Neural synchrony indexes impaired motor slowing after errors and novelty after white matter damage

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A B S T R A C T

In humans, action errors and perceptual novelty elicit activity in a shared frontostriatal brain network, allowing them to adapt their ongoing behavior to such unexpected action outcomes. Healthy and pathologic aging reduces the integrity of white matter pathways that connect individual hubs of such networks and can impair the associated cognitive functions. Here, we investigated whether structural disconnection within this network because of small-vessel disease impairs the neural processes that subserve motor slowing after errors and novelty (post-error slowing, PES; post-novel slowing, PNS). Participants with intact frontostriatal circuitry showed increased right-lateralized beta-band (12–24 Hz) synchrony between frontocentral and frontolateral electrode sites in the electroencephalogram after errors and novelty, indexing increased neural communication. Importantly, this synchrony correlated with PES and PNS across participants. Furthermore, such synchrony was reduced in participants with frontostriatal white matter damage, in line with reduced PES and PNS. The results demonstrate that behavioral change after errors and novelty result from coordinated neural activity across a frontostriatal brain network and that such cognitive control is impaired by reduced white matter integrity.

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1. Introduction

Controlled behavior requires the ability to adapt ongoing actions to unexpected outcomes. For example, when driving a car, both one’s own actions (e.g., accidentally switching on the windshield wiper, “error”) and outside factors (e.g., a failing power steering, “novel”) can lead to unexpected action outcomes, which require immediate adaptation of behavior. Over the life span, the capacity to implement such cognitive control processes progressively diminishes (Braver and Barch, 2002; Harty et al., 2013; Hedden and Gabrieli, 2004; Verhaeghen and Cerella, 2002), which is further escalated by pathologic age-related processes, such as small-vessel disease (SVD) (Prins et al., 2005).

In healthy individuals, cognitive control after unexpected action outcomes is well characterized. Both errors and novels lead to slower reaction times on subsequent trials (post-novelty slowing, PNS, Barcelo, et al., 2006; Notebaert et al., 2009; Parmentier et al., 2011, post-error slowing, PES, Rabbitt and Rodgers, 1977) and engage a number of prefrontal, cingulate, and basal ganglia brain regions (Hester et al., 2004; Kerns et al., 2004; Polich, 2007; Ridderinkhof et al., 2004; Soltani and Knight, 2000). In fact, errors and novels engage a common distributed brain network (Wessel et al., 2012), which could explain why both types of events evoke similar behavioral changes (PES and PNS). However, it is not clear how exactly PES and PNS are implemented within this network and
how healthy or pathologic aging affects these cognitive control abilities.

Recent studies suggest that a right-lateralized frontostriatal motor inhibition mechanism could underlie PES and PNS (Danielmeier et al., 2011; Marco-Pallares et al., 2008; Wessel and Aron, 2013). This motor inhibition mechanism is engaged when actions have to be cancelled (Aron et al., 2007b, 2014) or slowed down (Chikazoe et al., 2009; Jahafari et al., 2010; Wessel and Aron, 2014; Wessel et al., 2013). Importantly, the anatomic regions that subserve this motor inhibition mechanism (right inferior gyrus, presupplementary motor area, and subthalamic nucleus, Aron et al., 2007a; Rae et al., 2015) are in fact part of the wider frontostriatal network that is active after both errors and novelty (Wessel et al., 2012). Activity of this mechanism can be measured using electroencephalography (EEG). When this mechanism is engaged, neural synchrony between frontocentral and right frontolateral brain areas is increased (specifically within the beta frequency band, i.e., 12–24 Hz, Swann et al., 2011, 2012), which ostensibly reflects communication between distant brain areas (Fries, 2005). Hence, the implementation of PES and PNS could crucially depend on the neural communication between the distant nodes of the brain network underlying this mechanism, which is indexed by right-lateralized beta-band synchrony.

