Monitoring of Self-Paced Action Timing and Sensory Outcomes After Lesions to the Orbitofrontal Cortex

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Abstract

Anticipation, monitoring, and evaluation of the outcome of one's actions are at the core of proactive control. Individuals with lesions to OFC often demonstrate behaviors that indicate a lack of recognition or concern for the negative effects of their actions. Altered action timing has also been reported in these patients. We investigated the role of OFC in predicting and monitoring the sensory outcomes of self-paced actions. We studied patients with focal OFC lesions (n = 15) and healthy controls (n = 20) while they produced actions that infrequently evoked unexpected outcomes. Participants performed a self-paced, random generation task where they repeatedly pressed right and left buttons that were associated with specific sensory outcomes: a 1- and 2-kHz tone, respectively. Occasional unexpected action outcomes occurred (mismatch) that inverted the learned button–tone association (match). We analyzed ERPs to the expected and unexpected outcomes as well as action timing. Neither group showed post-mismatch slowing of button presses, but OFC patients had a higher number of fast button presses, indicating that they were inferior to controls at producing regularly timed actions. Mismatch trials elicited enhanced N2b-P3a responses across groups as indicated by the significant main effect of task condition. Planned within-group analyses showed, however, that patients did not have a significant condition effect, suggesting that the result of the omnibus analysis was driven primarily by the controls. Altogether, our findings indicate that monitoring of action timing and the sensory outcomes of self-paced actions as indexed by ERPs is impacted by OFC damage.

INTRODUCTION

The OFC has been extensively studied, yet its role in performing the executive functions remains debated (e.g., Wallis, 2019; Stalnaker, Cooch, & Schoenbaum, 2015; Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009; Murray, O’Doherty, & Schoenbaum, 2007; Happaney, Zelazo, & Stuss, 2004; Rolls, 2004; Stuss & Levine, 2002; Stuss et al., 1983). Research has suggested a multifaceted role for the OFC in social cognition, emotion, and decision-making (Henri-Bhargava, Stuss, & Freedman, 2018; Hiser & Koenigs, 2018; Dixon, Thiruchselvam, Todd, & Christoff, 2017; Rolls & Grabenhorst, 2008). The OFC has been implicated in various tasks that require decision making and monitoring of outcomes, particularly in the online tracking of reward value (Hebscher & Gilboa, 2016; Wallis, 2012; Ullsperger & von Cramon, 2004; Walten, Devlin, & Rushworth, 2004). Patients with OFC lesions demonstrate both a reduced sensitivity to future consequences and a difficulty in learning from previous mistakes when engaged in decision-making tasks involving reward, despite overall seemingly normal intellectual and memory function (e.g., Floden, Alexander, Kubu, Katz, & Stuss, 2008; Murray et al., 2007; Bechara, Damasio, & Damasio, 2000; Bechara, Tranel, & Damasio, 2000; Bechara, Damasio, Tranel, & Anderson, 1998). Such findings have contributed to a prevalent view that the primary functions of the OFC are related to the regulation of emotion and motivation, with a strong emphasis on inhibitory control and reward-related processing (Rudebeck & Murray, 2011, 2014; Rolls, 2004; Roberts & Wallis, 2000; Dias, Robbins, & Roberts, 1996).

Recent findings have challenged models emphasizing only emotion regulation and behavioral inhibition as core functions of the OFC (Schuck, Cai, Wilson, & Niv, 2016; Rudebeck & Murray, 2014). There is growing support, especially from animal research, for the idea that the OFC generates predictions concerning the likely outcomes of impending stimuli, choices, and actions and represents an updated valuation of outcomes based on an individual’s current motivational state (Wikenheiser, Marrero-Garcia, & Schoenbaum, 2017; Wikenheiser & Schoenbaum, 2016; Rudebeck & Murray, 2014; Schoenbaum et al., 2009; Schoenbaum, Roesch, Stalnaker, & Takahashi, 2011).

The notion of emotion regulation and behavioral inhibition as core OFC functions may arise, in part, from prior studies of action outcome processing that used tasks where outcomes clearly had an emotional or motivational value (Ullsperger, 2017). Given the presence of signals in...
the OFC that are unrelated to reinforcement, this suggests that the OFC forms representations of the environment that extend beyond reward, including the specific cortical representation of sensory events and their outcomes (Gottfried & Zelano, 2011; Wallis & Miller, 2003; Schoenbaum & Eichenbaum, 1995). Neuropsychological studies in rodents have shown that OFC neurons can represent specific sensory features of both value-relevant and value-neutral outcomes (McDannald et al., 2014; Stalnaker et al., 2014). Furthermore, human fMRI studies indicate that the OFC signals outcome-related attributes beyond reward (Gottfried & Zelano, 2011). The emerging view of OFC function is that it forms and maintains a “cognitive map” of task space, which contains an updated representation of observable and unobservable task-relevant information (Schuck et al., 2016; Wikenheiser & Schoenbaum, 2016; Stalnaker et al., 2015; Wilson, Takahashi, Schoenbaum, & Niv, 2014). The OFC is thought to map relevant sensory, temporal, and contextual attributes needed to model and predict the environment, including the effects of choices and actions (Schuck et al., 2016; Farovik et al., 2015; Wilson et al., 2014).

A key role of the OFC in mapping and monitoring the entire environment or task space may entail not only predicting events and outcomes but also noticing breaches of expectation, that is, prediction errors (Petrides, 2007). Additional areas proposed to be involved in detecting and processing prediction errors include the right inferior lateral pFC (Chatham et al., 2012; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010), the motor system and cerebellum (Popa & Ehnner, 2019), and also the frontoparietal network (Visalli, Capizzi, Ambrosini, Mazzonetto, & Vallesi, 2019; Waskom, Frank, & Wagner, 2017). Noticing expectation violations may even occur across all levels of extended brain systems as proposed by the hierarchical predictive coding framework (Friston, FitzGerald, Rigoli, Schwartenbeck, & Pezzulo, 2017; Picard & Friston, 2014; Friston, 2005). A related proposal, concerning action-based predictive coding, is models of feedforward signaling. In these models, noticing breaches of expectation are based on the comparison of a copy of the motor command (i.e., effence copy) and its predicted sensory consequences (i.e., corollary discharge) to the actual performed actions and their sensory effects (Subramanian, Alers, & Sommer, 2019). These mechanisms enable us to discount sensations that result from our own actions. Supporting this view, studies find attenuated ERPs (i.e., N1 suppression) to self-generated relative to externally produced action outcomes, but accentuated responsiveness (i.e., N2b-P3a increase) to self-generated unexpected sounds in motor-to-auditory prediction tasks (e.g., Knolle, Schwartz, Schröger, & Kotz, 2019; Knolle, Schröger, & Kotz, 2013; Knolle, Schröger, Baess, & Kotz, 2012).

Different types of unexpected events (i.e., action errors, unexpected action outcomes, or unexpected perceptual events) recruit an extended fronto-basal ganglia network for suppressing ongoing behavior, as reflected in reactive motor slowing after unexpected stimuli (Wessel & Aron, 2017; Wessel, Klein, Ott, & Ullsperger, 2014). This network includes the subthalamic nucleus and dorsomedial and inferior frontal cortices, with additional engagement of dorsolateral and ventromedial pFC (Wessel & Aron, 2017). An fMRI study showed significantly enhanced activation in the OFC for unexpected, externally generated, action outcomes in comparison to self-generated errors. Other parts of the brain did not show a differential response to the two types of unexpected action outcomes (Wessel, Danielmeier, Morton, & Ullsperger, 2012).

