Nobody Expects the Unexpected

Unexpected Action Effects in Two Cortical Lesion Populations

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For my wife

Abstract

We recruited patients with orbitofrontal lesion (OFC; n = 18), right lateral prefrontal cortex lesion (LPFC; n = 9), and healthy age-matched controls (CTR; n = 22) to perform a self-paced, two-choice random generation task (adopted from Iwanaga & Nittono, 2010). We compared how each set of participants responded to the perceivable consequences of their voluntary actions while recording behavioral responses and electroencephalography (EEG). All participants repeatedly pressed both a left and a right button, but not at the same time. Each button was normatively associated with its own tone, a 1 kHz tone for right button presses and a 2 kHz tone for left button presses. Participants were instructed that their button presses should be random, in a measured manner, without overlap (roughly 1500 ms between presses), and that the tones that their button presses produced were task-irrelevant. After an initial 20 presses, a button press would occasionally produce the tone normatively associated with the other button ($p = 0.132$) and this condition was classified as a cognitive mismatch. The standard condition, when a button press produced its expected tone was classified as a cognitive match. Event-related potentials (ERPs) were extracted from the EEG recording in relation to these two conditions. In CTR participants cognitive mismatch trials elicited enhanced N1, N2, P3, and a late positive potential (LPP) components. The OFC group had an ERP that indicated they did not differentiate between instances of cognitive match and mismatch. The LPFC group had an ERP on cognitive mismatch trials that was not highly differentiated from cognitive match trials, except for a posterior P3a component. Comparisons between and within the different participant groups suggest that action effect outcome monitoring is severely undermined by orbitofrontal damage and is impacted, but not devastated in patients with LPFC lesion. These findings are discussed in relation to the performance monitoring neural network, predictive processing, the cognitive map of a state space, and action effect experimental paradigms in general.

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Introduction

If the job of the human brain at its most basic level is to facilitate survival, then it should enable a smooth interaction with the immediate external environment. If this is the case, then the detection of unexpected events must be a particularly tiresome and time-consuming task for our brains. In a perfectly predictable world, i.e., one without the unexpected, valuable cognitive resources would not be needed to contend with and respond to potentially dangerous unexpected events. Of course, this is not the case and the brain has evolved multiple resources for handling unexpected events.

Within cognitive neuroscience there is a range of different types of task paradigms that have been formulated to pry at the different seams that link the various types of unexpected events. A classic, the oddball paradigm, evokes behavioral and physiological reactions to unexpected events by inserting an occasional odd, hence the moniker, or missing tone into a sequence of expected tones (Debener, Makeig, Delorme, & Engel, 2005). Another style of eliciting unexpected event responses is through the use of a flanker task where a given stimulus is indicative of which button a participant should press; feedback is then provided and this feedback can be of an unexpected variety (Wang et al., 2010). While reactions to unexpected events have been well studied (for a review see: Ullsperger, Fischer, Nigbur, & Endrass, 2014), the types of paradigms are generally thought to impact cognition and behavior in different fashions (Wessel, 2018). Boiled down, the different types of unexpected outcome paradigms typically fall into three categories: error related (through the modulation of feedback), violation related (through the modulation of expectations), and surprise related (through the introduction of entirely new and unrelated stimuli) (Hughes, Desantis, & Waszak, 2013).

There are many ways to create these different types of unexpectedness, but for the purposes of this study we chose a paradigm that was used by Iwanaga & Nittono (2010) where they elicited an unexpected action effect in a unique manner. With only minor alterations we were able to use this paradigm to compare the effect of expected and unexpected action-effects when they were voluntarily elicited and were task-irrelevant. What is unique about this approach is that participants are not *responding* to a stimulus, that is, the participants *chose* which button they pressed. Additionally, participants were explicitly informed prior to beginning that the results of their button presses were of no relevance to the task and should therefore be ignored. This is equivalent to a scenario in which the outcome of an action is neither positive nor negative (i.e., neutral valence), the action itself was unforced (i.e., voluntary), and occasionally the action-effect has unexpected consequences (i.e., an unexpected outcome). A real-world analog might be a situation in which a person reaches out to pick up what they believe is a full container of milk. The initial action to pick up the milk container, which is in reality a quarter full, was designed with the expectation of a full milk container. When the quarter full milk container is lifted up it initially shoots up because the current motor program expected a heavier, full container and applied full container force to the lift. That the milk container is not full is irrelevant to the ultimate goal of adding milk to your coffee (valence), the action was self-initiated (voluntary), and the

weight of the container violated the expectation of a full container. Seemingly specific, this type of interaction with the world is common enough; think of trying to locate items on your desk without looking or believing that there is an extra step at the bottom of a staircase.

The three aspects of action-effect processing that this paradigm invokes are voluntary actions, valence neutral actions, and the violation of expectations. Within EEG research, there are two common approaches used to study the violation of expectation aspect inherent to this paradigm, there is the aforementioned oddball paradigm and also paradigms where violation arrives in the form of feedback (Wessel & Aron, 2017). In these paradigms, when and how a violation of expectation impacts consciousness is different. For an oddball paradigm the violation is immediate and unrelated to any internal (to the subject) reason or action. In feedback paradigms the violation is terminal and might be contingent on prior actions. Despite these temporal and contextual differences, there are arguments that advance the idea that a violation of expectation, regardless of when and how it occurs, is neurologically realized in the same or shared underlying anatomical neural network (Ullsperger et al., 2014; Wessel, 2018; Wessel & Aron, 2017; Wessel, Danielmeier, Morton, & Ullsperger, 2012). This theory of one network being responsible for handling all types of unexpected events arises largely from the performance monitoring (PM) literature (Wessel, 2012). A reduction of this PM theory is that A) all surprising events are unexpected this include errors, novel stimuli, and violations of expectations and B) there is a generic neural network that is dedicated to handling all of these different types of unexpected events (Wessel, 2018). For dissenting views see (Bouret & Sara, 2005; Gorelova, Seamans, & Yang, 2002). The central idea of this PM theory being, that although there may be many different types of unexpectedness, the human brain relies on only one neural network to respond to all of them.

The evidence that PM theories rely on for their interpretation is collated from computational modeling, prototypical event-related brain potential (ERP) responses, and independent component analysis (ICA; Alexander & Brown, 2014; Ullsperger et al., 2014; Wessel et al., 2012). Using ICA and a modified flanker task, Wessel et al. (2012) found that two components of an ERP that was evoked by either an unexpected novel event or an action error were not independent. This was in line with their hypothesis that the two components, an error related negativity (ERN) component and the N2/P3a component complex, are produced by the same neural generator and that unexpected novel events and action errors are treated by the brain as two instances of the same thing. Using event-related functional magnetic resonance imaging (fMRI), the ICA finding of a shared neural generator was tested and the results indicated that the posterior medial frontal cortex (pMFC), including the anterior midcingulate cortex (aMCC), were the most active during the task. The evidence from computational models similarly identifies a more generic network as responsible for responding to all types of unexpected events. Using a computational neural model, Alexander & Brown (2011) demonstrated that a model that treats errors and unexpected novel stimuli as a more general instance of an unexpected event performed better than models that had different methods for handling different types of unexpected events. This same highest performing model also showed that the generic class of unexpected event detection was underpinned by the dorsomedial prefrontal cortex (mPFC) and the aMCC working together to respond to unexpected events. What these findings indicate is that the prototypical

ERP morphologies elicited by unexpected events and errors is actually resultant from one network of cortical sources (See Ullsperger et al., 2014 for a review).

In a tangential stream, brain lesion literature generally supports this unified PM theory, but not without a little back bending. Usually taken as support, is the finding that the P3a (which is associated with rapid orienting, attentional processes, and automatic novelty detection) is reliably undermined in patients with frontal cortex damage (Knight 1984, Polich 2007) and that its sibling P3b component (a strong marker of a corrective action, updates in memory, and volitional target detection) is presumed to be generated by the temporal-parietal junction (Soltani & Knight, 2000; Yamaguchi & Knight, 1991). In contrast, the P3 was shown to be unaffected in subjects that had lesions to the parietal cortex, unlike the patients with lesions in the area of the temporo-parietal junction (Friedman, Cycowicz, & Gaeta, 2001; Knight, 1984). The diminished P3a in frontal lesion patients and the severe impact of temporo-parietal junction lesions on the P3a and P3b, suggest that a variety of neurological sources contribute to the P3a (Polich, 2007), but that the P3a in particular is the most stringently impacted by damage to frontal cortices, especially the dorsolateral prefrontal cortex (Daffner et al., 2000; Yamaguchi & Knight, 1991). Differentiating the debate, but preserving the primacy of the frontal cortices, a study that recorded the ERPs of LPFC and OFC lesion patients during an auditory novelty oddball paradigm found that both groups had a reduction of the P3a response to novel stimuli, an unaffected P3b, and that LPFC patients had an enhanced sustained negative slow wave (NSW) following novel sounds (Løvstad et al., 2012). The authors interpreted the attenuated P3a in both lesion groups as an altered orienting response to unexpected and task-irrelevant novel events, which was a new finding in lesion OFC patients. The finding of an enhanced NSW in LPFC patients for novel sounds in the same study, was understood as a specific to LPFC damage type of prolonged processing of task-irrelevant sounds. This OFC finding stands a bit at odds with another more recent study that showed that patients with lesions to the LPFC (infarctions to the middle cerebral artery) had ERPs that were almost devoid of both the ERN component and the N2/P3a component complex in response to errors and unexpected events (Wessel, Klein, Ott, & Ullsperger, 2014). While the missing P3a was a replication of earlier findings, the authors interpreted the abolished ERN and P3a as support for their hypothesis that perceptual novelty (unexpected event outcomes) and action errors are reliant on the same neuronal network: the prefrontal-cingulate performance-monitoring network (PCMN), without mention of the OFC or the Løvstad et al. (2012) findings.

As was mentioned, the idea and evidence that the neuronal architecture of unexpected outcomes is broadly one and the same, is an attractive and parsimonious model. Ontologically speaking, the existence of one neural network supporting responses to differing manifestations of unexpectedness is especially persuasive from a predictive coding perspective. The predictive coding model maintains that the brain is constantly and actively generating predictions about the "next" stimuli it will encounter (Clark, 2013). A pillar of predictive coding is the "free-energy" principle that asserts that because cognition is not cheap from a biological resource perspective, the brain occupies itself with detecting and minimizing errors in its predictions about incoming and soon to be encountered stimuli (Friston, 2010). Therefore, having a dedicated network that can handle a variety of differing mismatches (i.e., failed predictions) would be biologically cheaper than having a different

network for each different type of possible mismatch. Furthermore, the modality nonspecific nature of the P3a and ERN lend credence to the idea that one generic network is handling all events of the type 'unexpected' (Friedman et al., 2001; Wessel et al., 2014). The ability to synthesize what *is* unexpected, independent of its sensory source, is in keeping with the lesion literature (Knight, Scabini, Woods, & Clayworth, 1989; Yamaguchi & Knight, 1991) and plausibly indicates a frontal top-down signalling that is updating internal predictive models (for a review: Phillips, Clark, & Silverstein, 2015). The arrangement of hierarchical levels of internal predictive models implies that the neurological activity that causes unexpected event responses in the brain, like the P3a, is in turn driven by and driving processes at lower-levels of cognition. Without the requisite healthy frontal cortices this reciprocal unexpected event response relationship is imperiled.

Although the PM theories have so far been presented as theoretically in step with the current task paradigm, PM does not have much of a comment on the coincidence of voluntary action and unexpected outcomes. While there is evidence that damage to the prefrontal cortex is implicated in the inability to orient attention to novel events and plan requisite reactions, the inability to appropriately allocate attention is not necessarily how internal models or their predictions are generated (Daffner et al., 2000). The imperative difference is that how an internally generated model of action and its resulting effects are interpreted provided a violation would, prima facie, seem to be different than responding to or registering the occurrence of an unexpected event. That is not to say that there is not a literature base from which to draw, rather that they are separate (Bubic, Von Cramon, & Schubotz, 2010). Findings based on EEG studies of voluntarily generated actions in healthy individuals has shown that when stimuli are voluntarily produced, the occurrence of a unexpected action enhances the P3a (Nittono, 2006; Waszak & Herwig, 2007). There is also evidence that voluntary actions that are involved in the production of auditory stimuli result in an attenuated N1 (Horváth, 2015). Although Iwanaga & Nittono (2010), the source of this paradigm, contains no discussion of whether the co-occurrence of voluntary actions and their valence neutrality had an unique effect, they did ruminate on the possibility that the late positive potential (LPP) might be an indicator of higher level conceptual processing of expected outcome violation. Potentially, this could be associated with a process that is updating internal models about the predicted outcome of our own actions, but similarly to the original authors we are hesitant to over commit ourselves to this interpretation.

In this current study we investigated the "unexpected" by honing in on which frontal cortical resources could be distinguished as causally liable in unexpected event outcomes with two different lesion populations. The two populations recruited were composed of patients with either lesions to the right lateral or orbital prefrontal cortex (LPFC and OFC, respectively). The logic behind the choice of these two lesion populations is as follows: There exists a relatively well established link between LPFC damage and abolished or severely reduced ERP responses to unexpected events (Friedman et al., 2001; Wessel et al., 2014). There exists a less well established link between OFC damage and abolished or severely reduced ERP responses to unexpected events (Løvstad et al., 2012). There are very few reported studies (Wessel & Aron, 2017) that have tested prefrontal lesion populations while they were engaged in voluntary actions that occasionally produced unexpected event outcomes. Therefore: If there is a unique neurological response to voluntarily made actions

that produce task irrelevant outcomes that occasionally violate expectations, then (provided pre-existing findings from other studies) comparing the ERPs of these two lesion populations will reveal whether frontal cortical resources are relied on during these types of unexpected event detection. Conversely, if PM theories are on the right track and all events of an 'unexpected' flavor are subserved by a generic unexpected event detection network (that is heavily reliant on the LPFC; Wessel 2018), then the LPFC group and not the OFC group will manifest the impaired neurological response expected in these types of situations.

This paradigm, originally developed by Iwanga & Nittono (2010), used only young healthy controls and studied the ERPs of expected and unexpected event outcomes dependent on whether the current stimulus was different on the previous trial. In our analysis, we chose to focus on solely whether the stimulus was expected or unexpected; we treated all expected events as one condition and all unexpected events as another. To insure the validity of such an approach we have included results for the effect of stimulus sequence in our analysis, but they did not pertain to our hypothesis and therefore comment on what we found is limited.