However, testing the causal importance of neural synchrony in humans is difficult. Whereas gray matter damage allows testing the causal role of focal brain areas, testing the causal role of the integrity of a distributed brain network necessitates the investigation of changes in white matter pathways. From this perspective, the aging process allows unique insights. Both healthy (e.g., Andrews-Hanna et al., 2007; Barrick et al., 2010; Davis et al., 2009; Westlye et al., 2010) and pathologic aging (e.g., Damoiseaux et al., 2009; Prins et al., 2005) are characterized by reductions in white matter integrity. Here, we used small-vessel disease (SVD) as a model of structural white matter disconnection to study the causal role of right lateralized beta-band synchrony in PES and PNS. SVD is an aging-related disorder (Pugh and Lipsitz, 2002) characterized by vascular white matter lesions (Cummins, 1995) and lacunar infarcts (Okroglic et al., 2013), which lead to impaired long-range neural communication (Schaefe et al., 2014).

In our present study, EEG was recorded from participants with and without frontostriatal microlesions because of SVD (rated using the age-related white matter changes rating scale, ARWMC, Wahlund et al., 2001) during a hybrid error-noveltv task (Wessel et al., 2012, 2014). We predicted that beta-band synchrony between frontocentral and right frontolateral brain regions would be increased after errors and novelty in participants with intact frontostriatal white matter. We furthermore predicted that such synchrony would be decreased in participants with frontostriatal structural disconnections and that this decrease would be correlated with impaired PES and PNS.

2. Materials and methods

2.1. Participants

Twenty-eight native German speakers with corrected or corrected-to-normal vision were recruited from the participant databases of the Day Clinic for Cognitive Neurology in Leipzig and the participant database of the Max Planck Institute for Human Cognitive and Brain Sciences. We specifically recruited participants for whom we had existing ratings of white matter integrity and neuropsychological testing data (these subjects had been recruited as part of another study, Quinque et al., 2012, for which they underwent neuropsychological assessment and magnetic resonance imaging (MRI) scanning, but not all of the current participants ended up participating in Quinque et al., 2012). Participants were excluded based on history of neuropsychiatric disorders (e.g., stroke, craniocerebral injury, neurodegenerative diseases, and dementia) or substance abuse. Furthermore, 4 subjects had to be excluded after recruitment (2 because of technical problems, 1 because of excessive error rate [38%, z > 0.37, significant outlier using Grubbs test at p < 0.0001], and 1 because of difficulties following the task instructions), resulting in a final sample size of 24. Participants were then grouped based on whether they had focal white matter damage in frontal or striatal regions (see subsequently), leading to an even split of the 24 participants into 2 groups: a frontostriatal lesion group (for ease of reading, we will from here on refer to this group simply as the “lesion group”) and a control group without frontostriatal lesions (Table 1).

2.2. Procedure

T2-weighted and fast fluid-attenuated inversion recovery (FLAIR) images were independently rated by 2 experienced clinicians (MLS and ER) according to Wahlund et al. (2001). This assessment took place on average 10.5 months (standard error of the mean = 0.76) before study participation, as part of the recruitment for a prior study (Quinque et al., 2012) (we believe that this delay period is nonproblematic because longitudinal studies using the ARWMC show that the change in white matter that is to be expected in such a period is minor at best [Goos et al., 2010; Kapeller et al., 2003]. This was in line with the fact that our neuropsychological assessment showed no differences in any of the scales between the 2 time points [see Section 3]). Furthermore, any change in ARWMC would have worked against our results pattern because white matter damage can only reasonably progress in positive direction [i.e., toward more damage]. Hence, if there were indeed significant changes in ARWMC in our sample between the MRI and testing, they could have only led to a case in which some of the participants of our control group actually did have WM damage, which would reduce the group effect that we hypothesized). For further analyses, we used the mean of both raters’ scores. A white matter lesion was defined as a hyperintensity of >5 mm diameter in the T2-weighted and FLAIR images. Hypointense signal changes on both T2 and FLAIR images with a minimal diameter of 2 mm were rated as lacunes. White matter ratings consisted of global score (range 0–30) and regional subscores for frontal, parietooccipital.

Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unit</th>
<th>Lesion group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>y</td>
<td>62.42</td>
<td>1.80</td>
</tr>
<tr>
<td>Education</td>
<td>y</td>
<td>13.96</td>
<td>0.64</td>
</tr>
<tr>
<td>Gender</td>
<td>F/M</td>
<td>8/4</td>
<td>2/10</td>
</tr>
<tr>
<td>WML</td>
<td>Total</td>
<td>7.10</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td>Frontal</td>
<td>2.75</td>
<td>0.42</td>
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<tr>
<td></td>
<td>Basal G.</td>
<td>0.96</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>Par.-occ.</td>
<td>2.50</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>Temporal</td>
<td>0.67</td>
<td>0.25</td>
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<tr>
<td></td>
<td>Infratentorial</td>
<td>0.21</td>
<td>0.17</td>
</tr>
<tr>
<td>Lacunes</td>
<td>Total</td>
<td>1.83</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Frontal</td>
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<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Basal G.</td>
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<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Par.-occ.</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Temporal</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Infratentorial</td>
<td>0.46</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Key: Basal G., basal ganglia; F, female; M, male; par.-occ., parietooccipital; SEM, standard error of the mean; WML, white matter lesion; #, number.
Subjects signed written informed consent and then underwent a neuropsychological test battery (Consortium to Establish a Registry for Alzheimer’s Disease [CERAD+]1) with the following subtests: Mini-Mental Status Test (MMST), verbal fluency, phonemic fluency, and Trail Making Test (TMT) A and B. Participants underwent this test battery both at the time of the structural brain scans and the subsequent study time. The study procedure was approved by the local ethics committee (No. 204-10-1207/2010). After completion of the neuropsychological test battery, the EEG experiment was conducted. In sum, the whole procedure took 2.5–3 hours.

2.3. Task

The task (Fig. 1) was identical to our previous studies using the hybrid flanker–novelty paradigm (for complete details, see Wessel et al., 2012, 2014). In short, participants performed speeded responses to a letter-version flanker task (Eriksen and Eriksen, 1974). Each trial started with a fixation period of variable length (sampled from a uniform distribution of the values 0, 400, 700, 900, 1100, or 1500 ms), followed by the onset of an imperative stimulus (5-letter string containing the letters H, Z, S, and X as either flanker or target, respectively). The middle letter was defined as the target. The 2 outside letters on each side were the flanker stimuli and could either be congruent (mapped to the same response key) or incongruent (mapped to the other response key) with the target letter. The letter array was on the screen for 70 ms, and responses were made using a custom button box. Ten milliseconds after the response on each trial, a visual stimulus was presented. Participants were instructed to monitor a standard stimulus (upward triangle) for rare occurrences of rare ‘oddball’ stimuli, on which a third button had to be pressed (the oddball stimulus was a downward triangle, which occurred 4 times throughout the experiment and was included to ensure that participants monitored the feedback. These trials were not analyzed). Unbeknownst to the participants, a third type of visual stimulus (novels) could be displayed following any correct response. Novels consisted of 1 of 100 different black-and-white silhouettes of everyday objects or animals, which matched the size and picture quality of the triangles. Novels were displayed at a rate matching each participant’s individual error rate. This way, 3 trial types of interest were generated: correct trials followed by standard stimuli (“standards”), correct trials followed by novel stimuli (“novels”), and erroneous trials followed by standard stimuli (“errors”). Four hundred twenty-four trials were performed in total.

2.4. EEG preprocessing

We recorded from 63 Ag-AgCl electrodes (EasyCap; Brain-Products, Garching, Germany) referenced against left mastoid, sampled at 500 Hz (22-bit resolution, amplifier: ReFa Porti-S32; TMS International), impedances were kept <5 kΩ. Analyses were conducted identical to our previous patient study (Wessel et al., 2014), using MATLAB 2010a (The Math Works, Natick, MA, USA) and EEGLAB (Delorme and Makeig, 2004). After import, data were filtered (0.5 Hz high-pass, 50 Hz low-pass, 2-way least-squares finite impulse response) and cut into segments (−500 to 2,500 ms relative to stimulus onset). Segments with nonstereotyped artifacts were rejected based on visual screening. Stereotyped artifact activity (saccades, blinks, and electrode artifacts) were removed using extended Infomax Independent Component Analysis (Bell and Sejnowski, 1995).