The contention that multiple regions of pFC play a role in the neuronal networks responding to unexpected events is in keeping with human lesion and EEG studies (Solbakk et al., 2014; Wessel et al., 2014; Lövstad et al., 2012; Turken & Swick, 2008; Daffner et al., 2000, 2003; Knight & Scabini, 1998; Knight, 1984). Our group has previously reported ERP indices of reduced attention to unexpected novel environmental sounds (i.e., unexpected perceptual events) in patients with lesions to either the lateral pFC or OFC (Lövstad et al., 2012). We have also showed altered ERP indices of monitoring and evaluation of action outcomes (stopping failure; i.e., action errors) in a stop-signal task despite unaffected stopping behavior in OFC lesion patients (Solbakk et al., 2014). A PET study in humans reported that the OFC responded to different types of breaches of expectation in attention tasks (Nobre, Coull, Frith, & Mesulam, 1999). Hence, lesion, electrophysiological, and neuroimaging studies indicate that the OFC is involved in predicting different perceptual events and action outcomes, and in monitoring and evaluating outcomes that deviate from the expected. This supports the proposal that the OFC is involved in creating and maintaining a cognitive map of task space (Schuck et al., 2016; Wikenheiser et al., 2016; Stalnaker et al., 2015; Wilson et al., 2014).

In this study, we examined this new perspective of the OFC by investigating whether patients with OFC damage are impaired with respect to predicting or monitoring the sensory outcomes of their actions compared to healthy participants. OFC lesion and control participants performed a task where both the decision about what action to make and the resulting action outcomes were of low complexity and valence-free. Using a modified version of a self-paced, two-choice random generation task (Iwanaga & Naito, 2010), participants engaged in simple self-initiated actions of their own choice, that is, deciding which button to press and when to press within a short time window. Each button press was paired with a specific tone. Occasionally, button presses produced unforeseen sensory outcomes that violated the previously established action–effect (i.e., button press and tone) associations. The task is an active, self-paced oddball paradigm using motor-to-sensory prediction. Voluntary actions evoke a sense of agency and a higher level of causal attribution processes instead of passively tracking sensorimotor outcomes (Moore, 2016). Unlike many studies of responses to outcome expectations, our
study did not rely on symbolic rewards as feedback. Rather, immediate action outcomes were valence-neutral acoustic stimuli and no performance feedback was provided. Corrective action in the event of an unexpected outcome was not required because action outcomes were defined as irrelevant to the task and participants were instructed to ignore the tones.

Our first goal was to replicate the ERP and behavioral findings from the original two-choice random generation study with healthy participants (Iwanaga & Nittono, 2010). This study reported an enhanced N2b-P3a complex and a late positive potential (LPP) in response to unexpected action outcomes accompanied by a slower button press response on the following trial (i.e., post-mismatch slowing). We refer to expected action outcomes (correct button press–tone pairing) as matches and unexpected action outcomes as mismatches. Knolle et al., employing a similar paradigm, investigated external versus self-generated deviants using EEG and found, in addition to the N2b-P3a complex, a reduced N1-suppression effect to self-generated deviants (Knolle et al., 2013). They interpreted this effect as a prediction error response resulting from the violation of a regular action outcome prediction. An increased N2b-P3a complex in response to unexpected action outcomes has also been reported by Wessel and colleagues (Wessel et al., 2012, 2014).

Our second goal was to investigate how individuals with focal lesions in the OFC processed the expected and unexpected effects of their actions, and whether this differed behaviorally or electrophysiologically from the healthy participants. We hypothesized that if OFC damage results in impaired prediction or monitoring of whether a prediction is met or violated, then their deviance-related ERPs (N2b, P3a) would not differ from their expected outcome ERPs. This might also be observable in reduced or absent behavioral slowing on the subsequent trial after encountering an unexpected outcome. Such results would support the recently formulated theory that the OFC is crucial for encoding expected outcomes independent of valence (Schuck et al., 2016; Wikenheiser & Schoenbaum, 2016; Rudebeck & Murray, 2014). Moreover, an inherent aspect of the random generation task is time perception and generation of regularly timed intervals. As earlier studies have reported altered timing performance in patients with damage to different subdivisions of pFC (Harrington, Haaland, & Knight, 1998; Berlin, Rolls, & Kischka, 2004; Picton, Stuss, Sallice, Alexander, & Gillingham, 2006), we also examined the overall timing of the motor acts.

METHODS
Participants

Eighteen adult patients with focal lesions to the OFC and 22 healthy controls were recruited to the study. Healthy controls were recruited through advertisement and personal contact, whereas patients were recruited through the Department of Neurosurgery at Oslo University Hospital. Inclusion of patients was based on the presence of lesions restricted to the OFC as indicated on pre-existing structural computer tomography and/or magnetic resonance imaging (MRI) scans. The healthy controls also underwent structural MRI scanning to ensure inclusion, and a neuroradiologist confirmed that their MRI images showed no signs of pathology.

The patients had OFC lesions because of resections of primary intracranial tumors or contusions because of traumatic brain injuries (TBIs) without signs of diffuse axonal damage. Exclusion criteria were a history of serious psychiatric disease, pre-/comorbid neurological disease, premorbid head injury, drug or alcohol abuse requiring treatment, IQ below 85, aphasia, auditory or visual sensory deficit, impaired motor function of the hands, or radiation therapy as part of treatment for brain tumor. The control participants were screened for neurological and neuropsychiatric health issues. All participants reported normal hearing, and normal visual acuity or vision corrected by optical lenses. Both patients and healthy controls underwent assessment of neuropsychological function with standardized and normed tests. This included estimation of general intellectual ability by means of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). No participant was excluded because of low intellectual ability (IQ) or otherwise impaired performance on standardized cognitive tests.

After study inclusion, three OFC and two healthy control participants were excluded because of technical or performance issues related to the experimental task (i.e., the random generation task). The EEG recording of one of the excluded controls had corrupted event triggers, and the data were not recoverable. The other excluded control did not follow the instruction to use both hands during the task (i.e., mainly used one hand). The three OFC participants were excluded because they had too few mismatch trials after rejecting trials with button interpress intervals faster than 700 msec or slower than 2500 msec (see Preprocessing of Behavioral Data section).

Our final study groups comprised 20 healthy controls and 15 patients with OFC damage. Participants were right-handed (94.3%), except one self-reported ambidextrous OFC patient and one left-handed control participant. Handedness was evaluated with the Edinburgh Handedness Inventory (Oldfield, 1971). Twelve of the patients had bilateral lesions, two had lesions localized to the right OFC, and one had damage in the left OFC. All patients were in the chronic phase of recovery, that is, at least 2 years post-tumor resection or trauma (mean = 7.7 years; range = 2–15 years). Details of the brain lesions are provided in Table 1. The final study groups did not differ significantly with regard to sex, age, years of education, or estimated IQ (Table 2).

All participants gave written informed consent before participating in the study. Healthy controls received 400
NOK (approximately 50 USD) for participation in the entire research project (neuropsychological assessment, EEG recording, and MRI scanning). Patients participated in conjunction with clinical follow-ups at the hospital's outpatient clinic. Their travel and accommodation expenses were covered. The study was approved by the Regional Committees for Medical and Health Research Ethics – South-East Norway and was performed in accordance with the principles stated in the Declaration of Helsinki.

