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The brain signs of wear and tear: Chronic stress associated alpha oscillations in the pregenual anterior cingulate cortex lead to fatigue

Sven Vanneste [a,b,c,*], Jan Ost [c], Dirk De Ridder [c,d]

[a] School of Psychology, Trinity College Dublin, Dublin, Ireland
[b] Global Brain Health Institute & Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
[c] Brai3n, Ghent, Belgium
[d] Unit of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

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ABSTRACT

Chronic stress or distress exerts profound effects on brain function, particularly in regions involved in emotion regulation and cognitive control. Here, we investigate the relationship between chronic stress, alpha oscillatory activity in the pregenual anterior cingulate cortex (pgACC), and fatigue in a large cohort (n = 589) comprising both healthy individuals and patients with neurological or psychiatric disorders. Using resting-state EEG, we identify a negative correlation between stress-related increases in pgACC alpha oscillations and the severity of fatigue. These findings suggest that chronic stress disrupts normal inhibitory control within the pgACC, potentially leading to heightened energy demands and fatigue. Our results advance the understanding of the neural mechanisms underlying stress-related fatigue and highlight pgACC alpha oscillations as a potential biomarker for assessing chronic stress effects on brain function.

Introduction

Chronic stress is increasingly prevalent in modern society and is a major risk factor for anxiety, depression and fatigue-related disorders (McEwen, 1998; McEwen et al., 2015; Sapolsky, 1996). While acute stress responses are adaptive and support survival, prolonged activation of stress systems leads to pathological allostasis and "wear and tear" on brain and body (De Ridder et al., 2016a; McEwen and Morrison, 2013; McEwen et al., 2016; Straub, 2017). These changes involve synaptic and dendritic remodeling, neurochemical alterations, and impaired recovery from distress, ultimately contributing to cognitive and emotional exhaustion (Gray et al., 2017).

Within a predictive (Bayesian) brain framework, stress can be conceptualized as uncertainty about how to safeguard physical, mental, or social well-being (de Berker et al., 2016; Peters et al., 2017). To reduce this uncertainty, the brain increases sensory sampling and mobilizes energetic resources via adrenergic, sympathetic, and corticoid mechanisms plasticity (Peters et al., 2017). While this is beneficial in the short term, persistent uncertainty forces prolonged high energy expenditure and can lead to exhaustion, manifesting clinically as anxiety and, with chronicity, depression and fatigue (De Ridder et al., 2014; Straub, 2017; Zhao et al., 2023; Zhao et al., 2024). This view echoes Selye's general adaptation syndrome, in which stress responses progress from an alarm phase to resistance and ultimately to exhaustion when resources are depleted (Peters, 2011; Selye, 1936; Selye, 1956).

The pregenual anterior cingulate cortex (pgACC) appears to occupy a central position in this stress–energy framework. As a key node of the default mode network, the pgACC is involved in self-referential processing and stimulus-independent cognition (Raichle, 2015; Raichle et al., 2001). It contributes to stimulus inhibition and the prevention of sensory overload (De Ridder et al., 2021; De Ridder et al., 2016b; Vanneste et al., 2018; Vanneste et al., 2024)), and in Bayesian terms is thought to encode the reliability of the current behavioural state while alternative policies are represented in dorsolateral prefrontal regions (Donoso et al., 2014; Seeley et al., 2007; Vincent et al., 2008). Under distress, the pgACC shows reversible volumetric reduction and synaptic reorganization (McEwen et al., 2016; Misquitta et al., 2021; Soares et al., 2012a), and its dysfunction has been linked to chronic pain, tinnitus, autonomic symptoms, and affective disturbances (Finnerup and Baastrup, 2012; Kano et al., 2019; Mohan et al., 2020; Song, 2015; Vanneste et al., 2019).

Importantly, stress-related changes in prefrontal function, including

* Corresponding author at: Lab for Clinical & Integrative Neuroscience, Global Brain Health Institute and Institute of Neuroscience, Trinity College Dublin, College Green 2, Dublin, Ireland.
E-mail address: sven.vanneste@tcd.ie (S. Vanneste).

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pgACC involvement, are reflected in alterations of EEG rhythmicity. Alpha oscillations, in particular, have been associated with stress, attentional control, and cortical inhibitory processes stress (Ehrhardt et al., 2022; Klimesch, 1999; Tran et al., 2007). Previous work has primarily examined alpha dynamics in acute or short-term stress contexts, such as exam stress, sleep deprivation, or cognitive stress tasks like the Stroop paradigm (Alonso et al., 2015; Ehrhardt et al., 2022; Lewis et al., 2007). However, the impact of chronic stress on resting-state alpha oscillations in the pgACC, and how such changes relate to fatigue, remains poorly understood.

Given the pgACC's role in stimulus inhibition, its vulnerability to chronic stress, and the energetic burden of persistent sensory and interoceptive processing, we hypothesize that prolonged distress is associated with a slowing of alpha oscillations in the pgACC, correlating with the severity of fatigue. Furthermore, we propose that under chronic stress, the pgACC may show altered connectivity with sensory and motor regions, reflecting a compensatory attempt to reduce environmental uncertainty that ultimately contributes to energetic depletion and exhaustion.

