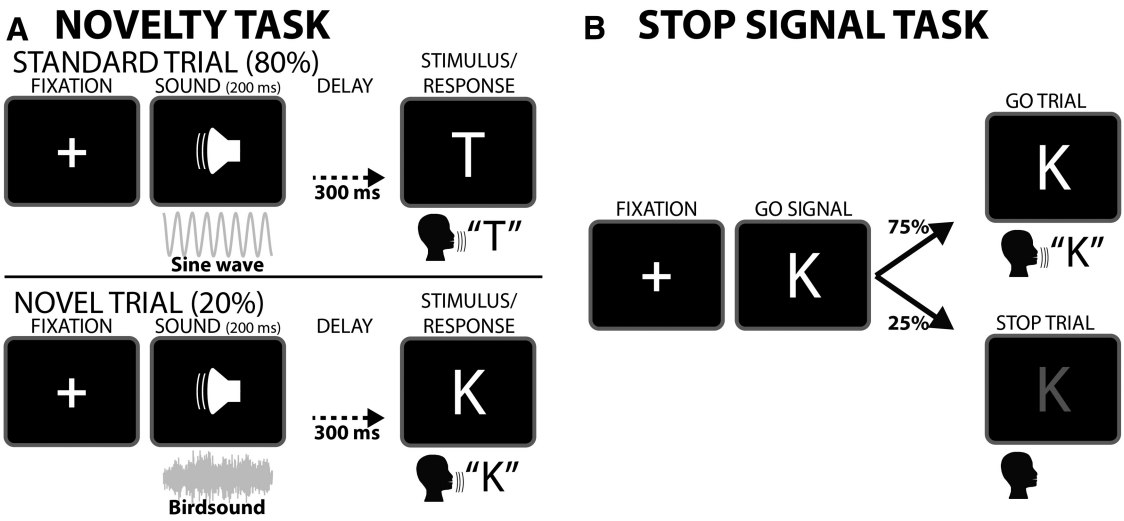

Figure 1. Task schematics. ***A***, Verbal reaction time task. ***B***, SST. Note that on stop-trials, the letter turned red.

hand (which was resting and not task related) while subjects performed the verbal novelty task. We predicted that CSE of the hand would be reduced following novels, indicating global suppression.

Materials and Methods

Experiment 1: behavioral

Participants. Twenty-four right-handed undergraduate students from the University of California, San Diego (UCSD), participated in the behavioral experiment in exchange for course credit; 20 were female. Mean age was 19.8 years (SEM: 0.34 years). Participants signed written informed consent, and the experiments were performed in accordance with the Declaration of Helsinki. The study was approved by the local ethics committee at UCSD (UCSD IRB #070617).

Experimental paradigm. A schematic of the paradigm can be found in Figure 1*A*. Each trial began with a central fixation cross, followed by a sound, then followed by a letter. Participants were instructed to respond as fast and accurately as possible according to one of two letters appearing on the screen (T or K, $p = 0.5$) by speaking the letter into a microphone. They were instructed that the letter would be preceded by a sound 500 ms before the letter (i.e., the stimulus onset asynchrony between the sound onset and letter onset was 500 ms). The duration of the sound was 200 ms. On 80% of all trials (standards), the sound was a 600 Hz sine wave. On 20% of trials (novels), one of 90 unique birdsong segments was presented instead. The participants were not informed of the presence of different sounds before the experiment. Birdsong segments were trimmed and normalized to match the sine wave stimuli in both amplitude envelope and duration. Letters were on the screen for one second. If participants did not respond within that time window, a "too slow!" message was displayed for 1 s. Overall trial duration was 3200 ms, plus a variable jitter (drawn from a uniform distribution containing the values 100, 200, 300, 400, and 500 ms). Trials were presented in a pseudorandom order: one constraint was that there could never be two novel trials in a row, and another constraint was that the first three trials had to be standards. Participants performed 450 trials equally divided into six blocks of 75 trials (15 of which were novel trials and 60 of which were standard trials).

Procedure and hardware. Participants sat in front of a 17 inch iMac personal computer (Apple) running MATLAB 2009b (MathWorks) and Psychtoolbox 3 (Brainard, 1997) for stimulus display. Participants rested their chins in a chin rest, and responses were recorded using a Logitech USB Microphone (Logitech International) placed in front of them. RTs were calculated in real time using a custom-made algorithm using the Psychtoolbox sound recording capabilities. At the beginning of the experiment, the microphone was gauged to the participants' voice amplitude level (in units of root mean square (RMS) power). RT was calculated online to display average RTs to the participants during the breaks in between blocks.

Analysis. Data were preprocessed by a human rater who checked each individual trial for the following: (1) accurate detection of speech onset by the on-line RMS algorithm and (2) accuracy of the participants' responses using a custom-designed MATLAB tool. Errors (e.g., saying T instead of K), partial errors (e.g., starting to say T instead of K but correcting before finishing speaking the initial letter), and misses (no response) were very rare (they accounted for <1% of all trials in every participant) and were omitted from further analyses. Trials in which RT estimates were inaccurately classified by the automated algorithm were rectified manually (if a clear speech onset was discernible) or discarded (in case of extraordinary amounts of noise, <5% of trials in all participants). RTs were then averaged per trial type (standard vs novel) and block (1 through 6) and subjected to a repeated-measures ANOVA using those two factors as independent variables. Individual comparisons between cells were calculated using paired sample t tests. In case of violations of the homoscedasticity assumption, degrees of freedom were corrected accordingly. All p values in the entire manuscript are two-sided unless otherwise specified.

Experiment 2: EEG

Participants. Fifteen right-handed undergraduate and graduate students from the UCSD participated in the EEG experiment for an hourly rate of $15. One participant had to be excluded because of a problem with the audio recording hardware, and another one had to be excluded because of excessive noise in the EEG recording (because of high resistances on the reference electrode that affected the entire recording), leaving a sample size of 13 (7 female). Mean age was 22.54 years (SEM: 1.25). Participants signed written informed consent, and the experiments were performed in accordance with the Declaration of Helsinki. The study was approved by the local ethics committee at UCSD (UCSD IRB #101176). None of the participants was in Experiment 1 or Experiment 3.