With these measures in hand we tested our hypothesis that patients with lesions to the OFC would not demonstrate a differentiated ERP or have induced motor slowing as a result of encountering a voluntarily induced task-irrelevant unexpected event outcome. This hypothesis draws from findings that damage to the OFC can manifest in reduced sensitivity to action outcomes (O'Callaghan et al., 2018). For the patients with a lesion to the LPFC, we hypothesized that there might be a diminished P3a for unexpected events (as has been shown before, e.g., Knight, 1984), but that the LPFC patients would have an ERP somewhat commensurate with the CTR group. In regards to behavior for the LPFC and CTR group, it was our belief that unexpected events would induce motor slowing for both groups. A less impacted P3a response should be consistent with the induced slowed motor response we expected. Lastly, we believed that we would replicate original findings (Iwanaga & Nittono, 2010) in our control population group, that is, an enhanced N2/P3 component complex and LPP component in response to unexpected- relative to expected event outcomes. In a more general rendering, our hypothesis was that intact frontocortical areas are necessary to register voluntary unattended event outcomes, specifically the OFC with, but not exclusively, LPFC involvement.

Methods

Participants

We recruited a total of 48 participants, 26 of whom where patients recruited from the Department of Neurosurgery at Oslo University Hospital - Rikshospitalet. Eighteen of the participants had MRI-verified focal orbitofrontal lesions because of resection of a primary intracranial tumor or contusion because of traumatic brain injury. Nine of the participants had MRI-verified focal right lateral prefrontal cortex lesions because of resection of a primary intracranial tumor. All patients were in the chronic phase of recovery from brain injury (at least 2 years post-tumor resection or trauma). Twenty-two healthy control participants were matched as closely as possible to the patients for age, sex, and level of

education. Lesion patient details can be seen in Table 1.

Screening of participants excluded any participant who had a history of serious psychiatric disease, drug- or alcohol abuse requiring treatment, premorbid head injury, pre-/comorbid neurological disease, substantial aphasia, visual neglect, or marked sensory impairment. All healthy control participants also received an MRI to ensure inclusion and a neuroradiologist affirmed that their structural MRI images revealed no signs of pathology. Participants gave written informed consent before participating in the study. Healthy controls received 400 NOK (approximately 50 USD) for participation in the entire research program (neuropsychological assessment, EEG, and MRI). The study was performed in accordance with the principles stated in the Declaration of Helsinki. The study and experimental procedures were approved by the Regional Committees for Medical and Health Research Ethics - South-East Norway.

Table 1: Details of included lesion patients. OFC lesion group in blue (n=15). LPFC, right, lesion group in green (n=9).

Patient	Group	Etiology	Age	Sex	Handedness	Laterality	IQ	Comment	Years Since Resction
1	OFC	Oligodendroglioma	39	M	Right	Right	121	F1, frontal pole	5
2	OFC	TBI	27	F	Right	Bilateral	122	Basal Frontal	13
3	OFC	Olfactory meningeoma	56	F	Right	Bilateral	119	Basal Frontal	11
4	OFC	Olfactory meningeoma	46	F	Right	Bilateral	116	Basal Frontal	7
5	OFC	Olfactory meningeoma	59	M	Right	Bilateral	112	Frontal pole bilateral	11
6	OFC	Olfactory meningeoma	56	F	Right	Bilateral	117	Bifrontal basal	11
7	OFC	Olfactory meningeoma	60	F	Right	Bilateral	82	Bifrontal basal	3
8	OFC	Olfactory meningeoma	59	F	Right	Bilateral	104	Bifrontal basal	12
9	OFC	Olfactory meningeoma	61	M	Right	Left	107	Left basal	7
10	OFC	Olfactory meningeoma	50	F	Right	Bilateral	129	Bifrontal basal	5
11	OFC	Olfactory meningeoma	62	M	Right	Bilateral	96	Bifrontal basal	12
12	OFC	Olfactory meningeoma	52	F	Right	Bilateral	97	Bifrontal, largest R	5
13	OFC	Ologo/astrocytoma	28	F	Right	Right	109	Medial frontopolar/frontobasal	2
14	OFC	Olfactory meningeoma	51	M	Right	Bilateral	107	Bifrontal basal	3
15	OFC	TBI	48	M	Right	Bilateral	Unknown	Bifrontal basal	8
16	Lateral	Falx Meningeoma	49	F	Right	Right	110	F1 Posterior	3
17	Lateral	Oligodendroglioma	65	F	Right	Right	108	MFG (46), near IFG	12
18	Lateral	Atypical low grade tumor	37	M	Right	Right	87	Right frontal malformations.	6
19	Lateral	Cavernous Hemangioma	39	M	Right	Right	91	F2	12
20	Lateral	Astrocytoma Grade II	45	F	Right	Right	90	F1	2
21	Lateral	Ganglioglioma	24	F	Right	Right	101	F2 lateral and pituitary adenoma	14
22	Lateral	Ganglioglioma	49	F	Right	Right	129	F2	5
23	Lateral	Cavernous Hemangioma	64	F	Right	Right	122	Small posterior F2	12
24	Lateral	Glioma Grade II	40	M	Right	Right	119	None	2

Demographics

The mean age for all participants was 46.4 years old (STD 13.62 years). The mean age for all lesion participants was 48.6 years (STD 11.84). Mean age for the CTR group was 45.1 years (STD 15.5). Mean age for the OFC group was 50.2 years (STD 10.8) and mean age for the lPFC group was 45.8 years (STD 13 years). Twenty-eight participants were female with a near equivalent amount of female participants for both lesion and control groups (OFC: 60%; LPFC: 66%; CTR: 62%, female). Apart from 1 unconfirmed ambidextrous participant and 1 left handed participant, all others were right-handed (93% right handed). All participants reported normal hearing, and normal acuity or vision corrected by optical lenses.

Lesion Reconstruction

Lesion reconstructions were based on structural MRIs obtained after study inclusion. Lesions were outlined on Fluid Attenuated Inversion Recovery (FLAIR) images for each participant's brain using MRIcron (www.mccauslandcenter.sc.edu/mricro/mricron/). High-resolution T1-weighted images were used to help determine the borders of the lesions. The resulting lesion masks were then transferred to normalized space using the Statistical Parametric Mapping software (SPM: www.fil.ion.ucl.ac.uk/spm/). Each lesion participant's brain was extracted from the T1 image using the FSL BET algorithm (FSL: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL), the extracted brain was masked with drawn lesion and was then normalized to the Montreal Neurological Institute (MNI) template using the SPM unified segmentation and normalization procedures. The transformation was then also applied to the individual participant's T1, FLAIR, and lesion mask images. Lesions were reconstructed under the supervision of a neurosurgeon (TRM). Figures 1 and 2 show the group lesion reconstructions for the OFC and LPFC groups, respectively. There was some overlap of OFC and LPFC lesion areas in the ventral PFC (see supplementary material figure 1 for all lesion reconstructions overlayed on one image).

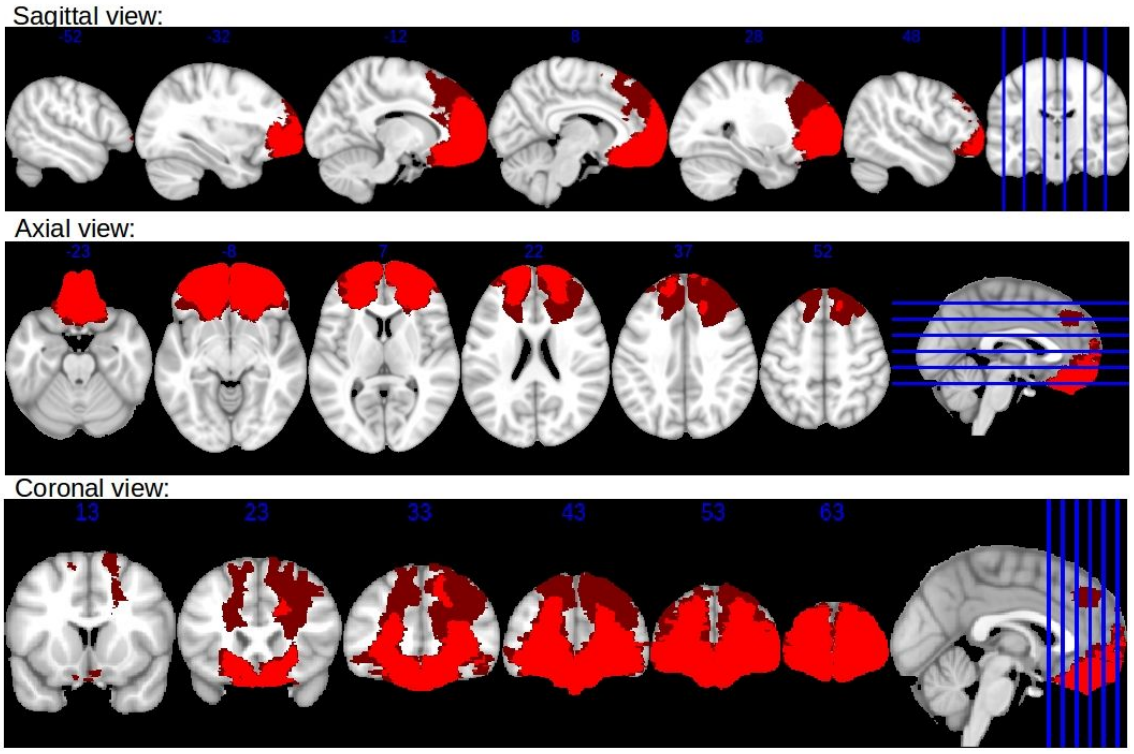

Figure 1: OFC group lesion reconstruction

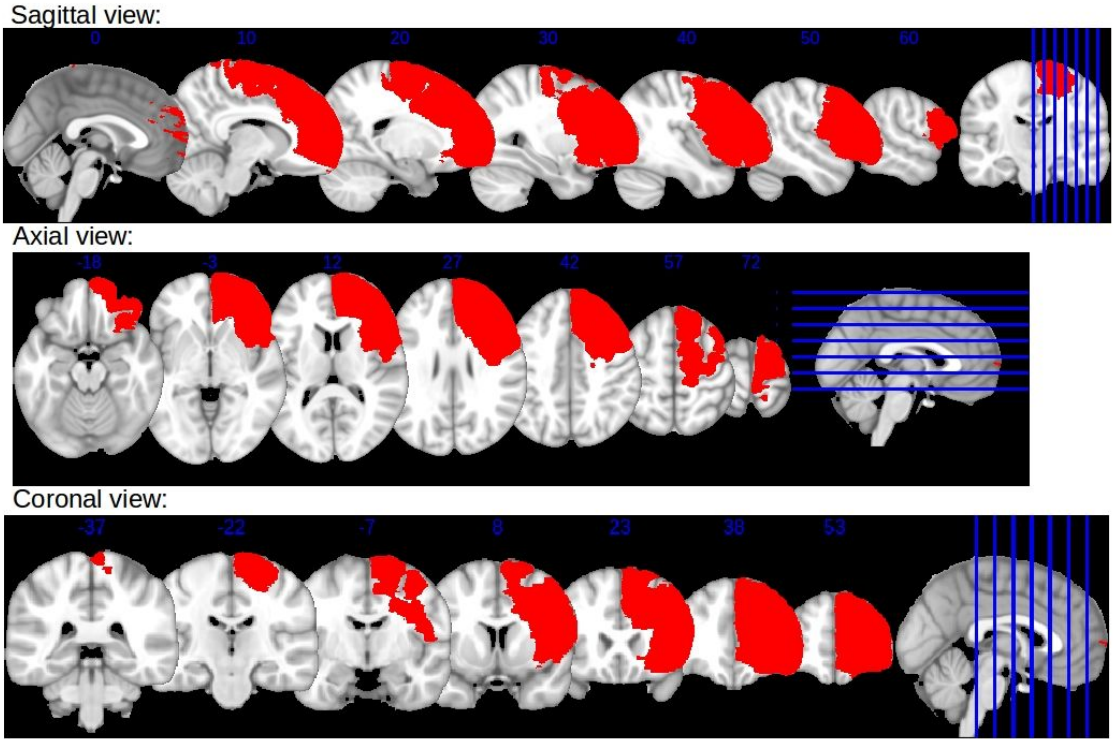

Figure 2: Right LPFC group lesion reconstruction

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 headcap which is constructed in accordance with the International 10–20 system. Two vertical electrooculography (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 offline importation were also placed on the left and right earlobes.

Experimental Design

Participants were instructed to randomly press one of two buttons on a response box using the left and right index fingers. The participants were also told that presses should occur at a regular but self-paced tempo of one press per 1-2 s and that they should press both buttons with approximately equal probability. When participants pressed either the right or left button a 70 ms long 1000-Hz or 2000-Hz tone was played through speakers situated in front of the participants (Figure 3). They were told prior to beginning the experiment that the tones were unrelated to how they were pressing the buttons and that the tones should be ignored.

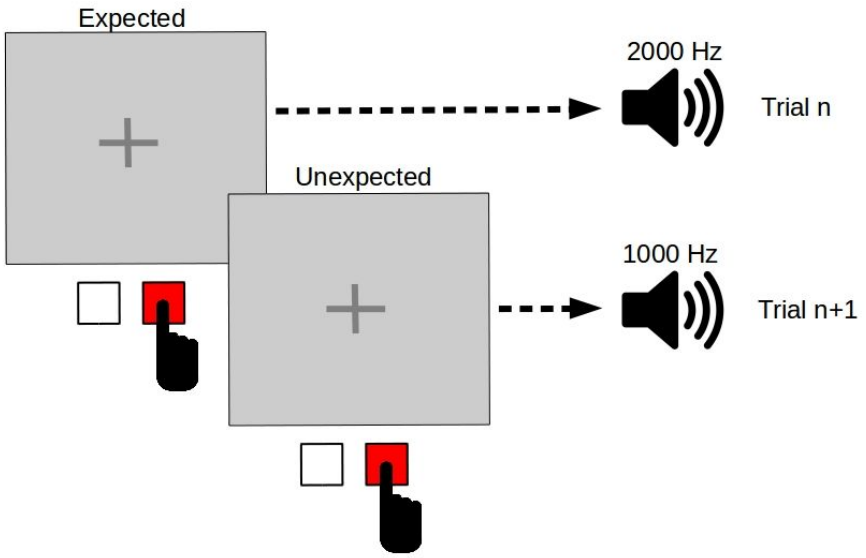

Figure 3: If on a given trial the right button was pressed it would normally produce a 2000 Hz tone, this was an expected event, a cognitive match trial. Whereas if on a given trial the right button was pressed and a 1000 Hz tone was produced, which was typically associated with a left button press, the event was unexpected, a cognitive mismatch trial.