The present study aims to test these hypotheses by systematically examining pgACC alpha activity and connectivity at rest in individuals exposed to chronic stress, and by relating these neural measures to subjective fatigue. By linking stress-related energetic demands, pgACC dysfunction, and alpha oscillatory dynamics, this work seeks to clarify the neural mechanisms underlying stress-related fatigue and identify potential biomarkers and targets for intervention in stress-induced cognitive and emotional exhaustion.

Methods and materials

Subjects

A total of 589 participants (age: 49.17 ± 17.34 years; males: 298; females: 286) were recruited for this study. See Table 1 for summarizing demographics and clinical characteristics. All patients were screened by a neurologist, neurosurgeon and/or psychiatrist at the brai3n clinic and research center in Ghent, Belgium. The study was in accordance with the ethical standards of the Helsinki declaration (1964) and was approved by the institutional ethics committee of the University Hospital Antwerp (UZA OGA85).

The healthy control group denied having ever experienced any neurological or neuropsychiatric conditions. In order to rule out pulsatile tinnitus, Meniere's illness, otosclerosis, and chronic headache, tinnitus subjects underwent screening by a tinnitus specialist. Brain tumors and other neurological conditions were also disregarded. Every patient with tinnitus had it for longer than a year. Patients with chronic pain complaints were evaluated by a pain expert for neuropathic pain caused by deafferentation (i.e., peripheral nerve, root, or central tract lesions).

Assessments

Fatigue severity scale

The Fatigue severity scale (FSS) is a 9-item scale that measures the severity of fatigue and how much it affects the person's activities and lifestyle in patients with a variety of disorders. The FSS scale is a self-report scale that is easy to administer and can be completed quickly with minimal effort. The items are scored on a 7-point scale with 1 = strongly disagree and 7 = strongly agree. The common way of scoring is based on mean of all the scores with minimum score being 1 and maximum score being 7. Cut-off score of 4 or more considered indicative of problematic fatigue. The FFS has been shown to be reliable and well validated (see Supplementary Materials).

Beck depression Inventory

The Beck Depression Inventory-II (BDI) provides information about depressive feelings and consists of 21 questions (Richter et al., 1998). Each answer being scored on a scale value of 0 to 3. Higher total scores indicate more severe depressive symptoms. The standardized cutoffs used differ from the original: 0–13: minimal depression; 14–19: mild depression;20–28: moderate depression; 29–63: severe depression. The BDI-II is positively correlated with the Hamilton Depression Rating Scale with a Pearson r of 0.71, showing good convergent validity. The test was also shown to have a high one-week test–retest reliability (Pearson's $r = 0.93$), suggesting that it was not overly sensitive to day-to-day variations in mood. The test also has high internal consistency ($\alpha = 0.91$) (Beck et al., 1996; Beck, 1996).

Hospital anxiety and depression scale

To measure anxiety we used the Hospital Anxiety and Depression Scale (HADS). The HADS is a self-report questionnaire that measures core symptoms of anxiety and depression without including physical symptoms. It is a short questionnaire of 14 questions, in which a score from 0 to 3 is given for each item. The scale addresses feelings in the past four weeks and consists of an anxiety scale and a depression scale with both 7 items. The higher a patient scores on this questionnaire, the more symptoms he/she experiences. Scores below 8 for anxiety and depression are considered normal. (0–7 normal, 8–10 mild, 11–14 moderate, 12–21 severe). Most factor analyses demonstrated a two-factor solution in good accordance with the HADS subscales for Anxiety (HADS-A) and Depression (HADS-D), respectively. The correlations between the two subscales varied from 0.40 to 0.74 (mean 0.56) (Bjelland et al., 2002). Cronbach's alpha for HADS-A varied from 0.68 to 0.93 (mean 0.83) and for HADS-D from 0.67 to 0.90 (mean 0.82). In most studies an optimal balance between sensitivity and specificity was achieved when caseness was defined by a score of 8 or above on both HADS-A and HADS-D. The sensitivity and specificity for both HADS-A and HADS-D of approximately 0.80 were very similar to the sensitivity and specificity achieved by the General Health Questionnaire (GHQ). Correlations between HADS and other commonly used questionnaires were in the range 0.49 to 0.83.

Distress numeric rating scale

The numeric rating scale (NRS) was used for distress to measure how stress people perceived in the last two weeks. This was assessed using a 10-point scale going from 0 = no distress to 10 = severely distressed).

Table 1
See Table 1 for summarizing demographics and clinical characteristics.

265 healthy control subjects
324 patients: • 63 patients with tinnitus • 20 with attention deficit disorder • 62 with chronic pain • 24 with anxiety • 42 with a major depression • 45 with chronic fatigue syndrome or burnout • 9 with a traumatic brain injury

Data collection

Before the recordings began, all participants gave written informed consent. Each individual completed a routine EEG session primarily intended for diagnostic evaluation and neuromodulation treatment. Resting-state EEG activity was collected with a Mitsar amplifier over a 5-minute period from 19 predefined scalp sites in the same recording room.