Experimental paradigm. The novelty task was performed exactly as described above. In addition, we used a basic version of the stop-signal paradigm (Logan et al., 1984) in the verbal domain. Here, participants were again instructed to respond as fast and accurately as possible according to a letter appearing on the screen (T or K, $p = 0.5$) after an initial fixation period (1000 ms). Participants again had 1000 ms to respond (a "too slow!" message was displayed in case this time was exceeded). However, they were instructed that on a subset of trials, a visual stop signal would inform them to attempt to stop their response. The stop signal consisted of the letter turning from white to red color after a variable time interval (the stop-signal delay, SSD). Stop signals appeared on 25% of trials, with an initial delay of 200 ms, which was adapted on a trial-by-trial basis to achieve a probability of successful stopping of 0.5. To this end,

the SSD was prolonged by 50 ms after each successful stop trial, and shortened by 50 ms after each failed stop trial. Individual SSD staircases were used for T and K. Stop trials were presented pseudorandomly interspersed with go trials, with the constraint that no more than three stop trials could occur in a row. Overall trial duration was 2500 ms. Participants performed a total of 400 trials, divided into 10 blocks. Participants were instructed that stopping successfully in case of a stop trial and going quickly in case of a go trial (no stop signal) were equally important. In the breaks between the blocks, the participants were informed of their RT. Additionally, the experimenter was presented with information about the stopping success rate and the mean SSD of the last block to be able to instruct participants to adapt their behavior to not overly favor cautious over quick responding (or vice versa).

Procedure and hardware. The sound recordings and preprocessing was done for both the novelty task and the SST as described for Experiment 1. We recorded EEG data using a 64-channel BioSemi system (BioSemi Instrumentation) at 512 Hz sampling rate with eight additional electrodes placed on the bilateral mastoids and canthus, as well as below and above each eye. Recordings were performed in a copper-shielded, sound-attenuated chamber (with a pair of speakers and the recording microphone being the only two line-powered devices in the chamber). Stimuli were presented on a NEC MultiSync FB2141SB CRT monitor (NEC) placed in a Faraday cage. The data were on-line referenced to the BioSemi CMS-DRL reference. All offsets from the reference were kept $<25\ \mu V$. Participants performed the novelty task first and the SST second. This was done so not to bias them toward using the stopping system in the novelty task in any way.

RT analysis. For the novelty task this was done as described for Experiment 1. RT analysis for the SST was done in a similar manner, with the initial audio preprocessing identical to the novelty task. RTs were averaged for go-trials and failed stop-trials separately. Stop-signal reaction times (SSRT) were computed using the mean method (Verbruggen and Logan, 2009). This relies on a valid race model of going and stopping, which assumes that failed stop-trial RTs are faster than correct go-trial RTs. This was tested on the group level by using a *t* test, and on the individual level by comparing median go to median failed-stop RTs. Also, the efficacy of the SSD staircasing algorithm was assessed by testing whether any participant's stopping probability deviated from 0.5 across blocks. To this end, the stopping success rate was quantified block by block for each of the 10 blocks, and these values were then tested against 0.5 using a Wilcoxon signed rank test. All subjects fulfilled both these criteria and were hence included in the analyses.

EEG preprocessing. Data were preprocessed using custom routines in MATLAB 2012a (MathWorks). ICA and dipole fitting (DIPFIT 2.2) were performed using functions from the EEGLAB toolbox (Version 9; Delorme and Makeig, 2004). On import into MATLAB, the data were re-referenced to the arithmetic average of the mastoid electrodes. The continuous time series were filtered using symmetric two-way least-squares finite impulse-response (FIR) filters with a low-pass cutoff of 0.5 Hz and a high-pass cutoff of 50 Hz. The time series were then visually inspected for channels with obvious nonstereotypic artifacts (e.g., spurious drift or other noise); such channels were excluded from further processing. The remaining channel data were visually inspected for segments with nonstereotyped artifact activity (e.g., from gross movement or spurious muscle activity). Such segments were removed from further analysis. Segments with stereotyped artifact activity (e.g., blinks and saccades) were retained in the data, as ICA is ideally suited to isolate these artifacts from the EEG (Jung et al., 2000a,b). After artifact removal, the data were re-referenced to the common average, and subjected to a temporal infomax ICA decomposition algorithm (Bell and Sejnowski, 1995; with extension toward sub-Gaussian sources, Lee et al., 1999) as implemented in EEGLAB. The resulting component matrix was screened for components representing stereotypic artifacts (blinks, saccades, and electrode artifacts) using outlier statistics (procedure as described previously; Wessel et al., 2012). Such components were removed. The remaining components were fitted with individual inverse dipole-solutions using the DIPFIT 2.2 algorithm as implemented in EEGLAB. As components whose equivalent dipole solutions are nondipolar usually represent nonbrain signals (as defined by a residual variance of their equivalent dipole solution of >15%; Delorme et al., 2012), such components were also removed. The automatic classifications based on these criteria were visually screened for inaccurate classifications and manually rectified if necessary. The remaining nonartifact components were subjected to further analyses.

EEG analysis. To extract event-related spectral perturbation (ERSP) and event-related potentials (ERPs), the preprocessed component data were subsequently cut into segments ranging from −500 to 1000 ms around the respective events for each task (successful stop-trials, failed stop-trials, and go-trials in the SST; novel, and standard sounds in the novelty task). Activity was then averaged with respect to the events in question. To generate ERSP data, the entire time series was filtered using two-way least-squares FIR filters with low and high cutoffs either according to the frequency band in question (0.5–4 Hz for delta, 4–8 Hz for theta, and 8–12 Hz for alpha), or using 50 linearly spaced individual frequencies ranging from 1 to 50 Hz (±0.5 Hz) for full-spectrum ERSPs. The data were then transformed into frequency space using a Hilbert transform, whose absolute value represents an analytic signal for the frequency band in question. All data were converted from arbitrary units into percentage change from baseline, by subtracting the average activity from 500 ms preceding the event in question (baseline) to the event itself from the signal within each segment, and subsequently dividing by the baseline (and multiplying by 100).

IC selection. To select brain components that represent the stopping network usually found in the SST, we defined selection criteria based on previous literature using EEG data of the SST (for review, see Huster et al., 2013). No clear-cut, singular signature has yet been determined; however, studies have consistently reported medial frontal delta and/or theta activity as potential markers of stopping-network activity (Yamanaka and Yamamoto, 2010; Nigbur et al., 2011; Schmiedt-Fehr and Basar-Eroglu, 2011). Hence, we modified a previously published automated IC selection algorithm (COMPASS; Wessel and Ullsperger, 2011) to screen components automatically, using the previously established knowledge about EEG signatures of stopping in the SST. To be able to qualify as a stopping component, an IC needed to show both: (1) a frontocentral radial topography (maximum IC weight at electrodes Cz, FCz, FC1, FC2, or Fz; topographical criterion), as well as (2) significantly stronger activity for successful compared with failed stop-trials in the theta and/or delta frequency bands (functional criterion).

"Significantly stronger activity" was operationalized such that candidate components had to have a stretch of data of at least a 100 ms duration within the first 500 ms following the stop-signal onset during which activity was greater for successful compared with failed stop-trials at $p < 0.01$ (false discovery rate (FDR) corrected; Benjamini and Hochberg, 1995).

