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REVIEW

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The influence of mental fatigue on brain activity: Evidence from a systematic review with meta-analyses

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Abstract
The occurrence of mental fatigue during tasks like driving a vehicle increases risk of injury or death. Changes in electroencephalographic (EEG) activity associated with mental fatigue has been frequently studied and considered a promising biomarker of mental fatigue. This is despite differences in methodologies and outcomes in prior research. A systematic review with meta-analyses was conducted to establish the influence of mental fatigue on EEG activity spectral bands, and to determine in which regions fatigue-related EEG spectral changes are likely to occur. A high-yield search strategy identified 21 studies meeting inclusion criteria for investigating the change in EEG spectral activity in non-diseased adults engaged in mentally fatiguing tasks. A medium effect size (using Cohen's g) of 0.68 (95%CI: 0.24–1.13) was found for increase in overall EEG activity following mental fatigue. Further examination of individual EEG spectral bands and regions using network meta-analyses indicated large increases in theta ($g = 1.03$; 95%CI: 0.79–1.60) and alpha bands ($g = 0.85$; 95%CI: 0.47–1.43), with small to moderate changes found in delta and beta bands. Central regions of the scalp showed largest change ($g = 0.80$; 95%CI: 0.46–1.21). Sub-group analyses indicated large increases in theta activity in frontal, central and posterior sites (all $g > 1$), with moderate changes in alpha activity in central and posterior sites. Findings have implications for fatigue monitoring and countermeasures with support for change in theta activity in frontal, central and posterior sites as a robust biomarker of mental fatigue and change in alpha wave activity considered a second line biomarker to account for individual variability.

KEYWORDS
alertness, alpha wave activity, beta wave activity, brain activity, delta wave activity, drowsiness, electroencephalography, fatigue, mental fatigue, meta-analyses, theta wave activity

1 | INTRODUCTION

Mental fatigue is known to be a primary risk for accidents and injury when driving a vehicle, flying an aircraft or when operating production line machinery (Borghini, Astolfi, Vecchiato, Mattia, & Babiloni, 2014; Lal & Craig, 2002). It is believed to be a risk factor in at least 40% of road crashes (Fletcher, McCulloch, Baulk, & Dawson, 2005) and for transport and storage industries there are high rates of work-related fatigue deaths with approximately 15 per 100,000 reported (Mitchell, Driscoll, & Healey, 2004). It has been advocated that indicators or biomarkers of mental fatigue could be used to warn people of their fatigue status and thus preventing fatigue-related accidents from occurring (Borghini et al., 2014; Lal & Craig, 2002). A potential neural biomarker that has received frequent research attention involves change in spectral electroencephalography (EEG) signals associated with mental fatigue (Craig, Tran, Wijesuriya, & Nguyen, 2012). However, there are diverse methodologies and findings raising questions about whether change in spectral EEG can be used as a suitable and reliable biomarker or indicator of mental fatigue. Therefore, through a systemic review and meta-analyses, the main objective of this article is to determine the reliability of changes in brain wave activity as a biomarker of mental fatigue.

1.1 | The nature and definition of mental fatigue

The human state of wakefulness lies on a biological, cognitive, and behavioral spectrum, in which one experiences alertness at one extremity, and sleep at the other (Scammell, Arrigoni, & Lipton, 2017). The wakefulness state depends on a complex interaction of neurobiological and psychophysiological processes (Constantinople & Bruno, 2011; Harrington, 2012; Van Dongen & Dinges, 2000). The degree of wakefulness is believed to be related to autonomic and endocrine processes, as well as the neuromodulation of cortical processing by noradrenergic and cholinergic pathways (Chaudhuri & Behan, 2004; Constantinople & Bruno, 2011; Scammell et al., 2017). It is regulated by one's "biological or circadian clock" located in the suprachiasmatic nuclei of the hypothalamus and influenced by circadian rhythmicity such as time of day or night (Van den Pol & Dudek, 1993; Van Dongen & Dinges, 2000). Other influencing factors including genetics, health status, age, physical exertion, and cognitive and emotional processes including perceived reward/cost versus effort (e.g., cost vs. reward; boredom vs. motivation), anxiety and mood (Craig, Tran, Wijesuriya, & Boord, 2006; Kurzban, Duckworth, Kable, & Myers, 2013).

Fatigue has been defined as a "biological drive for recuperative rest" that may include feelings of sleepiness as well as physical and mental elements, with mental fatigue viewed as a state of consciousness lying within the wakefulness spectrum (Craig, Tran, Wijesuriya, & Middleton, 2012; Williamson et al., 2011). Mental fatigue has been described as "a gradual and cumulative process… associated with a disinclination for any effort, a general sensation of weariness, feelings of inhibition and impaired mental performance" (Borghini et al., 2014) and "as a decline in the ability and efficiency of mental and/or physical activities that is caused by excessive mental and/or physical activities" (Ishii, Tanaka, & Watanabe, 2014). However, definitions of mental fatigue abound. Since fatigue is a dynamic event involving subjective, mental, behavioral, neural, and physiological processes that interact over time across different tasks and environmental contexts, it is often difficult to agree upon an operational definition (Fonseca, Kerick, King, Lin, & Jung, 2018).

It is important to provide an acceptable definition that can be applied to the studies featured in the review and meta-analyses. However, first, it will be a helpful exercise to determine what mental fatigue is not. Mental fatigue should be distinguished from the debilitating pathological fatigue commonly suffered by people with chronic disease and neurological disorder, such as multiple sclerosis, depression, chronic fatigue syndrome, cancer (Chaudhuri & Behan, 2004), and those with severe injuries such as spinal cord injury (Craig, Tran, Wijesuriya, & Middleton, 2012). Mental fatigue should also be differentiated from muscular fatigue, a state associated with continued and sustained contraction of a muscle, leading to muscle glycogen depletion, low oxygen and increased levels of lactic acid (Allen, Lamb, & Westerblad, 2008). Mental fatigue should also be differentiated from a condition called daytime sleepiness, commonly occurring from sleep disorder or disturbance, and defined as the propensity to fall asleep during the day (Berlowitz, Spong, Gordon, Howard, & Brown, 2012; Craig, Rodrigues, Tran, Guest, & Middleton, 2018).

For this review, we define mental fatigue as a subjective wakefulness state in which they begin to feel mentally tired, drowsy and sleepy, experienced during periods of sustained demand in which a person is required to concentrate and focus their attention on a cognitive or behavioral task of some nature such as sitting for an examination, driving a vehicle or operating machinery (Craig et al., 2006). In certain cases, mental fatigue may be associated with motivational states or negative feelings like anxiety, frustration, and boredom, with the person experiencing aversion to continue performing a task (Boksem, Meijman, & Lorist, 2005; Craig et al., 2006; Lorist, 2008). Effort-reward imbalances are also known to occur, for example, a person's performance will deteriorate when mentally fatigued, even if there may be motivation to perform the task (Boksem & Tops, 2008; Kurzban et al., 2013). A consequence of mental fatigue is an elevated risk of performance decrements, that is, difficulties maintaining satisfactory levels of behavioral and mental functioning, leading to increased risk of errors and incorrect decisions (Lorist, 2008). Some argue that mental fatigue differs somewhat to a state of "sleepiness" (i.e., in non-diseased persons), in that a sleepiness state may be further along the wake-sleep continuum than mental fatigue (Phipps-Nelson, Redman, & Rajaratnam, 2011). However, the authors contend that it would be highly challenging to distinguish reliably between the two states given the subjective nature of assessing mental fatigue and sleepiness. Future research may need to clarify any supposed differences.

