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Neural mechanisms of mental fatigue elicited by sustained auditory processing

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ABSTRACT

Despite growing evidence that prolonged episodes of effortful listening can lead to mental fatigue, little work has been done to examine the patterns of brain activation associated with listening over time. In order to gain a better understanding of the nature of listening-related mental fatigue, this study characterized the effects of sustained auditory processing on brain activation in 19 adults with normal hearing. A 50-min, auditory choice paradigm served as the fatiguing task. Mental fatigue was quantified using subjective (self-report) and behavioral (response time and accuracy) measures, as well as event-related potential (ERP) measures indexing motivation (error-related negativity; ERN) and general arousal (N1). Additional electrical neuroimaging analyses were carried out on ERP datasets. Subjective and behavioral results confirmed that participants became fatigued during the auditory task (data from the first 25 min compared with the second 25 min). ERPs revealed changes in neural activity consistent with decreased arousal (reduced N1 amplitude). Topographical analyses indicated decreased brain activation, without a change in underlying neural network configuration. Regions of decreased brain activation, as estimated via electrical neuroimaging, suggested a decrease in attention to task stimulus-response characteristics (reduced activation in regions associated with the dorsal attention network). The decrease in mean N1 amplitude revealed a significant, positive correlation with subjective report of reduced motivation. These findings support existing cognitive and neurophysiological models that suggest mental fatigue builds over time on task, and affects motivation to influence task performance. Furthermore, this study shows sustained auditory processing can elicit mental fatigue, and that dorsal parietal activity might provide a useful method of measuring its effects.

1. Introduction

Current usage of the term mental fatigue ranges in meaning from an adaptive process that aids in goal selection (Boksem and Tops, 2008; Hockey, 2013), to a clinically disruptive phenomenon with a central nervous system etiology (Chaudhuri and Behan, 2000; Gay et al., 2016). Mental fatigue has been shown to affect both physical and cognitive performance (Hopstaken et al., 2014; Marcora et al., 2009), and to arise from sustained, demanding activity – either physical or cognitive in nature (Cook et al., 2017; van der Linden et al., 2003; for review see: Hornsby et al., 2016). While definitions vary widely, the present study concerns itself primarily with mental fatigue as an adaptive process, as outlined in the motivation control theory of fatigue proposed by G. Robert Hockey (MCT; Hockey, 1997, 2013). According to the MCT, the function of mental fatigue is to interrupt ongoing behavior to allow for reassessment of existing goals and actions. Fatigue-related task interruption can be accompanied by a variety of psychophysiological phenomena, such as feelings of tiredness, increased distractibility, and decreased motivation to continue task performance. The utility of mental fatigue manifests as protection against excessive commitment to a specific goal, in favor of a more balanced (and beneficial) allocation of effort. For instance, an animal foraging for food in a location with abundant resources needs not expend much effort in finding food; however, as resources in the area become depleted, more foraging effort is required. Because mental fatigue builds under conditions of unfavorable effort/reward ratios, the animal will eventually cease foraging behavior to reassess its environmental options. Attention to cues other than the foraging task might reveal a nearby area with more plentiful resources, whereupon the animal can change locations and improve the return on its effort (Dill, 1983; Kamil and Roitblat, 1985).

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Similar effort/reward scenarios involving more complex, goal-directed behavior have also been described in humans (e.g., Boksem and Tops, 2008; Hockey, 1997; Kool and Botvinick, 2014; Kurzban, 2016). For instance, Kool and Botvinick (2014) showed that cognitive effort serves as a perceived cost, while cognitive rest provides reward. Consistent with this view, performing a listening task in the presence of background noise has been shown to increase cognitive effort (perceived cost) in participants with normal hearing and hearing loss (Picou et al., 2017; Picou and Ricketts, 2014). Correspondingly, a growing body of literature suggests that sustained listening under a variety of adverse listening conditions (e.g., in noise, degraded stimuli, hearing impairment) can also lead to mental fatigue (e.g., Key et al., 2017; Alhanbali et al., 2017; Bess and Hornsby, 2014; Gellerstedt and Danermark, 2004; Hétu et al., 1988; Hornsby, 2013; Kramer et al., 2006). For instance, Antons et al. (2012) found that 20 min of listening to degraded audio resulted in greater mental fatigue than listening to intact audio for the same duration. Specifically, the alpha band activity (8–10 Hz) of the electroencephalogram (EEG) was greater during the last 10 min of listening, compared with the first 10 min. Alpha activity has been shown to be inversely related to cognitive processing and to increase with development of mental fatigue (e.g., Adrian and Matthews, 1934; Craig et al., 2012; Rowland et al., 1985). Antons et al. (2012) also found higher self-report of mental fatigue after listening to degraded audio compared with intact audio, supporting the interpretation of their electrophysiological results. Key et al. (2017) showed that children became fatigued after engaging in two hours of demanding speech-processing tasks presented in background noise. Fatigue was quantified subjectively (increased self-report), behaviorally (slowed visual response times over task duration), and physiologically (decreased attentional processing). Attentional processing was indexed by the P3b component of the event-related potential (ERP), which revealed a smaller amplitude at the end of the fatiguing task compared with the beginning of the task (for review of the P3 see Polich, 2007). Yet, despite the mounting evidence of listening-related mental fatigue, little work has been done to investigate the changes in brain activation during sustained, effortful listening.

Much of the available information about the neural mechanisms associated with mental fatigue comes from studies of clinically disruptive states, such as those experienced by patients with chronic fatigue syndrome (CFS). Chaudhuri and Behan (2000, 2004) attribute mental fatigue in this population to a disruption of the motivational processes supported by the striato-thalamo-cortical loop. They argue that a decrease in dopaminergic drive to the association loop of the basal ganglia leads to a loss of the motivational signal otherwise provided to the frontal lobes to guide behavior. Consistent with this mechanism, anatomical tracing studies have established dopaminergic projections between limbic structures and the ventral striatum, describing the interconnectivity as the point of synthesis for motivation and action (e.g., Haber et al., 1990; Mogenson et al., 1980).

Recently, Gay et al. (2016) reported that in adults with CFS, subjective reports of fatigue correlated with decreased functional connectivity between the salience network (SN) and the default mode network (DMN) during resting state (see also Boissoneault et al., 2016; Wortinger et al., 2016). The SN, comprised of the insula and anterior cingulate cortex (ACC), is thought to identify behaviorally relevant stimuli and allocate processing resources (Menon and Uddin, 2010; Uddin, 2015). The DMN is a neural network associated with self-referential thought (e.g., envisioning the future), and shows deactivation during externally-focused, goal-directed behavior (Buckner and Carroll, 2007; Raichle et al., 2001). In short, the SN acts as a switch to deactivate the internally-focused DMN in order to engage networks associated with task-relevant, outwardly-focused behavior (Uddin, 2015). The decreased functional connectivity between the SN and DMN associated with fatigue may lead to persistent DMN activation and the inability to direct cognition to an external task. Kool and Botvinick (2014) suggest DMN activation might signal engagement in temporary reward behavior (i.e., rest) during prolonged task performance, consistent with MCT predictions of increased distractedness and allocation of cognitive resources away from a fatiguing task over time.

It seems reasonable that brain regions comprising the SN and DMN might also play a role in mental fatigue elicited in typical adults. For example, Boksem and Tops (2008) proposed a neurophysiological model of elicited mental fatigue that also implicates ventral striatum dopamine as providing the motivational signal to carry out an action. They suggest the ACC modulates striatal dopamine and thus motivational control of behavior (e.g., Cohen et al., 2000; Paus, 2001; Weissman et al., 2006). Consistent with these findings, Hockey (2013) speculated the neural substrate subserving the ongoing cost/benefit analysis during task performance is the ACC; specifically via its roles in performance evaluation and effort recruitment (Botvinick, 2007; van Veen et al., 2001). Thus from psychological and neurophysiological standpoints, the ACC is a prime candidate for studying elicited mental fatigue within the framework of the MCT.

As a non-invasive method of quantifying changes in brain activity, ERPs can provide an indirect window into ACC activation patterns and serve as an index of its associated cognitive processes. For instance, the ERN is a response-locked ERP that appears as a negative deflection over frontomedial sites following error commission (Falkenstein et al., 1991; Gehring et al., 1990), and dipole source estimation studies consistently identify the ACC as a likely neural generator of the ERN (e.g., Dehaene et al., 1994; Holroyd et al., 1998; van Veen and Carter, 2002). Lorist et al. (2005) showed a reduction in ERN amplitude elicited by 2 h of flanker task performance. Reduced ERN amplitude over time was interpreted as signaling reduced performance monitoring (i.e., reduced ACC activity). Consistent with ERN findings, post-error slowing, a behavioral index of response preparation, indicated impaired strategic adjustments following error commission, confirming impaired performance monitoring (see also Themanson et al., 2012). Boksem et al. (2006) also showed that ERN amplitude decreased with time on task, and that ERN amplitude increased with subsequent re-motivation immediately following 2 h of task performance. The initial decline in ERN amplitude is consistent with funneling cognitive resources away from a task with an unfavorable cost/benefit ratio (e.g., brought about by prolonged time on task), and is also consistent with resources being reallocated when the cost/benefit ratio was improved by increasing participant motivation (e.g., increased financial reward for task performance). Due to the proposed central role of the ACC in mental fatigue, and the evidence establishing the ERN as an index of its activation, this study used ERN amplitude as one neurophysiological measure of mental fatigue.

Mental fatigue is also associated with decreased attention, withdrawal of cognitive resources from a task, and engaging in “mind-wandering” type thought. Therefore, this study also investigated mental fatigue by indexing changes in attention and arousal using the auditory N1. The N1 has been shown to consist of overlapping components, proposed to originate from several neural sources that subserve different functions (e.g., Giard et al., 1994; Näätänen and Picton, 1987). In their extensive review, Näätänen and Picton (1987) demonstrate that the N1 indexes general arousal as well as signals a non-specific call for attention. For instance, Escera et al. (2003) asked participants to classify visual stimuli occurring 300 ms after presentation of irrelevant auditory stimuli. Auditory stimuli consisted of pure tones (80%) and complex sounds that were either unidentifiable noise bursts or recognizable, environmental sounds (20%). The results showed identical N1 enhancement in response to both the identifiable and unidentifiable types of novel sounds, acting as a general trigger for attention based on detection, while P3 amplitude increased only to identifiable novel sounds (orientation of attention).