During the session, participants sat comfortably in a well-lit, sound-attenuated room with their eyes closed. EEG electrodes were placed according to the international 10–20 system at 19 fixed scalp locations, and electrode impedance was kept below 5 kΩ throughout. To ensure consistency in the recordings, participants were asked to refrain from consuming alcohol for 24 h prior to the session and to avoid caffeinated drinks on the day of the EEG.

Preprocessing

To ensure data quality, participants' attentiveness was monitored to mitigate potential EEG alterations due to fatigue or external influences. The EEG signal underwent specific filtering parameters (high-pass at 0.15 Hz and low-pass at 200 Hz) using WinEEG software version 2.84.44 (https://mitsar-eeg.com/product/wineeg-advanced/, Mitsar, St. Petersburg, Russia).

A meticulous artifact inspection was conducted, and all transient artifacts indicative of eye blinks, eye movements, jaw tension, teeth clenching, or gross body movements were manually removed from the EEG signal. Artifacts were defined as EEG features that deviate from activity generated by neural sources. Specifically: (1) Some artifacts are confined to particular frequency ranges (e.g., above a certain frequency) and were attenuated using standard frequency filtering.(2) Line-noise artifacts at discrete frequencies such as 50 Hz (or 60 Hz in the USA) and their harmonics were removed using notch filters. (3) Artifacts restricted to specific time periods, such as those produced by eye blinks, were identified by visual inspection, and the corresponding time segments were excluded. (4)Artifacts arising from one or a few localized sources, yielding stereotyped spatial patterns (i.e., occupying a subspace of the signal space), were removed by estimating their characteristic topographies (artifact subspace) and projecting them out of the data.(5) When artifacts and genuine brain signals could be assumed to be sufficiently statistically independent, they were separated and removed using independent component analysis (ICA). (7) Artifacts with a characteristic temporal profile (e.g., exponential decay) were modeled parametrically; their parameters were fitted to the data, and the modeled artifact contribution was then subtracted. (8) Additionally, artifacts with specific temporal structures, such as exponential decay, were modeled, and their parameters were fitted and removed from the data.

Following artifact removal, the average EEG duration was compared across different groups, including healthy controls and individuals with various conditions such as tinnitus, chronic pain, Parkinson's disease, major depression, attention deficit hyperactivity disorder, alcohol addiction, obsessive–compulsive disorder, and food addiction. However, no significant differences were observed among these groups based on this analysis ($F = 0.92$, $p = 0.63$).

Source localization

Exact low-resolution brain electromagnetic tomography (eLORETA) was used to estimate intracerebral electrical activity. As part of the standard preprocessing, the EEG data were transformed to a common average reference prior to running the eLORETA algorithm (Pascual-Marqui, 2002). eLORETA computes neuronal electric activity as current density (A/m^2) without requiring any prior assumptions about how many sources are active. The solution space and leadfield matrix were the same as those implemented in the LORETA-Key software (https://www.uzh.ch/keyinst/loreta), which uses updated realistic electrode coordinates (Fuchs et al., 2002; Jurcak et al., 2007) and a boundary element model based on the standard MNI-152 brain (Montreal Neurological Institute, Canada). The eLORETA-Key anatomical template divides the neocortical MNI-152 space (including the hippocampus and anterior cingulate cortex) into 6,239 voxels of 5 mm^3, using probabilistic information from the Demon Atlas (Lancaster et al., 2000). Co-registration ensures accurate mapping between MNI-152 space and the Talairach and Tournoux coordinate system.

Using eLORETA, we estimated scalp-recorded activity in the alpha band (8–12 Hz). Anatomical labeling of significant clusters was performed with the tools provided in the eLORETA software package. Although eLORETA has been criticized for having lower spatial resolution than functional MRI and for limitations in resolving the hippocampus and cortical gray matter (Mulert et al., 2004), its validity is supported by convergent findings with invasive recordings from implanted electrodes in epilepsy patients (Zumsteg et al., 2006a,b) and with cognitive event-related potentials (ERPs) Further studies have shown that eLORETA can reliably localize activity in deep brain regions such as the subgenual anterior cingulate cortex (Pizzagalli et al., 2004) and the mesial temporal lobe (Zumsteg et al., 2006c).

Region of interest

The log-transformed electric current density was calculated for the regions of interest (ROIs) for the alpha (8–12 Hz) frequency band. The ROIs in the present study are pgACC, As the voxel-size of each region of interest has the dimension 5 mm^3, we only used this voxel. We do not differentiate between left and right due to their proximity to the midline. Due to volume conduction, laterality is harder to differentiate for areas close to the midline.