Five blocks were run for each participant and each block consisted of 159 trials. The first twenty trials of each block were designated as a baseline period during which the button-tone combination did not vary and each button press elicited a predetermined tone. In trials following the initial 20 there was an infrequent occurrence ($p = 0.132$) that a button press would produce the tone associated with the other button, which we refer to as cognitive mismatch trials. There were 21 cognitive mismatch trials in each block and two cognitive mismatch trials never occurred in succession. Prior to the beginning of each block a gray circle (3 degrees in diameter) was presented to the participant at a fixed tempo of 200 ms on and 1000 ms off to help establish a regular button press speed. Following the gray circle, participants were presented with a grey cross that they were told to fixate on during the task, which did not change for the remainder of the block.

Data preprocessing

The two conditions analyzed were: cognitive match (CM) and cognitive mismatch (CMM). The CM condition was defined as when the participant pressed either response button and the tone that was played matched their expectations, an expected event 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 the trial was defined as a cognitive match trial. The CMM condition was defined as when the participant pressed either of the response buttons and the tone that was played did not align with what they expected, an unexpected event 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 the trial was defined as a cognitive mismatch trial.

Inherent in the paradigm there are four different experimental conditions. Beside the CM and CMM trials, it would be possible to investigate whether stimulus sequence had an impact. Because our hypothesis did not include a strong a priori notion as to whether the effect of stimulus sequence would be relevant to any particular lesion group, analysis of

stimulus sequence was run in order to insure that an effect of stimulus sequence would not infiltrate and obscure our investigation of CM and CMM. We will comment on the effects of stimulus sequence in the discussion. The results of the stimulus sequence analysis indicated a need to take the mean of the trials that were stimulus repetition and CM (CM and SR) and stimulus change and CM (CM and SC). The same was true for stimulus repetition and CMM (CMM and SR) and stimulus change and CMM (CMM and SC). This more conservative approach was deemed appropriate because if all CM trials were simply treated as one type without considering the effect of stimulus sequence within the trial, stimulus sequence effects became present in the results. To control for this, all CM-SR trials were isolated and all CM-SC trials were isolated per electrode and per participant. The CM-SR and CM-SC trials were then added together and divided by the total number of participants. This is a standard way to study main effects in EEG paradigms (Cohen, 2014; Kirk, 2015; Mensen & Khatami, 2013; Myers, Well, & Jr, 2010).

Preprocessing for behavioral data was relatively straightforward. First, trials were excluded that had a button press interval that was shorter than 700 ms or longer than 2500 ms. Trials were then grouped by condition and the mean button press interval per condition was computed. In order to formulate a normalized value for comparing the button-press intervals, we took an average of the first 20 trials wherein there were no CMM events. The average of the first 20 trials (per block) was then subtracted from the mean button press intervals of the CM and CMM trials per block (Iwanaga & Nittono, 2010). For example patient N performed 5 blocks of 159 trials. First, we took the mean button press interval of the first twenty trials for block one. Second, we took the mean button press interval for CM trials on block one and the mean button press interval for CMM trials on block one. Finally, we subtracted the mean of the first twenty trials from the CM average and subtracted the mean of the first twenty trials from the CMM average. The resulting two values were the normalized CM button press interval for block one and the normalized CMM button press interval for block one. We performed this process for each participant and for each block.

For the preprocessing of the EEG the two conditions, CM and CMM, ERP's were computed at all scalp electrode locations over a total time window of 900 ms. The 200 ms period prior to button presses was defined as a baseline, which was relative to the 700 ms window of interest that followed the button press and contained the auditory event. The latency between the onset of the button press and when the tone was heard was 35 ms (SE 5 ms). In order to avoid overlap between trials, trials where the time between button presses was under 700 ms were eliminated. This reduced the initial number of participants that were eligible for inclusion. Following exclusion on behavioral grounds, EEG data were preprocessed using custom written scripts and EEGLAB functions (Delorme & Makeig, 2004) in MATLAB (Natick Massachusetts). EEG data were originally recorded using an active reference (CMS-DRL) and each data record was re-referenced to linked earlobes during importation into MATLAB. After being imported, data were bandpass filtered from .05 Hz to 35 Hz, down-sampled to 250 Hz, average referenced, and epoched around button presses. Using automated rejection tools and visual inspection individual noisy electrodes were rejected; an average of 3.68 electrodes were rejected from each participant dataset. 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 750 +/- μvolts. Lastly, data was common referenced again to account for removed data segments, baseline corrected (from -200 ms to event onset marker), and rejected electrodes were interpolated.

Exclusion of participants

Although we recruited 18 OFC participants and 22 control participants, we had to exclude 3 OFC and 2 control participants. One of the 2 excluded control participants EEG recording had corrupted event triggers and the data were not recoverable. Of the remaining participants that were excluded, they were excluded because they did not have enough CMM trials after rejecting trials with button presses intervals under 700 ms or over 2500 ms. While it appeared that the control participant did not understand the instructions, all of the OFC patients demonstrated an inability to maintain a regular tempo and sped through the task too quickly. All OFC participants had a higher than control and LPFC trial rejection due to short button press intervals. OFC participants lost 20.4% of all trials as a result of speeding, LPFC participants lost 9.28 % of all trials for this reason, and control participants lost 7% of trials (see Table 3). This is not atypical for OFC patients as they have been shown to have trouble keeping time (Picton, Stuss, Shallice, Alexander, & Gillingham, 2006).

Statistical Analysis

Behavioral data was collected in the form of button press intervals. Because the task was self-paced, there was not a response time to analyze. Rather, we used the amount time between button presses, the interval, as a behavioral measure of task demands. Each patient completed 5 blocks of 159 trials (total of 795 trials for each participant). All behavior results were subjected to either t-tests or repeated measures analysis of variance (rmANOVA).

After the initial preprocessing of EEG data, statistical analyses were performed using nonparametric permutation cluster testing (Maris & Oostenveld, 2007; Mensen & Khatami, 2013). The advantage of using nonparametric cluster-based statistical tests is that they do not require the researcher to limit the number of data points submitted to statistical analysis. Parametric statistical tests typically require an a priori assumption about which sensors and time points will best demonstrate the conditional effect they are investigating (Groppe, Urbach, & Kutas, 2011). Such assumptions are made necessary in virtue of the extremely conservative methods available to control for multiple comparisons in parametric tests, e.g. Bonferroni correction (Cohen, 2014). What a Bonferroni correction for multiple comparisons is controlling for is the family-wise error rate (FWER), the rate at which false discoveries are being made and with an increasing number of comparisons there is an increasing FWER. To handle the increasing FWER, the Bonferroni correction is used and this essentially adjusts the alpha level proportional to the number of comparisons being made. In our study we have epochs composed of 225 samples and 64 electrodes; if we wanted to analyze all data points parametrically a Bonferroni correction would adjust the alpha level to $3.5*10^{-6}$. To escape the conservative Bonferroni correction it is typical to reduce the number of electrodes and time points used during parametric statistical analysis, thereby decreasing the number of comparisons and the severity of the Bonferroni correction (Mensen, 2012). Additionally, a researcher must also accept certain assumptions about their data's homogeneity of variance, sphericity, and normality of all included variables if they wish to use a rmANOVA design. Although this is not the apt venue to delve into the issues that arise from these assumptions and data reductions, the limitations of parametric statistical testing have been implicated in the inability to replicate findings and the inflation of significant results that have risen to the fore in critiques of current psychological research (Bakker & Wicherts, 2011; Ioannidis, 2005; Sterne & Smith, 2001).

Comparatively, nonparametric methods do not require the same strict assumptions about the structure of the data (Ashby & Alfonso-Reese, 1995) and can incorporate as many data points as are computationally viable (Mensen & Khatami, 2013)[1]. Utilizing nonparametric methods and cluster-based statistical tests together, further ameliorates the issues that parametric statistical testing present. Cluster methods as standardized for EEG by Maris & Oostenveld (2007), incorporate the knowledge that activity at one electrode site will naturally be present at adjacent electrode sites (Blair & Karniski, 1993; Maris & Oostenveld, 2007). Taking into account this property of electrophysiology, cluster-based testing groups significant electrode sites if they are 1) defined as neighboring, and 2) above an initial statistic that was computed during the permutation of the data, which is essentially t-values that are representative of the null hypothesis.[2]

Specifically for this dataset, the final corrected statistical values were computed using threshold-free cluster enhancement (TFCE). TFCE was originally validated for use with fMRI datasets and has now been adapted for EEG (Mensen & Khatami, 2013; Smith & Nichols, 2009). The TFCE method is superior to other cluster-based statistical tests because it does not require an assumption about what a reasonable threshold should be for defining cluster inclusion (point 2 in the above paragraph), which eliminates another assumption and brings us closer towards true objectivity. Another benefit is that TFCE is extremely interpretable. The tables and bar graphs that are rather standard in the EEG literature have the unfortunate effect of either (in the former case) requiring a high degree of statistical knowledge to make sensible, or (in the later case) reducing the data to a singular space time point just to visualize an effect. TFCE does not require either of these limiting factors because the full breadth of data being analyzed are available for visualization, which has the desired effect of making the data and their statistical tests more comprehensible in a single glance (Mensen, 2012). TFCE has been independently validated by different research groups, adapted to fit the needs of varying statistical tests, and already is a standard statistical tool within the fMRI community (for EEG specific validation see: Mensen & Khatami, 2013; Pernet, Latinus, Nichols, & Rousselet, 2015).[3]

Results

Behavioral Results

For each participant, the interval between button presses was recorded to determine whether CM or CMM events caused any behavioral effects. The results can be seen in Table 2. There was no significant main effect of either factor on button press intervals or their interaction [Group: $F(2,82) = 0.6854$ $p = 0.5067$, Condition: $F(1,82) = 0.0305$ $p = 0.8619$; Group x Condition: $F(2,42) = 0.0067$ $p = 0.9933$].

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1 Prior to modern GPU and CPUs, permutation testing was a time consuming endeavor. See the introduction and first chapter of Armand Mensen's PhD Thesis: "Valid, Sensitive, and Interpretable: A Novel Approach to EEG Analysis" (2012) for a more in depth and accessible account (Mensen, 2012).

2 This explanation is overly simplistic and only brushes the surface of the underlying processes that are involved in generating this family of statistical tests. I recommend Mensen 2012 for more detail and depth than I can provide here.

3 A search using Google Scholar for "TFCE EEG" returned 374 papers since 2012 that analyzed EEG data using TFCE. Another search for "Threshold-Free Cluster Enhancement" returned 3,060 papers since 2012, which indicates the prevalence of TFCE within the fMRI literature.

When comparing within the groups, no preference for pressing one button in particular emerged, and the occurrence of a CM or CMM trial did not elicit a pattern of participants pressing another button or the same button on the following trial (See Table 2). The mean button press interval for each block can be seen in column four of Table 2, and in column 5 the results of an repeated measures ANOVA can be seen that was run to confirm that no one block of trials was significantly different from any other block.

Table 2: Results of behavioral measures for each group.

	Percentage left button presses (SE)	Percentage same button press following CM (SE)	Percentage same button press following CMM (SE)	Mean press interval after rejecting < 700 ms trials, per block (ms)	Mean press interval F-values per block	t-test results for CM vs CMM	Total rejected trials as a result of button-press interval criteria (700ms>press>2500ms)
OFC	49.6% (0.7)	53% (4.9)	53.8% (5.3)	1045.9	F(4,70) = 0.45 p = 0.7708	t-stat = 0.0986 df = 28 sd = 344.76 p = 0.9221	2424 of 11880 20.4%
				892.1			
				899.2			
				876.5			
				886.6			
LPFC	49.8% (0.9)	42.1% (6.8)	42.6% (6.8)	964.7	F(4,40) = 0.18 p = 0.945	t-stat = 0.2646 df = 16 sd = 156.6 p = 0.795	588 of 6333 9.28%
				891.8			
				934.5			
				849.6			
				852.9			
CTR	48.9% (0.9)	52% (3.0)	53.4% (2.7)	1104.1	F(4,95) = 0.04 p = 0.9967	t-stat = 0.1946 df = 38 sd = 117.05 p = 0.8468	1119 of 15840 7.06%
				1088.5			
				1090			
				1092.4			
				1087.2			

Despite none of the comparisons being significant, we did note that in the normalized plot of the button press intervals it was clear that the behavior was different for controls and OFC patients, despite being statistically insignificant (see Figure 4). Control group behavior was suggestive of post cognitive mismatch slowing instead, which is in keeping with the behavior seen in relation to this task in earlier studies (Iwanaga & Nittono, 2010). Another complicating issue was the rapidity of the OFC group's button presses during the task. Our criteria for trial inclusion automatically rejected numerous OFC trials on the grounds that their button-press intervals were under 700 ms.

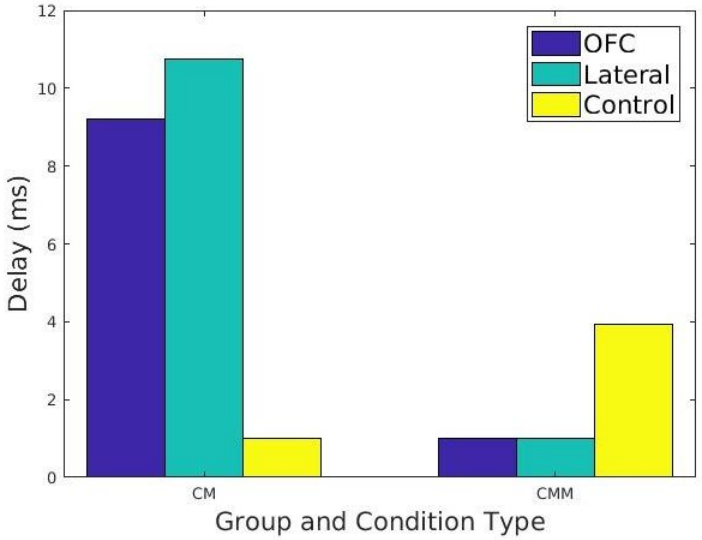

Figure 4: On the left are the three participant groups' mean button press interval for cognitive match (expected outcome) trials and on the right are the mean button press intervals for cognitive mismatch (unexpected outcome) trials. None of the comparisons were significant ($p < .05$).

ERP Results

Between Groups

Because the behavioral results indicated that there was not a significant difference between the three groups in the terms of performance between conditions, we ran analyses to determine whether there was an ERP difference that was unique to one group or widespread. We approached the analysis using a combination of t-tests and ANOVAs and all results reported are corrected for multiple comparisons. Starting with a similar design as was used to assess behavioral results, we used a TFCE ANOVA (henceforth just tANOVA), that allowed us to compare the F-values and p-values at each individual time point (-200 ms to 700 ms) at each individual channel between the three groups.