Arguably, this increased performance decrement experienced during mental fatigue can be explained by diminished cortical processing of "top-down" resources resulting in reduced capacity to perform goal-directed behavior and attend to tasks effectively (Lorist, 2008). In addition, mental fatigue will result in a deterioration of the afferent-efferent closed-loop system (bottom-up, top-down), that is, one's ability to perceive incoming afferent signals (e.g., sounds, shapes, smells, nociception), leading to slowed reactions and less effective decision making about one's choices and attention to what is important in one's immediate context (Boksem et al., 2005; Corbetta & Shulman, 2002). For example, when a person drives a vehicle for extended time periods, they will experience mental fatigue and sleepiness. As explained above, this will result in a reduced capacity to process incoming afferent information necessary to drive safely and efficiently (Boksem et al., 2005; Lorist, 2008). Essentially, when fatigued, the driver's ability to process continuous incoming information about the driving environment (e.g., speed of the vehicle and surrounding vehicles, speed limits, traffic threats, road surface condition and safety, sound of the motor, etc.) will be challenged and weakened. Consequently, top-down resources will be diminished, affecting their awareness of the changing driving environment, their ability to estimate a safe distance between their vehicle and the vehicle in front, ability to predict when to brake, recall traffic rules, and calculate directions, and so on, resulting in performance decrements and raising the possibility of accidents and injuries. Furthermore, mental fatigue often results in intensified exertion and mental effort in attempts to improve efficiency, though at the expense of capacity to process cognitively, potentially leading to anxiety and frustration (Boksem et al., 2005; Craig, Tran, Wijesuriya, & Middleton, 2012).

1.2 | Neural oscillations

The EEG signal reflects the summation of the inhibitory and excitatory postsynaptic potentials of neural nerve cells (Santamaria & Chiappa, 1987). The rhythmic activity of large groups of neurons is believed to be a rudimentary means of communication between cortical cell groups (Klimesch, 1996; Steriade, Gloor, Llinás, Lopes da Silva, & Mesulam, 1990). The cortical electrical field potentials are measured using scalp electrodes and when quantifying the EEG signal, it can be transformed into spectral bands. That is, delta wave activity (1–4 Hz), theta wave activity (4–7.5 Hz), alpha wave activity (7.5–13 Hz; sometimes divided into lower alpha: 7.5–10 Hz, and upper alpha: 10–13 Hz), beta wave activity (14–30 Hz), and gamma activity (>30 Hz). These bands have been shown to be sensitive to the wakeful/sleep states, and consequently, EEG is considered a potential biomarker for the wakefulness to sleep spectrum (Aeschbach et al., 1999; Craig, Tran, Wijesuriya, & Middleton, 2012; Ishii et al., 2014; Klimesch, 1996; Santamaria & Chiappa, 1987; Scammell et al., 2017).

EEG synchronization and desynchronization activity in theta, alpha and beta bands occur with various cortical activities in specific regions of the brain. Synchronization of EEG activity refers to the co-activation of very large numbers of neural cells resulting in increased amplitude in the frequency of the EEG spectrum (Clayton, Yeung, & Cohen Kadosh, 2015). Increased theta and alpha wave amplitude (synchronization) has been found to be associated with the onset of fatigue (Barwick, Arnett, & Slobounov, 2012; Borghini et al., 2012; Craig, Tran, Wijesuriya, & Middleton, 2012). Interestingly, alpha wave synchronization has also been shown to be related to top-down activity such as demanding internal cognitive processing in frontal brain regions (Benedek, Bergner, Könen, Fink, & Neubauer, 2011). Desynchronization involves reduced amplitude of the EEG wave and generally associated with the increased cortical activity or an alert non-fatigued brain (Benedek et al., 2011; Klimesch, 1996).

1.3 | EEG as an indicator/biomarker of mental fatigue

Mental fatigue is a significant safety problem in many industries. There is a need to establish reliable biomarkers that are suitable for countermeasure monitoring systems, some options being EEG, heart signals, eye movements (electrooculography), and videoing facial movement. EEG being sensitive to cognitive functions are likely to be influenced by mental fatigue and thus a promising biomarker (Borghini et al., 2014; Clayton et al., 2015; Santamaria & Chiappa, 1987; Scammell et al., 2017; Wijesuriya, Tran, & Craig, 2007). Consequently, changes in the EEG spectral bands concomitant with the onset of mental fatigue have been extensively studied and published in the research literature (e.g., see studies listed in Table 1). However, if change in EEG spectral bands is ever to be considered a valid and reliable indicator to be used within mental fatigue monitoring or countermeasure systems there needs to be clarification of the reliability of change in the four main EEG bands, such as the size and direction of change. For example, some studies find increases in alpha and theta contingent with mental fatigue, while others do not (Craig, Tran, Wijesuriya, & Middleton, 2012; Jap, Lal, Fischer, & Bekiaris, 2009; Tanaka et al., 2012). This was one purpose of this study. Clarification also needs to occur regarding in which cortical regions these EEG changes are occurring and therefore where best to measure the signals.

1.4 | Objectives

The primary objective of this article, therefore, was to address the following questions: (a) Are mental fatigue associated changes in brain wave spectral oscillations in delta,

TABLE 1 Details about studies that met inclusion criteria

Authors; year of publication	*N* and sex	Mean age (yr); *SD* or range	Fatiguing task	EEG sites recorded; sites used in the meta-analysis	Time on task and quality scores
Awais, Badruddin, and Drieberg (2014)	9 adult students	–	Simulated driving	19 sites; O1, O2, P3, P4	1 hr 50 min; 2,5
Caldwell, Hall, and Erickson (2002)	10; 9 males	31.2; 26–46	Simulated flying	25 sites; Fz, Cz, Pz	2 hr testing sessions; 26 hr sleep deprivation; 2,3,4
Campagne, Pebayle, and Muzet (2004)	46 males	20–70	Simulated driving	F3, C3, P3, O1	2 hr 49 min; 1,2,3
Cao, Wan, Wong, Cruz, and Hu (2014)	21 students	21–29	Exposure to visual stimuli	Oz	Up to 1 hr; 3
Craig, Tran, Wijesuriya, and Middleton (2012))	48, 25 males	31.5; 12	Simulated driving	32 sites; Fz, Cz, Pz	2 hr; 1,2,3,4,5
Dasari, Shou, and Ding (2013)	10 males	24; 4	Simulated flying	128 sites; Fz, Cz,Pz	2 hr; 2,5
Fan et al. (2015)	10 males	20–28	Cognitive task	19 sites; Fz, Cz, Pz	1 hr; 1,2,4,5
Gharagozlou et al. (2015)	12 males	20–30	Simulated driving	13 sites	Around 1 hr; 1,2,4
Jagannath and Balasubramanian (2014)	20 males	23; 4	Simulated driving	21 sites; F3,F4,P3,P4, O1,O2	1 hr; 1,2
Jap et al. (2009)	52, 36 males	28; 10	Simulated driving	30 sites	1 hr; 2,4
Jap, Lal, and Fischer (2011)	50 males	44; 9	Simulated driving	FP1–FP2, T3–T4	0.5 hr; 2,3,4
Lal and Craig (2002)	35, 26 males	34; 21	Simulated driving	19 sites	Up to 2 hr; 1,2,3,4
Macchi, Boulos, Ranney, Simmons, and Campbell (2002)	8, 7 males	40.9	Simulated driving	8 bipolar sites	2 hr; 2,3
Perrier et al. (2016)	24, 12 males	26.9; 3.4	Real driving	7 sites used for frontal, central, posterior regions	0.5 hr plus sleep deprivation; 1,2,3,4
Phipps-Nelson et al. (2011)	12, 8 males	32.7; 6.9	Simulated driving	F3, F4, C3, C4, P3, P4, O1, O2	2 hr; 1,2,3,4
Simon et al. (2011) (see also Schmidt et al., 2009)	10, 6 males	27.5; 24–36	Real driving	64 sites; 9 sites in frontal & central, 11 in posterior	2 hr 23 min; 2,3,4,5
Tanaka et al., 2012	18 males	30; 11	Cognitive tasks	11 sites; Fz, Cz, Pz,	2 hr; 1,2,4
Torsvall and Akerstedt (1987)	11 train drivers	42; 27–58	Real driving	O2–P4	4.5 hr; 1,2,3
Trejo et al. (2015)	16, 12 males	26.9; 7	Cognitive task	32 sites; Fz, Pz	Up to 3 hr; 1,2,5
Wascher et al., 2014	14, 7 males	23.4; 21–27	Cognitive task	60 sites; FCz, POz	4 hr; 1,3,5
Zhao, Zhao, Liu, and Zheng (2012)	13 males	25.8; 22–27	Simulated driving	32 sites; FZ, Cz, Pz	1.5 hr; 1,2,3,4,5

Note: Quality Score: The greater number of scores indicates higher quality: 1 = mental fatigue defined; 2: mental fatigue assessed; 3: Circadian effects controlled; 4: participants asked to refrain from substances that will influence EEG; 5: sophisticated EEG cleaning strategies used to remove noise.

theta, alpha, and beta bands, reliable indicators/biomarkers, regardless of the sustained task used to produce mental fatigue? (b) Depending on the spectral band, does change in brain wave activity occur more reliably in some cortical regions? To obtain answers to these questions, we report results of a systematic review with meta-analyses of studies that investigated changes in the EEG spectral bands associated with the onset of mental fatigue.