Using these–fairly agnostic, yet clear-cut–selection criteria, at least one component was found in every participant, with one exception. In that participant, visual inspection revealed a component that fulfilled the necessary functional criterion of successful > failed stopping for at least 100 ms at $p < 0.01$, yet its topographical activity maximum was slightly too anterior (electrode site AFz). Instead of rejecting this participant, this component was selected manually and the participant was included. However, excluding this participant did not qualitatively alter any of the significances presented in the following. Of the 13 participants, 3 had two components that met the two criteria. In these cases (which are probably the result of overfitting of the IC model), the IC activities were averaged in these participants for all subsequent analyses. A group average of stop-task-related activity can be found in Figure 2. Individual IC topographies for each participant can be found in the results section.

Stopping-related activity in the novelty task. We then investigated activity in these stopping-related components on the different types of trials in the novelty task. To test whether activity in the brain network for successful outright action-stopping was increased on novel compared with standard trials, we tested the full-spectrum ERSP on novel versus standard trials in only the successful-stopping-related ICs (as identified by the rationale explained above). Full-spectrum ERSPs were tested for significant differences using *t* tests for each time point and each frequency individually, and corrected using the FDR procedure ($p < 0.05$, two-sided; all unless otherwise specified). For purposes of consistency with

the ERP literature (which operates in channel space), we also back-projected these components into channel space and quantified the ERP at electrode FCz. The ERP was tested for amplitude differences sample by sample using sample-wise *t* tests and applying FDR correction in the time domain ($p < 0.01$).

We also tested whether activity in the successful-stopping-related components was greater for parts of the experiment in which the novel trials induced larger amounts of motor slowing. This was done to test whether any of the EEG signatures are predictive of the amount of novelty-induced slowing. Since the behavioral data indicated that slowing was greatest in Block 1 (in fact, novelty-induced slowing effects were only significant in this block) and smallest in Block 6, we tested the ERSPs, as well as the ERP back-projection at FCz, using the same statistical methodology as explained for the earlier contrasts, but this time comparing the differences between novels and standards in Block 1 versus Block 6.

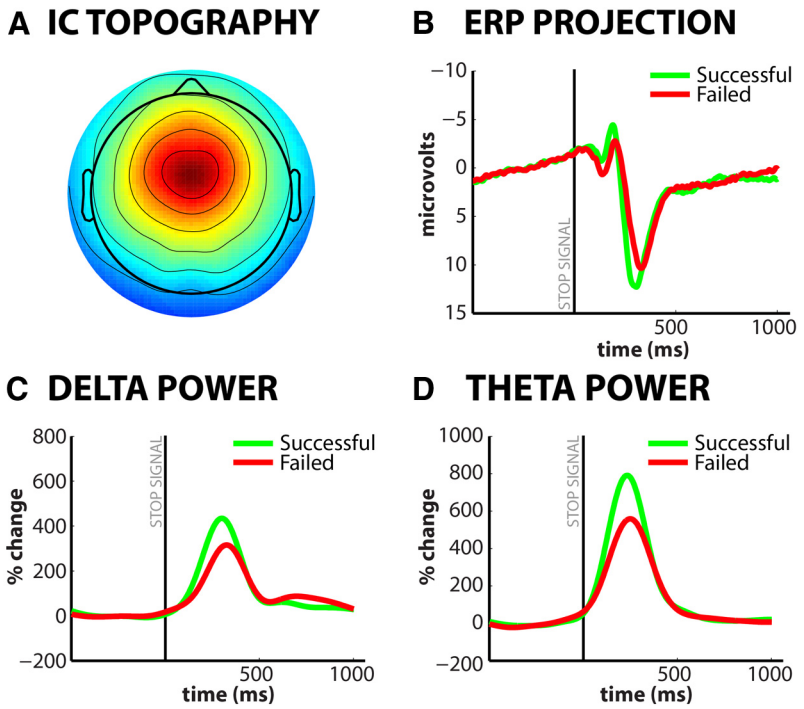

Figure 2. Successful-stopping-related independent components; group average. ***A***, Mean topographical distribution of IC weights. Since sign of the weight matrix is arbitrary, all weight matrices were flipped to show positive activity at electrode FCz. ***B***, ERP projection at electrode FCz. ***C***, Delta-band (0.5–4 Hz) power. ***D***, Theta-band (4–8 Hz) power.

Experiment 3: TMS

Participants. Fourteen (10 female) right-handed undergraduate and graduate students from the UCSD participated in the TMS experiment for an hourly rate of $15. Mean age was 22.21 years (SEM: 0.95). Participants signed written informed consent and underwent TMS safety screening. The experiments were performed in accordance with the Declaration of Helsinki. The study was approved by the local ethics committee at UCSD (UCSD IRB #071912). None of the participants was in Experiments 1 or 2.

Experimental paradigm. The novelty task was performed exactly as described above, except now TMS was performed in the sound-to-letter interval, while electromyography (EMG) was recorded (see below for details) from the hand, which was task irrelevant and at rest. For the SST, several studies now show that successfully stopping an action not only reduces motor-evoked potential (MEP) amplitudes of the effector that needs to be stopped, but also reduces MEP amplitudes in effectors that are not engaged in the task at all, and are actually at rest (Badry et al., 2009; Cai et al., 2012; Majid et al., 2012; Wessel et al., 2013). This "global" reduction of MEP during stopping occurs not only in relation to trials without successful stopping, but also compared with an intertrial interval (ITI) baseline in which all effectors are at rest. This indicates true suppression, as opposed to mere relative differences in excitation. Here, we investigate whether the stopping system (which is shown in Experiment 2 to be active following unexpected events), exerts its suppressive influence in a global fashion following unexpected events, similar to a global stop. Using the same logic as for the SST, we measured MEPs from the hand, which was irrelevant to the verbal novelty task, and which was resting comfortably on the table next to the participant.

We note that TMS introduced a second auditory stimulus (the "'click" from the TMS stimulator) that followed the sound before the onset of the imperative letter stimulus on each trial. Unlike the sound, the auditory signal from the TMS stimulator was the same every trial. It has been shown that in paradigms like the novelty task used here, inserting a stereotypic additional signal between the sound and the imperative stimulus reduces (or abolishes) novelty-induced slowing effects (Parmentier et al., 2008). Hence, we expected diminished (or abolished) behavioral slowing effects in this paradigm compared with the two earlier experiments. However, even if that is the case, the experiment was identical to the two previous experiments until the TMS measurement was obtained in each trial. Consequently, the TMS measurement will probe the same mechanism as the EEG experiment, yet RT, as well as measurements of RT–TMS relationships, might be affected by a reduction in novelty-induced slowing caused by the presence of the TMS stimulation.