Corbetta and Shulman (2002) describe two distinct attentional networks, one involved in preparation and goal-directed stimulus/response selection (the dorsal network), and one that does not involve top-down selection that is specialized for stimuli that are unexpected or salient (the ventral network). They suggest interaction between the two systems allows for orienting and attending to behaviorally relevant stimuli. Because mental fatigue affects central processing, and the dorsal attention network engages top-down selection, it is worthwhile to include a component of the ERP sensitive to attention. Thus, while the ERN indexes a cortical region thought to be involved in behavioral monitoring and allocation of cognitive resources, the N1 is associated with orienting attention towards task stimuli as well as general arousal; processes potentially affected by ACC signaling. The present study therefore recorded two ERP components thought to index two different levels of cognition affected by mental fatigue. Importantly, this study complimented the hypothesis-driven findings obtained from traditional ERP measures with data-driven microstate and neuroimaging methods that permitted estimation of specific neural generators (described in Section 2.8).

In summary, the purpose of this study was to characterize changes in brain activation associated with mental fatigue elicited by sustained auditory processing in adults with normal hearing. We investigated mental fatigue within the framework of the MCT by (1) using subjective questionnaires to quantify perceived fatigue, (2) tracking behavioral performance using measures of accuracy and response speed, and (3) assessing cognitive processing using event-related potentials and electrical neuroimaging techniques. We hypothesized that mental fatigue would result in (1) self-report of fatigue and demotivation, (2) reduced processing speed and accuracy, (3) reduced ERN and N1 amplitudes, and (4) decreased activation in brain regions associated with error-monitoring and attention/arousal as estimated via electrical neuroimaging methods.

2. Materials and methods

2.1. Participants

Data from 19 adult volunteers (aged 18–30 years; mean = 22.4 years; 10 males; 9 females) were analyzed for this study. A total of 28 participants were originally recruited from Vanderbilt University and the surrounding Nashville area, with a total of 9 participant exclusions. Four participants had to be excluded from the study without completing the task: 3 were noncompliant with hairstyle restrictions to achieve proper impedances with the electrode cap, and 1 was unable to perform the task (i.e., practice score of less than 70%). Three participants did not commit a sufficient number of errors for a stable ERN waveform. Data from two further participants were excluded after completing the full study due to excessive noise throughout the EEG. All participants were screened to confirm normal hearing using pure tones presented at 25 dB HL at octave frequencies (250–8000 Hz), bilaterally. All volunteers met this criterion with the exception of 1 person who presented with a mild, low-frequency hearing loss, bilaterally. Statistical analyses with and without this participant's data revealed no differences, therefore the data were included in all analyses. Participants were right-handed or mixed-handed (20 right-handed; 1 mixed-handed), as determined using the Edinburgh Handedness Inventory – Short Form (Veale, 2014). There was no history of neurogenic or otologic disease, as evidenced by self-report. Participants were compensated for their time. This study was approved by the Vanderbilt University Institutional Review Board.

2.2. Subjective measures

Subjective data were collected and stored using Research Electronic Data Capture tools (REDCap; Harris et al., 2009) hosted at Vanderbilt University. Subjective fatigue was assessed using two inventories completed immediately preceding and immediately following the behavioral task. The first instrument consisted of three questions written by the authors to probe states directly relating to the MCT; namely, motivation, task engagement, and willingness to continue the task (see Table 1). Responses were made using sliders on a visual analog scale ranging from 0 to 100 (low to high, respectively), in increments of 1. Verbal anchors were positioned at the minimum and maximum endpoints of the slider.

Table 1
Subjective questions written by the authors. Responses were made using an onscreen slider with values ranging from 0 to 100, in increments of 1. Verbal anchors were positioned at the endpoints of the slider.

Question	Verbal anchors
How motivated or unmotivated are you to continue this task?	Very unmotivated – Very motivated
How engaged are you in this task?	Very disengaged – Very engaged
How willing or unwilling are you to continue this task?	Very unwilling – Very willing

The second subjective measure included subscales of the Profile of Mood States (POMS; McNair et al., 1971). The POMS is a validated, 65-item inventory used to assess various mood states, including tension, depression, anger, vigor, fatigue and confusion. Items within a given subscale describe feelings that people have (e.g., “Worn out” or “Energetic”). Participants select a number, using a five-point Likert scale ranging from zero (Not at all) to four (Extremely), that best describes how they are feeling right now. Only the fatigue (7 questions) and vigor (8 questions) subscales were administered.

2.3. Task and stimuli

The behavioral task required participants to determine whether trains of three pure tones contained a specific stimulus combination. Trains consisted of various permutations of 400 Hz and 800 Hz pure tones, with every train containing at least one tone of each frequency. The stimuli were presented monaurally, and could occur in the right or left ear. Right- and left-ear trials were equiprobable. Participants were instructed to respond with a right-handed key press (the “1” key on the number pad of a standard QWERTY keyboard), regardless of right or left ear presentation, when at least two out of the three tones presented were 800 Hz. Conversely, participants respond with a left-handed key press (the “z” key of the same keyboard), again regardless of presentation ear, when at least two of the three tones presented were 400 Hz. These instructions were counterbalanced with half the participants making key presses in the reverse order (i.e., right-handed responses to 400 Hz and left-handed responses to 800 Hz).

Each of the three pure tones in a train was 250 ms in duration. Each tone was gated by raised-cosine ramps of 10 ms and presented with a 0 ms interstimulus interval, for a train duration of 750 ms. A 500 ms burst of Gaussian noise served as a cue before each trial, followed by silence. The cue-to-trial silent interval was jittered within 500–800 ms. A single trial consisted of the Gaussian noise cue and silent interval, followed by a pure tone train. Participants were required to make speeded responses within 1750 ms post stimulus presentation. A response immediately triggered a jittered intertrial interval of 800–1100 ms before a new trial began. If no response was made within 1750 ms post stimulus, participants heard a buzzer letting them know they responded too slowly and that the trial was scored as incorrect. The buzzer was a sawtooth wave with a fundamental frequency of 150 Hz and a duration of 340 ms.

All stimuli were routed through a soundcard (Sound Blaster Z; Creative) and presented through ER-3A insert earphones (Etymotic, Elk Grove Village, IL) using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Pure tones were presented monaurally at 70 dB SPL, to achieve approximately equal perceived loudness between 400 and 800 Hz, according to Fletcher and Munson (1933). The cue and buzzer were presented 70 dB SPL through the same system, bilaterally.

2.4. Procedure

Participants were instructed to abstain from caffeine and alcohol for at least 12 h prior to the study session. Sessions began at either 9:00 or 13:00 to avoid testing during circadian spikes and to limit variability due to normal diurnal changes in cortisol (Kirschbaum and Hellhammer, 1989). Recruitment materials and task instructions stated the purpose of the study was to "measure brain activity during a listening task" so that participants were unaware of the fatigue component (participants were debriefed at the end of the session). Upon entering the EEG laboratory participants were asked to surrender watches and cell phones to the experimenter for the duration of the testing, and were provided no other means to track time. The duration of the study was given as no longer than 4 h.

Following placement of the electrode net, participants began a short practice session. Task instructions were provided on a computer screen and emphasized response accuracy to obtain the most robust ERN (Gehring et al., 1993). Participants were also instructed to time eyeblinks and movements to occur between trials. A fixation cross was provided to discourage wandering eye movements. The practice session consisted of two parts. The first part provided feedback immediately following responses to familiarize participants with the task, and the second part provided no feedback. The task itself provided no feedback, to avoid confounds from the feedback-related negativity (e.g., Luu et al., 2003). The average score from the second half of the practice session was displayed only to the experimenter. Participants with a mean practice score of less than 70% were excluded from the study, as a high number of errors has been shown to be inversely related to ERN amplitude (Hajcak et al., 2003; Luck and Kappenman, 2011). The entire practice session lasted approximately 5 min.

Once the practice session was completed, participants filled out electronic versions of the two subjective questionnaires (described in Section 2.2). Directly following completion of the questionnaires, participants began the test session. Mean task duration was approximately 50 min to complete 880 trials. Immediately following completion of the behavioral task, participants filled out a second set of the subjective questionnaires. For statistical analysis, the session data were split into first half (block 1) and second half (block 2) in order to assess the effects of fatigue on task performance and cognitive processing over time. Each block consisted of 440 trials, and lasted approximately 25 min.

2.5. Behavioral measures and analyses

First, task performance was assessed by calculating the percent of correct responses for each block. Second, processing speed was assessed using response times, measured as the latency from trial onset to key press. Incorrect trials and response times under 100 ms were discarded. Reaction times are reported as Winsorized means (a robust estimate of central tendency; Wilcox, 2005) to account for outliers in the data set. Comparisons between blocks were conducted using bootstrapped, pairwise *t*-tests. All bootstrap analyses consisted of 10,000 samples. Effect sizes are reported as Cohen's *d*, with small, medium and large effect sizes of $d = 0.2$, 0.5 and 0.8, respectively (Cohen, 1988). Statistical analyses were performed using *R* version 3.3.2 (R Core Team, 2016).

2.6. ERP acquisition and pre-processing

The continuous electroencephalogram (EEG) was recorded using a high-density electrode net consisting of 128 Ag/AgCl electrodes embedded in soft sponges (Geodesic Sensor Net; Electrical Geodesics Inc.). Data were acquired using NetStation software (Electrical Geodesics, Inc., version 5.1.2). The EEG was sampled at 1000 Hz, and band-pass filtered online from 0.1 to 100 Hz. The recording was referenced to Cz during acquisition, and re-referenced offline to the average voltage across all electrodes.