2 | METHOD

2.1 | Inclusion criteria

Inclusion criteria for the systematic review and meta-analyses consisted of: (a) Studies conducted after 1980 that investigated brain wave activity (EEG) changes in non-diseased adults (aged 18+), in tasks designed to generate mental fatigue (i.e., over an extended period of time expected to result in mental drowsiness), such as simulated driving or performing cognitive tests. (b) Studies presented mean EEG spectral data in at least one of the four major bands (delta, theta, alpha, and beta rhythm activity), in the form of EEG amplitude (magnitude) or power (square of the amplitude) change scores, from an alert to a fatigued state. It should be noted that only studies that provided EEG spectral amplitude or power change data were used in the meta-analyses. Studies that provided results only in the form of an inferential statistical test for change over time (e.g., a one-way repeated measures ANOVA *F*-value) were not used in the meta-analysis, given a pre-post repeated measure *F*-value cannot be directly converted to a mean difference effect size quantifying change in brain activity (Cohen, 1988). (c) Studies reporting cortical site(s) from which the EEG was recorded using either monopolar or bipolar assessment. (d) Studies published in peer-reviewed journals or refereed conference papers, or research reported in a doctoral thesis, and (e) Studies published in English.

2.2 | Search procedure

The systematic review and meta-analyses were conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). To perform a comprehensive systematic review of the literature concerning EEG spectral activity changes associated with the onset of mental fatigue, a high yield search strategy was utilized. Medical Subject Headings (MeSH) vocabulary thesaurus was used with terms naming descriptors in a hierarchical structure that permitted searching at different levels of specificity. Search terms used in conjunction with "fatigue," "alert," "tiredness," or "drowsiness" included "mental," "cognitive," or "health." Brain activity terms included "EEG," "electroencephalography or electroencephalogram," "brainwaves or brain waves," while the terms "delta, theta, alpha and beta" were used in conjunction with "rhythm, wave or activity." Multiple search engines were used to maximize chances of finding studies that met the above inclusion criteria. Search syntax and strategies were tailored to the unique capabilities of each search engine. Medline (via OVID), PsychInfo and IEEE search engines were first employed using combinations of the above keywords. Google Scholar was employed last, using the broad search term "mental fatigue, drowsiness and brain wave activity, EEG." The Google search involved reading the title and abstract of the first 1,000 papers detected by the Scholar search, and then the search was continued sequentially until no new relevant papers were detected in 200 papers. Additionally, we also sourced relevant studies in reference lists of systematic reviews as well as published conference papers.

2.3 | Meta-analyses computations

EEG data included in the analyses were generated by diverse research groups using different methodologies (e.g., recruitment, types of participants, and EEG equipment and assessment strategies). Given this diversity, it was expected that heterogeneity will be large, that is, a large amount of between-study variability in addition to existing within-group variability (Borenstein, Hedges, Higgins, & Rothstein, 2009; Higgins, Thompson, Deeks, & Altman, 2003). Estimated heterogeneity was calculated using I^2 (the proportion of observed variance that reflects real differences in effect size) and tau-squared (τ^2; an estimate of the standard deviation of the distribution of true effect sizes), both of which provide information on the amount of heterogeneity beyond sample differences (Borenstein et al., 2009; Higgins et al., 2003). An I^2 of 0% indicates no observed heterogeneity, 25% low, 50% moderate and >75% indicates high heterogeneity (Higgins et al., 2003). If I^2 is large, it becomes worthwhile to explore with additional meta-analytic techniques (Borenstein et al., 2009). The effect size index used for all outcome measures was Hedge's *g*, the standardised mean difference between the alert and fatigued conditions, correcting for small-sample bias. The effect of each study was weighted by the inverse of its variance, the variance being composed of both within and between study variance.

Robust variance estimation (RVE) meta-analyses were conducted to determine an overall effect size (across all frequencies and regions) for spectral change in the studies meeting inclusion criteria. RVE meta-analyses were then conducted on each of the four frequency bands separately to examine the effect sizes for each individual frequency band. Given the dependent nature of EEG measurements RVE was chosen as it manages dependent effects by mathematically adjusting the standard errors of the effect sizes to account for dependence (Hedges, Tipton, & Johnson, 2010). This allows the inclusion and synthesis of all estimated effect sizes simultaneously eliminating the need to average or select only one effect size per study. In contrast, traditional meta-analysis models assume independent effect sizes, with a common approach for handling multiple effect sizes, resulting in an averaging of the study effect sizes, which leads to a loss of information (Fisher & Tipton, 2015). The outcome of the RVE meta-analysis is a random-effects weighted average, similar to traditional meta-analyses, while including all available information (Fisher & Tipton, 2015).

Network meta-analysis (also called mixed treatments comparison or multiple treatments comparison meta-analysis) is an extension of the standard pairwise meta-analysis allowing comparisons of multiple interventions to be calculated in a single analysis of all the relevant studies (Caldwell, Ades, & Higgins, 2005; Leucht et al., 2016; Zhang et al., 2014). Network meta-analysis was used in the current study so that changes in the four spectral bands associated with mental fatigue could be analyzed together, allowing direct comparison of change in the bands. It also enabled the comparison of change in EEG spectral activity in multiple cortical regions associated with mental fatigue. Therefore, a two arm-based network meta-analysis was conducted, first, to estimate and compare changes in the four EEG frequency band associated with mental fatigue, and second, to compare changes in EEG spectral activity in the cortical regions associated with mental fatigue. To assist in visualizing the multiple distributions of frequency band and cortical region by effect size, posterior probability density plots are provided. These are based on a probability distribution of the EEG spectral data, performing a function similar to histograms, though presenting and describing the four EEG frequency bands and the cortical regions.

All statistical analyses were performed using R version 3.5.2 (R Core Team, 2013) and RStudio version 1.1.442 (RStudio Team, 2015). Metafor package (Viechtbauer, 2010) was used to calculate effect sizes and the robumeta package (Fisher & Tipton, 2015) used to calculate the RVE for the overall effects of the meta-analysis. The pcnetmeta R package (Lin, Zhang, Hodges, & Chu, 2017) was used for the network meta-analysis, which involved a random effects model with a Bayesian framework, enabling the estimation of the effects of the different arms used for EEG analysis (e.g., the four spectral bands).

2.4 | Quality analysis of the selected studies

The authors agreed the following criteria were important for the scientific quality of the papers selected for the meta-analyses: (a) The study provided an operational definition of mental fatigue. (b) An assessment for mental fatigue was conducted pre and post-intervention. (c) Circadian rhythm confounding effects were addressed in the experimental design, for example, participants were assessed at a standard time each day. (d) Participants were asked to refrain from using substances prior to the study that may possibly confound the mental fatigue task, such as coffee and (e) cleaning strategies were employed to improve the signal-to-noise ratio of the EEG. This is due to EEG being an extremely small signal (millionths of a volt), and artifact sources (e.g., electrical power, radar, eye and head movement, heart signals, and so on) having a critical influence on the integrity of the EEG signal. Each criterion was awarded one point, for a maximum score of 5 points, with higher scores indicative of higher scientific quality. All studies meeting inclusion criteria for the meta-analyses were examined for these quality indicators and quality ratings of 3 or above were considered acceptable for scientific quality. Table 1 contains the quality scores for each study.