EMG recording. Surface EMG was recorded from the first dorsal interosseous muscle of the right hand via Ag–AgCl HydroGel electrodes (Lead-Lok). A ground electrode was placed over the distal end of the ulna. The signal was amplified using a Grass QP511 Quad AC Amplifier (Grass Technologies), with a recording bandpass filter between 30 and 1000 Hz (60 Hz notch). The amplified data were sampled using a CED Micro 1401 MK-II acquisition system (sampling rate: 2000 Hz) and recorded using CED Signal software (Version 4; Cambridge Electronic Design).

TMS procedure. CSE was measured using MEPs elicited by TMS. TMS was performed using a Magstim 200-2 system (Magstim) with a 70 mm figure-of-eight coil. Hotspotting was performed to identify the hand stimulation locus and correct intensity. The coil was first placed 5 cm lateral and 2 cm anterior to the vertex and repositioned to where the largest MEPs were observed consistently. Resting motor threshold (RMT) was then defined as the minimum intensity required to induce MEPs of amplitudes exceeding 0.1 mV peak-to-peak in 5 of 10 consecutive probes (Rossini et al., 1994). TMS intensity for the experimental stimulation was then adjusted to 110–120% of RMT (mean intensity = 58% of maximum output; min = 44%, max = 72%). An EMG sweep was started 150 ms before every TMS pulse to obtain an estimate of baseline EMG activity for later artifact correction. TMS was time locked to one of three times (150, 175, and 200 ms) following the onset of the sound on each trial. These values were generated from our prior experience of when MEP suppression is expected during outright verbal action-stopping in the SST (Cai et al., 2012). Stimulation time points alternated in a fixed sequence, for both trial types separately. Also, to obtain an estimate of baseline CSE, we stimulated in the ITI on 30 trials (5 per block).

EMG analysis. MEPs were identified from EMG using in-house software developed in MATLAB. Trials were excluded if (1) the RMS power of the EMG trace 150 ms before the TMS pulse exceeded 0.01 mV (since such prestimulus noise can contaminate the MEP measurement), (2) the MEP amplitude on a given trial exceeded ±1 mV (which is beyond the resolution of the amplifier and leads to saturation), or (3) the MEP amplitude did not exceed 0.01 mV (trials in which no MEP was elicited, mostly due to coil misplacement or miss-

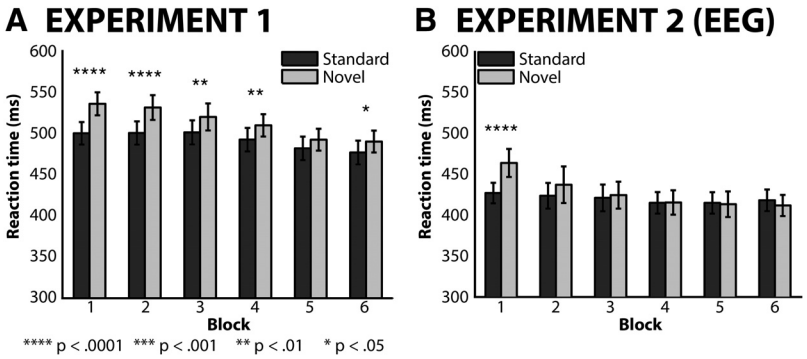

Figure 3. Behavioral results from the novelty task. ***A***, Experiment 1. ***B***, Experiment 2 (EEG). Note that the sample size in Experiment 1 is significantly larger than the sample size of Experiment 2, which is why significant RT slowing in Experiment 2 is limited to the first block. Error bars denote SEM.

ing stimulation due to, e.g., coil overheating). MEP amplitude was quantified using a peak-to-peak rationale, measuring the difference between maximum positive and negative amplitudes within a time period of 10–50 ms following the pulse. Both automated artifact rejection and MEP quantification were visually checked for accuracy on each individual trial for every dataset by a rater who was blind to the respective trial type. Exclusions were rare. We removed an average of 10.71 trials (SEM: 6.02) from each participant based on all criteria combined. MEP amplitudes were normalized by the individual participants' baseline MEP (resulting in numbers >1 in case of relative excitation compared with baseline and numbers smaller than one indicating suppression). Those values were averaged for each trial type and time point individually, and tested against each other using a 2 × 3 ANOVA (factors TRIAL TYPE and TIME POINT) and individual *t* tests in case of a significant interaction.

Results

Experiment 1: behavioral

As expected, RT was significantly slower for novel compared with standard trials, as indicated by a main effect of TRIAL TYPE ($F_{(1,23)} = 28.8$, $p < 0.0001$). RT also decreased as a function of BLOCK ($F_{(5,115)} = 9.02$, $p < 0.0001$). There was also a significant BLOCK × TRIAL TYPE interaction ($F_{(5,115)} = 5.96$, $p < 0.0001$), indicating that the difference between novels and standards wore off over time. Individual comparisons revealed that there was significant novelty-induced slowing for Blocks 1, 2, 3, 4, and 6 (Block 1: $t_{(23)} = 6.84$, $p < 0.0001$, $d = 0.54$; Block 2: $t_{(23)} = 4.72$, $p < 0.0001$, $d = 0.44$; Block 3: $t_{(23)} = 3.45$, $p < 0.01$, $d = 0.25$; Block 4: $t_{(23)} = 3.51$, $p < 0.01$, $d = 0.26$, $d = 0.16$; Block 6: $t_{(23)} = 2.57$, $p < 0.05$, $d = 0.2$). RT results can be found in Figure 3*A*.

The results clearly establish a post-novel slowing effect for this verbal paradigm. This is consistent with many prior studies (Parmentier et al., 2008, 2011; Ljungberg and Parmentier, 2012). This sets the stage to examine if motor slowing in this paradigm can be explained by a brain network for outright action-stopping.

Experiment 2: EEG

Behavioral

In the SST, mean RT was 557 ms on go-trials and 496 ms on failed-stop trials ($t_{(12)} = 14.99$, $p < 0.0001$). Error rates (0.11%, SEM: 0.04) and miss rates (0.48%, SEM: 0.17) were low. Average SSRT was 256 ms (SEM: 6), mean SSD was 301 ms (SEM: 13.4), and the average stopping success rate was 0.52 (SEM: 0.49). Hence, the RTs met the requirements of the race model at the group level. On the individual level, each participant's median RT on go-trials was longer than the failed-stop trial RT, with none of the participants showing success rates significantly different from 0.5. Hence, all participants' datasets fulfilled the requirements of the race model.