Lesion Reconstruction
Lesion reconstructions were based on structural MRI scans acquired after study inclusion. The lesions were manually outlined on Fluid Attenuated Inversion Recovery images (1 × 1 × 1 mm³ resolution) for each participant's brain using MRicron (www.mccauslandcenter.sc.edu/mricron/mricron/). High-resolution T1-weighted images were used to help determine the borders of the lesions. The resulting lesion masks were transferred to normalized space using the Statistical Parametric Mapping software (SPM12: www.fil.ion.ucl.ac.uk/spm/). The image of each participant's brain was extracted from T1-weighted images using the FMRI Software Library Brain Extraction Tool algorithm (FMRI Software Library: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). The extracted brain image was masked with the drawn lesion and then normalized to the Montreal Neurological Institute template using the SPM unified segmentation and normalization procedures. The transformation was then also applied to the individual patient's T1, Fluid Attenuated Inversion Recovery, and lesion mask images. Lesions were reconstructed under the supervision of a neurosurgeon (T. R. M) and a neurologist (R. T. K). Figure 1 shows the aggregate lesion reconstructions for the OFC group and the average percentage of lesioned tissue within each Brodmann's area (BA).

Experimental Setting and Recording Hardware
Participants were seated in a Faraday-shielded room 70 cm from an LCD monitor with a 60-Hz refresh rate. EEG was recorded at 1024-Hz sampling rate using a 64-channel BioSemi Active Two system with electrodes placed using the BioSemi head cap, which is constructed in accordance with the International 10–20 system. Two vertical EOG electrodes were placed above and below the right eye, and two horizontal EOG electrodes were placed at the participants' left and right canthi. Two reference electrodes for later off-line importation were also placed on the left and right earlobes.

Experimental Design
Participants performed a self-paced, two-choice random generation task similar to the task used by Iwanaga and

<table>
<thead>
<tr>
<th>Patient</th>
<th>Etiology</th>
<th>Years Since Resection/Injury</th>
<th>Lesion Size (cm³) Per Hemisphere</th>
<th>Affected BA Per Hemisphere</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>1</td>
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<td>5</td>
<td>0</td>
<td>22.9</td>
</tr>
<tr>
<td>2</td>
<td>TBI</td>
<td>13</td>
<td>59.7</td>
<td>97.6</td>
</tr>
<tr>
<td>3</td>
<td>Olfactory meningioma</td>
<td>11</td>
<td>56.4</td>
<td>61.5</td>
</tr>
<tr>
<td>4</td>
<td>Olfactory meningioma</td>
<td>7</td>
<td>11.6</td>
<td>36.7</td>
</tr>
<tr>
<td>5</td>
<td>Olfactory meningioma</td>
<td>11</td>
<td>3.1</td>
<td>5.4</td>
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<tr>
<td>6</td>
<td>Olfactory meningioma</td>
<td>11</td>
<td>1.3</td>
<td>7.5</td>
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<tr>
<td>7</td>
<td>Olfactory meningioma</td>
<td>3</td>
<td>2.6</td>
<td>47.4</td>
</tr>
<tr>
<td>8</td>
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<td>12</td>
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<td>36.2</td>
</tr>
<tr>
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<tr>
<td>10</td>
<td>Olfactory meningioma</td>
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<tr>
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<tr>
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<td>60.3</td>
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<tr>
<td>13</td>
<td>Low grade glioma</td>
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<td>6.4</td>
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<tr>
<td>14</td>
<td>Olfactory meningioma</td>
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<td>22.5</td>
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<tr>
<td>15</td>
<td>TBI</td>
<td>8</td>
<td>13.9</td>
<td>21.9</td>
</tr>
</tbody>
</table>

A blank cell is used when there was no lesion in a given hemisphere. Lesions that comprise < 0.2 cm³ in any given BA are not reported.
Nittono (2010). Participants were given three rules to follow: 1) that they should randomly press one of two buttons on the response box using their left and right index fingers (Figure 2), 2) that their presses should occur at a regular self-paced tempo of one press every 1–2 sec (trials with button interpress intervals of less than 700 msec or more than 2500 msec were not included in the later data analyses), and 3) that they should press both buttons with approximately equal probability. Prior to the start of each block, a gray circle (3° in diameter) was presented 10 times (stimulus duration = 200 msec; ISI = 1000 msec) to help participants establish an idea of what a regular button press speed (1–2 sec) should be. This was followed by a gray fixation cross on the screen that participants were told to fixate on for the remainder of the block. The appearance of the fixation cross was also the cue for participants to start pressing buttons. The entire task consisted of five blocks and 795 trials (one block = 159 trials), and participants were allowed to take a short break after the third block.

When participants pressed either the right or left button, a tone that was 70 msec in duration was played through speakers situated in front of where the participant sat. The latency between when the button was pressed and when the tone was heard was 35 msec (SE = 5 msec). Participants were informed that the tones were not relevant to the task and should be ignored. The first 20 trials of each block were designated as a baseline period during which the button presses produced the tone they were supposed to, that is, a 1000-Hz tone for a right button press and a 2000-Hz tone for a left button press. We refer to trials where a button was pressed and the resulting tone matched the established pattern as match. After the initial 20 trials, there was an infrequent occurrence that a button press would produce the tone that had been established as associated with the other button. These trials we refer to as mismatch (p = .151; 15.1% for mismatch trials, and p = .849; 84.9% for match trials). In total, there were 21

| Table 2. Characteristics of the Healthy Control Group and the Group with Lesion to the OFC |
|------------------------------------------|----------|--------|
|                                        | CTR      | OFC    |
| N (% female)                            | 20 (55)  | 15 (67) |
| Age in years (SD)                        | 43.0 (14.2) | 50.4 (11.6) | ns |
| Education in years (SD)                  | 15.7 (2.4) | 13.9 (2.5) | ns |
| Total IQ (SD)                            | 113.4 (9.8) | 109.9 (12.4) | ns |

Comparison of the percentage of females (chi-square test), age, years of education, and IQ between the two groups (one-way ANOVA). Values given are means, with standard deviation (SD) in brackets. The mean value for total IQ is given in IQ scores. CTR = control group; ns = not significant.

Figure 1. Lesion reconstructions for the patient group. (A) depicts aggregate lesion overlay maps in axial view for the patients with orbitofrontal lesions (OFC). The color code (from 0 to 1, i.e., 0–100% overlap) for the group overlay indicating the percentage of shared lesion coverage across patients. The more red/purple the color, the greater the lesion overlap. Neurological convention is followed with the right side of the brain being on the right side of the image and vice versa. (B) shows percentage of damaged tissue within each BA. BAs with less than 2% damage are not presented.
mismatch trials in each block and two mismatch trials never occurred in succession. Stimulus presentations and response recordings were done using E-Prime software, Version 2.0 (Psychology Software Tools).

Data Preprocessing

The two task conditions analyzed were match and mismatch. The match condition was defined as when the participant pressed a response button and the tone that was played matched their expectation: an expected action outcome. For example, if the participant pressed the left response key that typically produced the 1000-Hz tone and the 1000-Hz tone was heard, then the trial was defined as a match trial. The mismatch condition was defined as when the participant pressed either of the response buttons and the tone that was played did not align with their expectations: an unexpected action outcome. For example, if the participant pressed the left response key that typically produced the 1000-Hz tone and the 2000-Hz tone was heard (which corresponds to the tone typically produced by the right response key), then the trial was defined as a mismatch trial.