The first test run was a 3x2 tANOVA. Factor A was condition (Cognitive Match and Cognitive Mismatch), factor B was group (CTR, Lateral, and OFC), and the final factor was the interaction of A and B. The results indicated, similarly to the behavioral results, there was a significant main effect of condition, but the effect of group and the interaction of group and condition (AxB) was not significant. For the effect of condition, five significant clusters emerged, three positive clusters and two negative clusters.[4] As can be seen in figure 5, the significant differences between the conditions are present in the N1 range (100-199 ms), N2 range (200-250 ms), P3 range (270-390 ms), and the LPP range (400-700 ms). Only clusters with a p-value below 0.025 are included for the 3x2 tANOVA.

In temporal order, the first significant cluster spanned 34 channel-sample pairs over 4 unique channels and ranged from 168 ms to 212 ms. The peak significant point occurred at channel TP8, a right temporal-parietal channel at 180 ms ($F(1,42) = 24.9357$, $p = 0.0041$). The second significant cluster spanned 351 channel-sample pairs over 29 unique channels

[4] It can be the case that a two clusters represent the same significant activity, especially if the clusters are disparate produced by a single dipole. For more detail, see section 5.4.1 in Mensen, 2012 and our own discussion in Discussion: ERP Polarity Inversion.

and ranged from 224 ms to 372 ms. The peak value in cluster two occurred at channel FCz, an frontocentral channel at 244 ms ($F(1,42) = 30.3437$, $p = 0.0002$). The third significant cluster spanned 4 channel-sample pairs over 1 unique channel and ranged from 252 ms to 264 ms. The peak significant point occurred at channel P10, a right posterior-occipital channel at 114 ms ($F(1,42) = 24.8742$, $p = 0.0199$). The fourth significant cluster was composed of points spanning 147 channel-time pairs over 15 unique channels and ranged from 304 ms to 392 ms. The peak significant point was found at channel FC3, a left frontolateral channel at 340 ms after the tone onset ($F(1,42) = 31.0686$, $p = 0.0005$). The fifth significant cluster spanned 3 channel-sample pairs over 1 unique channel and ranged from 640 ms to 648 ms. The peak significant point occurred at channel CP6, a right posterior temporal-parietal channel at 644 ms ($F(1,42) = 23.1618$, $p = 0.0266$).

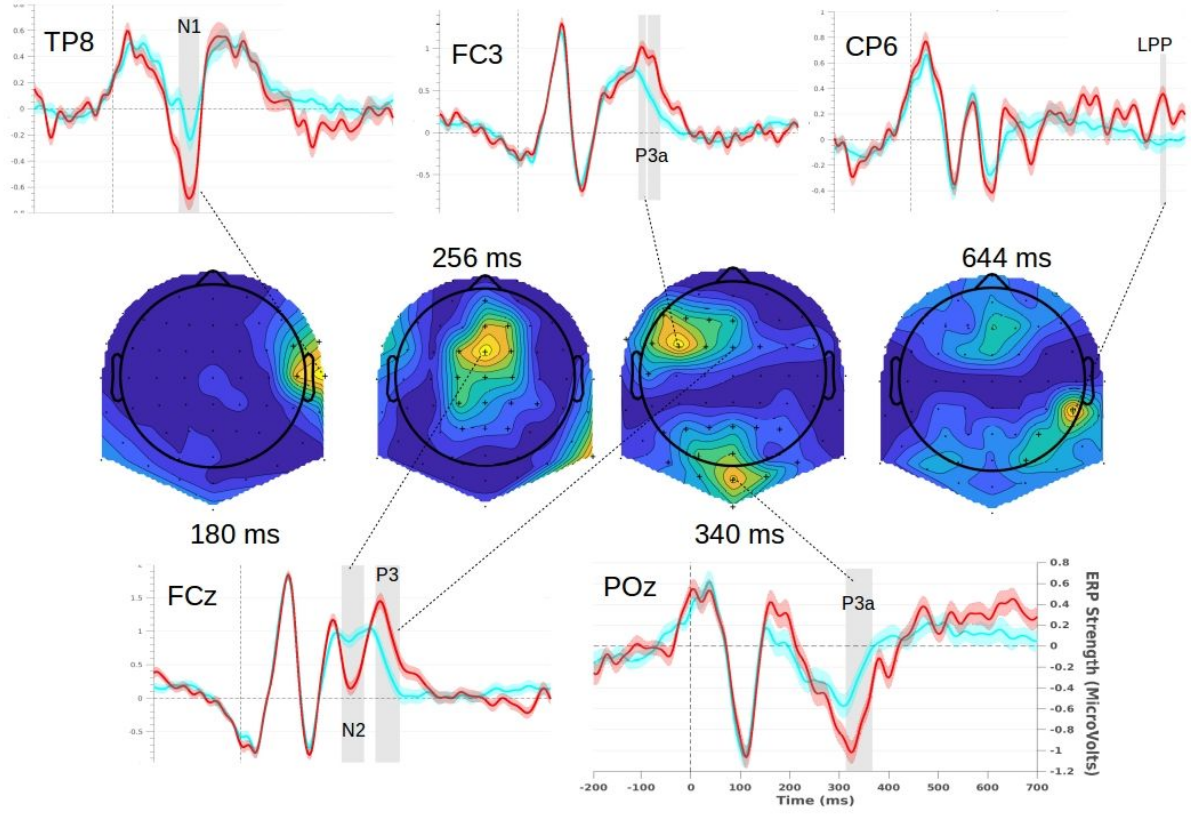

Figure 5: 3x2 tANOVA results. The five significant clusters and the correlated peak channel for each cluster. Topographic plots show the results of the TFCE statistic. The gray shaded areas indicate where there was a significant difference and shaded areas around the ERP waveforms are the calculated standard error. Each ERP ranges from -200 ms before event (tone) and 700 ms after. Significant electrodes are marked with an '+' in the topoplot.

Following these results it was necessary to determine whether these condition effects were true for every group. To assess this we ran a tANOVA to compare each group to each other: CTR and LPFC, CTR and OFC, and LPFC and OFC. All the results indicated a similar significant difference for condition and insignificant results for the effect of group and the interaction of group and condition. Of all of the 2x2 tANOVAs that we ran, it was the comparison of LPFC and OFC that stood out, because they were the least significant (or most insignificant) of all of the tests for the effect of group ($p = .8476$), and for the effect of

condition (p = 0.014). All other comparisons were highly significant for the effect of condition p <= 0.0038, and all comparisons for the effect of group were highly insignificant p >= 0.3750. This indicated that perhaps there was something unique to either the LPFC or OFC group that was skewing the effect of condition unlike the other comparisons. This necessitated using independent t-tests to compare condition by condition and between each group. For each group we compared ERPs on a given condition by submitting the entire epoch for the t-test and then corrected for multiple comparisons using the TFCE method. From these, a significant finding emerged that showed that CTR and OFC participants did not have similar ERPs for the cognitive match condition. Had we had a stronger hypothesis about when effects would be observable, we could have honed in on a specific time window and performed a more classic statistical test, but rather we were obliged to use the entire 900 ms epoch.

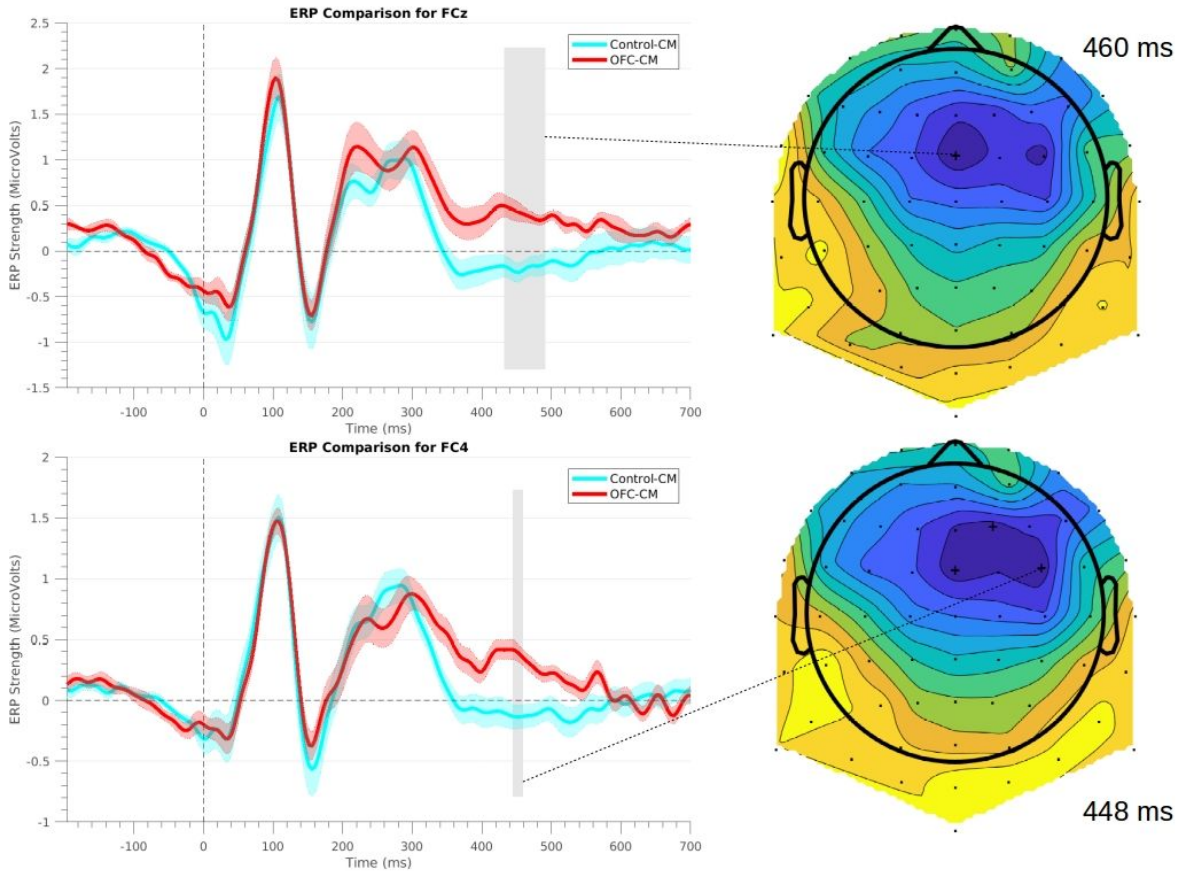

Figure 6: Peak electrodes of significant clusters for independent t-test comparison of CTR cognitive match (blue) and OFC cognitive match (red). Grey shaded bars indicate significant areas and ERP waveform shaded areas are the calculated standard error. Significant electrodes are marked with an '+' in the topoplot. Topoplot shows the TFCE t-test statistic. Note: significant electrodes in the bottom topoplot are members of the top cluster. The bottom cluster was composed of only one unique 1 channel, FC4.

The results of the independent t-test corrected for multiple comparisons using 10,000 permutations for CTR and OFC cognitive match ERPs were two significant clusters within a relatively similar time window. The first significant cluster was composed of 3 channel-sample pairs over 1 unique channel and ranged from 448 ms to 456 ms. The peak

significant point occurred at channel FC4, a right frontocentral lateral channel at 448 ms (T(1) = -4.0406, p = 0.0481). The second significant cluster was composed of 19 channel-sample pairs over 2 unique channels and ranged from 432 ms to 488 ms. The peak significant point occurred at channel FCz, a frontocentral mid-line channel at 460 ms (T(1) = -4.2385, p = 0.0394). These results were indicative of the LPP component and were not evident from the initial tANOVA that was run, which showed a much later (644 ms) significant difference. The ERPs of the peak significant channels are shown in Figure 6.

All tANOVA results for the main effect of condition are visualized in Figure 7. The top row of Figure 7 (A), contains the significant clusters that the 3x2 tANOVA returned and are represented by the gray significance bars in Figure 5. The remaining tANOVA tests (rows B - C Figure 7) were all 2x2 tANOVAs. The comparison of variance for the effect of condition involving CTR and LPFC revealed significant clusters that were similarly in line with the 3x2 ANOVA, no significant value was found for either the main effect of group or the interaction of group and condition. The removal of the OFC group from the comparisons seems to have increased the number of significant samples. Row C in Figure 7 contains the comparison of variance for the effect of condition involving CTR and OFC. With the LPFC group removed, the LPP significant effect disappears and the number of significant samples decreased. The final row, D, in Figure 7 contains the comparison of variance for the effect of condition involving LPFC and OFC. The effect of removing the CTR group from the comparison is dramatic. Without including the CTR group there is no significant finding for samples within the N1 window, the N2 window, or the LPP window.

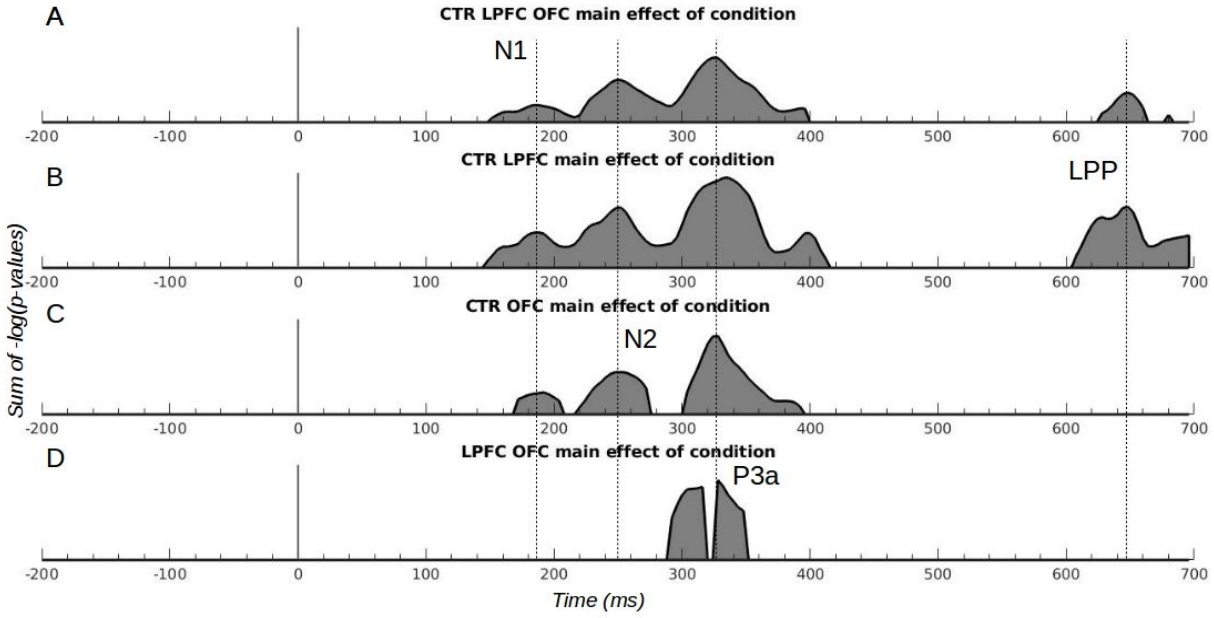

Figure 7: The sum of the -log of the p-values resulting from tANOVAs, specifically significant clusters shown. A line is drawn through all plots through the four most consistent significant clusters that emerged from the tANOVAs and their correlated ERP components noted. No Y-Axis is provided because the sum of -log(p-values) only suffices as convenient way to visualize p-values in a more intelligible way than a 0 to 1 value. All plots are with the main effects Group and Condition. The factor of condition is always constituent of CM and CMM. A) significant clusters of a 3x2 tANOVA. Groups were CTR, OFC, and LPFC. B) significant clusters of a 2x2 tANOVA. Groups were CTR and LPFC. C) significant clusters of a 2x2 tANOVA. Groups were CTR and OFC. D) significant clusters of a 2x2 tANOVA. Groups were LPFC and OFC.