2.5. Neural synchrony

Neural synchrony was quantified as phase-locking value (PLV, Lachaux et al., 1999). Data were first transformed to current-source density using a MATLAB toolbox (Kayser and Tenke, 2006). This is done to reduce volume conduction between remote electrode sides, which can lead to artificially inflated PLVs. Afterward, the data were filtered into 21 linearly spaced frequencies ranging from 4 to 24 Hz (2-way least squares finite impulse response filters) and transformed into the frequency domain using a Hilbert transform. The phase angle of the Hilbert transform was then used to quantify PLV separately for each trial type and frequency. PLV was quantified between 3 clusters of electrodes, 1 frontocentral cluster (FCz and C2), and 2 frontotemporal clusters (FC6 and FT8 for right lateralized and FC5 and FT7 for left lateralized), in the time range of 500 ms after the response. The electrodes for the clusters were chosen because (a) they are in closest anatomic proximity to the proposed nodes of the stopping network (presupplementary motor area and right inferior frontal cortex, respectively, Aron et al., 2007a, 2007b); (b) they overlap with the clusters that showed an increased beta-power response in a scalp EEG study of motor inhibition in Parkinson’s disease (Swann et al., 2011); and (c) these exact electrodes (FCz and C2 for the frontocentral cluster and FC6 and FT8 for the right frontotemporal cluster) showed the greatest beta coherence during successful motor inhibition in scalp EEG recordings of the stop-signal task, measured in >50 healthy individuals (J.R. Wessel, unpublished observations, 2014).

2.6. Event-related potentials

To ensure that any potential group differences in PES and PNS were not caused by perceptual or motor processes, we tested whether neural markers of these processes differed between the 2
groups. To test the integrity of perceptual processing, we analyzed the amplitude of the occipital visual N1 event-related potential (ERP) (Haider et al., 1964), which followed the onset of the target in the flanker task. To test the integrity of motor processing, we analyzed the response-locked lateralized readiness potential (LRP; Vaughan et al., 1968). We hypothesized that these sensory and motor ERPs would be unaffected by frontostriatal disconnections.

To derive the N1, we quantified the average ERP deflection at electrodes O1 and O2 after target onset in the flanker task, separately for both groups. We quantified the ERP amplitude in 2 typical ways: as peak amplitude between 150 and 200 ms after target onset and in a trough-to-peak fashion, in which we subtracted the amplitude of the preceding trough of the ERP (in the time range from 80 to 120 ms after target onset) from that peak amplitude. The N1 was baseline-corrected to a period lasting from −100 to 0 ms before stimulus onset.

To derive the LRP, we subtracted the average ERP deflection at electrodes ipsilateral from the response hand (FC3 for left-handed responses and FC4 for right-handed responses) from the average electrodes O1 and O2 after target onset. This was done for a time range of −700 to +300 ms with respect to response commission. We quantified the LRP amplitude as both mean amplitude and peak amplitude in the time range 200 ms before the response. The LRP was baseline-corrected by subtracting the mean activity of the entire epoch.

2.7. Statistical analyses

Mixed-design 3 × 2 analysis of variance (independent variables [IVs]: trial type [standard, error, novel; within-subjects]; group [lesion, control: between-subjects]) were used to assess errors on basic reaction time (RT). Measurements of post-trial RT adaptations were calculated using the following formulae, which account for differences in correct-response RT between subjects and provide a normalized and unbiased measurement of RT change:

\[
PES = 100 \frac{\text{med}(cCRT_{err+1}) - \text{med}(cCRT_{sta+1})}{\text{med}(cCRT_{sta+1})}
\]

\[
PNS = 100 \frac{\text{med}(cCRT_{nov+1}) - \text{med}(cCRT_{sta+1})}{\text{med}(cCRT_{sta+1})}
\]

These formulae expresses PES and PNS as % change in compatible correct-trial RT caused by errors or novels on the preceding trial (Wessel et al., 2014). Error rates, error-correction rates (correct button pressed after the error but still within the deadline), and miss rates (no response) were tested between groups using 2-sided t tests. PES and PNS, per our hypothesis, were tested in 1-sided fashion. All tests were conducted using the appropriate corrections in case of violations of the respective homoscedasticity assumptions.