Preprocessing of Behavioral Data

Behavioral data were collected in the form of button press intervals. Because the task was self-paced, there was no response time to analyze. Rather, we analyzed the amount of time between button presses, that is, the interval, as a behavioral measure of the self-paced task demand. First, trials were excluded that had button press intervals shorter than 700 msec or longer than 2500 msec, in order to remove behavioral outliers with respect to the experimental task (“keep a steady pace with a button press interval of 1–2 sec”) and to avoid overlap between trials for the analyses of the ERPs. The mean and standard error (SE) button interpress intervals for each of the five blocks before and after rejecting timing outliers can be seen in Table 3. Trials were then grouped by condition, and the mean button press interval per condition was computed. In order to define a normalized baseline value for the button press intervals, we used the arithmetic mean of the first 20 trials of each block, which had no mismatch events. We then subtracted the average of the first 20 trials from the mean button press intervals per block (Iwanaga & Nittono, 2010). We performed this process for each participant and for each block to derive normalized button press intervals per condition.

Preprocessing of EEG Data

EEG data were preprocessed using custom written scripts and EEGLAB functions (Delorme & Makeig, 2004) in MATLAB. EEG data were recorded using an active reference (CMS-DRL), and each data record was rereferenced to linked earlobes during importation into MATLAB. After import, data were bandpass filtered from .05 to 35 Hz, down-sampled to 250 Hz, rereferenced to common average, and epoched around button presses. ERPs of the match and mismatch conditions were computed at all scalp electrode locations over a total time window of 900 msec. The 200-msec period before button pressing was defined as a baseline, which was relative to the 700-msec window of interest that followed the button press and contained the auditory event. Using automated rejection tools and visual inspection, individual noisy electrodes were rejected. An average of 3.68 electrodes were rejected from each participant data set. Before interpolating missing electrodes, Blind Source Separation EOG and EMG correction algorithms were run to control for ocular and muscular artifacts (Gomez-Herrero et al., 2006). Further visual inspection and automated methods were then used to reject epochs with clear movement artifacts and amplitudes greater than 75 ± μVolts. Lastly, data were once again rereferenced to the common average to account for removed data segments; baseline corrected (from −200 msec to event onset marker) and rejected electrodes were interpolated.
Behavioral data from the experimental task were subjected to mixed model or repeated-measures ANOVA, or t tests. To examine whether the interval between button presses was the same across the five blocks of trials, we performed for each group a repeated-measures ANOVA with block as a five-level within-subject factor. To investigate whether button presses following mismatch trials was slower than button presses following match trials, the duration of the interval between button presses was subjected to a 2 × 2 mixed model ANOVA with the between-subjects factor of group (OFC vs. control) and the within-subject factor of condition (match vs. mismatch). To compare differences in the numbers of rejected trials for the behavioral data between groups (i.e., outliers with respect to the length of the button press intervals), independent-samples t tests were conducted for the number of rejected trials. Alpha was set to .05.

After preprocessing of EEG data, statistical analysis of between-groups differences were performed using a 2 × 2 mixed model ANOVA. Based on our theoretically driven hypothesis that the ERPs of the OFC would not clearly differentiate between expected (i.e., match) and unexpected (i.e., mismatch) action outcomes, planned within-groups analyses were also performed, using dependent-samples t tests. All statistical analyses of the EEG data were combined with nonparametric permutation cluster testing (Mensen & Khatami, 2013; Maris & Oostenveld, 2007). All final corrected statistical values were computed using a type of nonparametric cluster-based statistical test called the threshold-free cluster enhancement (TFCE; Mensen & Khatami, 2013; Smith & Nichols, 2009). TFCE differs from other cluster-based statistical tests as it does not require an a posteriori assumption concerning what a reasonable threshold should be for defining cluster inclusion (Mensen, 2012). This allows TFCE to capture more of the underlying natural dynamics of neural activity that might be obscured when using other permutation methods that privilege significant clusters exhibiting strong peaks or activation (Mensen & Khatami, 2013). TFCE achieves this using a weighted average derived from the calculated t values. The resulting TFCE values are then scaled in extent (or width) and height in relation to the cluster they originated from, in essence making a TFCE value more reflective of "clusteredness" and enhancing broad or less strong clusters in relation to their neighborhood of origin (Mensen & Khatami, 2013; Smith & Nichols, 2009). TFCE is a standard statistical tool within the fMRI community (for EEG-specific validation, see Pernet, Latinus, Nichols, & Rousselet, 2015; Mensen & Khatami, 2013).

**RESULTS**

**Behavioral Results**

The mean and SE button interpress intervals for each of the five blocks constituting the random generation task can be seen in Table 3. A repeated-measures ANOVA showed that no single block of trials was significantly different from the others in terms of duration of interval between button presses (OFC: F(4, 70) = 0.215, p = .759; control: F(4, 95) = 0.042, p = .997). All of the following analyses of button interpress intervals were performed on the means across blocks.

A mixed model ANOVA showed no significant main effect of either group or condition on button interpress intervals.
following the action outcomes (group: \( F(1, 66) = 1.799, p = .185 \); condition: \( F(1, 66) = 0.023, p = .879 \)). In addition, there was no significant interaction between the two factors (Group × Condition: \( F(1, 33) = 0.015, p = .902 \)). Thus, the lack of a significant main effect for condition, and also for the interaction with group, indicates that there was no slowing of motor responses following unexpected action outcomes (mismatch) for either group.

Our criteria rejected numerous trials for the OFC patients because their button press intervals were below 700 msec or above 2500 msec. The large number of rejected trials of OFC patients is indicative of timing difficulties, because the participants were not fulfilling the experimental task demands during those trials (“keep a steady pace with a button press interval of 1–2 sec”). The number of rejected trials per group can be seen in Table 3. Overall, the OFC group had a significantly higher mean number of rejected trials (20.3% in total, with 19.8% of the match trials and 21.7% of the mismatch trials being rejected) compared to the control group (6.6% in total, with 6.5% match trials and 6.7% mismatch trials; \( t(33) = 2.398, p = .022 \)). The difference in rejected trials between the groups was largely the result of an increased number of too short button press intervals produced by the OFC group (group median of rejected trials across match and mismatch conditions = 571 msec).

Table 3 shows that the groups had no preference for pressing one button in particular. Both groups used the left and the right buttons at an approximately equal rate (see “Button Press %” in Table 3). The table also shows that the occurrence of a match or mismatch trial did not elicit a pattern of participants pressing another button on the same button on the following trial.

Although both groups followed the instruction to use the left and right button with equal probability, patients with OFC damage had difficulty maintaining a steady pace of button presses within the exclusion criteria and had a significantly higher number of fast button presses (i.e., short button interpress intervals) compared to the control group.

**ERP Results**

**Between-Group Analyses**

A 2 × 2 tANOVA showed a significant main effect of condition, but the effect of group and the Group × Condition interaction was not significant (for the effect of group, the peak value was found at FCz at 432 msec; \( F(1, 33) = 11.25, p = .368 \); for the interaction effect, the peak value was found at channel AF8 at 412 msec; \( F(1, 33) = 18.92, p = .57 \). Four significant clusters emerged for the condition effect. Only clusters with a \( p \) value ≤ .025 are reported for the main condition effect in the following section.