In the novelty task, as in Experiment 1, RT was numerically slower for novel compared with standard trials; however, the main effect of TRIAL TYPE did not reach significance ($F_{(1,12)} = 1.6$, $p = 0.23$). Again, RT decreased as a function of BLOCK ($F_{(5,60)} = 2.88$, $p = 0.02$). Importantly, there was a significant BLOCK × TRIAL TYPE interaction ($F_{(5,60)} = 7.61$, $p < 0.0001$), indicating that the difference between novels and standards wore off over time. Individual comparisons revealed that there was significant novelty-induced slowing for Block 1 ($t_{(12)} = 5.37$, $p < 0.001$, $d = 0.75$), but not the other blocks (all ps > 0.25). RT results can be found in Figure 3*B*.

Notably, overall RT was shorter in Experiment 2 compared with Experiment 1. We attribute this to the likely greater motivation of subjects in Experiment 2. The participant sample in Experiment 1 consisted of UCSD undergraduates who were recruited via automated software and who were participating for course credit. In contrast, the sample in Experiment 2 consisted of participants who were recruited through flyers and e-mail, and also via a pre-existing database of motivated participants willing to undergo EEG, and who were being paid for participation. Importantly, however, despite the faster overall RTs of participants in Experiment 2, the decisive within-group difference between novel and standard trials was unaffected by these overall differences in base RT. Indeed, Block 1 for Experiment 1 had an effect size of $d = 0.54$, and this was $d = 0.75$ for Experiment 2. Thus the effect size of the difference between novel and standard trials was even greater in Experiment 2, despite the faster overall RTs. The fact that significance values are smaller for Experiment 2 thus relates to the much smaller sample size compared with Experiment 1 ($N = 13$ vs $N = 24$).

EEG

Full-spectrum ERSPs (Fig. 4*A*) show increased activity in the successful-stopping-related ICs on novels versus standard trials in the delta, theta, and alpha frequency ranges (critical p value after FDR correction: 0.006). In the sound-to-letter interval (500 ms following the sound), the following between condition differences were significant: delta (0.5–4 Hz) in the time range from 0 to 500 ms following the tone, theta (4.5–8 Hz) from 186 to 500 ms post-tone, and alpha (8.5–12.5 Hz) from 129 to 368 ms. Strikingly, every participant showed significantly increased activity in the stopping network on novels compared with standard trials in one of the three frequency bands ($p < 0.01$; Fig. 5). The ERP projection at FCz also shows significant differences, with the novel trials showing a greater P3 wave in the time range from 232 to 357 ms following the tone (Fig. 4*B*; critical p value after FDR correction: 0.003).

In addition, we compared the activity within this system between the first and the last block. Slowing following novel trials was greatest in the first block (which, in the EEG dataset, was in fact the only block that showed significant slowing), and smallest in the final block, and hence, greater novel-related activity in the tone-letter interval would indicate a direct relation between the neural signature and the degree of motor slowing. This was in-

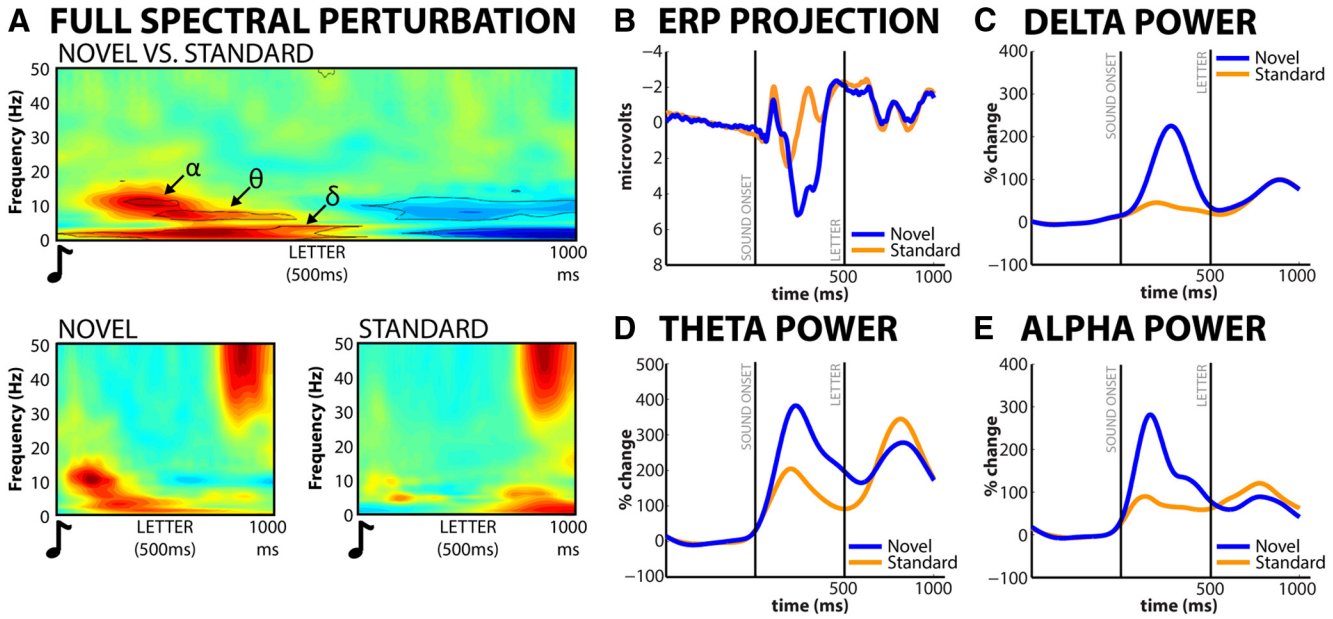

Figure 4. Activity of successful-stopping-related independent components for the novelty task. ***A***, Full frequency band ERSP. Colors indicate percentage change from baseline (warm colors, increase; cold colors, decrease). Black outlines denote significance at $p < 0.05$ (FDR corrected). ***B***, ERP projection at electrode FCz. ***C***, Delta-band (0.5–4 Hz) power. ***D***, Theta-band (4–8 Hz) power. ***E***, Alpha-band (8–12 Hz) power.