Within Group

Because of the significant difference between CM OFC and CM CTR, we performed follow-up dependent t-tests within each group to compare conditional ERP differences. The resulting three t-tests were informative in relation to how each group's responses varied between themselves for a given condition. All within group t-tests were performed using 10,000 permutations to correct for multiple comparisons using the TFCE method.

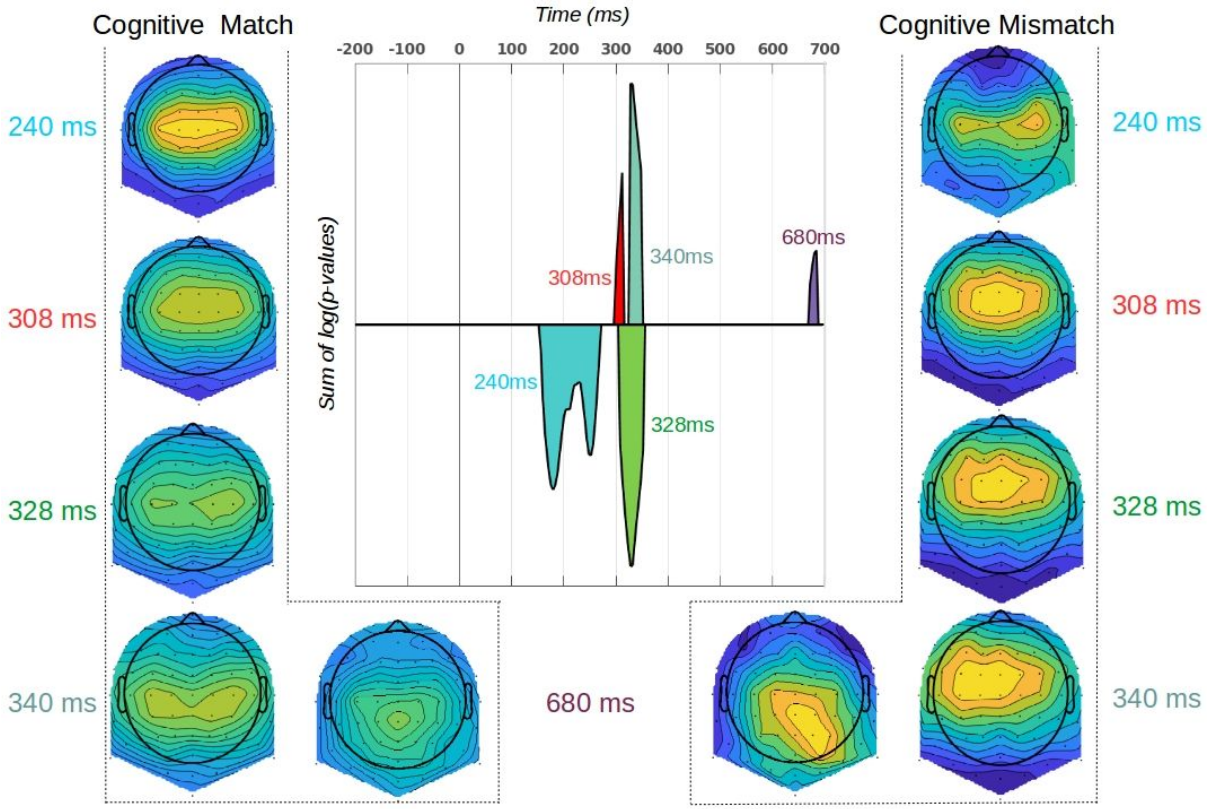

Figure 8: Within group dependent t-test of Controls for Cognitive Match and Mismatch. Scalp EEG topography for Cognitive Match (left side) and Cognitive Mismatch (right side) at the peak significant point for each of the five significant clusters. Center plot: Y-axis is the sum of the log of the p-values for each cluster (the sum of the log of a p-value = 1 is 0 and the log of a p-value = 0.05 is equal to +/- 2.9957. This is essentially a nice way to visually represent p-values). Only the significant p-values that contribute to a cluster are shown. Whether or not a cluster is negative or positive is arbitrary and has no relation to the constituent p-value.

The results from testing the CTR group when comparing their ERPs for CM and CMM, showed that there were five significant clusters where p <= 0.025, see Table 3 for statistical results, and Figure 8 for a visual representation of the significant clusters and the topoplots at those cluster time points, and Figure 9 for the midline electrode FCz ERP plot comparing the two conditions. The peak points and channels where the CTR participants ERPs' diverged depending on condition was illustrative in that four of the five clusters replicated the original findings of (Iwanaga & Nittono, 2010), and added the additional perspective of what was occurring on a more global level rather than the activity that was occurring at the select few electrodes and time windows that were chosen for inclusion in the

original statistical analysis. Exemplary of the benefit of using a statistical test like TFCE is that the N1 component that was not previously noted, was clearly a significant portion of the ERP evolution. This was in keeping with previous findings (Tomé, Barbosa, Nowak, & Marques-Teixeira, 2015).

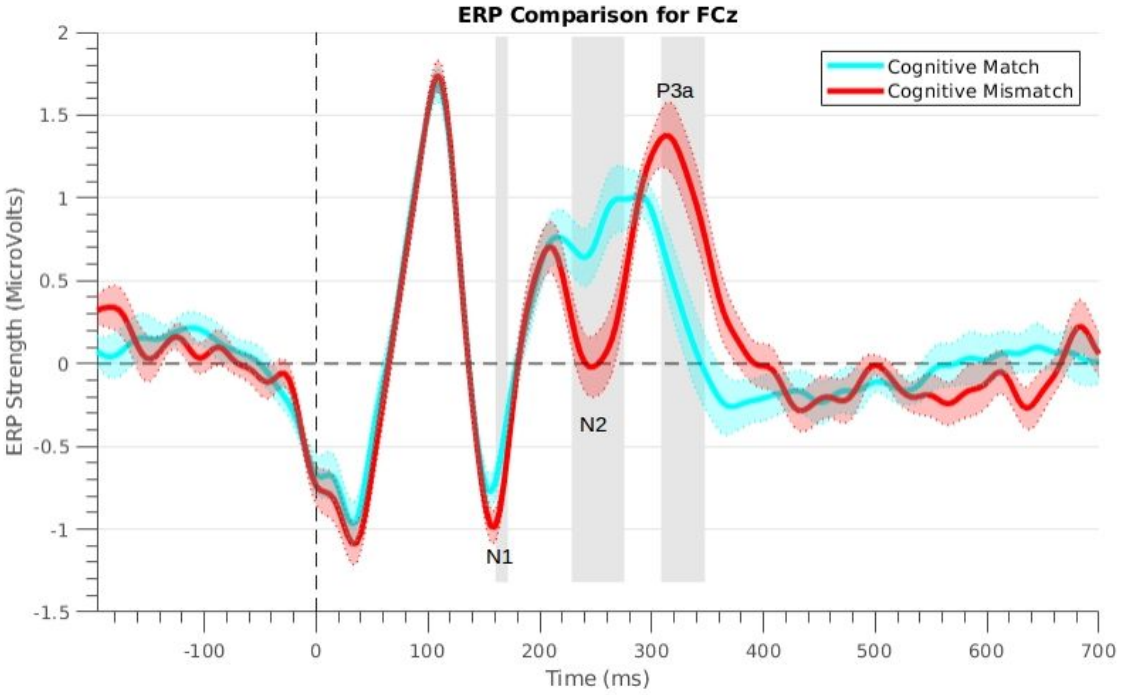

Figure 9: FCz electrode ERPs for Cognitive Match (blue) and Cognitive Mismatch (red) within group dependent t-test for CTR. Shaded areas around the ERP waveforms are the calculated standard error. Shaded gray bars indicate a significant difference between the two conditions. Cluster 1 contributes to the first and second significant period.

For the LPFC group the results of the dependent t-test comparing CM and CMM, highlighted a single significant cluster that was composed of 2 channel-sample pairs over 1 unique channel and ranged from 300 ms to 304 ms. The peak significant point occurred at channel PO8, a right posterior occipital channel at 300 ms ($T(1) = 10.8975$, $p = 0.0192$), see Figure 10. Although just shy of being significant (peak p-value at 0.0535), another cluster was present closer to the midline sites, peak electrode P2, that emerged at 292 ms. This cluster seems to capture the origin of the spread of EEG scalp activity that manifests as a significant cluster 8 ms later at electrode PO8 (see Table 3 for more details).

Table 3: Significant clusters for the CTR and LPFC groups. Dependent t-tests within group comparing CM and CMM conditions, multiple comparisons controlled for using 10,000 permutations. Cells in blue only show significance at trend level $p < 0.05$.

Cluster	Time Range (ms)	Peak Channel	Peak Time (ms)	Cluster Size	Unique Channels	T-Stat T(1) at Peak	P-Value at Peak
1-CTR	160 – 272	FC1	240	208	22	4.7128	0.0021
2-CTR	304 – 316	P5	308	4	1	6.2105	0.0105
3-CTR	312 – 356	FC3	328	58	8	-5.5630	0.0042
4-CTR	332 – 352	Oz	340	12	4	4.3143	0.0214
5-CTR	676 – 668	P4	680	4	1	-5.3013	0.0226
1-LPFC	292-296	P2	292	2	1	7.6648	0.0535
2-LPFC	300-304	PO8	300	3	1	10.8975	0.0192

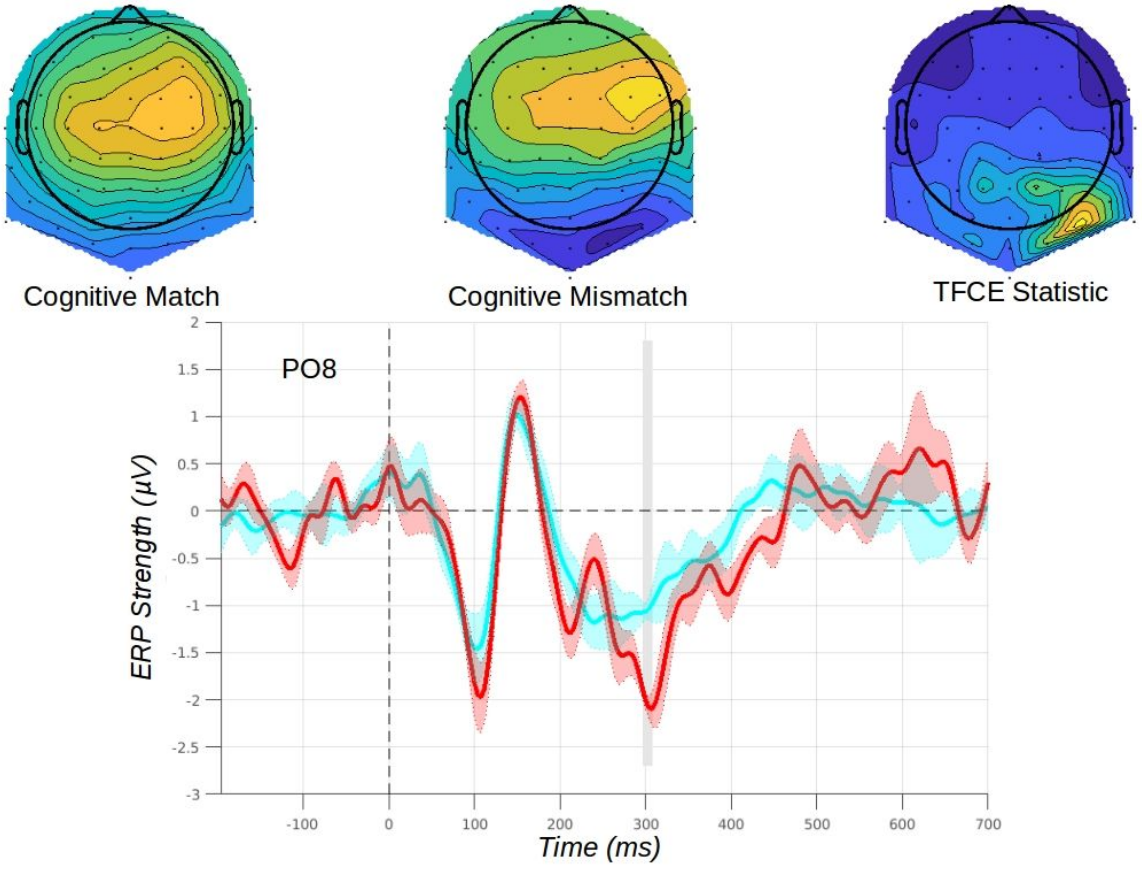

Figure 10: LPFC group dependent t-test result for comparing ERPs of CM and CMM at 300 ms at electrode PO8. Cognitive Match waveform in blue and Cognitive Mismatch waveform in red. Shaded area around the ERP waveforms is the calculated standard error. Gray shaded bar at 300 ms denotes the portion of the ERP that was significant.

For the final comparison of OFC CM and CMM using dependent t-tests, the results were insignificant. This was in keeping with our hypothesis that the OFC participants would not distinguish between the two conditions. The peak significant p-value was .5195 indicating that across the board, the ERPs of the OFC participants were extremely similar regardless of whether there was an unexpected action outcome or not (See Figure 11, left row).