There were four significant clusters that demonstrated a main condition effect of match versus mismatch. In temporal order, the first significant cluster, composed of three channel–sample pairs over one unique channel, started at 180 msec (after the button press) and ended at 188 msec. The peak significant channel and sample in the cluster occurred at channel T8, a right temporal channel, at 184 msec, \( F(1, 33) = 23.42, p = .021 \). This effect is in keeping with a difference in N1 amplitude between the two conditions, most likely driven by increased amplitude to mismatch trials. The second significant cluster was composed of 49 channel–sample pairs over five unique channels and lasted from 228 to 276 msec. The peak channel in Cluster 2 occurred at FC1, a left lateral fronto-central channel at 240 msec, \( F(1, 33) = 21.13, p = .008 \), and this condition effect seemed to be driven by an increased N2b in the mismatch compared to the match condition. The third significant cluster was composed of 76 channel–sample pairs over 10 unique channels and lasted from 308 to 360 msec. The peak channel in the third cluster was FC5, a left lateral fronto-central channel, at 332 msec, \( F(1, 33) = 27.01, p = .002 \). This condition effect is indicative of an increased P3a response to unexpected action outcomes. The fourth significant cluster was composed of 29 channel–sample pairs spanning five unique channels and lasted from 316 to 360 msec. The peak channel was Oz, a midline occipital channel, at 344 msec after the tone onset, \( F(1, 33) = 26.95, p = .004 \), which also showed an increased P3a response to unexpected action outcomes.

These significant clusters are driving task condition differences in the N1 range (100–199 msec), N2b range (200–250 msec), and P3a range (270–390 msec), reflecting enhanced amplitudes for mismatch compared to match trials. Because the omnibus TFCE statistics showed no significant effects involving the group factor, this indicates that the occasional errors in the established motor-to-sensory predictions (i.e., mismatch trials) were detected by control and OFC participants. Given our a priori hypothesis that patients with OFC damage would have ERPs that do not clearly differentiate between expected and unexpected action outcomes, we conducted planned within-group analyses to identify whether either group showed a significant main effect of condition when studied individually.

**Within-Group Analyses of the Task Condition Effect**

We conducted planned dependent \( t \) tests within each group to compare ERP differences for the mismatch versus match conditions. All within-group \( t \) tests were performed using 10,000 permutations to correct for multiple comparisons using the TFCE method. The results from comparing the control group ERPs for match and mismatch trials showed that there were five clusters with a significant condition effect (\( p ≤ .025 \)). See Figure 3A–3E for a visual representation of the clusters and the corresponding topographic plots, and Table 4 for cluster size, \( t \) values, and significance at each channel-time peak for each cluster.
As can be seen at left and midline fronto-central sites in Figures 3 and 4, the ERP waveforms of the control group followed each other closely in the early sensory responses to the action effects (i.e., tones), but started to significantly diverge around the peak of the N1 and then again at the N2b. The first cluster encompassed a time range of 160–272 msec and 22 unique channels with a peak time of 240 msec and a peak channel at FC1, \( t(19) = -4.713, \) \( p = .003 \).

Table 4. ERP Cluster Results from TFCE \( t \) Tests for the Healthy Control Group

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Time Range (msec)</th>
<th>Peak Channel</th>
<th>Peak Time (msec)</th>
<th>Cluster Size</th>
<th>Unique Channels</th>
<th>( t ) Values at Peak</th>
<th>( p ) Values at Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>160–272</td>
<td>FC1</td>
<td>240</td>
<td>208</td>
<td>22</td>
<td>(-4.713)</td>
<td>.003</td>
</tr>
<tr>
<td>2</td>
<td>304–316</td>
<td>P5</td>
<td>308</td>
<td>4</td>
<td>1</td>
<td>(-6.211)</td>
<td>.012</td>
</tr>
<tr>
<td>3</td>
<td>312–356</td>
<td>F3</td>
<td>328</td>
<td>58</td>
<td>8</td>
<td>5.563</td>
<td>.005</td>
</tr>
<tr>
<td>4</td>
<td>332–352</td>
<td>Oz</td>
<td>340</td>
<td>12</td>
<td>4</td>
<td>(-4.314)</td>
<td>.021</td>
</tr>
<tr>
<td>5</td>
<td>676–668</td>
<td>P4</td>
<td>680</td>
<td>4</td>
<td>1</td>
<td>5.301</td>
<td>.021</td>
</tr>
</tbody>
</table>

Table 4. ERP Cluster Results from TFCE \( t \) Tests for the Healthy Control Group

Dependent-samples \( t \) tests within-group comparing match and mismatch condition. Cluster extent as well as location and significance of cluster peak values are reported.

\( ^a \) Results are corrected for multiple comparisons using cluster-based permutation TFCE statistics (10,000 permutations).

Figure 3. Significant clusters for the healthy control group (A–E). Dependent \( t \) tests within-group comparing match and mismatch condition, multiple comparisons controlled for using 10,000 permutations. The match ERP waveform is depicted in blue and the mismatch waveform in red. Shaded areas around the ERP waveforms represent the calculated SEs. Gray shaded bars denote the portion of the ERP waveform that showed a significant difference between match and mismatch trials at that time range. To the right of the ERPs, the corresponding topographic scalp maps at the peak significant time point for each cluster are shown for match and mismatch conditions, along with the result of the TFCE statistical comparison of the two conditions.
p = .003, revealing a significantly increased N1 and N2b for the mismatch condition in comparison to the match condition (Figure 3A, Table 4, and Figure 4). The increased amplitude of the N1 for the mismatch condition did not occur at the cluster peak channel (Figure 3A), but is evident, for example, at channel FCz (Figure 4, left).

The second, third, and fourth clusters occurred in time ranges between 304 and 352 msec, included, respectively,

Figure 4. Participant groups from left to right: healthy control (CTR) and OFC lesion group grand average ERP waveforms at midline electrodes (from top to bottom: Fz, FCz, Cz, Pz). The time range is from −200 to 700 msec. ERPs from match trials are in blue, and ERPs from mismatch trials are in red. Shaded areas around the waveforms represent the calculated SE. Gray shaded bars indicate times when the electrode was part of a cluster showing significant task condition differences for the healthy control group (p ≤ .025). The OFC group showed no significant effect of task condition on ERPs.
The main condition effect of the 2 × 2 tANOVA for the and mismatch trials using dependent tests showed no significant results, indicating that the ERPs of the participants with OFC lesion were similar regardless of whether there was an unexpected action outcome or not (see Figure 4, right). At fronto-central scalp locations, the peak of the P3a and a large part of its descending slope distinguished between action outcomes. The P3a was enhanced and peaked about 40 msec later for tones signaling unexpected compared to expected action outcomes. The control participants also had significant task condition differences in the P3a range at left posterior and midline occipital sites.

It is noteworthy that the topography of the P3a shows a polarity switch in electrodes posterior of and including CPz, which was not reported by Iwanaga and Nittono (2010). This was evident for all participants regardless of group affiliation and over both hemispheres. Although a true polarity switch is difficult to ascertain without performing a source localization analysis, a switch in polarity is suggestive of a low-frequency dipole (Jentzsch & Sommer, 2001). The location of the switch (at CPz, in the vicinity of motor cortices) is suggestive of a motor cortex dipole being responsible. The current experimental task (rapid button presses of both hands) likely invokes a motor source and could produce such a polarity switch. The inversion does not affect the interpretation of the P3a component, because it was consistent and evident across participants.