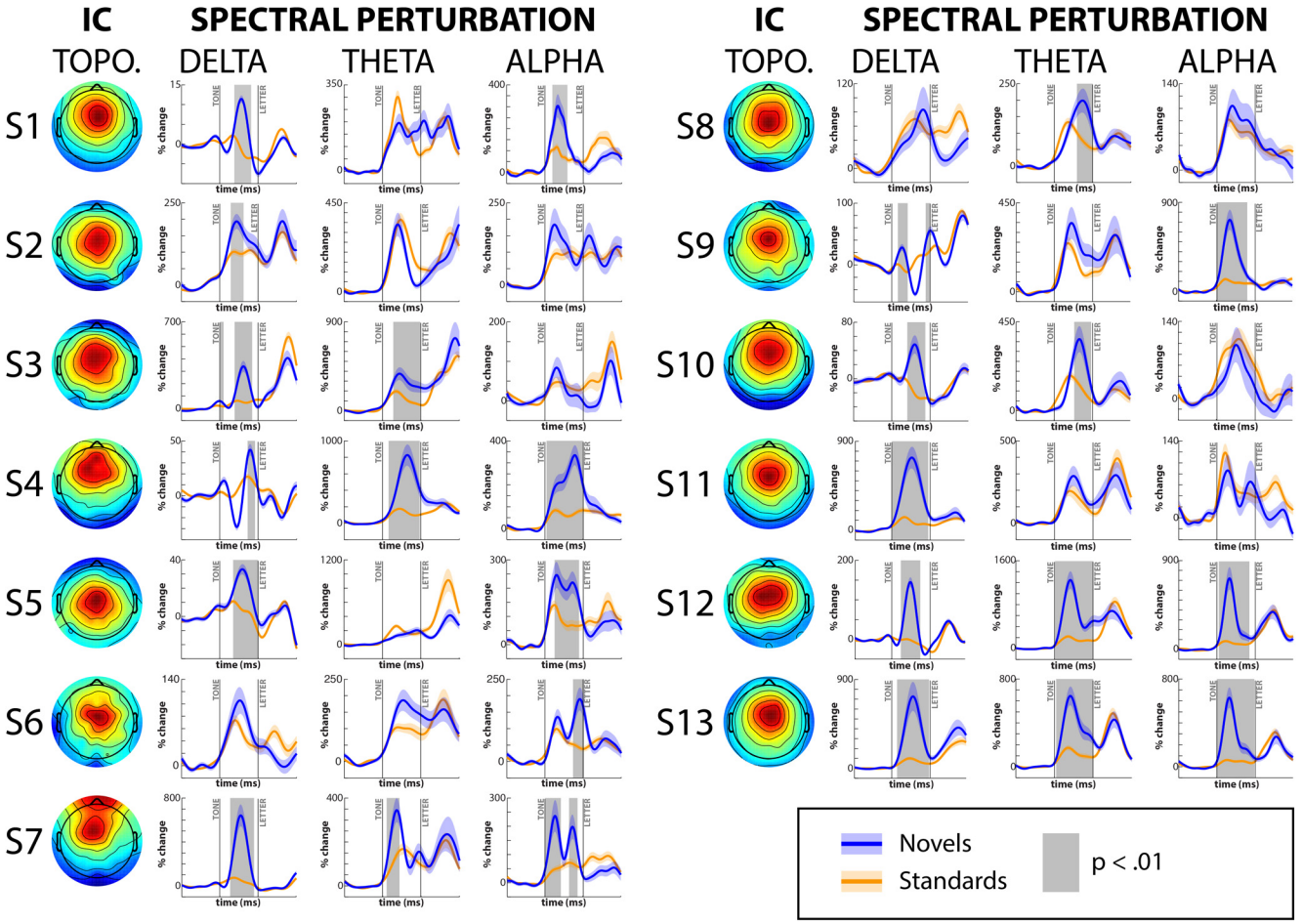

Figure 5. Individual participants' activity of successful-stopping-related IC activity on the novelty task. IC topographies represent the topographical distribution of the IC weight maps (rectified to show positivity at electrode FCz). Wave boards show individual frequency band activity for novels and standard trials in the three frequency bands that showed significantly enlarged activity on novel trials on the group level. Shading represents SEM.

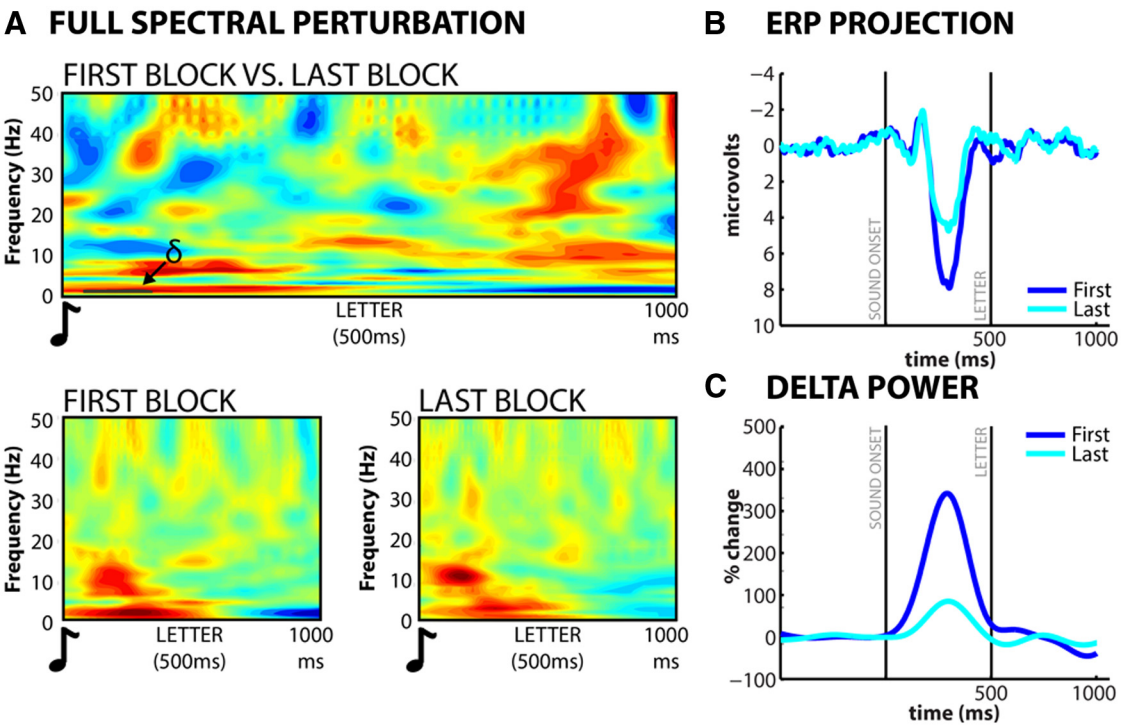

Figure 6. Comparison of novel-related activity in the novelty task based on experimental block. First block showed significant behavioral slowing; last block did not. All parts show difference between novel and standard trials. ***A***, Full frequency band ERSP. Colors indicate percentage change from baseline (warm colors, increase; cold colors, decrease). Black outlines denote significance at $p < 0.05$ (FDR corrected). ***B***, ERP projection at electrode FCz. ***C***, Delta-band (0.5–4 Hz) power.

deed the case for the successful-stopping-related ICs: the full-spectrum ERSP (Fig. 6*A*) reveals significantly increased activity in the delta band ($p < 0.05$ one-sided, FDR corrected to a two-sided critical p of 0.0004) from 35 to 147 ms (Fig. 6). The P3a-ERP at FCz, which showed significant differences between novels and standards in the overall comparison (see above) also showed significant differences with respect to this contrast (Fig. 6*B*): in the first block, where slowing was significant, the novel-standard P3a difference was significantly more positive compared with the last block in the time range from 252 to 262 ms, 277 to 291 ms, and 304 to 318 ms (however, none of these stretches survive FDR correction for multiple comparisons).