Data pre-processing and analysis were performed using Cartool (Brunet et al., 2011; brainmapping.unige.ch/cartool) and a custom package (Moore, 2015) implemented in *R*. The continuous EEG was low-pass filtered at 8 Hz for the ERN, and 30 Hz for N1 analyses. The more aggressive low-pass filtering for the ERN was due to the high prevalence of alpha contamination (typically 8–12 Hz). Line noise was removed using a notch filter at 60 Hz. For the response-locked ERN, the EEG was segmented to include baselines 100 ms prior to the response and 400 ms after the response (total epoch duration of 500 ms). Epochs for the stimulus-locked N1 began 100 ms prior to the stimulus onset and ended 800 ms post stimulus onset to capture the entire length of the pure tone train (total epoch duration of 900 ms). Visual inspection, combined with an artifact rejection criterion of ± 80 μV, occurred manually on a trial-by-trial basis to remove epochs contaminated by eyeblinks and other noise. The mean accepted error trials for the ERN were 12.5 (range: 6–26) for the first half, and 13.94 (range: 6–30) for the second half. The number of error trials used for analysis did not differ significantly between blocks, maintaining a constant ERP signal-to-noise ratio independent of behavioral performance. Mean epochs accepted for the N1 were 82.84 (range: 52–123) for the first half, and 64.16 (range: 36–105) for the second half. Bad channels were interpolated using 3D splines before averaging (Perrin et al., 1987). On average, 11 of the 128 channels were interpolated (range: 7–14). Averaged data were baseline-corrected by subtracting the mean pre-response or pre-stimulus voltage (for the ERN and N1, respectively) on a channel-by-channel basis.

2.7. ERP analyses

Exploration of the electrophysiological data began with analysis of the ERP waveforms. The mean amplitudes of the grand mean ERNs from each block were compared using bootstrapped, pairwise *t*-tests. ERN mean amplitude was calculated using a window of 0–100 ms after the onset of a key press (Luck and Kappenman, 2011). For waveform analyses, the ERN was measured using a frontocentral electrode cluster (electrodes 5, 6, 11, 12) corresponding approximately to Fz of the 10–20 system, consistent with existing literature (Gehring et al., 1993; Weinberg et al., 2015). Only correct trials occurring before error trials were considered (correct-before-error; CBE) to maintain equal signal-to-noise ratios across trial types.

The mean N1 amplitude difference was also compared across blocks. Because each trial consisted of a 3-tone train of sinusoids, 3 N1 peaks were evident in the stimulus-locked averages (Fig. 4A). The mean amplitude window for each peak was defined as ± 30 ms surrounding the time point at 100 ms post stimulus onset (Vaughan and Ritter, 1970). Thus, N1 windows were 70–130 ms, 320–380 ms, and 570–630 ms for the first, second and third N1 windows, respectively. For waveform analyses, the N1 was measured using an electrode cluster near FCz (electrodes 6, 7, 13, 107 and 113).

2.8. Electrical neuroimaging analyses

The ERP data were also subjected to a series of procedures collectively referred to as electrical neuroimaging (Murray et al., 2008). Electrical neuroimaging makes use of the scalp voltage field in its entirety (as recorded by a dense electrode array) to interpolate topographic maps at each sampled point. The topographic maps inform about changes in the scalp voltage field over time, which in turn identifies windows of interest for estimating neural generators. The benefits of these procedures include (1) completely data-driven selection of latency windows, (2) means to discriminate between differences in brain activation due to changes in neural network configuration (global dissimilarity) versus changes in response strength (global field power), and (3) linear inverse solutions to visualize and statistically analyze likely intracranial sources giving rise to observed scalp voltage maps. While the spatial resolution of inverse solutions is quite limited

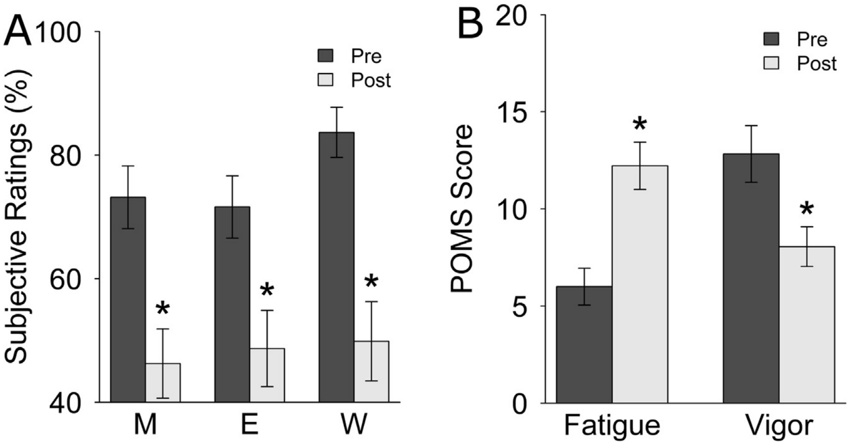

Fig. 1. Bar plots showing the mean data for both subjective measures. (A) Subjective Ratings refer to questions written by the authors. Lower values reflect less motivation, engagement and willingness to continue the task. (B) POMS Scores refer to the fatigue and vigor subscales from the Profile of Mood States. Higher values mean more fatigue and vigor, respectively. Error bars depict standard error of the mean. Asterisks indicate a significant difference between pre- and post-conditions.

compared to hemodynamic neuroimaging techniques (e.g., fMRI), source estimations can be quite useful when considered in conjunction with existing imaging studies and when correlated with behavioral measures.

All electrical neuroimaging procedures were performed using Cartool (Brunet et al., 2011). First, scalp field power was quantified as the standard deviation of all average-referenced electrodes at a given time point. This produced a global measure of cortical activation strength referred to as global field power (GFP; Lehmann and Skrandies, 1980). GFP was calculated for each time point in mean individual data, and contrasted using paired *t*-tests. To correct for multiple comparisons, a criterion of 11 consecutive data points (i.e. > 11 ms) was required to reach significance (see Table 1 from Guthrie and Buchwald, 1991; note also Blair and Karniski, 1993 for an alternative approach). Results of the paired *t*-tests were used to identify specific latencies where scalp field power differed significantly across blocks for further analyses. Next, global dissimilarity (DISS; Lehmann and Skrandies, 1980) was used as a measure of topographical change, but statistical analyses revealed no significant findings.

Last, the neural generators giving rise to the scalp voltage fields were estimated using local autoregressive averaging (LAURA; for review see Michel et al., 2004). LAURA builds on the minimum norm solution, a general brain source estimation method, by imposing constraints on electrical current propagation based on biophysical laws, such the inverse square law of electromagnetic theory (Grave de Peralta Menendez et al., 2004). LAURA is based on a distributed source model, meaning a priori knowledge of the actual number of dipole sources in the brain is not required; instead, a 3D grid of fixed-position solution points represents the possible sources of current in the intracranial space. Specifically, the inverse space consisted of 4024 nodes evenly distributed within the gray matter of the Montreal Neurological Institute average brain (Brett et al., 2002). Localization accuracy was on the order of the grid size (6 mm).

Cartool was used to down-sample all EEG data to a 111-channel electrode montage for use with a 111-channel inverse solution. Neural generators were estimated during the window identified from the GFP analysis. Following recommendations from Thelen et al. (2012), prior to calculating the inverse solution, ERP data within the window was averaged across time, resulting in a single data point for each participant and condition, serving to increase the signal-to-noise ratio for each participant's data. Only sources meeting two statistical criteria were considered reliable. The first criterion required clusters to consist of at least 17 contiguous nodes (equivalent node-level *p*-value of $p \leq 0.0002$, corresponding to an estimated full-width half maximum of 6 mm). The second criterion required *t*-values of the differences across blocks to reach a statistical criterion of $t_{crit}(18) = 2.55, p = 0.02$, which removed nodes greater than ± 2 standard deviations from the mean in order to reduce the effect of such potentially spurious sources. Source estimations were plotted using the Montreal Neurological Institute (MNI) average brain in MNI space (Brett et al., 2002).

2.9. Correlation analyses

Due to the ordinal nature of our subjective data, relationships between brain activation, behavior, and subjective questionnaires were analyzed using a non-parametric correlational approach (Spearman's rho; Myers et al., 2010). Neural responses were represented by the mean difference (block 1 – block 2) in current magnitude (i.e., current source density, or CSD) in brain regions identified by the inverse solution for each participant. The difference in CSD was used to represent the change in brain activation between the first and second block, with positive values indicating a decrease in activation (fatigue) and negative values indicating an increase in activation. CSD differences were compared against mean differences in (1) behavioral measures, (2) subjective ratings from the authors' questionnaire, and (3) POMS subscale scores.

3. Results

3.1. Subjective data

Mean subjective data are presented in Fig. 1. Data from 1 participant were not available for analysis due to technical error. Data from the remaining 18 participants showed a highly significant decrease in (1) motivation to continue the task ($t(17) = 6.89$, $p < 0.0001$, $d = 1.62$); (2) level of engagement in the task ($t(17) = 6.42$, $p < 0.0001$, $d = 1.51$); and (3) willingness to continue the task ($t(17) = 6.5$, $p < 0.0001$, $d = 1.53$), as assessed by the authors' questions from Table 1. The authors' questions were significantly correlated with each other (r_s value range: 0.70–0.82).

Results from the POMS support the findings from the custom questionnaire. The POMS fatigue subscale showed an increase in fatigue as measured before and immediately following the task ($t(17) = -5.03$, $p < 0.001$, $d = 1.18$), while the POMS vigor subscale revealed a significant decrease ($t(17) = 5.57$, $p < 0.0001$, $d = 1.31$). The pre-task POMS fatigue and vigor scores reported here were within 1 standard deviation of the normative data for this population (i.e., primarily college students; Nyenhuis et al., 1999), suggesting a representative subject pool. Only post-task POMS vigor scores decreased by more than 1 standard deviation of the normative data for this population, suggesting vigor was the more sensitive POMS scale for this task.