Following the P3a, unexpected action outcomes additionally evoked a sustained LPP with a parietal distribution in the 600–700 msec time range in the control group (Figure 3E). It was significantly larger to unexpected action outcomes than to expected action outcomes at a right parieto-occipital location. This was supported by the fifth cluster, which encompassed a time range between 676 and 688 msec and one unique channel (P4) with a peak time of 680 msec, \( t(19) = 5.301, p = .021 \). Peak points and channels where the control participants’ ERPs diverged depending on condition was illustrative in that four of the five clusters replicated the original findings of Iwanaga and Nittono (2010). A benefit of using a statistical test like TFCE is that the N1 component, which was not noted by Iwanaga and Nittono, could be clearly identified as a significant portion of the ERP evolution (Figure 4, left). This is in keeping with previous findings (Tomé, Barbosa, Nowak, & Marques-Teixeira, 2015) and with a study that reported an enhanced N1 component for self-generated deviant sounds (Knolle et al., 2015).

For the OFC lesion group, the comparison of match and mismatch trials using dependent \( t \) tests showed no significant results, indicating that the ERPs of the participants with OFC lesion were similar regardless of whether there was an unexpected action outcome or not (see Figure 4, right).

In summary, the within-group analysis revealed that the main condition effect of the \( 2 \times 2 \) tANOVA for the between-group analysis is dominated by the condition effects of the control group. This is visualized in Figure 4, illustrating match and mismatch condition ERPs at four central midline electrodes for the two groups.

**DISCUSSION**

We examined how patients with lesions to the OFC and healthy controls responded to the sensory outcomes of their voluntary actions. Both groups performed the task in a similar manner, except that the OFC patients had difficulty maintaining a steady button press pace, resulting in a higher number of trials rejected primarily because of too short button press intervals. Neither group showed the predicted slowing of button presses after unexpected action outcomes. The overall mixed-design analysis did not reveal significant ERP differences between the groups, indicating that lesion patients as well as controls had differential responses to action outcomes that were incongruent versus congruent with the learned standard action–outcome association. Planned within-group analysis showed, however, that only the healthy group had a significant effect of task condition, suggesting that the result of the omnibus analysis was driven more by the control group than the OFC lesion group. The lack of significant effects between groups in the overall analysis may be because of the high variability of ERPs within the OFC group, but alternatively that OFC damage does not unequivocally disturb processing of action outcomes of the sort studied here. The findings are further discussed with respect to current theoretical accounts of the role of the OFC in action monitoring and in forming cognitive maps of task space.

**Behavioral Results**

The participants engaged in a fairly simple experiment that was a variation of a self-paced two-choice random generation task (Iwanaga & Nittono, 2010). The results showed that some task performance measures were similar across the study groups. Despite no performance feedback, both the patients and the healthy controls kept track of their button presses, as indicated by the approximate equal number of left and right button presses. However, the OFC patients were inferior to controls at producing regularly timed motor acts. OFC patients had difficulty following the task rule requiring a spacing of 1–2 sec between each button press and pressed at a faster rate than controls. Three patients had to be excluded from ERP analysis because they had too many trials rejected because of how close their button presses were to each other. Previous studies have found altered time perception and production in OFC lesion patients. Berlin et al. reported that patients with damage to the OFC stopped sooner than healthy controls when reading numbers aloud, provided that they had been instructed to stop when they thought 90 sec had elapsed (Berlin...
et al., 2004). The patients also estimated that more time had passed during that same interval. These findings were interpreted as reflecting a faster subjective sense of time (Berlin et al., 2004). Aberrant internal timing processes might even partially explain the myopic discounting of future reward associated with OFC damage, leading to problems anticipating the long-term consequences of choices, biasing decisions toward more immediate reward (Peters & D’Esposito, 2016; Sellitto, Ciaramelli, & di Pellegrino, 2010). The increased number of fast button presses observed in our OFC patients may have multiple causes. It may relate to a core deficit in the ability to cognitively quantify the amount of time that has elapsed (Picton et al., 2006), or it may reflect a deficit in executive functioning such as reduced inhibitory control/impulsivity (Berlin et al., 2004). Despite this, our results do not support a problem with general monitoring. While a difficulty with controlling the tempo of button presses was apparent, the monitoring of the equivalent distribution of left and right presses was not impeded.

We also examined whether action outcomes that did not match the learned button press–tone association impacted the interpress interval. Our prediction was that healthy participants would have transient slowing of button presses immediately following an action effect outcome mismatch, that is, post-mismatch slowing (Iwanaga & Nittono, 2010). For OFC lesion patients, we hypothesized that a problem with detecting unexpected outcomes or monitoring action effects would leave button press intervals unaffected. The behavioral data did not support our hypothesis that healthy controls, but not OFC patients, would show post-mismatch slowing. Post-mismatch slowing was neither evident for healthy controls nor for OFC-injured participants. The lack of slowing in the healthy participants could be because of the differences in participants’ ages compared with the Iwanaga and Nittono study. Participants in the latter study were in their 20s (mean age = 21.7 years), whereas our control participants matched in age to OFC patients were older (mean age = 43 years) and had a wider age distribution. It is known that increased age can contribute to changes in information processing speed and executive function. Most studies on post-error slowing reported that slowing occurs in both young and older adults (Pereiro, Bustamante, Cisneros, & Juncos-Rabadán, 2018; Czernochowski, 2014; Ruitenber, Abrahamse, De Kleine, & Verwey, 2014; Dutilh, Forstmann, Vandekerckhove, & Wagenmakers, 2013; Jackson & Balota, 2012; Friedman, NSSler, Cywicz, & Horton, 2009; NSSler, Friedman, Johnson, & Bersick, 2007; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000), with significantly increased post-error slowing in older compared to young participants in some of the studies (Pereiro et al., 2018; Ruitenber et al., 2014; Dutilh et al., 2013; Jackson & Balota, 2012; Friedman et al., 2009; Falkenstein et al., 2000). Based on the aging literature, age may not account for the lack of a post-mismatch button press delay in our study, but, other than age, we are not aware of major differences in our experimental task design and that of Iwanaga and Nittono (2010).

Electrophysiological Results

Although the two conditions of our experimental design did not have a differential impact on the participants at the behavioral level (i.e., no post-mismatch slowing of button presses), the cortical responses were modulated by the manipulation of the sensory outcome of the self-initiated actions as observed in ERPs that differentiated between match and mismatch trials. We replicated the ERP findings of Iwanaga and Nittono (2010) in controls finding an enhanced N2b-P3a complex for mismatched tones. This supports the notion that unexpected self-generated action effects are not ignored even if they are defined as task irrelevant (Adachi, Morikawa, & Nittono, 2007; Waszak & Herwig, 2007; Nittono, 2006). The OFC group showed a less clearly differentiated ERP response to the two types of action outcomes.