For the neural synchrony analyses, we computed the following comparisons: First, we tested whether there was increased frontocentral to right frontolateral beta-synchrony after errors and novelty. This was done by comparing response-locked PLV between errors, novels, and standard trials in the control group. Because PLV is sensitive to trial numbers, we selected a random sample of standard trials that matched the number of errors and novels for each subject in these analyses. Second, we tested whether these effects were right lateralized. This was done by comparing these contrasts (errors and novels vs. standards in the control group) between the frontocentral and right frontolateral ROIs and the frontocentral and left frontolateral ROIs. All these tests were conducted using sample-by-sample paired t tests for each individual frequency and time point. Third, we then tested whether the extent of synchrony between frontocentral and right frontolateral electrode sites predicted the amount of PES and PNS across participants using an individual differences approach. We correlated each participant’s mean response-locked PLV data on errors and novel trials with their PES and PNS value, respectively. This was done using a sample-by-sample Spearman correlation for each individual frequency and time point. Finally, we tested whether beta synchrony was decreased in the lesion group compared with the control group. This was done by comparing both the basic contrasts (errors and novels vs. standards PLV between frontocentral and right frontolateral clusters) and the lateralized contrasts (errors and novels vs. standards between frontocentral and right frontolateral clusters compared with frontocentral and left frontolateral clusters) between the 2 groups, again using sample-by-sample t tests for each individual frequency and time point. Figs. 2–4 show neural synchrony thresholded at p < 0.01 (1 sided). The relevant beta-band analyses that were significant at this threshold also showed significant beta differences at a frequency-wise false discovery rate (Benjamini and Hochberg, 1995) corrected threshold of p < 0.05 (with one exception, which was significant as an false discovery rate corrected trend at p < 0.1, see Section 3.3).

3. Results

3.1. Neuropsychological measures

The lesion group showed significantly worse performance compared with the control group in verbal fluency (t(22) = 2.62, p = 0.02) and TMT-A (t(22) = 2.18, p = 0.04) and marginally worse performance in phonemic fluency (t(22) = 1.73, p < 0.1) and TMT-B (t(22) = −1.98, p = 0.06). No group differences were found in MMST (t(22) = 0.47, p = 0.64) and the TMT-B/TMT-A quotient (t(22) = 0.22, p = 0.83, Table 2).

Importantly, a comparison of the neuropsychological testing data between the time point of the structural scan and of the study (see previously) showed no significant change in any of the test scores between both time points (verbal fluency: 23.71 vs. 24.71, t(23) = −1.11, p = 0.28; phonemic fluency: 14.83 vs. 14.25, t(23) = 0.89, p = 0.38; MMST: 28.92 vs. 28.46, t(23) = 1.55, p = 0.13; TMT-A: 39.38 vs. 42.5, t(23) = −1.07, p = 0.3; TMT-B: 89.96 vs. 93.04, t(23) = −0.47, p = 0.64; and TMT-B/TMT-A: 2.45 vs. 2.39, t(23) = 0.22, p = 0.83).

3.2. Behavior

No group differences were found with respect to error rates (t(22) = 0.36, p = 0.73) or error-correction rates (t(22) = 0.01, p = 0.99, Table 2). Also, despite somewhat slower RTs in the lesion group, a 3 × 2 analysis of variance showed no influence of either group or trial type on RT (group: F(1,22) = 1.78, p = 0.2; trial type: F(2,44) = 0.56, p = 0.58; group × trial type: F(2,44) = 0.73, p = 0.49). However, the lesion group did exhibit a marginally elevated miss rate (t(22) = 1.88, p = 0.073).