Seed-based phase synchronization

Phase synchronization between time series from different spatial locations is typically taken as evidence of functional connectivity. In particular, "lagged phase coherence" between two sources can be viewed as the extent of cross-talk between the brain regions generating the source activity (Congedo et al., 2010). When two areas oscillate coherently with a phase delay, this cross-talk can be interpreted as information exchange mediated by axonal transmission.

Any dependence measure is, however, strongly affected by an instantaneous, non-physiological component caused by volume conduction (i.e., the spread of electric or magnetic fields from primary current sources through biological tissue to the sensors (Pascual-Marqui, 2007b). To address this issue, Pascual-Marqui and colleagues (Pascual-Marqui, 2007a; Pascual-Marqui et al., 2011) proposed a method that removes this confounding factor. This dependence measure can therefore be applied jointly to any number of brain regions, i.e., distributed cortical networks, whose activity is estimated with eLORETA. Linear dependence (coherence) between multivariate time series is defined as the sum of lagged and instantaneous components. These measures are non-negative, equal zero only under independence, and are defined in the frequency domain. In the present context, alpha-band (8–12 Hz) lagged linear connectivity was computed using a seed in the pgACC.

Statistical analyses

Assessments

Pearson correlations were conducted between distress, depression, anxiety and fatigue. To further identify the relationship between these variables we applied a path analysis. According to our hypothesis, the relationship between distress and fatigue might be mediated through anxiety and depression. SPSS AMOS was used to test the goodness-of-fit of path models and estimate the parameters using maximum likelihood estimation. Six models were tested.

Whole brain

The approach employed in this study is a non-parametric permutation test, which involves estimating the empirical probability distribution for the max-statistic through randomization under the null hypothesis comparisons (Nichols and Holmes, 2002). This method is utilized to address multiple testing concerns, accounting for the numerous tests conducted across all voxels and frequency bands. As this method is non-parametric, its validity does not hinge on assumptions of Gaussianity (Nichols and Holmes, 2002). The comparisons across the entire brain were conducted using eLORETA, employing multiple voxel-by-voxel comparisons utilizing a logarithm of F-ratio. The significance threshold for all tests was determined through a permutation test involving 5000 permutations. Specifically, comparisons were made between healthy controls and the patient groups (low and high fatigue).

Region of interest

A Pearson correlation was calculated between the region of interest and the fatigue severity scale for the alpha frequency band for all patients. Furthermore, a partial correlation was conducted between the region of interest and the fatigue severity scale for the alpha frequency band for all patients, controlling for distress, anxiety and depression.

A univariate ANOVA was conducted including the three groups (control, low and high fatigue) as independent measures and the log transformed current density for the pgACC at the alpha frequency band as the dependent measure.

Seed-based phase synchronization

To determine differences in seed-based phase synchronization between the three groups (control, low and high fatigue), we performed F-statistics for independent groups with a corrected threshold $p < 0.05$, which were also corrected for multiple comparisons by conducting eLORETA-built-in voxel-wise randomization tests (5000 permutations).

Results

Assessments

A Pearson correlation analysis revealed a significant positive correlation between fatigue, and depression, anxiety, and distress, respectively (see Table 2), indicating that severe fatigue goes together with increased depression, anxiety and distress.

A path analysis further shows that distress seems to mainly modulate anxiety, that is modulating depression, that is modulating fatigue (see Table 3).

To explore the effect of fatigue on the brain, we divided the patient group into low versus high fatigue groups. We used the norm scores with a cut-off score of 4 or more to be considered problematic fatigue. Of the 324 patients, 189 patients were assigned to the low fatigue group and 135 patients to the high fatigue group. A comparison shows that the high fatigue group has increase scores on depression, anxiety and distress in comparison to the low fatigue group (see Table 4).

Correlation analysis between brain activity and fatigue

A correlation analysis revealed a negative correlation between fatigue and pgACC, the left and right dorsal lateral prefrontal cortex, and the left and right intraparietal sulcus for the alpha frequency band (r = -0.31, $p < 0.05$; see Fig. 1). As a secondary analysis we conducted a regression analysis including fatigue and patient group as independent variables and whole brain activity for the alpha frequency band as dependent variables. This analysis revealed a effect for fatigue (β = -0.13, $SE = 0.03$, t = -4.28, $p < 0.05$; see Fig. 1), but not for condition (β = 0.003, $SE = 0.025$, $t = 0.13$, $p = 0.90$). We see alpha activity in the pgACC as well as in the left and right dorsal lateral prefrontal cortex.

This analysis was further confirmed by a region of interest analysis. Revealing that the fatigue severity correlated negatively with the log-transformed current density of the pgACC for the alpha frequency band (r = -0.38, $p < 0.001$; see Fig. 1). To further confirm this latter finding, a partial correlation was conducted between fatigue and the log-transformed current density of the pgACC for the alpha frequency band, controlling for depression, anxiety and distress. This analysis confirmed that there was still a significant negative relationship (r = -0.14, p = 0.024), indicating the more severe the fatigue, the less log-transformed current density of the pgACC for the alpha frequency band was present, or vice versa. Controlling for condition, the partial correlation analysis demonstrated a significant negative correlation ($r = –.26$, $p < 0.001$), suggesting that increasing fatigue severity corresponded to decreasing log-transformed current density in the pgACC for the alpha frequency band.