3 | RESULTS

Figure 1 summarizes the study selection procedure based on PRISMA guidelines (http://www.prisma-statement.org/). The Medline, PsychInfo, and IEEE searches produced 805 relevant studies. From this total, 164 studies were selected for full-text reading after inspecting titles and abstracts. The broad Google Scholar search produced 17,300 results, however, only the first 1,200 abstracts were inspected as no new studies meeting the inclusion criteria were found in 200 papers in the search after the first 1,000 papers were examined. Only 4 additional studies were found in the Google Scholar search and one study was found from the reference list of a review paper, resulting in 169 papers requiring detailed inspection. After careful inspection, 65 papers were selected for additional reading. This resulted in a further 44 papers being excluded, leaving 21 meeting inclusion criteria. All 21 studies were conducted with "non-diseased" samples who participated in protracted mental tasks leading to mental fatigue (which also potentially encompasses feelings of sleepiness or boredom etc). It was assumed from the Method described in the 21 studies that all participants were alert at the beginning of the task when EEG was begun to be assessed, and that they gradually became tired as they participated over time while exerting mental effort, regardless of the type of task (i.e., driving or cognitive tests). Studies were selected where it was clear that participants were assessed over time from an alert to a tired/mentally fatigued state. Of these 21, 9 papers only provided an overall cortical change in EEG spectral data, while 12 papers provided information on change in EEG spectral activity in specific cortical regions

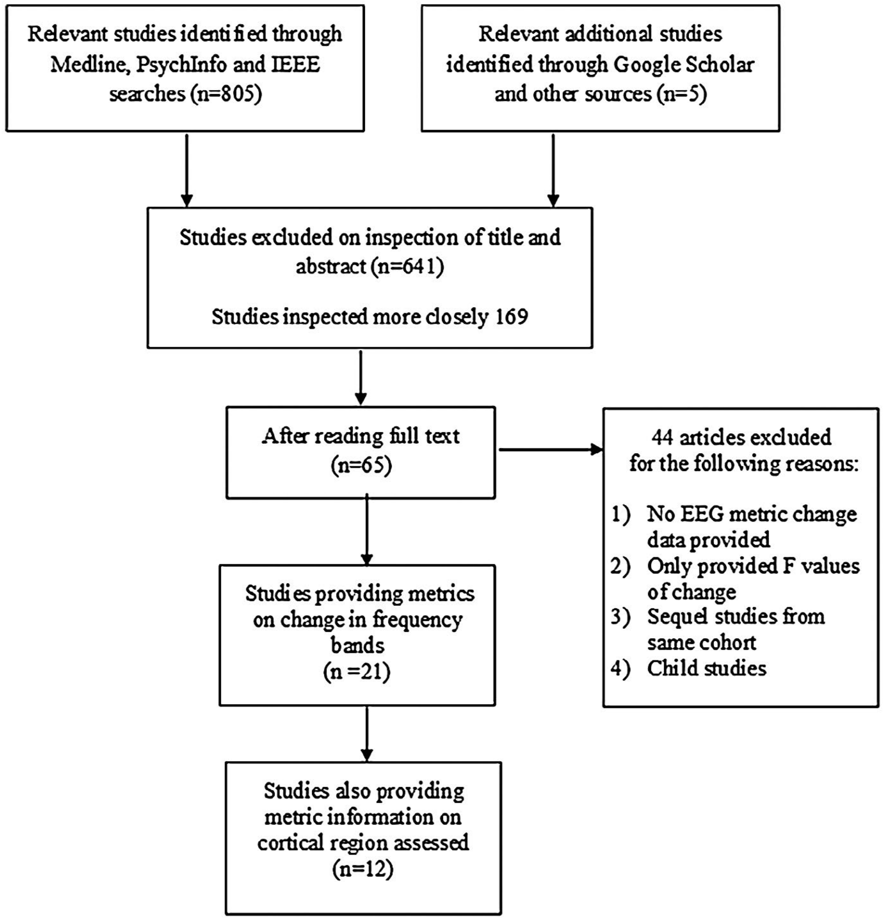

FIGURE 1 Flow diagram showing search results and selection/exclusion process of the studies eligible for inclusion

rather than a single change measure over the entire cortex. Table 1 provides detail on cortical sites used to measure EEG in the 21 studies including the assessment of the quality of the study. Where data from multiple sites was provided in the 12 studies, where possible, data from Fz, Cz, and Pz were extracted and used to summarize change in frontal, central, and posterior regions.

3.1 | Results of the RVE meta-analysis

An RVE meta-analysis examining change in all EEG spectral changes from the 21 studies found a medium to large effect size (g = 0.68; 95% confidence interval or CI: 0.24–1.13, $p < .01$). As expected, heterogeneity was large with an I^2 of 91.1 and τ^2 1.05. This was followed by four additional RVE meta-analyses examining change in each of the individual four bands. Inspection of the forest plots in Figures 2-5 show the range of observed effect sizes for change in each of the four spectral bands associated with mental fatigue. For delta wave activity change, a moderate non-significant effect size was found ($g = 0.62$; 95%CI: −0.34–1.57, $p = .17$). Figure 2 shows a forest plot with effect sizes for delta wave activity change in 9 of the 21 studies. Heterogeneity was large with an I^2 of 92.2 and τ^2 1.2. For theta wave activity change, a large significant effect size was found (g = 1.0; 95%CI: 0.56–1.44, $p < .001$). Figure 3 shows a forest plot with effect sizes for theta wave activity change in 19 of the 21 studies. Heterogeneity was large with an I^2 of 83.6 and τ^2 0.54. For alpha wave activity change, a moderate to large significant effect size was found ($g = 0.76$; 95%CI: 0.20–1.33, $p < .05$). Figure 4 shows a forest plot with effect sizes for alpha wave activity change in 21 studies. Heterogeneity was large with an I^2 of 91.9 and τ^2 1.2. For beta wave activity change, a small non-significant effect size was found (g = 0.03; 95%CI: −0.76–0.83, p = .93). Figure 5 shows a forest plot with effect sizes for beta wave activity change in 12 studies. Heterogeneity was large with an I^2 of 93.9 and τ^2 1.5. The high heterogeneity found for overall EEG activity and for each band indicates the 21 studies come from varied populations (for instance, due to variation in methodology) and that therefore it was judicious to perform additional meta-analyses, such as network meta-analyses and subgroup analyses (Borenstein et al., 2009).

3.2 | Network meta-analysis: Spectral bands

Figure 6 shows the network meta-analysis forest plot allowing for a direct comparison of the four spectral bands