With respect to PES and PNS, the control group showed significant PES (t(11) = 2.21, p = 0.05, d = 0.94) and PNS (t(11) = 2.18, p < 0.05, d = 0.93), as predicted, both with large effect sizes. The lesion group, however, showed neither effect, even when tested one-sided (PES: t(11) = 1.22, p > 0.1; PNS: t(11) = 0.58, p > 0.28). When directly testing differences between the groups, PES differences were nonsignificant (t(22) = 0.3, p = 0.38), whereas differences in PNS were significant (t(22) = 1.91, p < 0.05, d = 0.81).
3.3. Neural synchrony

Neural synchrony results can be found in Figs. 2–4. As can be seen in Fig. 2, beta synchrony in the control group was increased for both errors and novels compared with standards (Fig. 2A). Furthermore, these effects were significantly greater for fronto-central to right-lateral electrodes compared with fronto-central to left frontolateral electrodes (Fig. 2B). Additionally, the amount of beta coherence between the fronto-central and right frontolateral cluster was highly (>0.7) correlated with the amount of post-trial behavioral change across all subjects (Fig. 3): participants with greater post-error or post-novel slowing showed stronger increases of beta synchrony between the right frontolateral and fronto-central cluster after the response (unlike all other statistics in this section, the PNS correlation only survived correction for multiple comparisons at \( p < 0.1 \)). This was the case for both errors and novels. Last, Fig. 4 shows that right-lateral beta synchrony after both errors and novels was reduced in the lesion group compared with the control group (Fig. 4A), and the same was true for the lateralized contrast (Fig. 4B).

Taken together, these results show that, as predicted, beta synchrony was selectively increased for errors and novelty, was
lateralized to the right side, was predictive of post-trial RT change on both types of trials across subjects, and was decreased in the lesion group compared with controls.

3.4. Event-related potentials

The posterior visual N1 to the imperative flanker-task stimuli showed no group differences, neither when quantified trough to peak ($t(11) = 0.11, p > 0.9, d = 0.05$) nor when quantified as peak amplitude alone ($t(11) = 0.35, p > 0.73, d = 0.17$). The LRP also showed no group differences, neither when quantified trough to peak ($t(11) = 0.14, p > 0.89, d = 0.06$) nor when quantified as mean amplitude ($t(11) = -0.23, p = 0.82, d = 0.11$). The ERP plots can be found in Fig. 5. This analysis shows that our 2 groups did not differ with regard to neural activity related to perceptive or motor processing.

4. Discussion

In this study, we show that a right-lateralized mechanism for motor inhibition, whose activity is indexed by EEG coherence between frontocentral and right frontolateral scalp regions, is crucially involved in behavioral change after unexpected action outcomes—namely, PES and PNS of reaction times. The study shows, for the first time, that right-lateralized EEG coherence is increased specifically after errors and novelty. Even more importantly, such right-lateralized EEG beta-band coherence predicted the degree of both PES and PNS across participants. Finally, this functionally important EEG coherence was reduced in patients with white matter lesions, which was correlated with a relative impairment of such behaviors in these participants. Together, these results link physiological effects of pathologic aging (reductions in white matter integrity) to well-established behavioral effects of such aging (reductions in cognitive control ability) and provide a sensible neural measurement (EEG coherence) that links both of these phenomena.

In this study, we specifically tested a recent proposal that suggest that a right-lateralized brain mechanism for motor inhibition could underlie PES and PNS (Marco-Pallares et al., 2008; Wessel and Aron, 2013). A core characteristic of this mechanism is that its frontocentral and right frontolateral nodes communicate in the EEG beta-band during motor inhibition (Swann et al., 2011, 2012). Our unique sample of participants with neural disconnection enabled us to directly test this hypothesis. First, we established that both errors and novelty were indeed followed by

![Table 2 Descriptive statistics of neuropsychological measurements and behavioral results separately for each group](http://www.memoryclinic.ch)
increased frontocentral to right frontolateral beta coherence. We also showed that this is not the case for left frontolateral regions. Second, we used an individual differences approach to show that the magnitude of right-lateralized beta-band coherence predicted the amount of PES and PNS between subjects. Third, we showed that frontostriatal white matter damage, as hypothesized, led to reduced functional beta-band (~20 Hz) coherence between frontocentral and right frontolateral electrode sites after both errors and novelty (the nonlateralized group difference plot shows some additional differences in lower beta/high alpha frequencies). Hence, we could demonstrate, for the first time, that right-lateralized mechanism operating in the beta band is involved in the implementation of post-trial reaction time changes after both errors and novelty.