Brain activity differences for fatigue

A whole-brain analysis comparing the high-fatigue group with healthy control participants revealed a significant decrease in alpha activity in the high-fatigue group. Reduced alpha activity was observed in the pregenual anterior cingulate cortex (pgACC), the left and right dorsolateral prefrontal cortex, the posterior cingulate cortex, and the precuneus ($F = −3.21$, $p < 0.05$; see Fig. 2).

A direct comparison between the high- and low-fatigue groups showed a similar pattern. The high-fatigue group exhibited significantly lower alpha activity in the pgACC, the left dorsolateral prefrontal cortex, and the right intraparietal sulcus ($F = −2.89$, $p < 0.05$; see Fig. 2).

Given the central role of the pgACC, we conducted a univariate ANOVA focusing specifically on this region. This analysis showed a significant effect of fatigue level on alpha frequency ($F = 3.71$, p = 0.024). The high-fatigue group demonstrated a lower mean alpha frequency ($M = 5.14$, $SD = 0.77$) compared to both the control group (M = 5.55, $SD = 0.79$) and the low-fatigue group ($M = 5.68$, $SD = 0.85$). Importantly, this effect remained significant after controlling for patient group, indicating that the observed differences in pgACC alpha frequency are not attributable to diagnostic status.

Seed-based pgACC connectivity

To clarify the functional role of the pgACC, we performed a seed-based connectivity analysis. When comparing participants with high fatigue to healthy controls, the high fatigue group showed significantly reduced functional connectivity between the pgACC and the right dorsolateral prefrontal cortex, the posterior cingulate cortex, and the hippocampus in the alpha frequency band ($F = 3.23$, $p < 0.05$; see Fig. 2). A similar pattern was observed when comparing the high and low fatigue groups. That is, individuals with high fatigue again exhibited significantly decreased connectivity between the pgACC and the right dorsolateral prefrontal cortex, the posterior cingulate cortex, and the hippocampus in the alpha band ($F = 2.95$, $p < 0.05$; see Fig. 2). In contrast, we also observed increased connectivity between the pgACC and both the posterior cingulate cortex and the hippocampus, suggesting that fatigue may be associated with a complex reorganization of pgACC-centered networks rather than a uniform decrease in connectivity.

Table 2
Correlations between fatigue (FSS), depression (BDI), anxiety (HADS) and distress (NRS).

	Depression	Anxiety	Distress
Fatigue	0.55***	0.29***	0.42***
Distress	0.22**	0.32***	
Anxiety	0.55***		

FSS: Fatigue Severity Scale; BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; NRS: Numeric Rating Scale; *** $p < 0.001$.

Table 3
Path analysis.

Modal	χ^2	p	GFI	AGFI	RMSEA	CFI	AIC	BIC
S-A-D-F	**3.10**	**0.217**	**0.90**	**0.48**	**0.04**	**0.99**	**19.06**	**48.01**
S-D-A-F	69.74	< 0.001	0.99	0.97	0.35	0.75	85.74	114.70
S-A-F-D	114.45	< 0.001	0.83	0.16	0.45	0.59	130.45	159.41
S-D-F-A	105.23	< 0.001	0.87	0.17	0.44	0.69	128.45	159.41
S-F-A-D	69.74	< 0.001	0.99	0.97	0.35	0.72	85.74	114.70
S-F-D-A	85.12	< 0.001	0.81	0.57	0.74	0.79	58.24	112.17

S: Distress; A: Anxiety, D: Depression; F: Fatigue. Comparison of CFI, AIC, BIC across models provides a possibly optimal model. Abbreviations: GFI, goodness of fit index; AGFI, adjusted GFI; RMSEA, root mean square error of approximation; CFI, comparative fit index; AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 4
A comparison between patients who score low or high on fatigue for depression (BDI), anxiety (BAI) and distress (NRS).

	Low Fatigue	High Fatigue	*F-value*
Depression	4.81 (3.18)	7.71 (3.91)	45.81***
Anxiety	8.90 (5.81)	11.26 (5.78)	10.93***
Distress	4.02 (2.52)	5.92 (2.71)	35.60***

BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; NRS: Numeric Rating Scale; *** $p < .001$.

Discussion

This study identifies two associations between neurophysiological patterns and mental fatigue: (1) reduced alpha activity within the pgACC and (2) increased alpha-band functional connectivity originating from the pgACC. These findings suggest that the pgACC acts as a major hub in stress related fatigue, and alpha activity within the pgACC is deficient in chronic stress. This alpha deficiency is associated with decreased alpha power in the central executive network, a network involved in externally oriented cognition, i.e. cognition to deal with a changing environment (Vincent et al., 2008). Like the body's immune system is protective against symptoms of bodily disease, the central executive network is postulated to be protective against symptoms of mental disease (Cole et al., 2014). And indeed, a lesion map associated with depression overlaps with the central executive network (Padmanabhan et al., 2019).