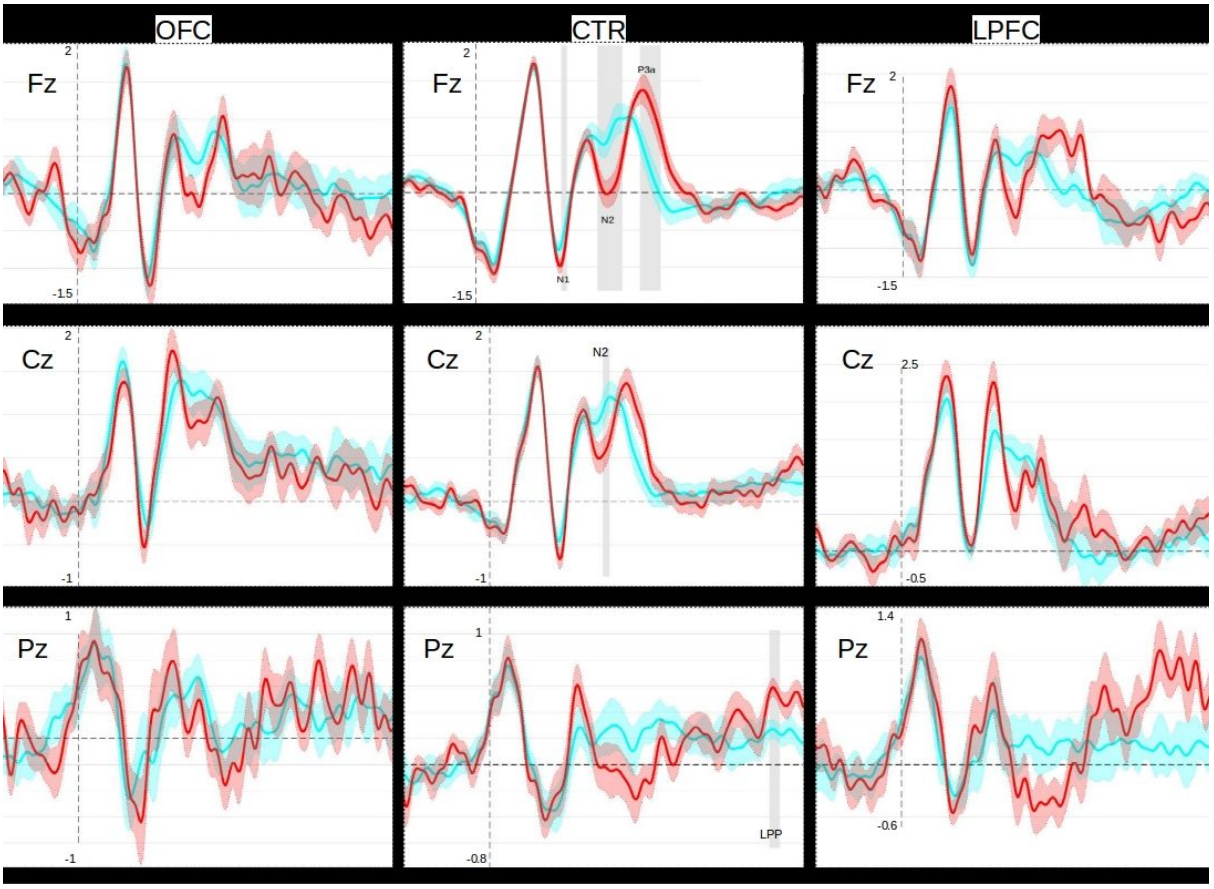

Figure 11: Participant groups (from left to right: OFC, CTR, LPFC) midline electrodes (from top to bottom: Fz, Cz, Pz). Time range is from -200 to 700 ms. Cognitive match trials are in blue and cognitive mismatch trials are in red, shaded areas around waveforms are the calculated standard error. Gray shaded bars indicate times when an electrode was part of a significant cluster ($p < 0.05$).

Stimulus Sequence

For completeness' sake, we also ran identical tests comparing stimulus sequence: tANOVA 3x2, tANOVA 2x2 between each group, independent t-tests, and dependent t-tests. Because tones were either identical to the tone from the previous trial (stimulus repetition; SR) or different from the previous trial (stimulus change; SC), there were an additional two conditions: SC and SR. There was a significant difference for stimulus sequence when compared within group and tANOVAs. Importantly, there was no significant difference for independent t-tests between groups for either SC or SR. The results can be seen in the supplementary materials.

Discussion

The results of our study broadly indicate that the OFC in healthy individuals is active in situations where task-irrelevant unexpected event outcomes resulted from voluntary actions. A similar but less conclusive finding was also true of the LPFC, but damage to the LPFC did not abolish the P3a component to unexpected outcomes. In lesion LPFC patients, the P3a was still present, but at posterior parietal-occipital sites. The age-matched CTR participants demonstrated four significant ERP components that differentiated CM and CMM trials: the N1, N2, P3a, and LPP. Neither the N1, N2 or LPP was present for CMM trials in either lesion group.

The following discussion is broken up into two parts. The first part of the discussion, is a comparison with the source article, Iwanga & Nittono (2010). We will use where our two studies intersect as a means to try and derive what normative processing of CM and CMM trials looks like and we will also comment on the differences that exist between the two studies. In the second part of the discussion, we will summarize what instances of CM and CMM look like for lesion LPFC and OFC patients and transition to a more general discussion of what these findings indicate for the healthy processing of CM and CMM. A few final words will then be offered about future directions.

Differences from the source material

N1 Amplitude and Latency

All components *except* the N1 were found by Iwanga & Nittono (2010), albeit latencies for the components in our study were temporally delayed. The later latencies in our study are most likely attributable to the age of our participants. The effect of age on ERP components has been shown to delay component onset and the mean age in Iwanga & Nittono (2010), was 21.7 years while ours was 46.4 years (STD 13.3; Riis et al., 2009; Wessel, Klein, Ott, & Ullsperger, 2014). The significant N1 component in our results is intriguing and perhaps requires further investigation as to whether it is the result of age or the voluntary actions required by the task. The N1 component observed in our study was only found within the CTR group, had an enhanced amplitude on CMM trials, and had a fronto-central distribution. These type of increase in N1 amplitudes has been seen in other studies that were testing older participant responses to deviant stimuli (Tomé, Barbosa, Nowak, & Marques-Teixeira, 2015) just as there have also been findings that the auditory N1 is attenuated during self-induced tone production (Horváth, 2015). It is known that in an oddball paradigm deviant sounds produce enhanced N1 responses compared to standard sounds (Näätänen, 1990), and studies that combined deviant tones with self-induced tones documented a decrease in the suppressive effect of voluntary actions on the N1 component (Knolle, Schröger, & Kotz, 2013). From a purely visual inspection of the midline sites depicted in Iwanga & Nittono (2010), there does not seem to be any difference between conditions in the N1 window. Whether or not this is the case is hard to determine without access to the original data, but potentially had the full range of electrodes been included and analyzed individually a N1 finding may have emerged. We will revisit the N1 findings in our study in the discussion below.

ERP Baseline Period

A necessary comment is required about the early negative-going potential that is evident in the first 35 ms after the event onset or zero-point in our EEG epochs. Whether this activity is a Bereitschaftspotential or another form of a lateralized readiness potential (LRP), we are unsure (Jahanshahi et al., 1995; Leuthold et al., 1996). When the actual tone became audible, in our task, was reliably delayed by 35 ms after button press. The event marker that was inserted into the EEG record following a button press was used as the zero point for our analysis, but if we were to shift the baseline period forward by 35 ms it would coincide with the peak of this early negative-going potential (See Figure 12). This negative-going potential was not evident in the paper by Iwanga & Nittono (2010). Our interpretation is that it is the result of participants in our implementation of the task using two hands rather than one to press the response box buttons. Because the event marker that was inserted into the EEG recording was contingent on there being a button press, the amplitude increase prior to the event marker is highly indicative of a readiness potential (Masaki, Wild-Wall, Sangals, & Sommer, 2004). We kept our original baseline period of 200 ms rather than shifting it forward 35 ms because this early negative-going potential was not evident at all electrodes, was not always perfectly aligned with 35 ms, and was not always of the same amplitude for CM and CMM conditions. The former point is perhaps the most important because high variation in baseline periods can attenuate or amplify the ERP in varyingly confounding ways during baseline normalization (Luck, 2005). To insure that the region of the ERP that we were interested in (0 - 696 ms), was not artificially influenced we kept the 200 ms baseline period because it was overall more consistent.

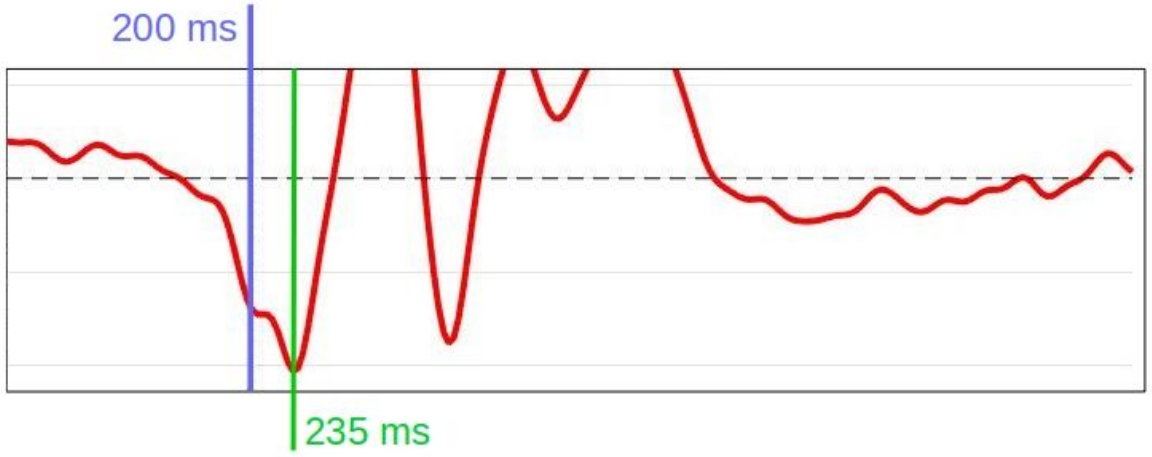

Figure 12: Visualized difference between when the event onset marker was inserted into the EEG record (200 ms) and when the tone was heard by participants (235 ms). Note - the EEG event marker was only inserted into the EEG record following a button press, not before.

ERP Polarity Inversion

Another difference between the source paper data (Iwanaga & Nittono, 2010) and our own was that there was a polarity switch that was visible in electrodes posterior of and including CPz. This was evident for all participants regardless of group over both hemispheres. While the true source of the polarity switch is difficult to ascertain without performing a source localization, a switch in polarity is suggestive of a bipolar source or a strong low frequency dipole being responsible (Jentzsch & Sommer, 2001). Given the

location of where the switch occurs within our group, it is highly probable that the polarity switch is the result of a motor cortex dipole. We arrived at this suggestion solely because of the boundary of the polarity switch (roughly a line running from left to right between central and parietal electrodes), which is typically directly over motor cortices. With a rapid button press task that requires both hands, a motor source is being invoked and could manifest as polarity switch such as we observe. The inversion does not affect ERP interpretation, because it was consistent and evident for all participants (For clear example see Figure 10 center row Cz and Pz differences).

Stimulus Sequence Effects

As was mentioned in the "Methods" and the "Results" sections, there were two additional conditions that could have been possibly studied within this paradigm, stimulus repetition (SR) and stimulus change (SC). By including the SR and SC conditions it is possible to study cognitive match stimulus repetition (CMSR), cognitive match stimulus change (CMSC), cognitive mismatch stimulus repetition (CMMSR), and cognitive mismatch stimulus change (CMMSC). In the source paper by Iwanga & Nittono (2010) these were the conditions that were analyzed. While we did run our own analysis (see supplementary materials), our findings were a bit different. The most important difference being that, using FCz as an example, SR and SC had highly similar ERPs that varied predominantly in amplitude and not shape. It was not later in the epoch (~440 ms) that the SR and SC waveforms diverged (See supplementary materials for plot and more discussion). In the end we concluded that not considering SC and SR would not impact our own analysis and that averaging SC and SR CM trials (same procedure for CMM trials) inhibited the significant amplitude differences from skewing our own analysis.

Current Findings

In this study we have shown that the orbitofrontal cortices are a vital piece of the neurological architecture that enable humans to differentiate unexpected and expected events. This finding is in relation to unexpected events that occur as a result of voluntary actions and when the outcome of an action is valence neutral. Furthermore, we have demonstrated that the right lateral prefrontal cortices are also involved in unexpected event outcome monitoring, but that the right LPFC might not be recruited as heavily as the OFC for this particular type of unexpected event outcome. Behavioral findings were relatively inconclusive.

What can be called normative?

Using the CTR group and the original Iwanga & Nittono (2010) paper as a reference, we are justified in assuming that the healthy brain follows this temporal and topographical profile when faced with valence neutral voluntary unexpected event outcome. The first indicator of a CMM response in the human brain is an N1 component that is amplified in relation to CM responses. It appears topographically strongest at central right electrode sites. Perhaps from a similar source or part of a spreading activation, the next component that emerges is an N2 component that appears topographically strongest at central mid-line sensors. The N2 for CM trials is evident, but is attenuated relative to the CMM N2. The third component that is characteristic of a CMM response is a P3a component that does not last longer than 100 ms and is topographically strongest at left frontocentral sites. The final component of CMM neurological responses is the LPP (late positive potential) which

occurred maximally within our CTR group at 680 ms at left temporoparietal (possibly occipital) sensors; this is best exemplified in Figure 11.

Lesion Patient ERP Responses

With this working profile of CMM responses in the CTR group we first turn to the LPFC group; the only lesion group of the two to have a significant difference between their CM and CMM ERPs. The significant effect for the LPFC participants peaked at 300 ms, which is typically the P3a component window (Soltani & Knight, 2000) and appeared topographically at a unique location on the scalp (parietal occipital right, electrode PO8). There are minimal indications of a N2/P3 complex at mid-line central sites, but in keeping with earlier studies the amplitude is reduced in comparison to the CTR group amplitudes and was not strong enough to rise to significance levels (See Figure 11 center and right rows). What makes our finding of a posterior significant cluster for the LPFC group intriguing is that this cluster is active during the nominal P3a window and the P3a component is *not* typically seen at posterior sites, especially in patients with LPFC lesions (Daffner et al., 2000; Knight, 1984; Løvstad et al., 2012; Wessel et al., 2014; Yamaguchi & Knight, 1991). It has been reported that parietal activity is concurrent with prefrontal cortex activity in tasks placing a heavy demand on cognitive control, and that the parietal activity may possibly be the source of top-down driven signals (Esterman, Chiu, Tamber-Rosenau, & Yantis, 2009; Solbakk & Løvstad, 2014). Perhaps this is that type of parietal activity, which has been undisturbed or amplified in the LPFC participants. This interpretation is possibly supported by similar significant activity on CMM trials within the CTR group at a slightly different latency (328 ms to 344 ms) and at the same electrode. For the CTR group, the cluster that contains this electrode, PO8, is strongest at 308 ms and is located parietally left (peak at electrode P5). The cluster activation that starts over the parietal left region spreads over posterior regions during the next 36 ms and grows to first include adjacent occipital electrodes and eventually begins to recede by the time it reaches electrode PO8 by 344 ms.