In line with the idea that distributed brain networks are important for certain cognitive control functions, it has been shown that white matter damage is an important mediator of cognitive control deficits such as task switching (Gold et al., 2010; Zhu et al., 2015), working memory (Charlton et al., 2010), implicit learning (Bennett et al., 2011), top-down attention (Bennett et al., 2012), and inhibitory control (Coxon et al., 2012). It has also repeatedly been shown that decreased white matter integrity mediates the effect of age on such cognitive control functions (Borghesani et al., 2013; Holtrop et al., 2014; Madden et al., 2009; Samanez-Larkin et al., 2012; Ziegler et al., 2010). Our findings are in line with these studies and support the general interpretation that white matter integrity is a key marker of the preservation or impairment of function in the aging brain. Beyond this, our findings also point to a noninvasive measure that can be derived from the scalp (EEG coherence), which covaries with the degree of functional preservation (or impairment) of cognitive control (Pinal et al., 2015), here specifically following errors and unexpected events.

One potential limitation of the present study pertains to the regional specificity of the lesions in our sample. Although we specifically grouped our sample based on whether participants had lesions in frontal or striatal regions, the thusly selected frontostriatal lesion group also had an increased number of lesions in parietooccipital and temporal regions. We accounted for this in several ways. First, we showed that neither an early visual ERP originating in the parietooccipital region (the N1) nor the motor LRP differed between the 2 groups. This shows that differences in error and novelty processing between the 2 groups cannot be explained by differences in sensory or motor processing, that the groups did not differ with regard to these processes, and that there is a degree of specificity to the loss of neural function caused by the white matter lesions. Second, we showed that the loss of coherence in the lesion group was regionally specific to right frontolateral to frontocentral coherence: A control analysis of left frontolateral to frontocentral coherence revealed no such differences, as predicted by our hypothesis.

Another potential limitation is the inverse problem: Because activity at the scalp level is a mixture of underlying neural dipoles, which could contribute to the scalp EEG in an infinite number of different configurations, the exact region of origin of any given EEG signature is not clear. Specifically, it is impossible to say whether the beta synchrony between frontocentral and right frontolateral regions actually corresponds to the beta coherence between pre-supplementary motor area and right inferior frontal cortex, which is indicated by intracranial measurements of the inhibitory mechanism during outright stopping of actions (Swann et al., 2012). Although the current-source density method we used eliminates the contributions from very remote dipoles (Kayser and Tenke, 2006), we still have to refrain from making any precise statements regarding the exact anatomic underpinnings of our measured signals. We do, however, stress that the electrode sites we selected for the PLV analysis overlap with a scalp-EEG study of the stop-signal task, which showed beta activity during successful action stopping in those exact regions of the scalp (Swann et al., 2011). The 2 sites were furthermore identical to the sites of maximal beta coherence during outright action stopping in a sample of >50 healthy volunteers who performed different versions of an action-stopping task (J.R. Wessel, unpublished observations, 2014). Hence, although we refrain from making precise anatomic statements that are precluded by the usage of scalp EEG, we believe that our results suggest at a common neural substrate that is active in both the stop-signal task and during error/novelty processing. This is in line with suggestions made in several recent studies (Danielmeier et al., 2011; Marco-Pallares et al., 2008; Wessel and Aron, 2013).

5. Conclusions

The present study is important in multiple ways. First, it provides evidence for a right-lateralized neural motor inhibition mechanism underlying the slowing of reaction times after unexpected action outcomes such as errors or perceptual novelty. Second, it shows that the activity of this mechanism can be quantified using event-related right-lateralized EEG beta-band coherence, which varies in amplitude with the degree of PES and PNS. Third, it shows that white matter damage, in our case caused by SVD, can lead to functional impairments that can be indexed by EEG coherence.
Taken together, this study provides a crucial link between physiological effects of aging on the one hand and age-related reductions of cognitive control ability on the other hand. It also shows that EEG coherence is a sensitive, noninvasive measurement that links both of these phenomena and could hence potentially be suitable as an indicator of functional impairments of cognitive control in (pathologic) aging.

Disclosure statement
The authors have no conflicts of interest to disclose.

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