Our ERP results are also consistent with those of a study by Knolle et al. (2013) in healthy participants. In that study, unexpected self-generated action effects were assessed using a similar experimental paradigm that required participants to press a button at a regular tempo that occasionally triggered deviant tones. Similar to our results, they reported an enhanced N1, N2b, and P3a effect in response to mismatches (i.e., self-generated tone deviants). They interpreted the enhanced N1 as a reduced suppression effect that occurs when there is a mismatch between expected and actual outcomes (Knolle et al., 2013). The N1 suppression effect occurs for self-generated stimuli and is similar to neuronal processes related to motor-to-sensory predictions. N1 suppression has been repeatedly reported (Lange, 2011; Bää, Jacobsen, & Schröger, 2008) and has been theoretically conceptualized in the internal forward model (Wolpert, 1997). It suggests that, if an action is self-produced, an efference copy of the motor command is generated to predict the sensory consequences of an action, thereby reducing the processing activity related to the expected sensory outcome (Chen et al., 2011). If, in this case, outcome predictions were violated, the processing of this prediction error produced an enhanced N1 (i.e., a reduced N1 suppression effect), in addition to an N2b and P3a, as seen in other studies. Knolle et al. (2013) suggest that N2b and P3a effects indicate the cognitive detection of errors in self-generated deviants, because the N2b has been shown to reflect conscious detection of an infrequent variation of a stimulus (Horváth, Roeber, Bendixen, & Schröger, 2008; Nätäinen, Simpson,
Loveless, 1982), and that the P3a reflects attentional orienting after the detection of an unexpected and infrequent sound (Knolle et al., 2013; Linden, 2005). In line with these studies and our own, a fronto-central N2b-P3a complex after unexpected action outcomes has also been reported in two studies by Wessel et al. (2012, 2014) in the visual domain. In accord with this literature, we propose that the significant N2b and P3a effects in our healthy controls reflect cognitive processes related to the detection of an unexpected action outcome.

This interpretation is in keeping with studies showing how outcomes that violate expectations elicit particularly prominent ERP indices of attentional orienting and action effect monitoring. Variations of the N2 component are seen in diverse types of tasks that involve infrequently occurring deviants (Naätänen, 1992) and have been ascribed different functional roles depending on task demands. This includes the detection of perceptual novelty or mismatch (Folstein & Van Petten, 2008), aspects of action control such as response selection timing (Gajewski, Stoerig, & Falkenstein, 2008), and action monitoring, the latter even in tasks where action outcomes are defined as irrelevant to the task and are not treated as an error (Iwanaga & Nittono, 2010; Ullsperger, Nittono, & von Cramon, 2007). Unexpected action outcomes in our task amplified the N2b and impacted ensuing processing stages reflected in the P3a component peaking around 300 msec.

Two distinct, but related ERP components, P3a and P3b, are often found in response to unexpected deviants. A posterior P3b, elicited by expected task-relevant deviants, is thought to reflect voluntary top–down driven allocation of attentional resources (Polich, 2003; Kok, 2001). An earlier and more anteriorly distributed P3a to unexpected rare or novel stimuli is thought to represent involuntary bottom–up driven reorientation or capture of attention by possibly salient events (Daffner et al., 2000; Knight, 1984, 1991). This fronto P3a component is believed to reflect an evaluative aspect of an orienting response (Polich, 2007; Friedman, Cycowicz, & Gaeta, 2001; Soltani & Knight, 2000; Holdstock & Rugg, 1995), and the posterior P3a component is thought to index categorization processes (Friedman et al., 2001). In our study, the enhanced and delayed P3 both frontocentrally and posteriorly, to unexpected action outcomes, suggest a P3a component, especially because participants were instructed not to pay attention to the tones (Iwanaga & Nittono, 2010, Nittono, 2006). There is also no posterior maximum P3b response to task-relevant deviants, often seen in oddball tasks (e.g., Polich, 2007). This configuration of P3 responses to match versus mismatch outcomes in our study indicates that the two types of action outcomes received unequal attentional resources and depth of evaluative processing. This is further supported by scalp topography. P3s elicited by a mismatch had a predominantly fronto-central scalp topography, whereas match P3s were more evenly distributed over the scalp.

Subsequent to the enhanced P3a, within-group analyses indicated that the healthy control group had an amplified posteriorly distributed LPP (660–700 msec) to unexpected action outcomes. Studies by Nittono et al. suggest that the mismatch between the expected and actual action outcome is also reflected in the LPP, but at a higher, conceptual level of mismatch than the preceding mismatch indices (Adachi et al., 2007; Adachi, Morikawa, & Nittono, 2011; Iwanaga & Nittono, 2010). Debate continues over what composite cognitive processes generate positive slow waves during this late stage of outcome processing. The LPP is associated with working memory processes, cognitive processing following feedback, expectancy-mismatch related processing, and performance evaluation (Hölting, Lubahn, & Mecklinger, 2019; Glazer, Kelley, Pornpanathanangkul, Mittal, & Nusslock, 2018; Pornpanathanangkul & Nusslock, 2015; Garcia-Larrea & Cézanne-Bert, 1998). Regardless of what the exact functional correlates of the series of mismatch-related ERPs are, the results highlight that participants, and particularly the healthy controls, attributed special significance to action outcomes that were incongruent with their expectations and that even simple task-irrelevant tones were assigned outcome value.

Importantly, we hypothesized that if damage to the OFC leads to impaired anticipation, or monitoring of impending action outcomes, then patients would have deviance-related ERPs similar to their expected outcome ERPs. Our hypothesis was not supported by the results of the overall mixed model analyses as the patients did not differ significantly from their healthy counterparts, despite grand average ERP waveforms (Figure 4) giving an impression that the OFC group had ERPs to mismatches that did not differ from those two matches, particularly in the time window encompassing the P3a. The grand means do, however, indicate a degree of differential processing, and the two groups show a similar temporal distribution of waveform amplitudes, including a similarly delayed peak of the P3a to deviant action outcomes. Because of our a priori hypothesis that the neural responses of the OFC patients would not be as sensitive to the experimental manipulation as those of controls, we conducted planned within-group analyses to examine whether either group showed a significant main effect of condition when studied individually. We find it noteworthy that the OFC group showed no significant condition differences in the ERP waveforms that typically distinguish between expected and unexpected effects of self-initiated actions (Wessel et al., 2012, 2014; Knolle et al., 2013; Iwanaga & Nittono, 2010). This suggests that the main effect of condition in our omnibus analysis was driven more by the control group than the OFC group. Because the N1 and the N2b-P3a complex elicited by deviant outcomes in the OFC group did not differ clearly from the response to standard outcomes as seen in controls, this may indicate some impact of processes involved in connecting a chosen action to its outcome.
thereby leading to a weakened prediction error signal when action–outcome contingencies change.

Studies suggest that the OFC is crucial for signaling outcome expectancies and is thought to signal both predicted sensory features and perhaps external cues such as timing or probability, including the current value of expected outcomes. This implies that the OFC maintains a broad representation of all available information (both sensory and unobservable information) that defines the situation or task at hand, potential actions, and their association to probable outcomes (Niv, 2019; Zhou et al., 2019; Rudebeck & Murray, 2014; Schuck, Wilson, & Niv, 2018; Stalnaker et al., 2015; Schoenbaum et al., 2009; Schoenbaum & Roesch, 2005). We suggest that the difficulty of our OFC lesion participants to maintain a steady tempo of button presses, and their lack of strongly differential N2b-P3a responses to unexpected versus expected action outcomes, can be understood within this framework. Our findings provide some support to the contention that an intact OFC is necessary for normal monitoring of behavior when direct environmental cues are absent and only representations of task rules in working memory can be relied on. In our task, the short-term passage of time (i.e., interval timing) is a perceptually unobservable state likely supported by working memory, which keeps track of passing time and modulates choices about when to act (Rubia & Smith, 2004). Based on the findings from previous lesion studies of time perception and production (Picton et al., 2006; Berlin et al., 2004), and our OFC group’s difficulty with maintaining a regular button press tempo, we suggest that an intact OFC plays a role in maintaining temporal information needed to sustain a stable map of task space. This idea has recently been suggested by other authors (Schuck et al., 2018) and implies that a precise map is needed to optimize predictions about the effects of choices and actions and for monitoring and comparing the actual outcomes of actions to what was expected.