The correlation between alpha deficiency in the pgACC and fatigue may however not be causal. It is likely a consequence of attempts to reduce uncertainty by limiting stimulus inhibition, as every stimulus may be relevant to reduce the stress (De Ridder et al., 2016b). Consequently, the increased alpha functional connectivity with sensorimotor and parietal areas may be an attempt to gain more information from the environment in stressful, i.e. uncertain contexts. The fact that the ventrolateral prefrontal cortex (VLPFC) and the inferior parietal (IP) network are also more strongly connected in alpha suggests that more external input is required to reduce uncertainty, i.e. stress. The VLPFC and IP combine to form the ventral attention network, a network that circuit breaks top-down attention if a bottom-up distinctive environmental stimulus is detected (Corbetta et al., 2008; Corbetta and Shulman, 2002). Furthermore, alpha functional connectivity is increased in stress (De Ridder et al., 2011), and is a signature of maladaptive coping (Vanneste et al., 2014). As anxiety is related to decreased alpha functional connectivity (Yassine et al., 2024) and depression to either hyper- or hypo-connectivity (Fingelkurts et al., 2007; Huang et al., 2023), the increased alpha functional connectivity is likely a sign of exhaustion resulting from an inefficient way to cope (Vanneste et al., 2014) in an uncertain, stressful environment (De Ridder et al., 2011) rather than a sign of anxiety or depression.

An important question is how (di)stress, anxiety, depression and fatigue relate to one another. Our correlation analyses demonstrate that distress, anxiety, depression and fatigue are interrelated, but they do not in themselves establish the directionality of these associations. This issue is clinically relevant, as different stages may require different treatment approaches. Adapting Cannon and Selye's seminal work to a Bayesian brain model (Friston, 2010) and integrating the selfish brain concept (Peters, 2011; Peters et al., 2004), we propose a theoretical framework in which uncertainty about how to engage with the environment gives rise to a cascade of adaptations in the brain that may be expressed phenomenologically in different ways. In this view, the brain is constantly engaged in reducing uncertainty by minimizing prediction errors, a process that requires substantial energy (Peters et al., 2017). When uncertainty persists, these efforts may contribute to a state of chronic stress. The pgACC has been implicated in modulating cognitive and emotional responses to stress (Soares et al., 2012b). Uncertainty is experienced as stress when the brain is unable to reduce prediction errors about future outcomes, contributing to allostatic load—the cumulative wear and tear on the body and brain resulting from chronic stress

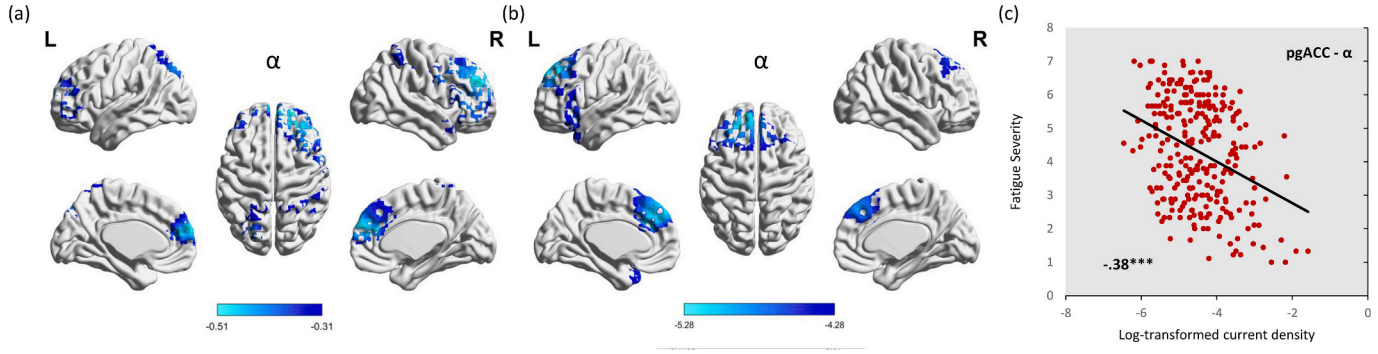

Fig. 1. (a) Negative correlation between fatigue and pregenual anterior cingulate cortex, the left and right dorsal lateral prefrontal cortex, and the left and right intraparietal sulcus for the alpha frequency band. (b) Secondary regression analysis including fatigue and patient group as predictors and whole-brain alpha-band activity as the outcome revealed a significant effect of fatigue showing alpha activity in the pgACC and the left and right dorsolateral prefrontal cortex. (c) Fatigue severity correlated negatively with the log-transformed current density of the pregenual anterior cingulate cortex for the alpha frequency band. *Note*: The brain figures where generated using BrainNet viewer (https://www.nitrc.org/projects/bnv).