Whether the significant cluster of activity present in the LPFC participants is reflective of compensatory activity due to cortical damage is difficult to ascertain. What should be noted is that for LPFC participants CMM trials did elicit a component in the P3 window at a posterior occipital site, and that N2 amplitudes and LPP amplitudes for the same criteria did not reflect the same activity as CTR participants. This result also stands in contrast to other lesion studies using LPFC participants. Wessel et al. 2014 tested novelty and error processing in LPFC lesion participants. Their focus was on ERN and P3a components, with the hypothesis that the LPFC was the cortical source for both of those components. While our LPFC participants had damage to right LPFC cortices, Wessel et al. 2014 had a predominately left LPFC participant group (left LPFC = 8, bilateral LPFC = 1). They found that the P3a component was almost completely abolished in their LPFC lesion group. Importantly, their LPFC lesion cohort had infarctions to the left middle cerebral artery (MCA) while the damage in our LPFC lesion group was more anteriorly located and was not as medial as the MCA. There was a similar behavioral finding that the LPFC patients in their study and our own LPFC patients did not exhibit the unexpected event induced behavioral slowing that CTR groups typically demonstrate. Despite task differences between the studies, our ERP finding of a posterior right significant cluster in the P3 time range does not bode well for their strong claim that all unexpected event outcomes responses solely rely on LPFC cortices. That is not to suggest that the PM theory that one generic neural network is responsible for all types of error, novelty, and unexpected event responses, rather that it

perhaps needs more refinement. This suggestion to refine this theory is given credence and a direction as we turn to the next group, the lesion OFC patients.

Our findings from the OFC lesion group are perhaps the most striking. Not only were they the only group to not have a significant difference between their CM and CMM ERPs, they were also the only group to vary significantly from the CTR group; a confirmation of our hypothesis. The difference that the OFC group had from the CTR group is intriguing because it was on CM trials and late within the epoch (LPP time window) where the effect was found. A difference in the CM ERP indicates that even on the *non*-violation trials the electrophysiological activity of the OFC group is distinct. The LPP component in Iwanga & Nittono (2010) was treated as possibly being an indicator of higher level conceptual processing of expected outcome violation. Adapting that interpretation to the OFC group's CM ERPs is a bit difficult when CM trials have no violation aspect to them. The implication being, that no matter the condition, the OFC patients were treating all event outcomes as requiring a higher level of conceptual processing. The further assumption is that damage to the OFC undermines the ability to appropriately gauge which events do and do not require more conceptual processing and that all events are treated like an unexpected event.

This does not seem to be a very viable conception. A simple refutation would be to point to the OFC group's behavioral results. There was no evidence of the behavioral slowing that is to be expected following an unexpected event, which is more suggestive of the OFC group not even "noticing" unexpected outcomes. Perhaps, if the OFC patients do not "notice" unexpected events, it is possible that they treated all events as expected. This too does not be seem to be very likely. Our results show that the ERPs of the CTR and OFC groups are more similar to each other on CMM trials than on CM trials. If not an indicator of higher level conceptual processing of expected outcome violation (at least for the OFC group), then what is the functional meaning of the LPP?

The remaining possibilities require disentangling the cognitive properties that defined the CM trials: voluntary choice (volitional control) and the valence neutral outcomes (task irrelevant). Starting with the latter, if the late positive potential is valence related, then its enhancement in the CM ERP of the OFC group would suggest the OFC group had a tendency to assign value, emotional or otherwise, to CM and CMM outcomes. Considering that all participants, were explicitly told that the outcomes of their actions were neither positive nor negative, the only possibility in this interpretation would be that the assignment of value was happening on CMM trials. Despite unexpected event outcomes having no positive or negative impact, if the CMM trial was eliciting *any* type of emotional response, then potentially the OFC group was assigning some emotional value to CMM outcomes (supposedly like the CTR) and also to CM outcomes. Damage to the OFC has been previously shown to hamper assessment of event outcomes (Maia TV & McClelland JL, 2004). Subjects with damage to the OFC are more inclined to treat all outcomes as equally positive or negative (i.e., Iowa gambling task, Bechara et al. 1997). Could this possibly be the source of LPP in the OFC group's CM ERP? The answer it seems, again, is no. The suggestion that assignment of value and the inability to do so properly is where the persistent LPP of the OFC group arises is undermined by findings that lesion OFC patients are sensitive to negative outcomes, despite not making the appropriate adjustments to thusly compensate (Fellows LK, Farah MJ., 2005). Because our assumption, in order for this scenario to work, was that the CTR participants were assigning some value to CMM trials and that the OFC participants were assigning that value arbitrarily for both CM and CMM, it would have to be the case that sensitivity to negative or positive outcomes was not a trait of a patient with OFC injury.

Perhaps then, the former possibility, is the LPP that the OFC group demonstrates on CM trials. That is, the persistent LPP is the result of some type of voluntary choice or volitional control processing deficit? Rather than the assignment of value being the manifested deficit, this suggests that the OFC group could be showing an inability to evaluate their own action outcomes. The persistent LPP in both CM and CMM trials for OFC participants would arise from the inability to compare their actions with their action outcomes, in essence an inability to reflect on the effect they are having. This would signal an inability to learn or predict their own action outcomes. For the CTR group, despite being told that their action outcomes were irrelevant to the task, the pattern of CM trials must have been internalized to some extent; otherwise CMM trials would not have been different from CM trials. It would seem that we have circled back to the suggestion of Iwanaga & Nittono (2010) that the LPP in healthy individuals reflected a high level conceptual evaluation of expectation mismatch (e.g., expectation → unexpected outcome = LPP). The only difference being that the reformulation of the LPP in healthy individuals is reflective of comparing a voluntary action with its outcome (e.g., voluntary action → unexpected outcome = LPP). Perhaps there is something special to voluntary actions not having their expected outcome, but a sense of agency or self determination is not undermined in OFC participants (David et al., 2008).

Alas, it would seem that all of the possibilities do not exactly fit the data. The fact that outcome value assignment is not undermined by damage to the OFC knocked down the suggestion that the persistent LPP was indicative of an inability to consider action outcomes as valence neutral. Of the remaining alternative possibilities for the persistent LPP, the suggestions were that either volitional control or expectation mismatch were responsible. The either-or distinction was perhaps a touch fallacious, at their base these two possibilities are likely to reflect a similar ability: to compare events and their outcomes. The ability to compare implies learning and forming predictions about upcoming events. How else would the difference between CM and CMM trials emerge within the CTR ERP? The CTR group learned that the status quo was CM trials. The violation of the predicted CM pattern elicited a whole host of components that were unique to CMM trials, despite being told that outcomes were neither positive nor negative. Although the OFC group had an ERP that did not indicate any significant differentiation between CM and CMM, which would suggest they did not learn what the standard was, the similarity between the OFC group CMM ERP and the CTR group CMM ERP implied that the OFC group treated all events as unexpected. The exception to this was the conflicting OFC group behavioral data that was devoid of the behavioral slowing that suggested they treated all events as unexpected. To resolve this paradox of whether the OFC group is capable of learning and predicting outcomes we can turn to findings that show that OFC damage does not undermine learning or predictive abilities. In a study of the OFC in rodents, it was found that OFC neurons did not signal prediction errors and that at the moment of unexpected reward it was midbrain dopamine neurons that signaled prediction errors (Takahashi et al. 2009). This was supported by other animal studies that similarly found that the OFC is not the source of prediction errors, even in cases of OFC dependent learning (Kennerley et al., 2011; McDannald et al. 2014; Takahashi et al. 2013). So, again, what functions does the LPP represent?

Perhaps the functional significance of the LPP is best explained by a recent theory that the function of the OFC is related to the maintenance of a cognitive map of the current task space (Stalnaker et al. 2015; Sharpe & Schoenbaum, 2016). The theory builds on the idea that a cognitive map is an associative structure that links events and their outcomes. This cognitive map would contain all the details that are necessary for being able to generate

predictions about upcoming events, including prior event properties like identity, context, specific features, temporal qualities, and so on. The building of the cognitive map could not be solely OFC-dependent, such a job is more likely attributable to a network of different cortical sites that could also contain information about event outcome rewards (past and present) or whether performance is being optimized for the current task space . Of note is that these two properties, reward assignment and performance monitoring, have been previously attributed to the OFC (Ostlund & Balleine, 2007; McDannald et al., 2011), but as our above discussion emphasised there is doubt as to whether these are truly OFC independent tasks. Rather, the role of the OFC is exactly that of a map: it represents the different connections and properties of the constituent components of the current task space, complete with a legend and a compass rose. As the components or properties of the current task space become available, the role of the OFC would be to maintain information about how they connect and relate to each other and how the resultant outcomes emerge from those associations (Schuck, et al. 2016).

It seems that this concept of the OFC being responsible for maintaining a cognitive map of the current task space meshes well with our data. To reiterate slightly, both the LPFC and OFC group did not demonstrate any of the behavioral slowing that follows an unexpected event, which is typically found in tasks like our own (Iwanga & Nittono 2010; Wessel & Aron 2017). This observation would seem to speak to a shared deficit in performance monitoring that has been associated with prefrontal cortices in past studies (Daffner et al., 2000). Because the behavioral slowing was absent in both groups, we cannot attribute this to a cognitive map deficit. What can, from the behavioral data, be attributed to a cognitive map deficit is the OFC group's inability to maintain a steady button press interval. Of the three groups tested the OFC group had an inordinate amount of trials rejected because they were below the 700 ms threshold. Attributing PM deficits solely to OFC damage (i.e. cognitive map maintenance) has already been discounted, but the inability to maintain a steady button press interval can be interpreted as resulting from a missing or damaged cognitive map. While the LPFC patients were clearly abiding by the one button press every 1 - 2 seconds rule, the OFC group was unable to. Interestingly, the OFC (and LPFC) group did press both the left and right buttons equivalently, but interpreting an action that already has a 50% likelihood of occurring is difficult.

From the EEG data we have the finding that the OFC group did not cognitively differentiate between expected and unexpected outcomes, whereas the LPFC group did have a significant P3 component to the unexpected tones. This finding is perhaps the most supportive of the theory that the OFC maintains a cognitive map of the current task space. In order to internalize and cognitively recognize that a pattern is emerging of what is to be expected and what is not, would require a working representation of the current task space. Our finding that the OFC group ERPs for CM and CMM trials could not be differentiated, correlates well with the concept of the OFC maintaining a cognitive map. The additional finding that task pattern violation was being identified by the LPFC participants is further support. Whether or not the the persistent LPP component observed in the OFC group could be related to a cognitive map deficit, is harder to definitively ascertain. Perhaps the persistent LPP was a result of other cortical sites attempting to reference or update the OFC. Alternatively, the enhanced LPP activity might reflect an inability to properly inhibit other cortical sources by the damaged OFC. It can be noted that the OFC group's ERP on CM trials was maximally different from the CTR group's CM ERP at frontal central sites and later in the epoch relative to event onset (~480 ms; Figure 6). The CTR group's ERP also had significant LPP activity, but it peaked over right parietal sites, was much later in the

epoch, and was strongest for CMM not CM trials (680 ms; Table 3 - fifth cluster and Figure 8 left side CM trials). This difference of location, time, and condition suggests that the OFC group's LPP activity had a frontal central source, was not an immediate response to event onset, was not as late as the CTR group, and was task independent; a profile that could be suggestive of malfunctioning frontal central cognitive process that would normatively integrate the properties of the most recent task event, that is, the maintenance of a cognitive map.

While we feel a bit overstretched on this interpretation, it does in a preliminary fashion make sense. Of course more testing is required, but given the literature and our findings this interpretation serves as a justifiable placeholder. From what we can tell, integrating the OFC into PM accounts would not be detrimental to the theory that there is one generic neurological response to errors or unexpected events. We are actually surprised that the OFC was not already considered part of the unexpected event response network given that having a cortical site like the OFC being responsible for maintaining a cognitive map works well with the "free-energy" principle (Friston, 2010). Showing that there is a location that acts as a referential node or hub that is centrally situated in relation to other cognitive resources would be a benefit for a hierarchical model. While we are not entirely comfortable with making a strong assertion about what the OFC does, we are comfortable in suggesting that it be given more of a role in future unified theories of unexpected event detection.

Conclusion and Future Directions

We have shown that damage to the OFC limits the brain's ability to properly attend to unexpected event outcomes in situations where actions are voluntarily made and valence neutral. Similarly, right LPFC damage impacts the same cognitive abilities, but the ERPs of the LPFC group still maintains some of telltale signs of the prototypical response to unexpected event outcome. While this finding perhaps tempers the strong claims of the PM theorists that the LPFC is pivotal to attending to unexpected event outcomes (Ullsperger, Fischer, Nigbur, & Endrass, 2014; Wessel, 2018), it does not completely undercut the theory. As was mentioned, we are potentially fond of the idea that one neural network supports broad cases of unexpected event outcomes. This idea is biologically sensible from a predictive coding perspective and seems to be partially corroborated from the present evidence. Given the current findings, either a reformulation of the neural network to include the OFC or a clear reason to differentiate unexpected event outcomes of the type elicited in our task would be required to salvage the strong claim about the LPFC in PM theories. This could be addressed in a variety of ways, but the format that we believe would be the easiest to justify is a new experiment that could differentiate LPFC and OFC activity given unexpected event outcomes. By combining a paradigm that produces an ERN component with a paradigm like our own, one could possibly see if the same neural source supports both unexpected event outcome and error-related outcome responses. The addition LPFC and OFC lesion participants would further clarify if the network that supports the ERP activity seen is local to all frontal cortices or particular to the task.