3.2. Behavioral data

Mean behavioral data are presented in Fig. 2. Consistent with existing fatigue literature, overall accuracy decreased from block 1 to

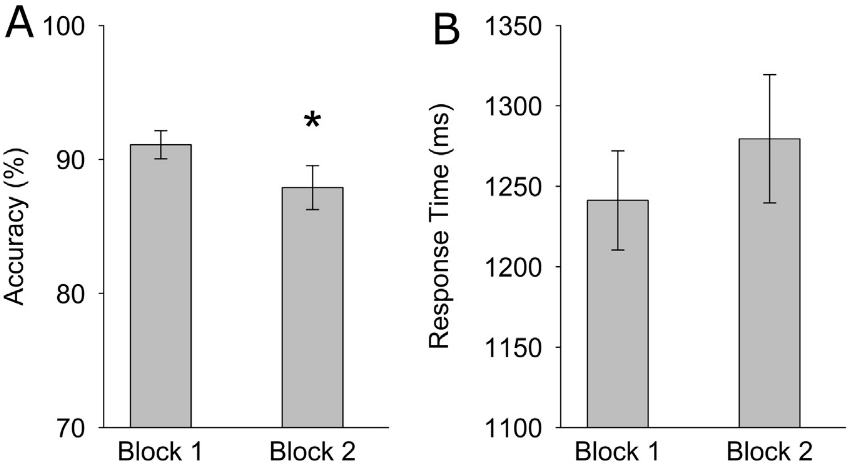

Fig. 2. Bar plots showing (A) mean accuracy and (B) response times for blocks 1 and 2. Error bars depict standard error of the mean. Asterisks indicate a significant difference between blocks.

block 2 (91.7% and 88.5%, respectively; $t(20) = 3.37, p < 0.001, d = 0.73$). However, while mean response time tended to increase over blocks, the trend did not reach statistical significance (1241 ms and 1279 ms for blocks 1 and 2, respectively; $t(20) = -1.86, p = 0.08, d = 0.41$).

3.3. *Event-related potential data*

The findings reported in this section are based on the hypothesis-driven methodology of traditional ERP analysis, which entails the use of predefined time windows and electrode clusters chosen a posteriori based on existing literature. Section 3.4 (immediately following) presents results from data-driven, electrical neuroimaging analyses that do not require experimenter selection of parameters, and allow for estimation of intracranial sources. Likewise, the Discussion maintains this separation when interpreting findings within the context of their respective literatures.

3.3.1. *ERN*

ERN grand averages were based on data from 16 participants. Three data sets were excluded due to excessive ocular artifacts resulting in fewer than 6 acceptable error trials in any block (Olvet and Hajcak, 2009; Pontifex et al., 2010). Fig. 3A and B display the grand average waveforms for error and CBE trials for each block. Fig. 3C shows the ERN difference wave for each block, which was used for statistical analysis. Despite the visual trend indicating lower ERN amplitude in block 2 compared with block 1, a pairwise *t*-test revealed no change in ERN amplitude ($t(15) = -2.2, p = \text{ns}, d = 0.1$), counter to the hypothesized reduction in amplitude across blocks. An F test to compare two variances revealed ERN variability did not differ significantly between blocks ($F_{2,15} = 1.84, p > 0.05$).

3.3.2. *N1*

Data from all 19 participants were used in the N1 analyses. Because each trial consisted of a 3-tone train of sinusoids, 3 peaks were evident in the stimulus-locked averages (see Fig. 4 A). Consistent with our initial hypotheses, planned comparisons revealed a significant decrease in amplitude from block 1 to block 2 for the first N1 window from 70 to 130 ms after the first tone onset ($t(18) = -2.2, p = 0.018, d = 0.5$); however, subsequent N1 windows (320 – 380 ms and 570–630 ms) did not show a difference in amplitude across blocks ($t(18) = -0.25, p = \text{ns}, d = 0.06$ and $t(18) = -1.22, p = \text{ns}, d = 0.28$ for the second and third windows, respectively).

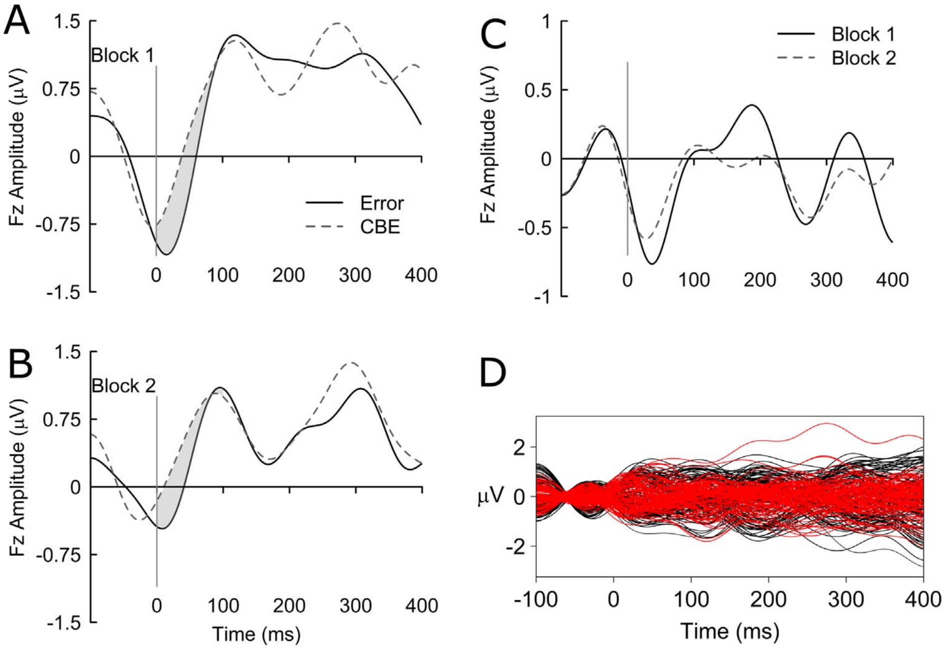

Fig. 3. ERN waveform data from the electrode cluster over Fz. Plots 3A and 3B show the grand average waveforms for error (solid line) and CBE (dashed line) trials for block 1 and block 2, respectively. The shaded regions show the difference between the waveforms within the time window of the ERN (0–100 ms). Plot 3C shows the grand average ERN difference waves (error – CBE) for block 1 (solid line) and block 2 (dashed line). Plot 3D shows the superimposed, grand mean difference waveforms for each of the 128 channels recorded. Waveforms from the first block are in black, and waveforms from the second block are superimposed in red. The thin, gray line at 0 ms in plots 3A–3C indicates the manual response (i.e., key press). Amplitude (ordinate axis) is given in microvolts. CBE = correct-before-error. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

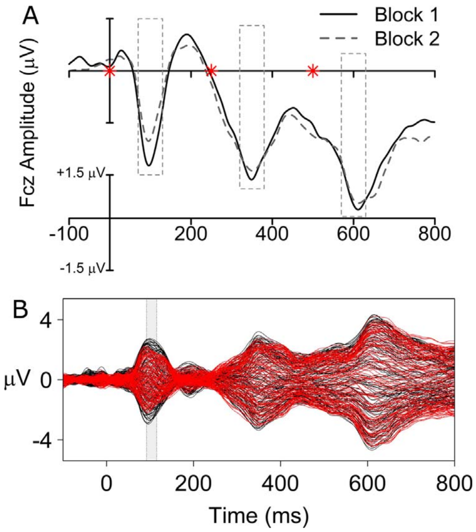

Fig. 4. N1 waveform data from the cluster of electrodes near FCz. The upper plot (A) shows the grand average waveforms for block 1 (solid lines) and block 2 (dashed line). The dashed boxes show the first, second and third N1 time windows respectively. The black line at 0 ms indicates the stimulus onset. Red asterisks show the onset of each tone in the 3-tone stimulus train. The bottom plot (B) shows the superimposed grand mean N1 waveforms for each of the channels recorded. The waveforms from the first block are in black, and waveforms from the second block are superimposed in red. Amplitude (ordinate axis) is given in microvolts. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.4. *Electrical neuroimaging data*

3.4.1. *ERN data set*

Paired *t*-tests revealed no significant differences in GFP (i.e., response strength), in agreement with ERN mean amplitude measures from traditional waveform analysis. Results of a non-parametric randomization test (referred to as topographical analysis of variance, or TANOVA; Murray et al., 2008) indicated no significant differences in ERN topographies across blocks, suggesting no significant changes in underlying neural generator configuration. Taken together, the electrical neuroimaging results suggest no significant changes in the scalp field strength (underlying neural synchrony) or configuration of cortical networks associated with error commission over time. Due to these non-significant findings, no further neuroimaging procedures were carried out on the ERN (e.g., source estimations).

3.4.2. *N1 data set*

Topographic analyses revealed a significant decrease in GFP from 92 to 115 ms post-stimulus onset (Fig. 4B, vertical shaded bar), which was within the time window used for waveform analysis based on previous N1 literature. Two additional GFP differences occurring after 250 ms post-stimulus onset (i.e., after the first tone presentation) were not considered: (1) to avoid potential premotor contamination because participants could begin to respond after the onset of the second tone in half the trials, and (2) to avoid changes in amplitude due to neuronal refractory periods (the interstimulus interval in pure-tone trains was 0 ms). There was no evidence of topographical differences between block 1 and block 2, as revealed by the TANOVA. These results suggest the same neural networks were active throughout the test session, but the neural response was reduced from block 1 to block 2.