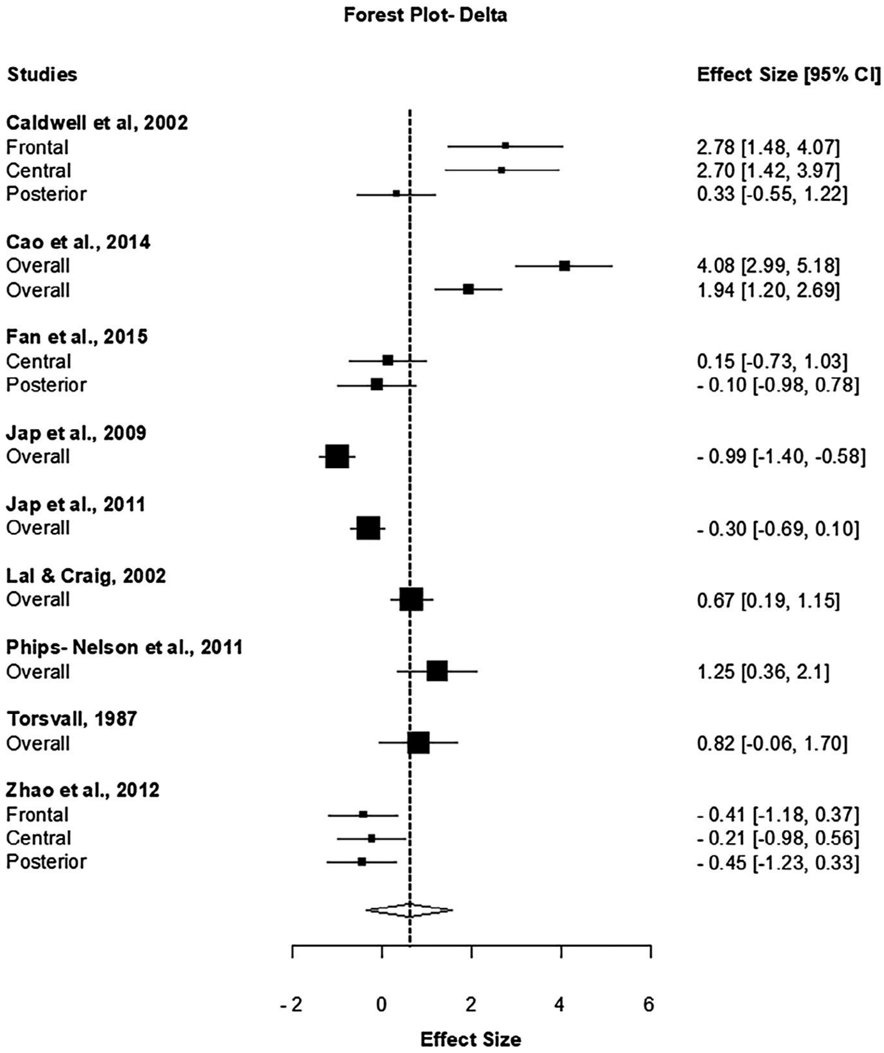

FIGURE 2 RVE forest plot for delta wave activity. 95% confidence intervals (95%CI) are in brackets. Width of the diamond shows 95%CI for the overall *g* of 0.62

associated with the onset of mental fatigue for all 21 studies. The effect sizes were largest in the theta (g = 1.03; 95%CI: 0.79–1.60) and alpha frequency bands (g = 0.85; 95%CI: 0.47–1.43). The delta band had a moderate effect size (g = 0.58; 95%CI: 0.09–1.42), while the beta band was found to have a small effect size (g = 0.23; 95%CI: −0.32–0.92). Figure 7 shows the density plot for the four frequency bands.

3.3 | Network meta-analysis: Regions

The changes in spectral EEG in the frontal, central and posterior regions were also explored using network meta-analysis in 12 studies only. Figure 8 shows the EEG effect sizes from the frontal, central, and posterior cortical regions associated with mental fatigue. The effect size was approaching large for the central region (g = 0.80; 95%CI: 0.46–1.21), and moderate for frontal (g = 0.64; 95%CI: 0.23–1.12) and posterior regions (g = 0.61; 95%CI: 0.21–1.06). Figure 9 shows the density plot for the change in EEG by regions.

3.4 | Sub-group network meta-analysis spectral bands by region

Figure 10 shows a sub-group network meta-analysis of change only in theta and alpha EEG spectral bands by region. This analysis shows that change in the theta band was large in frontal (g = 1.24; 95%CI: 0.44–1.95), central (g = 1.34; 95%CI: 0.44–1.96) and posterior sites (g = 1.12; 95%CI: 0.34–1.91). Alpha frequency band change was moderate to large if measured in central (g = 0.88; 95%CI: 0.26–1.48) and posterior sites (g = 0.76; 95%CI: 0.05–1.34), while moderate in frontal sites (g = 0.50; 95%CI: −0.46–1.36).

3.5 | Sub-group analyses controlling for type of fatiguing task

To confirm that driving (including 2 simulated flying) versus cognitive tasks were similar in EEG power change during the fatiguing task, the 21 studies were divided into

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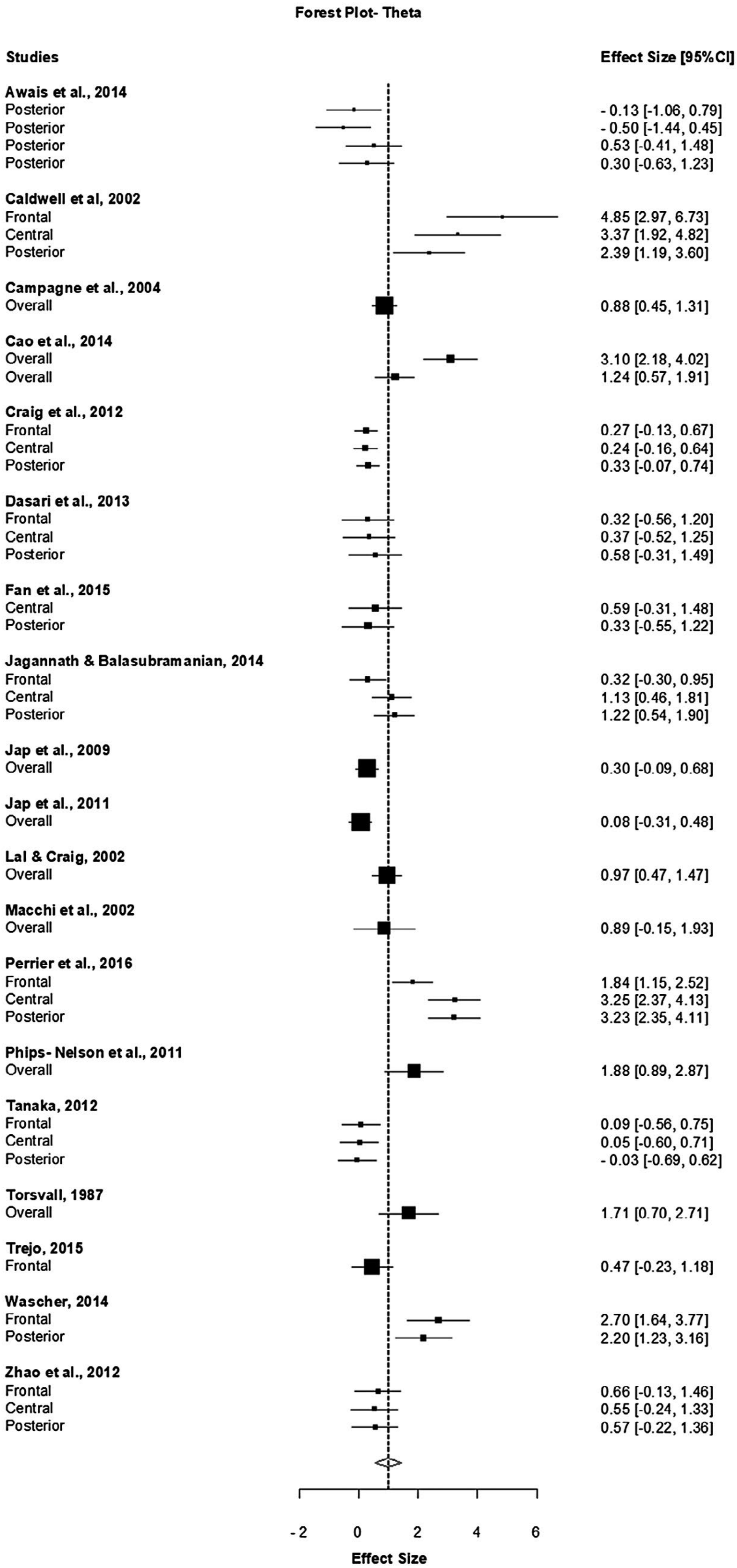

FIGURE 3 RVE forest plot for theta wave activity. 95% confidence intervals (95%CI) are in brackets. Width of the diamond shows 95%CI for the overall *g* of 1.0

those that utilized a driving protocol (simulated or real: 16 studies) versus a cognitive task protocol (5 studies). These two groups were then compared for theta and alpha spectral activity outcomes averaged across cortical sites. For theta activity, there were no significant differences between groups using a non-parametric test (Mann Whitney) for