Together, we used ICA of EEG data to show that the brain network that explains successful action-stopping in the SST is also more active following novels compared with standard trials in the novelty task. Successful-stopping-related ICs showed increased activity on novels compared with standards in the delta, theta, and alpha bands, and also showed an increased P3a-ERP. Furthermore, the degree of early delta activity (35–147 ms) related to the degree of motor slowing, as the delta-band difference between novels and standard trials was significantly greater in blocks of the experiment in which significant slowing was observed compared with the last block, in which slowing was absent. The same thing was true (to a lesser extent) for the P3a-ERP as well. Hence, we show that the brain network for successful stopping in an SST also explains slowing after novel trials. Based on these findings, we made a specific further prediction regarding the nature of motor slowing after novelty: since the brain network for outright action-stopping operates in a global, noneffector-specific manner (Badry et al., 2009; Cai et al., 2012; Majid et al., 2012; Wessel et al., 2013), such global motor suppression should also occur for motor slowing following novelty. To test this hypothesis, we collected TMS data during the novelty task, comparing CSE of the task-unrelated hand between novels and standards. We predicted reduced CSE of the task-unrelated hand for novels compared with standards.

Experiment 3: TMS

Behavior

As in Experiments 1 and 2, RT was numerically slower for novel compared with standard trials; however, the main effect of TRIAL TYPE did not reach significance ($F_{(1,13)} = 1.61$, $p = 0.23$). Again, RT decreased as a function of BLOCK ($F_{(5,65)} = 4.94$, $p < 0.001$). There was no significant BLOCK × TRIAL TYPE interaction ($F_{(5,65)} = 1.46$, $p = 0.21$). Planned comparisons revealed that despite the potentially counteracting effects of the stereotypic TMS sound, there was significant novelty-induced slowing for Block 1 ($t_{(13)} = 5.37$, $p < 0.001$, $d = 0.75$), but not the other blocks (all ps > 0.25).

CSE

There was no main effect of TRIAL TYPE ($F_{(1/13)} = 1.68$, $p = 0.22$) or TIME POINT ($F_{(2/26)} = 1.44$, $p = 0.26$). However, importantly, there was a significant TRIAL TYPE × TIME POINT interaction ($F_{(2/26)} = 4.3$, $p = 0.02$; Fig. 7). Individual comparisons show that on the first time point (150 ms), CSE was indeed significantly suppressed on novels compared with standard trials ($t_{(13)} = 3.18$, $p < 0.01$, $d = 0.7$; significant using Bonferroni correction at 0.05). Also, activity on novels was suppressed below baseline (i.e., 1) at this time point ($t = 2.2$, $p < 0.05$, $d = 0.87$). Additionally, the same analysis as for the EEG, i.e., comparing the amount of CSE suppression in Block 1 (which showed behavioral RT slowing on novels compared with standards) to Block 6 (no slowing), showed that relative TMS suppression on novel compared with standard trials was greater in Block 1 than in Block 6 (0.22 vs 0.004 mV, $t = 2.17$, $p < 0.05$, $d = 0.87$).

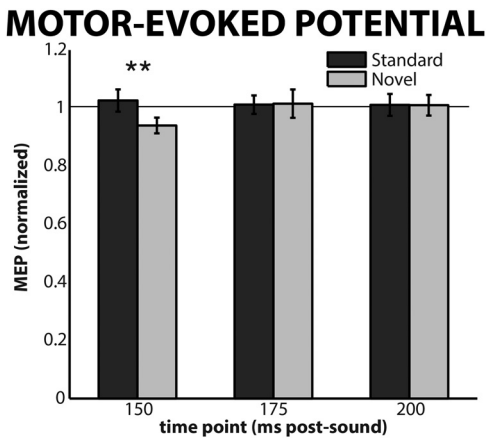

Figure 7. CSE as measured by the MEP (normalized by an ITI baseline) in the novelty task. Error bars denote SEM.

We used TMS of a task-unrelated muscle in the hand to demonstrate that CSE is globally suppressed after a novel trial in the novelty task, which was in fact the case at 150 ms following the onset of the novel tone (but not after 175 ms or 200 ms). Furthermore, the amount of global suppression on novel trials at the 150 ms time point was greater for time periods in the experiment during which novels caused a lot of motor slowing, compared with periods in which they did not. This parallels the finding from the EEG study, in which delta-band activity in the successful-stopping-related components showed the same effect.

Discussion

We show that motor slowing following unexpected events (novels) is explained by activity of a brain network for outright action-stopping. We isolated the brain signature for action-stopping by identifying an independent EEG signal component whose activity was greater for successful than failed stopping. We then examined activity patterns within this component in a verbal RT task in which occasional novel trials induced motor slowing. There was increased activity in the stopping component on novel compared with standard trials, and moreover this corresponded with the amount of motor slowing. Further, using TMS we show that CSE of the hand (which was task-irrelevant) was reduced following novel compared with standard trials, and also compared with an ITI baseline (indicating true suppression). Furthermore, the suppression was increased during stages of the experiment in which slowing was greater compared with stages in which slowing was reduced. Thus, a common mechanism is recruited by unexpected events and by outright stopping of action. This has substantial implications for a unified neural systems theory of unexpected events (including perhaps novelty, action errors, and prediction errors) in terms of an underlying global inhibition network. As unexpected events are well known to have non-motor (cognitive) effects, i.e., distractibility, our current results open the possibility that this is mediated via global inhibition.

Although our results only concern one kind of unexpected event–novel tones preceding verbal choice responses–several lines of evidence suggest a unitary mechanism for different kinds of unexpected events that evoke motor slowing. First, a recent study used both functional magnetic resonance imaging (fMRI) and EEG to show that the brain system that is active following action errors is also active following novels, and that both of those induced motor slowing (Wessel et al., 2012). Second, many EEG studies demonstrate similar signatures as the ones here (i.e., frontocentral theta and delta signals) following several different kinds of events, including action errors (Luu et al., 2004; Trujillo and Allen, 2007; Cohen, 2011; van Driel et al., 2012) and prediction errors (Cavanagh et al., 2010). However, only one study directly related this EEG activity to the degree of motor slowing (Cavanagh et al., 2010). Third, an EEG study likened brain activity for outright stopping to activity for motor slowing following action errors (Marco-Pallarés et al., 2008). Together, these studies argue that there is a common mechanism underlying motor slowing following many different kinds of unexpected events. Our current results suggest this common underlying mechanism could be the global inhibition network for action-stopping.