Intracranial source estimations were performed to discover likely

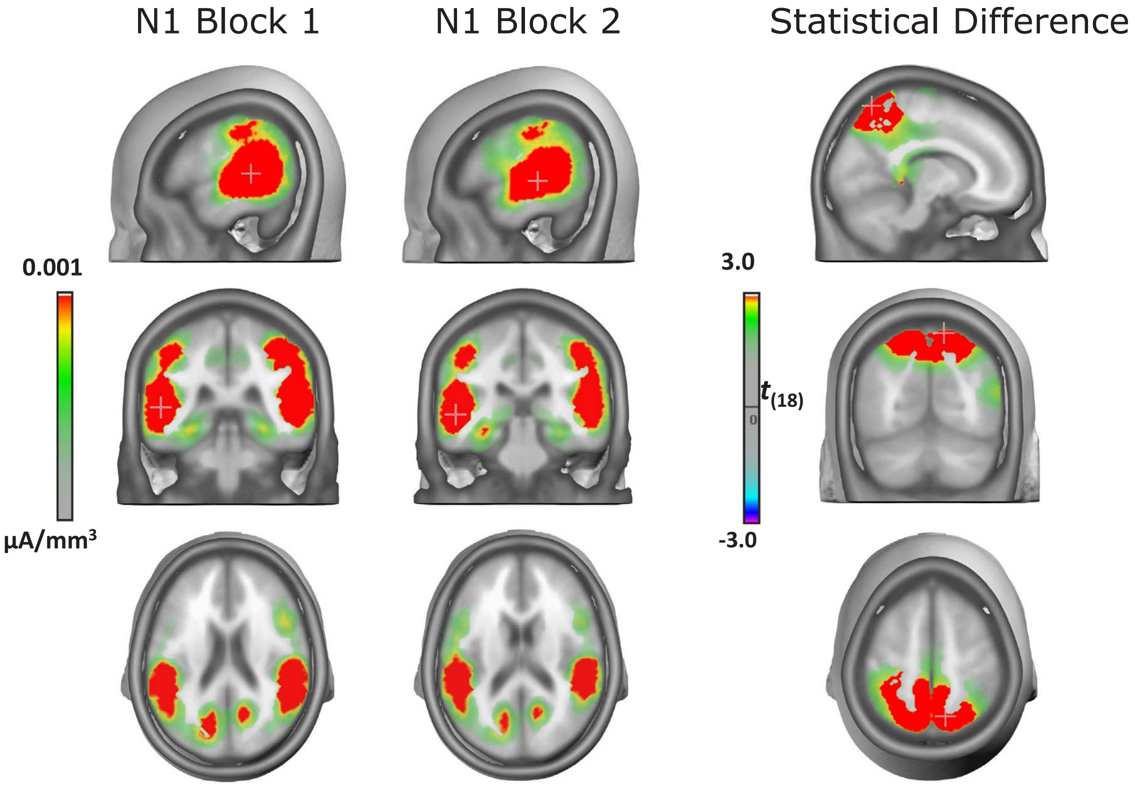

Fig. 5. Source estimation results. The two leftmost columns (labeled “N1 Block1” and “N1 Block 2”) show the mean brain activation for blocks 1 and 2, respectively. The point of peak activation is indicated by a white plus sign (BA 22; coordinates of maximal CSD = − 60, − 31, 8 and − 56, − 28, 2 for blocks 1 and 2, respectively). Rows show peak activation from sagittal, coronal and transverse views, respectively. The rightmost column (labeled “Statistical Difference”) shows the *t*-value map of the contrast between conditions. Warm colors denote greater activity in block 1 compared with block 2. The point of maximal difference between blocks is indicated with a white plus sign (BA7; coordinates of maximal *t*-value = 11, − 61, 60).

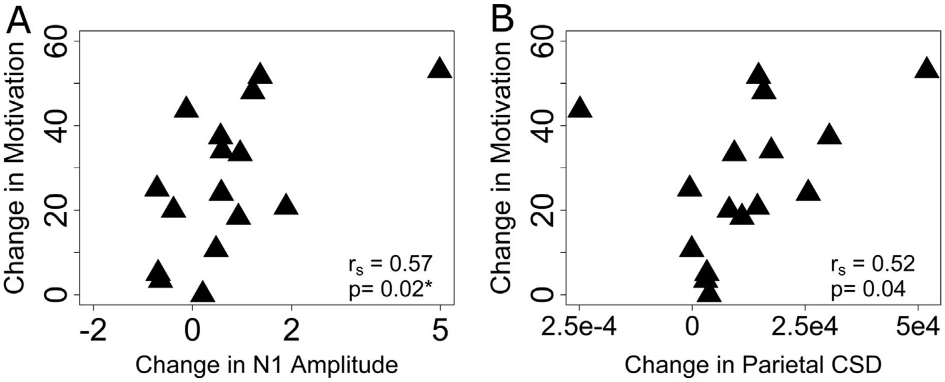

Fig. 6. Correlations between brain and behavior. 6 A plots the change in self-reported motivation (y axis; block 1 – block 2 in percent) as a function of change in N1 mean amplitude (x axis; block 1 – block 2 in µV). Self-reported motivation was calculated collapsed across the authors' questions. 6B plots the same motivation ratings from 6A, as a function of change in parietal cluster CSD (x-axis; block 1 – block 2 in µA/mm^3). Note increasing positive values denote a decrease in brain activation (N1 and CSD) and a decrease in motivation. CSD = current source density. *p*-values marked with an asterisk denote correlations that remained significant after correcting for multiple comparisons.

brain regions contributing to the GFP differences observed as a function of block number during the 92–115 ms window identified above. Both blocks revealed a large cluster of activation in the superior temporal gyri near the superior aspect of the temporal lobe (BA22; MNI coordinates of maximal *t*-value = − 60, − 31, 8 and − 56, − 28, 2 for blocks 1 and 2, respectively). This location borders the supratemporal plane, the estimated site of the auditory N1 from several dipole studies (for review see Näätänen and Picton, 1987). The point of maximal activation identified in this study is also consistent with auditory regions measured using the superior spatial resolution of the electrocorticogram over the same latency (e.g., auditory stimulus MNI coordinates at 100 ms = − 67, − 30, 17; Edwards et al., 2010). Mean activation for each block is shown in the 2 leftmost columns of Fig. 5 (labeled “N1 Block1” and “N1 Block2”, respectively). From top to bottom, rows show sagittal, coronal and transverse views.

Comparison of estimated sources from block 1 and block 2, using our temporal, spatial and statistical criteria, revealed a total of three significant clusters. The first was a large cluster with peak activation in the bilateral precuneus (BA7; MNI coordinates of maximal t-value = 11, − 61, 60), and included regions in the bilateral posterior cingulate cortex (PCC; BA23), left posterior inferior parietal lobule (pIPL; BA40), and bilateral posterior superior parietal lobule (pSPL; BA7). These regions have been associated with the dorsal attention and default mode networks (e.g., Fox et al., 2006; Spreng et al., 2009). The second, smaller cluster meeting all criteria was located in the right posterior temporal lobe (BA39; coordinates of maximal t-value = 41, − 51, 20), extending into the (1) superior temporal gyrus (STG; BA22) and (2) middle temporal gyrus (MTG; BA39). These regions have been associated with Wernicke's area, which is vital in the comprehension of speech sounds and receptive language (e.g., Damasio and Geschwind, 1984). The third cluster was identified in parahippocampal cortex, though we abstained from interpreting this cluster due to its deep, subcortical location and thus unlikely capture with electroencephalography.

Statistical analyses revealed decreased activity in block 2, compared with block 1, for both clusters considered for analysis ($t(18) = 2.55$, $p = 0.02$). Specifically, mean CSD for the large parietal cluster was 4.45 × 10^4 µA/mm^3 for block 1, and 3.32 × 10^4 µA/mm^3 for block 2. Mean CSD for the temporal cluster was 8.60 × 10^4 µA/mm^3 for block 1, and 6.74 × 10^4 µA/mm^3 for block 2. Statistical differences between maps (*t* values) are shown in the rightmost column of Fig. 5 (labeled “Statistical Difference”).

3.5. Correlation analyses

Correlation analyses were not performed on the ERN data set as our initial analyses revealed no significant differences between the two blocks. The relationship between the changes in N1 mean amplitude (block 1–block 2; 0.62 µV) and changes in subjective and behavioral data was explored. Changes in subjective and behavioral data were also compared to changes in mean CSD for each cluster (i.e., block 1–block 2; parietal cluster = 1.13 × 10^4 µA/mm^3; temporal cluster = 1.86 × 10^4 µA/mm^3).

The authors’ subjective questions were created to assess participant motivation to engage actively in the study task. Motivation was assumed to be reflected in the participants’ willingness to continue the task, their task engagement, and their stated level of motivation to complete the task. We tested the relatedness of these questions and POMS ratings using a principal component analysis (PCA) method. The PCA was calculated using singular value decomposition of the centered and scaled data matrix in base R. All three author questions loaded onto a single component, accounting for 64% of the variance in the subjective data. Individual factor scores from the single component were used in subsequent analyses of the authors' subjective questionnaire. The POMS fatigue and vigor subscales each loaded onto separate components (16% and 13% of variance, respectively) and were thus analyzed separately. A priori, planned significance tests were corrected for comparisons across the two clusters identified via LAURA (i.e., parietal and temporal) using the Bonferroni method ($p < 0.025$).

Correlation analyses revealed a significant relationship between the change in mean N1 amplitude and the authors’ motivation questionnaire ($r_s = -0.57$, $p < 0.025$; Fig. 6A). Specifically, as reported motivation decreased, attention and arousal (as indexed by the N1) also decreased. Contrary to expectations, there were no significant correlations between N1 amplitude and either POMS subscale, although the correlations were moderate and in the expected direction (see Table 2). Likewise, there were no significant correlations between changes in N1 amplitude and changes in either behavioral measure (i.e., accuracy or response time).

Correlation analyses between changes in CSD from the large parietal cluster and changes in subjective ratings of motivation revealed a moderate, initially-significant correlation ($r_s = 0.52$, $p = 0.039$; Fig. 6B). However, the correlation did not retain its significance after correcting for multiple comparisons for each cluster ($p > 0.025$).

Table 2
Results of correlation analyses (Spearman's rho) between changes in brain responses and changes in subjective and behavioral response data. Subjective motivation refers to the collapsed data from the authors' subjective questionnaire (i.e., the principal component reflecting Motivation, Engagement and Willingness subjective responses). Asterisks mark significant correlations ($p < 0.025$) after correcting for multiple comparisons for each cluster (i.e., parietal and temporal) using the Bonferroni method. CSD = current source density.