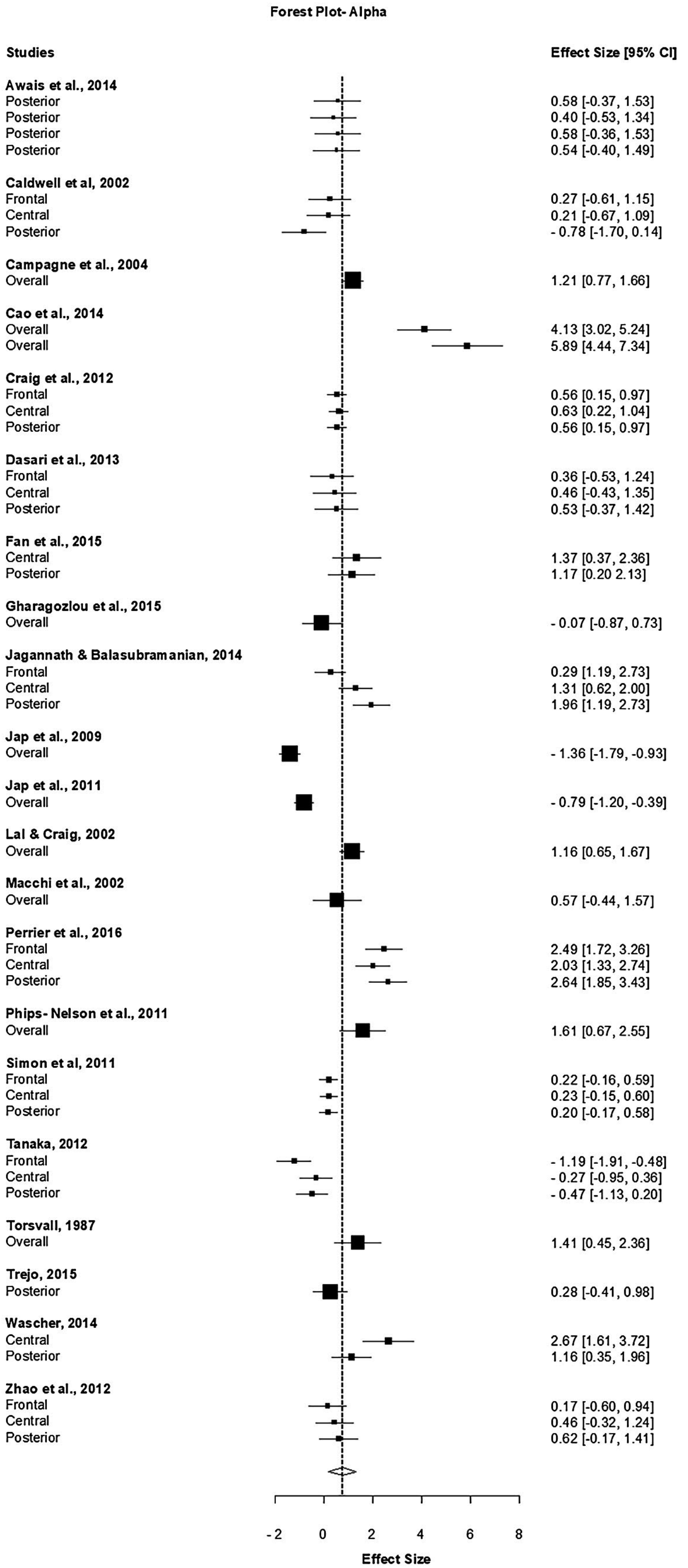

FIGURE 4 RVE forest plot for alpha wave activity. 95% confidence intervals (95%CI) are in brackets. Width of the diamond shows 95%CI for the overall g of 0.76

EEG power ($U = 14$, $z = 1.28$, $p = .21$). For alpha activity, there were no significant differences between groups using a non-parametric test (Mann Whitney) for EEG power ($U = 24$, $z = .37$, $p = .71$).

4 | DISCUSSION

This meta-analytic study investigated change in EEG spectral activity concomitant with mental fatigue in non-diseased

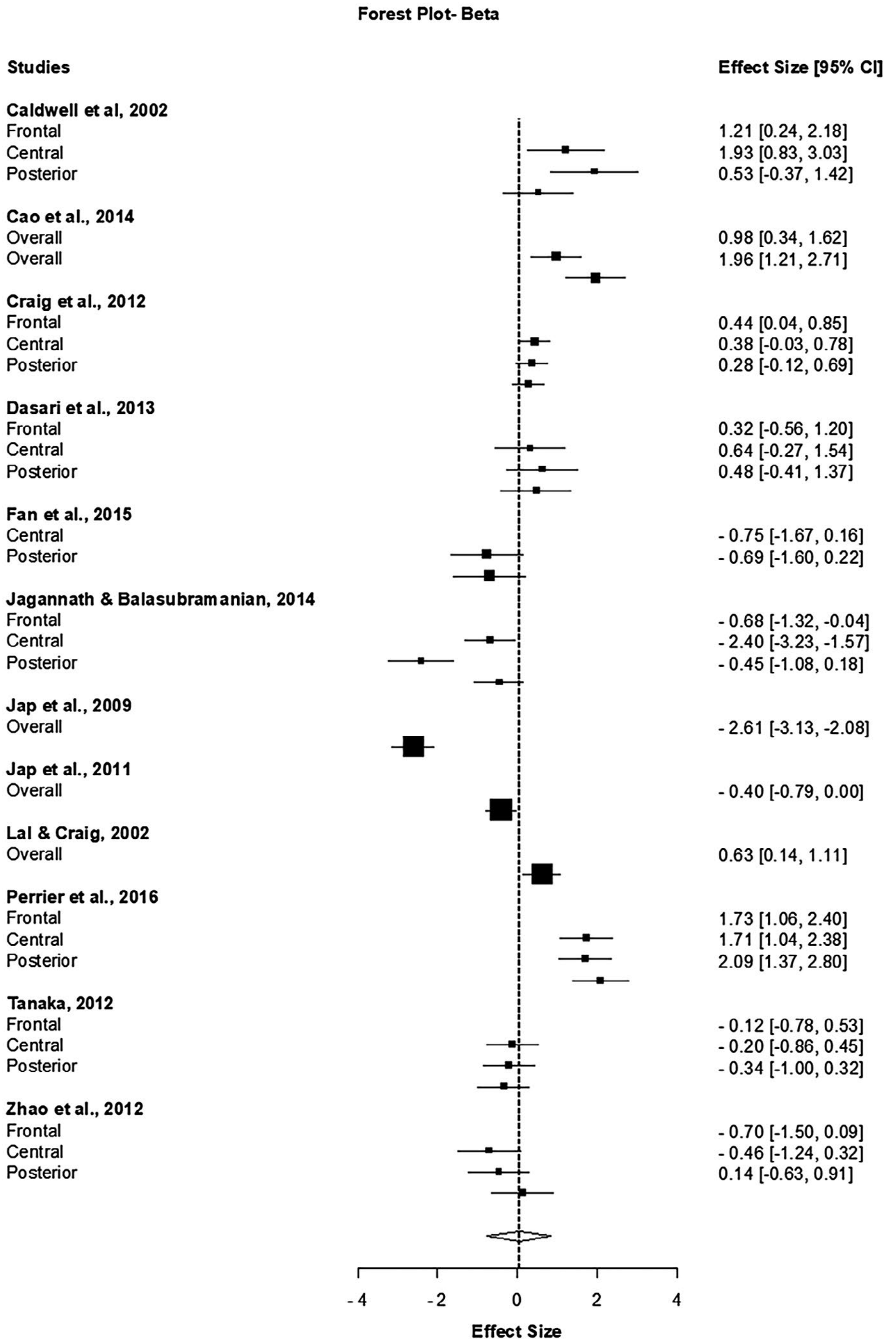

FIGURE 5 RVE forest plot for beta wave activity. 95% confidence intervals (95%CI) are in brackets. Width of the diamond shows 95%CI for the overall *g* of 0.03

adults. This is an important objective to achieve as there is no clarity from past studies whether change across the four bands is a reliable occurrence, nor is it clear where the regional changes are occurring. Furthermore, results from the meta-analyses can be used to determine whether EEG spectral change can be considered a reliable biomarker of mental fatigue. As argued, EEG spectral change has been considered a feasible biomarker that could be used to predict and warn a person when they become fatigued when exerting sustained mental effort (Chai et al., 2017). Change in EEG spectral data could, therefore, be used in a mental fatigue countermeasure device, possibly leading to reduced risk of accident and injury in a broad range of activities, such as aviation, transport industries, driving cars, or in shift work occupations such as medicine/nursing (Borghini et al., 2014; Scott, Hofmeister, Rogness, & Rogers, 2010; Sikander & Anwar, 2019). The findings presented in this article provide a firm indication of which EEG spectral band change is reliably occurring when a person mentally fatigues, as well as which cortical region would be best to measure change in EEG.