How unexpected events produce motor slowing

By linking unexpected events to the brain's stopping system, our results speak to controversies about how unexpected events produce motor slowing. One such debate is whether such slowing is automatic (involuntary), reactive (stimulus-driven), and possibly related to orienting (Notebaert et al., 2009), or whether it is a strategic (voluntary), planned (controlled) adjustment, especially in the case of post-error slowing (Brewer and Smith, 1984). Another debate concerns whether such slowing happens with or without awareness (Rabbitt, 2002; Endrass et al., 2007; Logan and Crump, 2010; Danielmeier and Ullsperger, 2011; Wessel et al., 2011).

The well known versatility of the stopping system could help resolve these debates. For example, nodes of the stopping network, such as the right inferior frontal cortex, the pre-supplementary motor area, and the subthalamic nucleus (STN) can be recruited automatically (Lenartowicz et al., 2011), reactively (for review, see Levy and Wagner, 2011), proactively (i.e., as a strategic brake; Jahfari et al., 2010; Swann et al., 2013; Zandbelt et al., 2013), and without awareness (van Gaal et al., 2010). These manifold ways in which regions of the stopping network are recruited mimics the diverse properties ascribed to unexpectancy-related motor slowing (automatic vs strategic, aware vs unaware). Our current findings motivate a parsimonious explanation: the stopping system universally produces motor slowing following many kinds of unexpected events.

Why unexpected events produce distractibility

It is striking that our current results show reduced CSE of the hand following novels in the verbal novelty task. This result echoes the finding that CSE is reduced for the hand following outright stopping of the voice (Cai et al., 2012). We interpret CSE reduction as a signature of global inhibition of the entire motor system. We suppose this is mediated via the STN of the basal ganglia, which is important for outright stopping (Kühn et al., 2004; van den Wildenberg et al., 2006; Neubert et al., 2010; Mirabella et al., 2012; Ray et al., 2012; Alegre et al., 2013), and which is purported to exert a massive effect on basal ganglia output (Hazrati and Parent, 1992; Gillies and Willshaw, 1998). We further suppose that the STN is also recruited by unexpected events. Consistent with this, fMRI reveals activation of a midbrain area (perhaps consistent with the STN) for both novels and action errors (Wessel et al., 2012), and a study in patients reported orienting signals in the STN (Bočková et al., 2011).

It is an interesting possibility that the STN could have such a widespread influence on basal ganglia output as to even effect non-motor representations (Gillies and Willshaw, 1998; Frank et al., 2007; Haynes and Haber, 2013). If so, this would provide a mechanistic basis for why unexpected events lead to disruptions of ongoing cognitive processing (Escera et al., 1998; Schröger and

Wolff, 1998; de Fockert et al., 2004). While such effects are often explained by attentional reorienting, as indexed by an enlarged P3a-ERP (Courchesne et al., 1975; Ranganath and Rainer, 2003; Polich, 2007), our study provides an elaboration; this attentional reorienting could be underpinned by a global inhibitory signal induced by the unexpected event, which then affects ongoing cognitive processing. The timing of the different physiological signatures of novelty processing in our current study supports this hypothesis: While the delta-EEG effects that vary with the degree of slowing reach significance almost immediately following the tones (0 ms for the overall novel vs standard comparison; 35 ms for the slowing vs lesser slowing comparison), P3a differences are significant only in later stretches of time (232 ms/252 ms). Situated chronologically between these two EEG phenomena is the CSE suppression, which is significant at 150 ms following sound onset, but no longer significant at 175 ms or 200 ms. This could mean that the early delta-EEG differences are a signature of the triggering of motor inhibition, which is then implemented globally via the STN (resulting in MEP suppression of the task-irrelevant hand), which then in turn influences the reorienting of attention (resulting in the differences in P3a-ERP).

Motor inhibition or infrequent signal detection?

An alternative interpretation of our EEG findings is that since both the SST and the novelty task involve the detection of an infrequent signal, this infrequent signal detection could be the decisive variable that drives the EEG component, rather than motor inhibition per se. Yet several considerations speak against this. First, the selection criterion that we used to extract the components from the SST was explicitly based on successful stopping. Specifically, each individual brain component in the EEG study showed significantly increased activity for successful compared with failed stopping, even though an (infrequent) stop signal appeared in both cases. Second, the components we describe also show an enlarged p300-ERP component in the SST (Fig. 2). This frontocentral p300 has recently been shown to increase significantly when stopping is incentivized, regardless of stop-signal frequency, i.e., it is not simply driven by the infrequency of the signal (Greenhouse and Wessel, 2013). Thirdly, it has been demonstrated behaviorally that the decisive factor that leads to motor slowing in this novelty task is not the infrequency of the novel trials, but instead their unexpectedness ("surprise," Parmentier et al., 2011). However, in the SST, stop signals are not unexpected. Thus, the EEG signature we observed here is probably not simply infrequency for the novel trials, and it is probably not simply unexpectedness for the stop-signal trails; we propose it instead reflects the common requirement for motor inhibition. In addition to our EEG findings, we show with TMS that there is a reduction of CSE on novel trials in the verbal task. Reductions of MEP amplitude are often taken to index true motor suppression, either compared with an evolving motor tendency/CSE increase during motor preparation (Coxon et al., 2006; van den Wildenberg et al., 2010), or compared with an ITI baseline when quantifying global motor stopping in the SST (Cai et al., 2012; Majid et al., 2012). Hence, in our study, the CSE reduction is also very likely indicative of true motor suppression; this further argues against a mere infrequent signal detection explanation of our findings.

While the above points strongly suggest that the common mechanism we identified is motor inhibition rather than infrequent signal detection, we acknowledge that these two processes are likely tightly integrated. Specifically, we suppose that the brain system for salience detection is tightly integrated with the brain system for motor inhibition to enable adaptive behaviors. Further, we suppose that any event that triggers the salience system might also automatically engage the inhibition system, whether the event is merely infrequent (oddball; Schröger and Wolff, 1998; Sharp et al., 2010; Chatham et al., 2012) or otherwise salient (Seeley et al., 2007; Ullsperger et al., 2010), making it difficult to explicitly experimentally disentangle motor inhibition and salience detection. Our contribution here is to show that a brain system for successful stopping in the SST also explains motor slowing after unexpected events that do not require an outright stop. For all the reasons we give above, we argue that the inhibition function of that network is the most parsimonious explanation for the effects, while acknowledging that salience detection and motor inhibition are likely tightly integrated.

Conclusion

We demonstrate that the neural system that is recruited when humans attempt to stop their actions outright is also recruited when unexpected events occur, and explains the slowing of motor responding induced by such events. This points to a ubiquitous (and flexible) system for motor inhibition–it can be voluntarily recruited to stop actions outright (as in the SST), and it can also be automatically recruited by unexpected events.

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