Altogether, we found that one aspect of performance related to following task rules is impacted (regular timing of button presses), but not another (equal ratio of left and right button presses) after OFC damage. Moreover, the typical enhancement of ERPs to unpredicted relative to predicted outcomes of self-initiated actions was less pronounced, but not absent in the patients. Recovery of function may have contributed to these results. Patients with extracerebral tumors, such as frontal meningioma, tend to make good recovery after resective surgery (Fountas et al., 2018; Liouta, Koutsarnakis, Liakos, & Stranjalis, 2016; Tucha et al., 2003), although presurgical deficits may persist (Rijnen et al., 2019). All participants in our OFC lesion cohort were in the chronic phase of recovery (at least 2 years post-tumor resection or trauma). This could be the reason why the patients did not show major deficits. The majority of the tumor patients did not have infiltrating intracerebral tumors (n = 2), but had benign tumors, slow growing olfactory meningiomas, that gradually exert increasing pressure and subsequent damage on the OFCs. Although the brain to a large extent returns into its normal shape and position after removal of the tumor, all patients in the current cohort had clear signs of OFC damage on their MRI scans taken at least 2 years postsurgery. An alternative, or complimentary, interpretation of our findings to that of recovery of function is that our experimental task, which places a low demand on controlled attention and working memory, is too easy to profoundly challenge the OFC, or that the neural systems necessary for monitoring the sensory outcomes of simple motor acts do not critically depend on the OFC. The fact that neither healthy controls nor patients exhibited post-mismatch slowing suggests that our experimental manipulation was not strong.

The ability to draw firm conclusions from this study is hampered by limitations related to sample sizes and experimental design. Our omnibus mixed model ANOVA did not confirm that the experimental manipulation pertaining to the sensory effects of self-generated actions (match vs. mismatch) modulated the ERP responses of the OFC lesion group significantly different from those of the control group. The small sample sizes that are typical in studies of rare focal lesions, including this study, may result in inadequate statistical power to detect subtle effects. Our patient sample size was, however, comparable to that of other published pFC lesion studies (e.g., Kam et al., 2018; Solbak et al., 2014; Funderud et al., 2015; Krämer et al., 2015; Voytek et al., 2010; Turk et al., 2008; Ullsperger, von Cramon, & Müller, 2002). Still, studies with modest sample sizes are more likely to be impacted by the larger interindividual differences in neural responses commonly observed in cohorts with neurological disorders (Seghier & Price, 2018) compared to demographically matched healthy control groups. The larger variability in ERP magnitudes in our OFC lesion group relative to the control group that can be seen in Figure 4 might contribute to explaining why the main effect of group and the interaction of group and condition in the mixed model tANOVA did not reach significance. A further limitation of our study could be related to the experimental paradigm as it may not create robust behavioral effects. As noted, neither the healthy control group nor the patient group showed the post-mismatch slowing after unexpected action outcomes that was reported in healthy young participants in the study by Iwanaga and Nittono (2010). An impact of the experimental manipulation was, however, observed in the electrophysiological responses to the deviant tones, supporting the view that breaches of expectation were detected at the brain level.

Conclusions

Using a self-paced, two-choice random generation task devoid of external cues and performance feedback, we broadly replicated the electrophysiological findings of the original study (Iwanaga & Nittono, 2010) in that rare,
unexpected action outcomes evoked a chain of deviance-related ERP deflections in healthy participants. Patients with OFC damage maintained some indication of preserved action-effect processing in their ERPs, but differentiated less clearly between expected and unexpected action outcomes. Although our analyses showed no significant between-group effects, the planned within-group analyses suggested that the condition effect was driven more by the healthy control group than the patient group. However, because the group comparison was not significant, we cannot draw a firm conclusion and this remains to be investigated in future studies. Neither patients nor controls showed post-mismatch slowing. Compared to controls, however, OFC patients had a larger amount of button presses that were faster than required for the task, indicating a difficulty with interval timing.

Altogether, the results support the contention that the OFC is engaged in monitoring behavior with respect to action timing. Based on our within-group analyses, we tentatively suggest that the OFC may also be involved in monitoring of the sensory outcomes of self-paced actions. This is in line with the recently suggested new perspective on the OFC, that is, its involvement in noticing breaches of expectation and updating predictions (Rudebeck & Murray, 2014; Schuck et al., 2016; Wikenheiser & Schoenbaum, 2016). However, further studies with more robust behavioral manipulations are needed to reveal the precise role of the OFC in outcome expectation and monitoring.

Acknowledgments

We are very thankful to all the patients and healthy controls who participated in this study. Professor Per Kristian Hol, Intervention Center at Oslo University Hospital, is acknowledged for his valuable help with clinical evaluation of the MRI scans of patients and healthy controls. We are grateful to Mari Sælid Messel for assistance with data collection and Sara Kruse Nossen for help with preparation of tables, figures, and references.

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Author Contributions

Anne-Kristin Solbakk: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Validation; Writing—Original draft; Writing—Review & editing. James Lubell: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing—Original draft; Writing—Review & editing. Alejandro O. Blenkmann: Conceptualization; Data curation; Investigation; Methodology; Software; Visualization; Writing—Review & editing. Maja Dyhre Foldal: Conceptualization; Data curation; Investigation; Writing—Original draft; Writing—Review & editing. Robert T. Knight: Conceptualization; Funding acquisition; Methodology; Resources; Software; Supervision; Writing—Original draft; Writing—Review & editing. Tor Endestad: Conceptualization; Funding acquisition; Investigation; Methodology; Resources; Supervision; Writing—Review & editing.

Funding Information

This study was supported by a grant from the Research Council of Norway (https://dx.doi.org/10.13039/501100005416) grant number: 240389 to A. K. S., T. E., and T. R. M., the Research Council of Norway through its Centres of Excellence scheme, grant number: 262762 RITMO, and RITPART International Partnerships for RITMO Centres of Excellence, grant number: 274996. R. T. K. was supported through National Institute of Neurological Disorders and Stroke (https://dx.doi.org/10.13039/100000065), grant number: NS21135.

Diversity in Citation Practices

A retrospective analysis of the citations in every article published in this journal from 2010 to 2020 has revealed a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience (JoCN)* during this period were M(an)/M = .408, W(oman)/M = .335, M/W = .108, and W/W = .149, the comparable proportions for the articles that these authorship teams cited were M/M = .579, W/M = .243, M/W = .102, and W/W = .076 (Fulvio et al., *JoCN*, 35:1, pp. 3–7). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article’s gender citation balance.

Ethics Statement

The study involving human participants was reviewed and approved by Regional Committees for Medical Research Ethics, South-East Norway. All participants provided written informed consent to participate in this study.
Data Availability

The ethical approval of the current study does not permit public archiving of the anonymized data sets generated and/or analyzed during the study. Readers can request access to the data sets supporting claims of the study by contacting the corresponding author Anne-Kristin Solbakk (a.k.solbakk@psykologi.uio.no).

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