	Change in mean N1 Amplitude		Change in parietal cluster CSD	
Subjective motivation	$r_s = 0.57$	$p = 0.02$*	$r_s = 0.52$	$p = 0.04$
POMS fatigue	$r_s = 0.39$	$p = 0.13$	$r_s = -0.36$	$p = 0.18$
POMS vigor	$r_s = -0.45$	$p = 0.08$	$r_s = 0.35$	$p = 0.19$
Accuracy	$r_s = 0.21$	$p = 0.39$	$r_s = -0.15$	$p = 0.53$
Response time	$r_s = -0.19$	$p = 0.43$	$r_s = -0.002$	$p = 0.99$

Similar to the pattern of N1 mean amplitude results, changes in mean parietal CSD revealed moderate-to-strong, but non-significant, correlations with changes in POMS scores, and low correlations with the change in behavioral measures. There was no relationship between changes in mean CSD of the temporal cluster and any measure.

4. Discussion

This study used the MCT of fatigue and supporting neurophysiological models as a framework within which to characterize the changes in brain activation due to mental fatigue, as elicited by sustained auditory processing. Taken together, the subjective, behavioral, and ERP results are consistent with a growing body of literature that shows continuous auditory processing can lead to mental fatigue. Data were divided into two, 25-min blocks representing the first and second halves of 50 min of continuous task performance. When block 2 was compared with block 1, questionnaires revealed self-report of increased fatigue and decreased motivation. Performance accuracy decreased across blocks, and reaction times trended toward slowing. Together these findings suggest an allocation of cognitive resources away from the task, or a failure to rally sufficient resources to engage in the task effectively. Counter to expectations, ERN amplitude did not differ significantly across blocks, although visual inspection revealed a trend of decreased amplitude from block 1 to block 2. This finding could suggest that error-monitoring remained essentially intact throughout the task, or, if an effect was present, it was too small (e.g., $d = 0.1$) to detect reliably given our sample size. In contrast, N1 amplitude in response to the first tone of the stimulus train decreased across blocks, consistent with reduced attention to the task stimuli and decreased arousal. Electrical neuroimaging analyses of the N1 dataset also showed a decrease in response strength (GFP) with no change in topographies (DISS) in auditory (sensory) and dorsal attention brain areas, indicative of a fatigue-related reduction in neural activation with no change in underlying neural networks across blocks. However, only the mean N1 amplitude was significantly correlated with self-report measures after correcting for multiple comparisons. There was an overall trend showing an association between changes in all subjective measures and changes in N1 mean amplitude and parietal CSD.

4.1. Associations between subjective measures and mental fatigue

It is noteworthy that the authors' motivation questionnaire was significantly correlated with brain activation, while the POMS fatigue and vigor subscales were not. The reasons for this discrepancy are unknown but may reflect, in part, differences in the specificity of the measures. The author-made questions focused *solely* on task-related perceptions (e.g., motivation to *continue the task*). This narrow focus is reflected in the results of the principal components analysis which found all author items loaded onto a single component. In contrast, the fatigue and vigor subscales of the POMS, which loaded as separate PCA components, are generic in nature; the POMS instructions ask participants more generally how they are feeling in terms of tiredness and energy level. Within the framework of the MCT, continued performance on a task despite the desire to stop (reduced motivation) is accompanied by factors such as increasing tiredness and distractibility, which, taken together, serve to interrupt task engagement. It is possible that participants were more aware of their desire to stop the task at hand, rather than their developing change in overall psychophysiological state. Such an explanation suggests future studies should carefully match the domains of subjective questionnaires to a specific definition of fatigue and the study task.

Furthermore, the POMS data were weakly-to-moderately correlated with N1 mean amplitude and parietal CSD, whereas the behavioral data were not correlated with either EEG measure. In other words, there was a general trend for the subjective data to indicate increased fatigue and decreased attention, that did not exist for the behavioral data. This trend suggests that the POMS could prove sensitive to changes in brain activation under different conditions, perhaps over longer task durations where more global changes in subjective fatigue/energy might play a larger role.

4.2. Electrophysiological measures and mental fatigue

4.2.1. ERN

Contrary to expectations, no significant fatigue-related changes in ERN amplitude were observed. In light of the significant decrease in behavioral performance accuracy, it is important to reiterate that the number of CBE and error trials used in the ERN averages did not differ significantly across blocks (i.e., the signal-to-noise ratios were equivalent). Taken together, continued performance monitoring despite the significant decrease in accuracy may indicate that participants were aware of committing more errors during the second block, but were not motivated enough to make corrective adjustments.

The time course of the change in ERN amplitude has proven inconsistent in the fatigue literature, possibly due to differences in the variety of tasks used. Previously, Kato et al. (2009) found a significant decrease in peak ERN amplitude between 0–20 and 20–40 min of performing a modified Go-NoGo task to elicit mental fatigue. However, Lorist et al. (2005) showed no significant decrease in peak ERN amplitude between 0–30 and 30–60 min of performing a fatiguing flanker task (a significant decrease was found between 30–60 and 60–90 min). Visual inspection of the waveforms in the current study revealed a trend toward decreasing over time. Thus, it is possible a longer task duration or additional participants would have revealed a significant decrease in ERN mean amplitude over a time course similar to Lorist et al. (i.e., from 60 to 90 min). Conversely, a different type of task (e.g., a response inhibition task) might have agreed more with the time course of Kato and colleagues, as the ERN is susceptible to task-specific influences (Riesel et al., 2013).

It should also be noted that the poor signal-to-noise ratio from the relatively small number of error trials comprising individual ERN averages could have contributed to the lack of statistical significance. This is unlikely because all data sets included in the analysis met the minimum number of errors trials suggested by the literature for the flanker task (6 trials; Foti et al., 2013; Olvet and Hajcak, 2009; Pontifex et al., 2010). There are no psychometric data for the number of trials required for a stable ERN using a Simon task; however, the auditory analog of the flanker task is arguably quite similar to the task used here (Chan et al., 2005). Additionally, because only correct trials occurring before error trials were used, and the number of trials used for each block did not differ statistically, it is unlikely ERN results were influenced by differences in signal-to-noise ratio between the blocks.

While our findings suggest that the ERN may not be sensitive to fatigue associated with sustained auditory processing, at least for the duration in our study, future studies using auditory tasks should investigate the effect of more robust averages and longer task durations to determine (1) whether the ERN is sensitive to fatigue elicited by sustained, effortful listening, and (2) whether fatigue develops over a similar time course across auditory and visual modalities.

4.2.2. N1

The decrease in N1 mean amplitude in the first time window likely reflected a decrease in task attention over time. The N1 has previously been shown to correlate with orienting attention to a relevant location triggered by stimulus presentation (e.g., Luck et al., 1990). In this study, participants attended to pure-tone trains that were randomly presented to either ear. This design likely elicited brain activation giving rise to the N1 upon orienting to the ear that received the first tone. Because all presentations were monaural, orienting spatial attention was only required at the beginning of a trial, perhaps explaining the greater N1 amplitude within the first latency window. Boksem et al. (2005) also found a decrease in N1 amplitude over time using a fatiguing visual attention task. They concluded fatigued participants were less able to orient attention to relevant targets, accounting for less accuracy over time. The decrease in N1 amplitude could be explained by decreased activation in the dorsal attention network, which is activated when humans attend to a location in preparation of a task-relevant stimulus (Corbetta and Shulman, 2002). The present experimental task was designed to elicit a state of anticipation following the Gaussian noise cue, as participants prepared for the pure-tone train (which was then decoded to determine a right- or left-handed response). The greater amplitude within the first N1 window during the first 25-min block likely reflected prestimulus, anticipatory spatial attention concentrated on the right and left ears. The neuroimaging results (discussed below in subsection 4.2.3) are consistent with brain regions associated with the dorsal attention network. Thus, the ERP results suggest the reduction in N1 amplitude over time was due to decreased attention and arousal that occurred as the task continued, consistent with the development of mental fatigue.

It could also be argued that the decrease in N1 amplitude was due to habituation; however, this seems unlikely for several reasons. First, habituation is thought to reflect the updating of a neuronal template based on stimulus repetition (Sokolov, 1963), but the order, frequency of appearance, and sidedness of the tones used in this study were random between presentations. Further, each pure tone train was separated by a decision process used to inform a behavioral response, and a Gaussian noise cue. It seems unlikely a pattern was established that led to habituation. Second, the data follow the refractory pattern described by Keidel and Neff (1976); namely, that amplitude reductions due to refractoriness occur immediately and stabilize following stimulus presentation (as opposed to a slower decline in amplitude characteristic of habituation). The second and third N1 windows show immediate amplitude reduction following the first N1 window, and do not differ statistically from one another (i.e., stability). For these reasons, we feel habituation did not drive the results. Instead, we interpret the reduction in first-window N1 amplitude as a decrease in general arousal due to the buildup of mental fatigue over time-on-task.

Similar to the present study, Boksem et al. (2005) showed a decrease in N1 amplitude during a 3-h visual attention task; however, Key et al. (2017) showed no change in N1 amplitude. The discrepancy could be due to methodological differences. Both the current study and Boksem et al. (2005) continuously recorded N1 responses to the stimuli during the fatigue-inducing task, while Key et al. measured ERPs before and after the fatiguing session, but not during. It could be that the processes underlying the N1 response recover rapidly; suggesting general arousal and orienting attention are less affected by fatigue. Indeed, Lorist et al. (2005) showed that higher-level processes were sensitive to fatigue while more reflexive actions (e.g., immediate error corrections) were not. Consistent with this notion, Key et al. found reduced P3b amplitudes (associated with voluntary attention) but not P3a amplitudes (associated with involuntary attention) following completion of a series of fatiguing listening tasks. An interpretation of these results consistent with the MCT is that changing a task can release lower-level processes from fatigue, but that higher-level functions are slower to recover. The increased resilience of lower-level functions compared to executive processes may prove to be an important consideration in future study design.