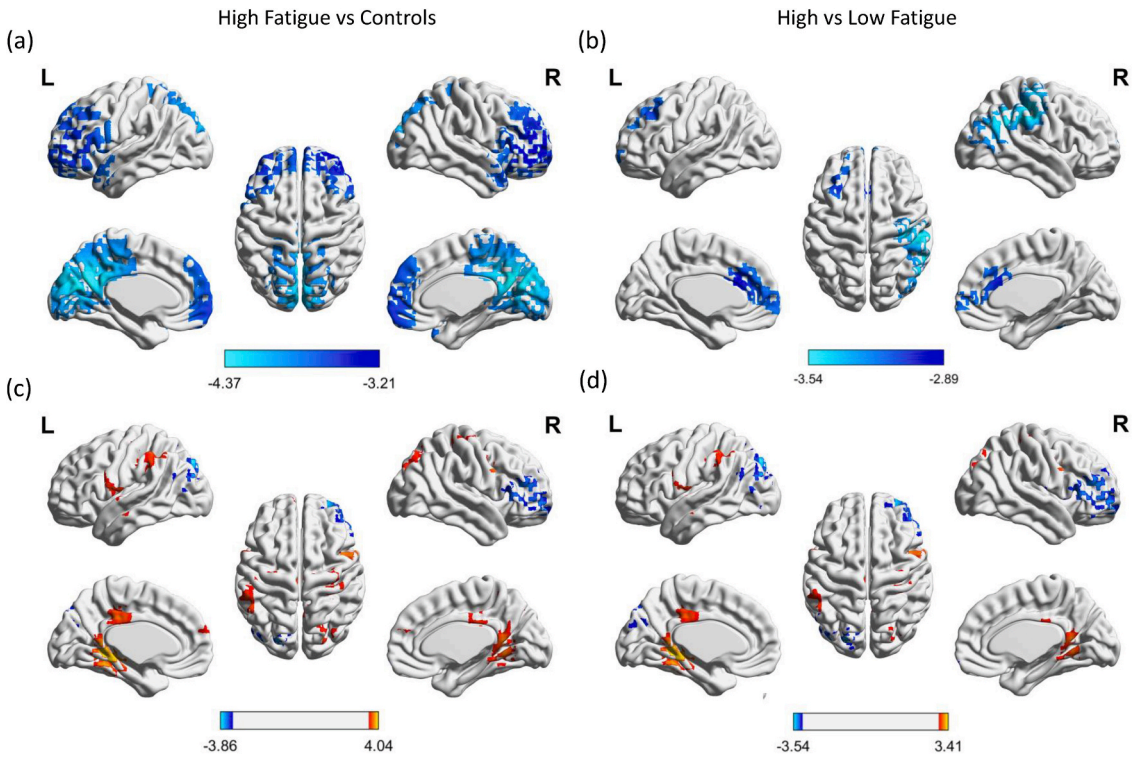

Fig. 2. (a-b) Whole brain analysis (a) Comparison between the high fatigue group and control subjects shows decrease alpha activity in the pregenual anterior cingulate cortex, the left and right dorsal lateral prefrontal cortex, the posterior cingulate cortex extending to the precuneus and the superior parietal cortex. (b) comparing the high fatigue group with the low fatigue group demonstrates decreased alpha activity in the pregenual anterior cingulate cortex, the left dorsal lateral prefrontal cortex, and the right intraparietal sulcus. (c-d) Seed-based phase synchronization (c) when comparing the high fatigue group with the control subjects a decreased phase synchronization between the pregenual anterior cingulate cortex and the right dorsal lateral prefrontal cortex group for the alpha frequency band is identified, as well as increased phase synchronization between the pregenual anterior cingulate cortex and both posterior cingulate cortex and the parahippocampus as well as increased phase synchronization with motor and primary sensory cortex, secondary sensory cortex, ventrolateral prefrontal cortex and temporoparietal junction (d) when comparing the high fatigue group with the low fatigue group a decreased phase synchronization between the pregenual anterior cingulate cortex and the right dorsal lateral prefrontal cortex group is demonstrated, as well as increased phase synchronization between the pregenual anterior cingulate cortex and both posterior cingulate cortex and the parahippocampus, as well as increased phase synchronization with motor and primary sensory cortex, secondary sensory cortex, ventrolateral prefrontal cortex and temporoparietal junction. *Note*: The brain figures where generated using BrainNet viewer (https://www.nitrc.org/projects/bnv).

(Peters et al., 2017). The pgACC is thought to be crucial for inhibiting irrelevant stimuli to prevent sensory overload, a function that may be compromised under prolonged stress (De Ridder et al., 2021; De Ridder et al., 2016b). This is consistent with our observation that chronic stress is associated with altered alpha oscillatory activity in the pgACC, which we interpret as reflecting the brain's attempts to manage increased sensory and cognitive load.