Although this already is asking a lot of future research, we assume that this is what must be undertaken given the methods available. Intracranial EEG research would be an additional entry point into this debate and perhaps be the best suited to handle these functional connectivity questions. The additional benefit of using intracranial methods would be the ability to assess parietal activity concurrent with an unexpected event outcome, provided that there is such electrode coverage. Similarly, patients with focal parietal lobe

damage could be recruited. This need for a fuller definition of unexpected event outcomes can partially be addressed using alternative methods like intracranial recordings, but in lieu of a patient group with drug-resistant epilepsy TFCE statistical methods offer another way to obtain the richer picture required. By not limiting analysis to mean amplitudes over multiple electrodes or not analyzing all electrodes and contributing time points, EEG research is hampering its own growth. TFCE offers a sensible and justifiable method that offers a possible solution to these qualms. What TFCE can not do is replace the fundamental pieces of the scientific method that uses hypothetical claims that require testing to assess their validity. In closing, we recommend that TFCE sees wider adoption, strong hypothetical claims about the neural network that could possibly support all instances of unexpected event outcomes, and the incorporation of the OFC into these accounts.

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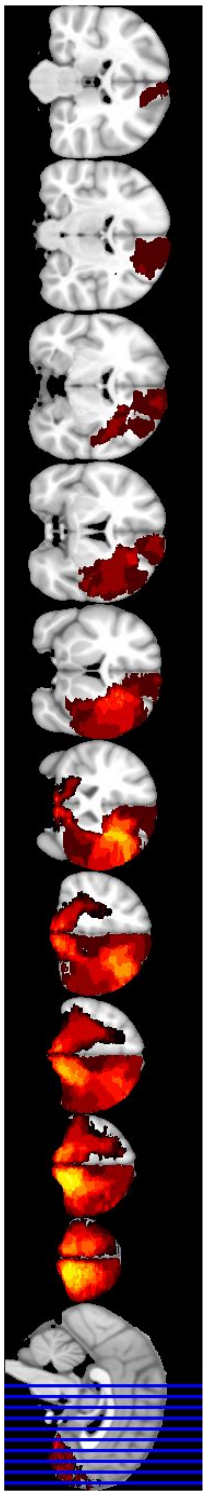
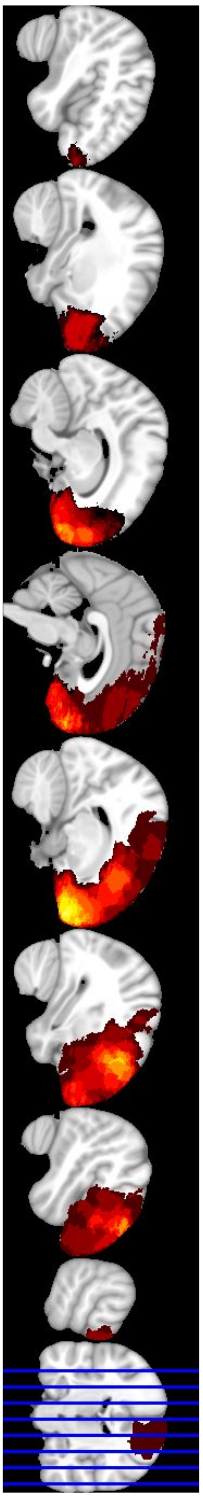
Supplementary Material

All Lesion Groups Overlay

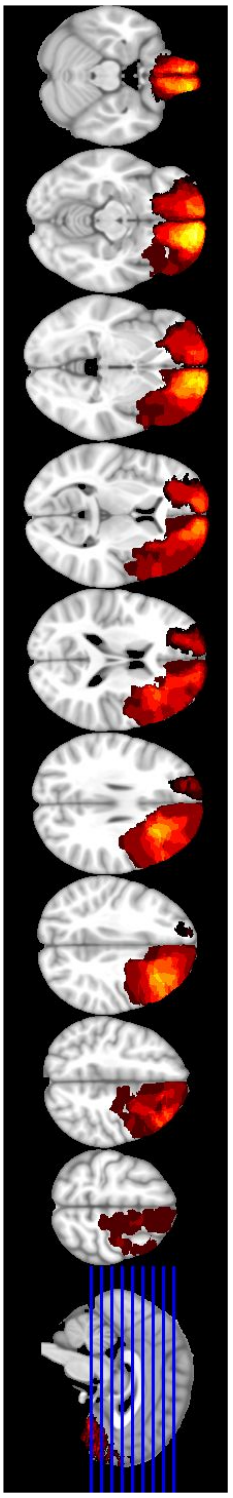
Coronal View:



Sagittal View:

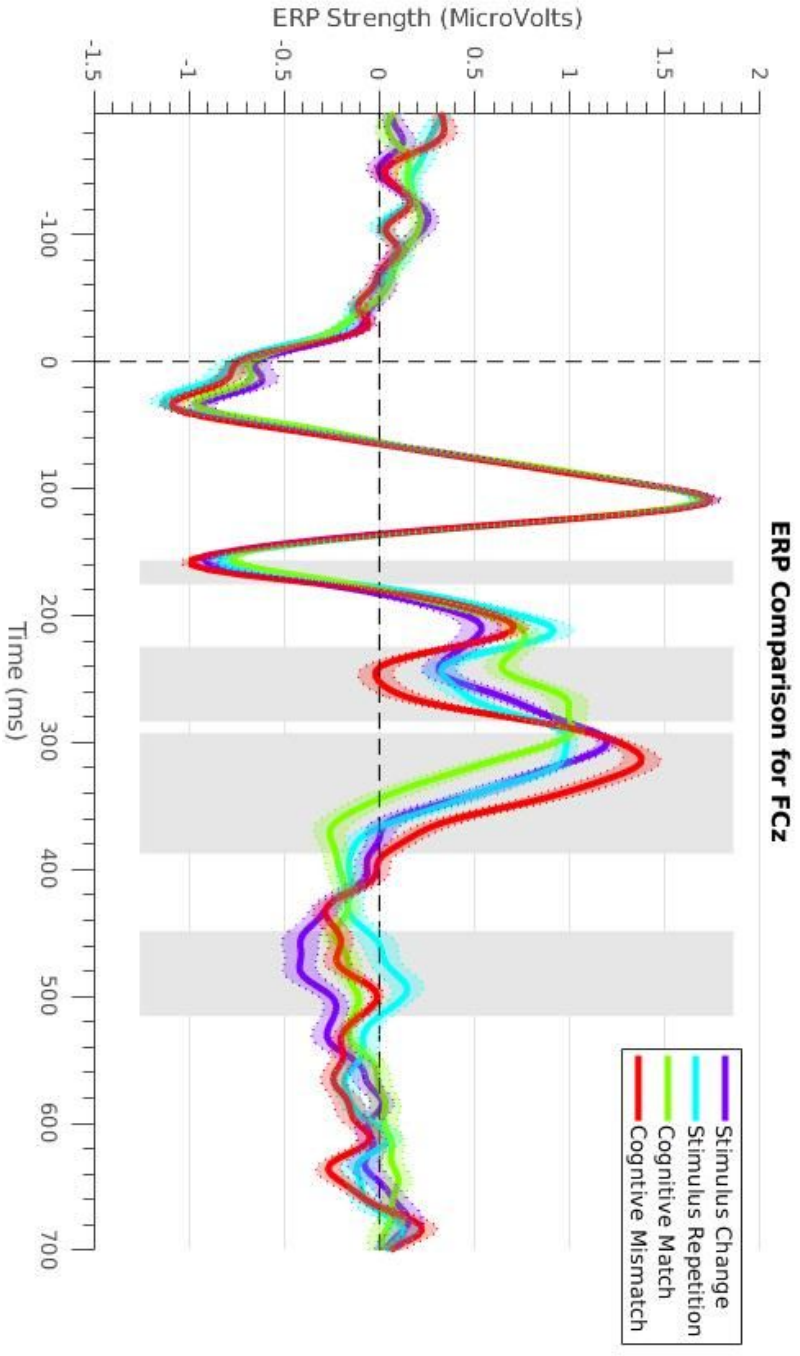


Axial View:



Supplementary Figure 1: All OFC and LPFC lesion maps overlaid on one standard brain MNI image. Intensity is indicative of degree of overlay.

Stimulus Sequence and Unexpected Event Comparison



Supplementary Figure 2: The plots of all CTR participants ERPs for the four possible conditions at electrode FCz. The conditions are: stimulus change (purple), stimulus

repetition (teal), cognitive match (green), cognitive mismatch (red); the shaded color appropriate area around each bar is the adjusted standard error of the within condition difference. The gray bars indicate when the electrode FCz was a member of a significant cluster and for how long. Note the P3a similarity between ERPs for stimulus change and cognitive mismatch and similarly for stimulus repetition and cognitive match P3a.

The original findings of Iwanga & Nittono (2010) for stimulus sequence are as follows. Using a parametric repeated measures ANOVA, the main and interaction effects of stimulus sequence were not significant in the N2 window except in the case of the three-way interaction of (CM vs. CMM) x (SR vs. SC) x (Left vs. Right electrodes). When they tested the simpler interaction of (SR vs. SC) x (Left vs. Right electrodes) for the N2 window (200 - 240 ms) the effect was not significant in cognitive match trials. For the P3 window (270 - 390 ms), stimulus sequence was significant for midline and lateral sites, but their interaction was not. For their last time window of interest, the LPP (400 - 700 ms), stimulus sequence was not significant.

Within our own analysis we found that SR and SC were significant for the CTR group using dependent T-Tests. We also ran a similar a tANOVA to test whether there was a main effect of condition that was significant. For the T-Test, only one significant cluster emerged that peaked at 472 ms at electrode C2 and started at 440 ms and lasted until 524 ms. The two inputs to the T-Test were SR and SC and we used 10,000 permutations to control for multiple comparisons. The results of the tANOVA, essentially a one-way ANOVA, showed that main effect of condition (CM, CMM, SR, and SC) was significant (See Supplementary Figure 2 above and Supplementary Table 5 below). Because the T-Test only revealed one significant cluster that peaked at 472 ms, we could conclude that any significant result extracted from the tANOVA that was prior to 472 ms was attributable to the introduction of the comparison of the CM and CMM conditions. Indeed, there was one cluster prior to this cutoff and it was a large cluster that encompassed the N1, N2, and P3 time windows. This implied that an amplitude and not component difference was the source of the significant difference.

Because we used TFCE to calculate our statistical tests we were able to analyze all channels and all time points, which did not limit us to using one mean value to represent an entire region (e.g., the mean value of all anterior channels or all right hemisphere channels). Our inclination is to attribute the findings of an effect of stimulus sequence to the statistical tests that were used by Iwanga & Nittono (2010). It is telling that post hoc and one-way testing did not reveal the stimulus sequence effects that the ANOVA testing for interactions did. A large selling point of TFCE is that we can visualize and compare the actual data with the statistical tests overlaid on the unadulterated data (Mensen & Khatami, 2013). TFCE is supposed to align with our intuitions about the data and not pop out any new results and in the case of stimulus sequence, this certainly seems to be true. The most interesting aspect of the stimulus sequence conditions for the CTR group was the difference in amplitude strength and the later significant portion of the ERPs, which matches with the LPP component. Because Iwanga & Nittono (2010) did not average the SR and SC conditions there is a potential for sequence effects to infiltrate and perhaps this contributed to their finding a significant effect for stimulus sequence in the P3 window. The inclusion of all trials of a stimulus sequence type, without taking an average of the contributing conditions, could dampen the effect that is contributed by match and mismatch trials and furthermore makes assessing where significance may originate difficult. Another possibility is the age of the

participants, whom in our case where older. It has been shown that P3 amplitude decreases at a rate of 0.18 µV per year (Picton, Stuss, Champagne, & Nelson, 1984). Although we did run the further tests to compare stimulus sequence between the groups, we have already strayed far from what our hypothesis covers and we will have to reserve further interpretation for another experiment.

Cluster Statistics for Stimulus Sequence

Supplementary Tables 1-4: Top table is the dependent t-test results showing only the peak p-value for the TFCE statistical comparison within group of stimulus repetition (SR) and stimulus change (SC); significant results highlighted in mauve. Second from top table is the independent t-test results showing on the peak p-value for the TFCE statistical comparison between groups per condition. Third from the top table contains the results of a tANOVAs with the main factors of Group and Condition; significant results highlighted in mauve and all other values are peak p-value for the effect. Bottom table, results for the main effect of condition from row one of the 3rd table (3x2 tANOVA: Group x Condition, (Control vs. Lateral vs. OFC) x (SR vs. SC)). The four clusters were significant at $p < 0.025$. Note that the clusters three and four are extremely early and clusters one and two are much later in the LPP component time window. Also observe that all clusters peak electrode is located at central sites. All results are controlled for multiple comparisons with 5000 permutations.

Dependent T-Test	SR vs. SC
Control	0.016897
Lateral	0.28604
OFC	0.0061988

Independent T-Test	SR	SC
Control vs. Lateral	0.85383	0.64697
Control vs. OC	0.35883	0.41902
Lateral vs. OFC	0.84463	0.88852

tANOVAs	Group	SR vs. SC	Group x (SR vs. SC)
Control Lateral OFC	0.74156	0.00025	0.26893
Control Lateral	0.73207	0.0876	0.44114
Control OFC	0.37753	0.000125	0.27856
Lateral OFC	0.83967	0.00262	0.5976

Control Lateral OFC	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Peak Channel	C2	C2	C4	C6
Peak Time (ms)	624	504	116	52
F(1,43) =	29.024515323	26.5268062438	30.8245934249	23.6430820773
P-Value at Peak	0.007248188	0.0002499375	0.000499875	0.0217445639
Cluster Size	13	128	206	9
Unique Channels	3	14	14	2
Unique Samples	6	25	33	8
Cluster Start Time (ms)	612	436	100	32
Cluster End Time (ms)	632	532	228	60

Supplementary Table 5: The significant clusters ($p < 0.025$) from a one-way tANOVA comparing CTR participants on all four conditions: CM, CMM, SC, and SR. These are the same clusters as seen at electrode FCz in supplementary figure 2. All results are controlled for multiple comparisons with 2500 permutations. Note the early onset and duration of cluster 4 (starts at 96 ms and ends at 546 ms). Also observe the short duration and late onset for clusters 1, 2, and 3.

Control CM CMM SC SR	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Peak Channel	'P4'	'F3'	'AF4'	'AFz'
Peak Time (ms)	684	652	564	256
F(3,19) =	15.967382631	9.7201738579	5.4450172994	12.6070791754
P-Value at Peak	0.0007993605	0.0247801759	0.048361311	0.0003996803
Cluster Size	62	10	5	2301
Unique Channels	9	2	2	64
Unique Samples	16	6	4	118
Cluster Start Time (ms)	640	640	556	96
Cluster End Time (ms)	700	660	568	564