4.2.3. *Electrical neuroimaging data*

As discussed in the previous Section (4.2.2), the reduction in N1 mean amplitude likely indicated reduced task-related attention in the dorsal attention network. Electrical neuroimaging techniques allowed for further interpretation of the ERP waveforms. Statistical analysis of mean brain activation from the N1 data set revealed an overall decrease in CSD during the second half of the task (block 2) compared with the first half of the task (block 1). In other words, the voxels identified by source estimations demonstrated greater current magnitude during the first block than the second block. Because current magnitude reflects neuronal activity, the decrease in CSD across blocks is consistent with a decrease in brain activation from areas identified using LAURA. Regions of significantly decreased CSD in block 2 included the precuneus, PCC, pIPL and pSPL, consistent with brain regions implicated in linking stimulus-response characteristics and orienting attention.

Corbetta and Shulman (2002) identify the dorsal attention network as existing (1) along the intraparietal sulcus (IPs), extending dorsally into the SPL, and anteriorly to the postcentral sulcus (BA7), and (2) in the dorsal frontal cortex where the precentral and superior frontal sulci meet (BA6). Fox et al. (2006) found that these brain regions also form a discrete network based solely on spontaneous neural activity, separate from a more ventral attention network proposed to subserve different facets of attention. MNI coordinates from their MRI study of the peak focus of the right posterior parietal region were 20, − 67, 51, compared with peak coordinates of 11, − 57, 53 for the present study (both in BA7; Talairach coordinates were converted using the yale.edu BioImage Suite).

Further conclusions relating to parietal brain regions are precluded by the relatively low spatial resolution of electrical neuroimaging. It should be noted, however, that this study did not identify frontal regions associated with the dorsal network. One explanation is that while the classic dorsal attention network typically involves frontal and parietal regions, humans have been shown to exhibit parietal-only activation when stimulus-response associations are simple or well-practiced (e.g., Shulman et al., 2002). It seems likely that the overall high performance levels and simplicity of the task account for the lack of frontal sites. Thus, taken with the other results, it appears reasonable to conclude this study captured a decrease in neural activity associated with orienting attention to task stimuli and response preparation. This finding supports the existing literature, such as the MCT of mental fatigue, suggesting decreased attention is one mechanism susceptible to fatigue-related interruptions in ongoing behavior. Additionally, this study provides physiological support for the hypothesis that sustained auditory processing can lead to decreased attention and mental fatigue. Considered with similar findings from visual ERP studies, there appears to be growing evidence that mental fatigue is a general, multimodal phenomenon.

4.3. *Limitations and future directions*

Overall our subjective data showed a positive association with ERP and neuroimaging data. However, substantial variability was present and only one of the two significant correlations survived correction for multiple comparisons, suggesting a need for additional participants. Another factor potentially obscuring brain-behavior associations was our choice of relatively long analysis blocks (i.e., first half versus second half). Examining task outcomes in narrower time windows (e.g., 10-min blocks) could better define an individual's performance/fatigue profile, perhaps enhancing our ability to observe brain-behavior associations. Unfortunately, the relatively low number of errors over the 50-min duration used in this study did not allow for finer division. Future studies could allow for potentially sparse observations by increasing the study duration or employing a task that yields more frequent errors. Finally, variability in our subjective results could reflect a lack of sensitivity in our subjective measures. The authors' questionnaire was more sensitive to brain-behavior associations than the more generic POMS, highlighting the importance of using task-specific measures. However, the clarity, reliability and validity of the authors' questions have not been systematically assessed and may not be optimal.

Importantly, our findings suggest that dorsal parietal activation may prove a useful indicator for quantifying brain-related changes in attention associated with mental fatigue, but future work is needed to clarify its role further. For instance, a study employing a greater number of shorter blocks may be able to quantify more accurately the time course of mental fatigue, perhaps capturing early neuronal activation over frontal sites associated with the dorsal frontoparietal attention networks.

5. Conclusions

Mental fatigue elicited by sustained auditory processing is associated with a pattern of changes in brain activation indicative of decreased attention in adults with normal hearing. Reduced N1 mean amplitude and parietal cluster activation was positively correlated with decreased motivation, willingness, and task engagement, hallmarks of mental fatigue. These findings shed light on possible neurophysiological mechanisms corresponding to the interruption of task performance proposed by the MCT. That is, decreased opportunity for cognitive rest likely works to skew the effort/reward ratio unfavorably, leading to demotivation and reallocation of attention away from a task. Further investigation into the relationship between mental fatigue, sustained listening, and the role of parietal brain regions is needed to understand better how these factors influence each other.

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References

Adrian, E., Matthews, B., 1934. The Berger rhythm: potential changes from the occipital lobes in man. Brain 57, 355–385.

Alhanbali, S., Dawes, P., Lloyd, S., et al., 2017. Self-reported listening-related effort and fatigue in hearing-impaired adults. Ear Hear. 38 (1), e39–e48.

Antons, J., Schleicher, R., Arndt, S., et al., 2012. Too tired for calling? A physiological measure of fatigue caused by bandwidth limitations. In: 2012 Proceedings of the Fourth International Workshop on Quality of Multimedia Experience Paper presented at the Quality of Multimedia Experience (QoMEX).

Bess, F.H., Hornsby, B.W., 2014. Commentary: listening can be exhausting—fatigue in children and adults with hearing loss. Ear Hear. 35 (6), 592–599.

Blair, R.C., Karniski, W., 1993. An alternative method for significance testing of waveform difference potentials. Psychophysiology 30 (5), 518–524.

Boissoneault, J., Letzen, J., Lai, S., et al., 2016. Abnormal resting state functional connectivity in patients with chronic fatigue syndrome: an arterial spin-labeling fMRI study. Magn. Reson. Imaging 34 (4), 603–608.

Boksem, M., Meijman, T., Lorist, M., 2005. Effects of mental fatigue on attention: an ERP study. Cogn. Brain Res. 25, 107–116.

Boksem, M., Meijman, T., Lorist, M., 2006. Mental fatigue, motivation and action monitoring. Biol. Psychol. 72, 123–132.

Boksem, M., Tops, M., 2008. Mental fatigue: costs and benefits. Brain Res. Rev. 59, 125–139.

Botvinick, M.M., 2007. Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. Cogn. Affect. Behav. Neurosci. 7 (4), 356–366.

Brett, M., Johnsrude, I.S., Owen, A.M., 2002. The problem of functional localization in the human brain. Nat. Rev. Neurosci. 3 (3), 243–249.

Brunet, D., Murray, M.M., Michel, C.M., 2011. Spatiotemporal analysis of multichannel EEG: cartool. Comput. Intell. Neurosci. 2011, 1–15.

Buckner, R.L., Carroll, D.C., 2007. Self-projection and the brain. Trends Cogn. Sci. 11 (2), 49–57.

Chan, J.S., Merrifield, K., Spence, C., 2005. Auditory spatial attention assessed in a flanker interference task. Acta Acust. U. Acust. 91 (3), 554–563.

Chaudhuri, A., Behan, P., 2000. Fatigue and basal ganglia. J. Neurol. Sci. 179, 34–42.

Chaudhuri, A., Behan, P., 2004. Fatigue in neurological disorders. Lancet 363 (9413), 978–988.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Lawrence Erlbaum Associates, Hillsdale, NJ.

Cohen, J.D., Botvinick, M., Carter, C.S., 2000. Anterior cingulate and prefrontal cortex: who's in control? Nat. Neurosci. 3, 421–423.

Cook, D.B., Light, A.R., Light, K.C., et al., 2017. Neural consequence of post-exertion malaise in myalgic encephalomyelitis/chronic fatigue syndrome. Brain Behav. Immun. 62, 87–99.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3 (3), 201–215.

Craig, A., Tran, Y., Wijesuriya, N., et al., 2012. Regional brain wave activity changes associated with fatigue. Psychophysiol 49 (4), 574–582.

Damasio, A., R., Geschwind, N., 1984. The neural basis of language. Annu. Rev. Neurosci. 7 (1), 127–147.

Dehaene, S., Posner, M.I., Tucker, D.M., 1994. Localization of a neural system for error detection and compensation. Psychol. Sci. 303–305.

Dill, L.M., 1983. Adaptive flexibility in the foraging behavior of fishes. Can. J. Fish. Aquat. Sci. 40 (4), 398–408.

Edwards, E., Nagarajan, S.S., Dalal, S.S., et al., 2010. Spatiotemporal imaging of cortical activation durin verb generation and picture naming. Neuroimage 50 (1), 291–301.

Escera, C., Yago, E., Corral, M.J., et al., 2003. Attention capture by auditory significant stimuli: semantic analysis follows attention switching. Eur. J. Neurosci. 18 (8), 2408–2412.

Falkenstein, M., Hohnsbein, J., Hoormann, J., et al., 1991. Effects of crossmodal divided attention on late ERP components. II. error processing in choice reaction tasks. Electroencephalogr. Clin. Neurophysiol. 78 (6), 447–455.

Fletcher, H., Munson, W.A., 1933. Loudness, its definition, measurement and calculation. Bell Syst. Tech. J. 12 (4), 377–430.

Foti, D., Kotov, R., Hajcak, G., 2013. Psychometric considerations in using error-related brain activity as a biomarker in psychotic disorders. J. Abnorm. Psychol. 122 (2), 520.

Fox, M.D., Corbetta, M., Snyder, A.Z., et al., 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc. Natl. Acad. Sci. 103 (26), 10046–10051.

Gay, C.W., Robinson, M.E., Lai, S., et al., 2016. Abnormal resting-state functional connectivity in patients with chronic fatigue syndrome: results of seed and data-driven analyses. Brain Connect 6 (1), 48–56.

Gehring, Coles, M., Meyer, D., et al., 1990. The error-related negativity: an event-related brain potential accompanying errors. Psychophysiology 27 (4), S34.

Gehring, W.J., Goss, B., Coles, M.G., et al., 1993. A neural system for error detection and compensation. Psychol. Sci. 4 (6), 385–390.

Gellerstedt, L.C., Danermark, B., 2004. Hearing impairment, working life conditions, and gender. Scand. J. Disabil. Res. 6 (3), 225–245.

Giard, M., Perrin, F., Echallier, J., et al., 1994. Dissociation of temporal and frontal components in the human auditory N1 wave: a scalp current density and dipole model analysis. Electroencephalogr. Clin. Neurophysiol. 92 (3), 238–252.