The selfish brain theory further emphasizes how the brain prioritizes its energy needs, especially under stress (Peters, 2011; Peters et al., 2004). Chronic stress may impose persistent demands on the pgACC to maintain inhibitory control, which, in our data, correlates with the severity of fatigue. Rather than implying a unidirectional causal effect, we suggest that as the brain continues to consume energy to manage uncertainty, resources may become depleted, contributing to cognitive and emotional exhaustion—a process that may be mirrored by the slowing of alpha oscillations in the pgACC. From this perspective, fatigue may not simply be a downstream symptom of stress, but could also be viewed as a correlate of the brain's energetic struggle to manage persistent uncertainty. This integration underscores the potential role of the pgACC in both emotional regulation and energy conservation, and suggests that chronic stress–related changes in this region may contribute to long-term cognitive and physical consequences (Misquitta et al., 2021; Soares et al., 2012a).

Irreducible uncertainty results in (di)stress, which can develop in anxiety in subacute settings and leads to depression in chronic settings, culminating in fatigue when exhausted. The path analysis confirms the sequence of clinical stages from stress to anxiety to depression to fatigue, in keeping with the theoretical Bayesian and selfish brain model. Our path analysis is consistent with a sequence of clinical stages from stress to anxiety to depression to fatigue. However, it is important to note that the model fit indices were only suboptimal. Thus, the proposed mediated pathway (stress → anxiety → depression → fatigue) should be regarded as a tentative, hypothesis-generating framework rather than a confirmed causal chain, and alternative pathways or bidirectional influences cannot be excluded.

This proposed model may be a final common pathway of many neurological and psychiatric disorders, as the study incorporated patients with chronic pain, chronic tinnitus, TBI, burn-out, post-viral chronic fatigue etc. As such, it may be a general adaption mechanism akin the Selye's concept. By integrating the selfish brain concept, depression and fatigue may be seen in a new perspective. Whereas they may be clinically maladaptive, from an energy point of view they may be adaptive. This has been proposed for chronic pain (De Ridder et al., 2022a), where acute pain is associated with an increase in energy expenditure of up to 60 %, and this reduces to 15 % in chronic pain (Straub, 2017). Similarly, chronic tinnitus may be a clinically maladaptive but energetically adaptive state (De Ridder et al., 2022b).

While individuals with chronic stress exhibited lower pgACC alpha power, this should not be interpreted as a causal "alpha deficiency" producing fatigue, but rather, it may reflect a downstream consequence of prolonged stress exposure or compensatory changes in sensory gating. The present findings highlight pgACC alpha oscillations as a potential

biomarker and neuromodulation target in stress-related fatigue, their translational value warrants careful consideration. First, chronic stress rarely occurs in isolation. Most clinical populations experience substantial comorbidity, including anxiety, depression, chronic pain, traumatic brain injury, and tinnitus—conditions well represented in our heterogeneous sample. While this diversity strengthens the ecological validity of the observed pgACC alterations, it raises questions regarding the specificity of pgACC alpha slowing. Our results suggest that reduced pgACC alpha activity correlates with fatigue even after statistically controlling for distress, anxiety, depression, and diagnostic category, yet the degree to which pgACC alpha reflects a shared transdiagnostic mechanism versus a disorder-specific signature remains to be tested. From a practical standpoint, implementing pgACC alpha measures as a clinical biomarker would require robust normative ranges, adequate test–retest reliability, and feasibility in everyday clinical EEG environments. The current study demonstrates reliable group-level effects but does not determine cutoff values or sensitivity–specificity thresholds needed for diagnostic or prognostic use. Likewise, while neuromodulation techniques—including neurofeedback, transcranial electrical stimulation, and transcranial magnetic stimulation—may be capable of targeting the pgACC indirectly, future studies must clarify whether modulating pgACC alpha can reliably induce symptomatic improvement and whether treatment effects generalize across comorbid populations. Finally, the translational pathway will likely require a precision-medicine approach. Given that pgACC dysfunction may represent a final common pathway in stress-related disorders, pgACC alpha activity could serve as a stratification marker to identify patients whose fatigue arises from chronic stress–induced inhibitory dysregulation. However, individuals whose fatigue stems primarily from inflammatory, metabolic, or sleep-related mechanisms may not exhibit the same pgACC electrophysiological profile. Future longitudinal, interventional, and multimodal neuroimaging studies will therefore be essential to establish the causal relevance, clinical utility, and generalizability of pgACC alpha activity across the complex landscape of comorbid stress-related conditions.

In conclusion, the current study attempts to unravel the relationship between (di)stress, anxiety, depression and mental fatigue. The pgACC appears as a crucial dysfunctional hub, and it is proposed that by not suppressing environmental stimuli in the brain, the brain is subsequently exposed to a persistent overload of stimuli that consumes extra energy, in the long run leading to mental fatigue. As such, decreased alpha activity may not only be a biomarker for fatigue, but also a target for neuromodulation approaches. As this may be a potential final common pathway for stress associated neurological and mental disorders, the implications may be extensive.

CRediT authorship contribution statement

Sven Vanneste: Writing – original draft, Visualization, Formal analysis, Conceptualization. **Jan Ost:** Project administration, Methodology, Investigation, Data curation. **Dirk De Ridder:** Writing – original draft, Validation, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroscience.2025.12.020.

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