The RVE meta-analyses across all frequency bands and regions revealed that increased EEG spectral activity occurs concomitant with mental fatigue (moderate effect size of 0.68). However, as this meta-analysis shows the overall effect size, it does not indicate in which frequency band change is reliably occurring. The individual frequency RVE

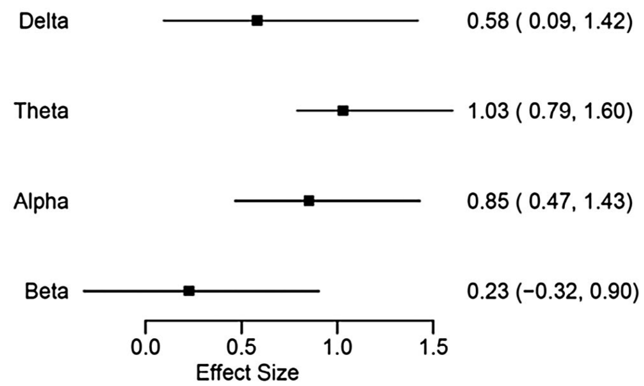

FIGURE 6 Forest plot for a comparison of size of change in the four spectral EEG bands associated with mental fatigue calculated using network meta-analysis. 95% confidence intervals (95%CI) are in brackets

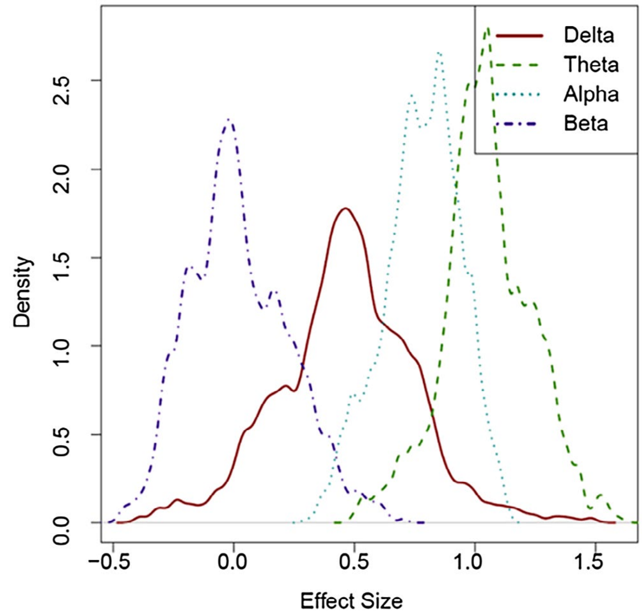

FIGURE 7 A density plot displaying posterior densities for estimates of effect sizes for EEG frequency bands delta, theta, alpha and beta

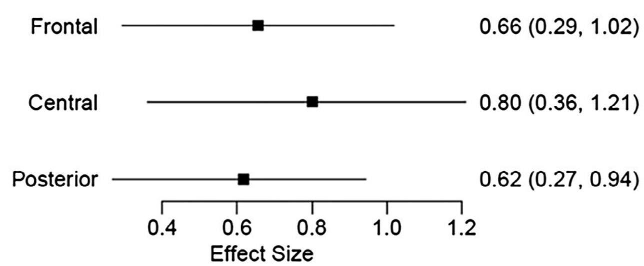

FIGURE 8 Forest plot showing a comparison of size of change in spectral EEG in frontal, central and posterior regions associated with mental fatigue calculated by network meta-analysis. 95% confidence intervals (95%CI) are in brackets

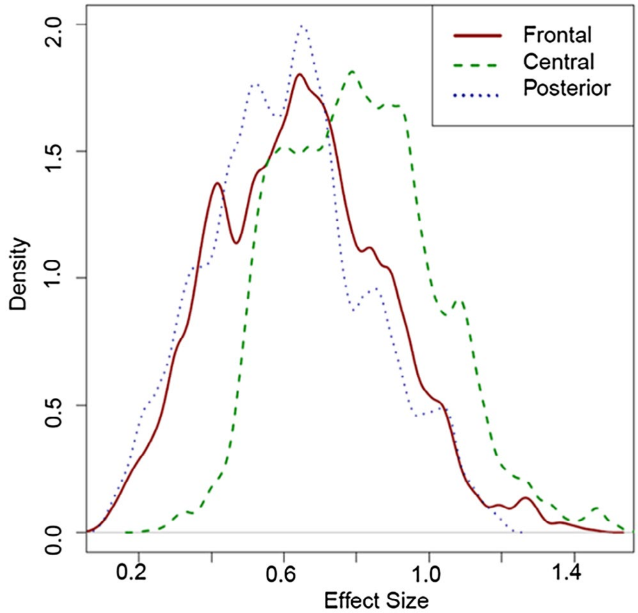

FIGURE 9 A density plot displaying posterior densities for estimates of effect sizes for frontal, central, and posterior EEG regions

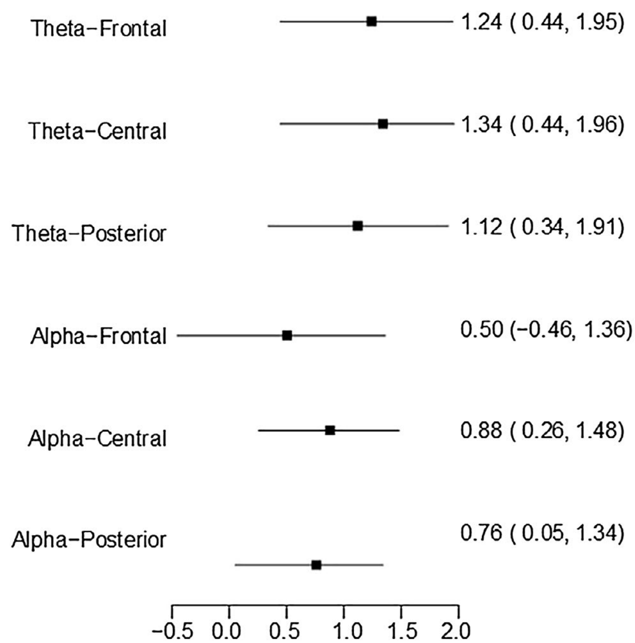

FIGURE 10 Sub-group network meta-analysis for a comparison of size of change only in theta and alpha EEG spectral bands by region. 95% confidence intervals (95%CI) are in brackets

meta-analyses provided evidence to answer this question. Large increases in theta wave activity and moderate-large increases were found in alpha wave activity concomitant with mental fatigue, while EEG spectral changes in delta and beta wave activity were shown to be unreliable and varied. Five of the nine studies that have examined changes in EEG delta, found increase in delta activity associated with mental fatigue, while four found changes in the opposite direction.

Interestingly, the study from Fan and Colleagues (2015) found increases in delta in the central region but decrease in posterior regions. Inconsistent results in delta activity could be a result of large ocular artifacts which are often in the same frequency band as delta activity, especially in regions closer to the front of the scalp. Inconsistent changes were also found with beta activity with half of the studies finding increases associated with mental fatigue. Some of the inconsistent results may be explained through the tasks used to fatigue participants, however, the type of task was shown not to influence EEG change significantly. Beta activity is thought to occur with increased cortical arousal associated with increased mental activity or effort, so increases in beta from simulated driving/flying tasks may be related to the exertion of mental effort to remain vigilant (Craig, Tran, Wijesuriya, & Middleton, 2012) whereas the decreased beta activity reported may be a result of cognitive tiredness.