Grave de Peralta Menendez, R., Murray, M.M., Michel, C.M., et al., 2004. Electrical neuroimaging based on biophysical constraints. Neuroimage 21 (2), 527–539.

Guthrie, D., Buchwald, J.S., 1991. Significance testing of difference potentials. Psychophysiology 28 (2), 240–244.

Haber, S., Lynd, E., Klein, C., et al., 1990. Topographic organization of the ventral striatal efferent projections in the rhesus monkey: an anterograde tracing study. J. Comp. Neurol. 293 (2), 282–298.

Hajcak, G., McDonald, N., Simons, R.F., 2003. To err is autonomic: error-related brain potentials, ANS activity, and post-error compensatory behavior. Psychophysiology 40 (6), 895–903.

Harris, P.A., Taylor, R., Thielke, R., et al., 2009. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inform. 42 (2), 377–381.

Hétu, R., Riverin, L., Lalande, N., et al., 1988. Qualitative analysis of the handicap associated with occupational hearing loss. Br. J. Audiol. 22, 251–264.

Hockey, R., 1997. Compensatory control in the regulation of human performance under stress and high workload: a cognitive-energetical framework. Biol. Psychol. 45, 73–93.

Hockey, R., 2013. The Psychology of Fatigue: Work, Effort and Control. Cambridge University Press, New York.

Holroyd, C.B., Dien, J., Coles, M.G., 1998. Error-related scalp potentials elicited by hand and foot movements: evidence for an output-independent error-processing system in humans. Neurosci. Lett. 242 (2), 65–68.

Hopstaken, J.F., Linden, D., Bakker, A.B., et al., 2014. A multifaceted investigation of the link between mental fatigue and task disengagement. Psychophysiology.

Hornsby, B., 2013. The effects of hearing aid use on listening effort and mental fatigue associated with sustained speech processing demands. Ear Hear. 34, 523–534.

Hornsby, B.W., Naylor, G., Bess, F.H., 2016. A taxonomy of fatigue concepts and their relation to hearing loss. Ear Hear. 37, 136S–144S.

Kamil, A.C., Roitblat, H.L., 1985. The ecology of foraging behavior: implications for animal learning and memory. Annu. Rev. Psychol. 36 (1), 141–169.

Kato, Y., Endo, H., Kizuka, T., 2009. Mental fatigue and impaired response processes: event-related brain potentials in a Go/NoGo task. Int. J. Psychophysiol. 72, 204–211.

Keidel, W.D., Neff, W.D. (Eds.), 1976. Habituation and Attention in the Auditory System Vol. 5 Springer, New York, New York.

Key, A.P., Gustafson, S.J., Rentmeester, L., et al., 2017. Speech-processing fatigue in children: auditory event-related potential and behavioral measures. J. Speech Lang. Hear. Res. 60, 2090–2104.

Kirschbaum, C., Hellhammer, D.H., 1989. Salivary cortisol in psychobiological research: an overview. Neuropsychobiology 22 (3), 150–169.

Kool, W., Botvinick, M., 2014. A labor/leisure tradeoff in cognitive control. J. Exp. Psychol. Gen. 143 (1), 131.

Kramer, S., Kapteyn, T., Houtgast, T., 2006. Occupational performance: comparing normally-hearing and hearing-impaired employees using the Amsterdam checklist for hearing and work. Int. J. Audiol. 45, 503–512.

Kurzban, R., 2016. The sense of effort. Curr. Opin. Psychol. 7, 67–70.

Lehmann, D., Skrandies, W., 1980. Reference-free identification of components of checkerboard-evoked multichannel potential fields. Electroencephalogr. Clin. Neurophysiol. 48 (6), 609–621.

Lorist, M., Boksem, M., Ridderinkhof, K., 2005. Impaired cognitive control and reduced cingulate activity during mental fatigue. Cogn. Brain Res. 24, 199–205.

Luck, S.J., Heinze, H., Mangun, G., et al., 1990. Visual event-related potentials index focused attention within bilateral stimulus arrays. II. Functional dissociation of P1 and N1 components. Electroencephalogr. Clin. Neurophysiol. 75 (6), 528–542.

Luck, S.J., Kappenman, E.S. (Eds.), 2011. The Oxford Handbook of Event-Related Potential Components. Oxford University Press, New York, New York.

Luu, P., Tucker, D.M., Derryberry, D., et al., 2003. Electrophysiological responses to errors and feedback in the process of action regulation. Psychol. Sci. 14 (1), 47–53.

Marcora, S.M., Staiano, W., Manning, V., 2009. Mental fatigue impairs physical performance in humans. J. Appl. Physiol. 106 (3), 857–864.

McNair, D., Lorr, M., DroppLemn, L., 1971. Profile of Mood States. Educational and Industrial Testing Service, San Diego, CA.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214 (5–6), 655–667.

Michel, C.M., Murray, M.M., Lantz, G., et al., 2004. EEG source imaging. Clin. Neurophysiol. 115 (10), 2195–2222.

Mogenson, G.J., Jones, D.L., Yim, C.Y., 1980. From motivation to action: functional interface between the limbic system and the motor system. Prog. Neurobiol. 14 (2), 69–97.

Moore, T., 2015. Event-related Potential (ERP) Data Exploration Made Easy. ⟨https://CRAN.R-project.org/package=erp.easy⟩.

Murray, M.M., Brunet, D., Michel, C.M., 2008. Topographic ERP analyses: a step-by-step tutorial review. Brain Topogr. 20 (4), 249–264.

Myers, J.L., Well, A., Lorch, R.F., 2010. Research Design and Statistical analysis. Routledge, New York.

Näätänen, R., Picton, T., 1987. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 24 (4), 375–425.

Nyenhuis, D.L., Yamamoto, C., Luchetta, T., et al., 1999. Adult and geriatric normative data and validation of the profile of mood states. J. Clin. Psychol. 55 (1), 79–86.

Olvet, D.M., Hajcak, G., 2009. The stability of error-related brain activity with increasing trials. Psychophysiology 46 (5), 957–961.

Paus, T., 2001. Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nat. Rev. Neurosci. 2 (6), 417–424.

Perrin, F., Pernier, J., Bertnard, O., et al., 1987. Mapping of scalp potentials by surface spline interpolation. Electroencephalogr. Clin. Neurophysiol. 66 (1), 75–81.

Picou, E.M., Moore, T.M., Ricketts, T.A., 2017. The effects of directional processing on objective and subjective listening effort. J. Speech Lang. Hear. Res. 60, 199–211.

Picou, E.M., Ricketts, T.A., 2014. The effect of changing the secondary task in dual-task paradigms for measuring listening effort. Ear Hear. 35 (6), 611–622.

Polich, J., 2007. Updating P300: an integrative theory of P3a and P3b. Clin. Neurophysiol. 118 (10), 2128–2148.

Pontifex, M.B., Scudder, M.R., Brown, M.L., et al., 2010. On the number of trials necessary for stabilization of error-related brain activity across the life span. Psychophysiol 47 (4), 767–773.

R Core Team, 2016. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria (Retrieved from https://www.R-project.org/).

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., et al., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. USA 98 (2), 676–682.

Riesel, A., Weinberg, A., Endrass, T., et al., 2013. The ERN is the ERN is the ERN? Convergent validity of error-related brain activity across different tasks. Biol. Psychol. 93 (3), 377–385.

Rowland, N., Meile, M., Nicolaidis, S., 1985. EEG alpha activity reflects attentional demands, and beta activity reflects emotional and cognitive processes. Science 228 (4700), 750–752.

Shulman, G.L., d'Avossa, G., Tansy, A., P., et al., 2002. Two attentional processes in the parietal lobe. Cereb. Cortex 12 (11), 1124–1131.

Sokolov, E.N., 1963. Higher nervous functions: the orienting reflex. Annu. Rev. Physiol. 25 (1), 545–580.

Spreng, R.N., Mar, R.A., Kim, A.S., 2009. The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. J. Cogn. Neurosci. 21 (3), 489–510.

Thelen, A., Cappe, C., Murray, M.M., 2012. Electrical neuroimaging of memory discrimination based on single-trial multisensory learning. Neuroimage 62 (3), 1478–1488.

Themanson, J.R., Rosen, P.J., Pontifex, M.B., et al., 2012. Alterations in error-related brain activity and post-error behavior over time. Brain Cogn. 80 (2), 257–265.

Uddin, L.Q., 2015. Salience processing and insular cortical function and dysfunction. Nat. Rev. Neurosci. 16 (1), 55–61.

van der Linden, D., Frese, M., Meijman, T.F., 2003. Mental fatigue and the control of cognitive processes: effects on perseveration and planning. Acta Psychol. 113 (1), 45–65.

van Veen, V., Carter, C.S., 2002. The timing of action-monitoring processes in the anterior cingulate cortex. J. Cogn. Neurosci. 14 (4), 593–602.

van Veen, V., Cohen, J.D., Botvinick, M.M., et al., 2001. Anterior cingulate cortex, conflict monitoring, and levels of processing. Neuroimage 14 (6), 1302–1308.

Vaughan, H.G., Ritter, W., 1970. The sources of auditory evoked responses recorded from the human scalp. Electroencephalogr. Clin. Neurophysiol. 28 (4), 360–367.

Veale, J.F., 2014. Edinburgh handedness inventory–short form: a revised version based on confirmatory factor analysis. Laterality 19 (2), 164–177.

Weinberg, A., Dieterich, R., Riesel, A., 2015. Error-related brain activity in the age of RDoC: a review of the literature. Int. J. Psychophysiol. 98 (2), 276–299.

Weissman, D., Roberts, K., Visscher, K., et al., 2006. The neural bases of momentary lapses in attention. Nat. Neurosci. 9 (7), 971–978.

Wilcox, R.R., 2005. Introduction to Robust Estimation and Hypothesis Testing, 2nd ed. Academic Press, San Diego, CA.

Wortinger, L.A., Endestad, T., Melinder, A.M.D., et al., 2016. Aberrant resting-state functional connectivity in the salience network of adolescent chronic fatigue syndrome. PLoS One 11 (7), 1–16.