To explore further and allowing for direct comparisons between the different frequency changes across the individual bands and in which region this change was occurring, network meta-analyses were then conducted. In comparison to the other bands, the largest and most consistent changes occurred in theta and alpha wave activity. Large increases in theta and moderate to large increases were found in alpha wave activity. In comparison, change in delta and beta wave activity was shown to cover a much larger confidence interval demonstrating more inconsistent results. Across all frequencies, most increase in spectral EEG was found to occur in central regions, with lesser increases found in frontal and posterior regions. Given that theta and alpha had the larger effect sizes in comparison to delta and beta, sub-group meta-analysis was conducted to examine the regional effect sizes for these two frequency bands. Large increases in theta wave activity occurred concomitant with mental fatigue across frontal, central and posterior regions, while moderate to large increases in alpha wave activity were found in central and posterior regions, with lesser increases found in frontal regions.

It is not surprising that EEG activity in central, frontal and posterior regions of the brain are highly affected by a fatiguing task. Fundamentally, as discussed in the Introduction, EEG during the wake-sleep cycle undergoes changes (notably in the theta and alpha spectrums) due to circadian and homeostatic processes, regulated by the circadian pacemaker in the suprachiasmatic nucleus of the hypothalamus, and corresponding with melatonin release (Aeschbach et al., 1999). This will influence most if not all neural regions. Further, evidence shows that slow EEG activity in the theta and alpha spectrums increase in frontal regions (e.g., posterior medial frontal cortex) during sustained attention (thus producing fatigue), with resultant phase synchronization connections communicating through central and posterior regions, exerting control over, for instance, cognitive, visual, and perceptual function (Clayton et al., 2015). Evidence also suggests that alpha activity is an index of top-down processing in frontal, central and posterior regions in which the cortex inhibits non-essential or conflicting processes, during sustained attention leading to fatigue (Bazanova & Vernon, 2014). Connectivity research has also shown strong brain networks exist between frontal, central, and posterior cortical regions when a person mentally fatigues (Fonseca et al., 2018; Liu, Zhang, & Zheng, 2010; Sun, Lim, Kwok, & Bezerianos, 2014).

These findings have implications for mental fatigue countermeasures as well as for theories that attempt to explain EEG spectral activity synchronization and desynchronization associated with mental function. Increased slow wave EEG activity in the 4–13 Hz frequency range (i.e., theta and alpha bands) can be considered reliable biomarkers of mental fatigue. Increases were found in almost all 21 studies in these two bands, except for a few studies where decreases were found (e.g., Jap et al., 2009, 2011; Tanaka et al., 2012). Explanations for why these studies found decreased 4–13 Hz activity rather than increased activity are not forthcoming. Nonetheless, we assert that increased theta activity (and to a lesser extent increased alpha activity) can be considered confirmed biomarkers of mental fatigue. Based on these findings, it is therefore recommended that theta activity be the front-line band targeted in frontal, central, or posterior regions, in a mental fatigue countermeasure device. Such a device could also target change in alpha activity in the countermeasure algorithm to account for individual variability. Additionally, countermeasure technology should utilize novel EEG processing strategies that can effectively classify increases in 4–13 Hz that occur over the cortex (e.g., remove artifact; improve recognition of changes). Countermeasure technology could also employ additional backup physiological measures such as heart rate, eye blink rate/ electrooculography, heart rate variability, and/or vehicular and hybrid features when driving (Borghini et al., 2012; Sikander & Anwar, 2019; Tran, Wijesuriya, Tarvainen, Karjalainen, & Craig, 2009).

Similar to mental fatigue, mental and cognitive activity has been shown to be associated with EEG 4–13 Hz cortical activity (Fonseca et al., 2018; Kiroy, Warsawskaya, & Voynov, 1996; Sauseng, Griesmayr, Freunberger, & Klimesch, 2010). For instance, increased power in slow-wave activity in the 4–13 Hz bands has been found to be associated with deterioration in mental performance (Borghini et al., 2014; Kiroy, Warsawskaya, & Voynov, 1996) and the findings of this meta-analytic study confirm this conclusion, given increased power in theta and alpha activity across the cortex was strongly associated with mental fatigue. Importantly, these increases occurred regardless of the type of fatiguing task studied. That is, a driving task (simulated or real) versus a cognitive test task. It is asserted here, therefore, that the type of task will more than likely not be a distinguishing factor for being associated with increased EEG spectral power in theta and alpha activity, as long as the task involves a protracted mentally fatiguing exercise. As discussed above in the network meta-analysis for regions, these increases are most likely to occur substantially in central cortical sites, followed by frontal and posterior regions. Connectivity research has shown that while coherence increased (generally believed to be associated with greater neural communication) during a mentally fatiguing task in frontal, central and posterior regions, it was concluded that this increase in coherence was associated with more "economical" but less efficient mental performance (Zhao et al., 2017). Furthermore, Fonseca and Colleagues (2018) have shown the early sleep cycle is associated with enhancement or suppression of EEG activity in different cortical regions (e.g., suppression of theta and alpha activity in occipital areas in those with good sleep vs. activation in those with poor sleep).

As argued earlier, mental fatigue compromises top-down cognitive/mental performance, and so an individual will be less able to perform as efficiently when dealing with complex mental tasks compared to when they are alert. This will normally lead to intentional or unintentional relaxation of mental effort achieved by various means, such as shutting eyes and napping, or redirecting one's attention to less demanding mental tasks. It may, however, also lead to increased effort to maintain mental performance, resulting in increased activity (Craig, Tran, Wijesuriya, & Middleton, 2012; Fonseca et al., 2018). However, activation versus suppression in EEG activity contingent with fatigue requires further research. For example, research also suggests that theta and alpha wave phasic synchronization impede memory processing and that increased power in these bands function as an inhibition mechanism across cortical areas (Klimesch, 1996; Sauseng et al., 2010).

There are several limitations to the findings of this review. One limitation is the number of studies that met the meta-analyses' selection criteria. However, the authors believe the 21 studies selected were sufficient to make valid conclusions about the influence of mental fatigue on EEG activity, and adequate to conclude that EEG spectral change is a reliable neural biomarker of mental fatigue. Results have indicated a significant medium to large global effect size and consistent increases in theta and alpha activity following mental fatigue. While only 12 studies included information on where EEG spectral change was occurring in specific regional areas (frontal, central and posterior) associated with mental fatigue, the findings provided in these 12 studies were largely in agreement. Therefore, the authors are confident that this meta-analytic study has provided evidence that theta and alpha activity reliably increases contingent with mental fatigue in frontal, central, and posterior regions. Quality was also a concern in many studies, however, 16 of the 21 studies did meet scientific quality based on our assessment. For example, very few studies conducted sophisticated cleaning of the EEG data to improve the signal-to-noise ratio (Tran, Craig, Boord, & Craig, 2004), while few studies addressed confounding factors that required controlling, like substances that could unnaturally alter EEG activity prior to the intervention, or circadian influences on the outcomes (Craig et al., 2006). Future studies must address these quality concerns. Heterogeneity was also a challenge, however, this led directly to the calculation of outcomes based on network and substudy meta-analyses.

In conclusion, the findings of the meta-analyses reported in this article have addressed the uncertainty regarding the biomarker status of EEG spectral change associated with mental fatigue. Increased theta wave activity should be considered a definite and valid neural biomarker of mental fatigue states across the frontal, central, and posterior cortical sites, and therefore can be confidently targeted in fatigue countermeasure technology. The findings suggest the neural biomarker status of increased alpha wave activity is less certain, though we do suggest it could be used as a second line indicator to account for possible individual variability. The findings also confirm that changes in delta or beta wave activity are less reliable as neural biomarkers of mental fatigue. The findings also provide some clarity on the association of slow-wave oscillations (4–13 Hz), mental fatigue and mental performance, confirming that increased 4–13 Hz is associated with decreased mental activity. Further research is needed to clarify the role of beta wave activity associated with mental fatigue, while the status of delta wave activity also needs exploration. The authors hope these results can be utilized to improve the development of fatigue countermeasure devices, and thus reduce risk of injury and death in activities demanding sustained mental effort.

CONFLICT OF INTEREST

None.

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