Coping with negative emotions under stressful conditions:

Predicting vulnerability and targeted interventions

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Since the moment we are born, and even while developing in the womb, we have to face a myriad of environmental challenges. How successfully we engage with these challenges is driven by both our genetic makeup and our ability to adapt to them, which synergistically operate to induce appropriate biochemical, physiological and behavioural changes when it becomes vital to escape or control potentially life-threatening stimuli.

In this context, resilience to environmental stress has been the subject of intense neurobiological and neurobehavioral research over the last few decades, and several studies have unveiled a multitude of biomarkers that have been suggested to predict how effectively an individual responds to stressful life events, in the short and long term.

For example, while some of us may tend to ignore that the Darwinian concept of "survival of the fittest" still applies to our modern societies, we can all certainly relate to how it feels when our expectations are not met or when we fail to reach our goals.

"Failing" is certainly not a pleasant experience. It is generally characterized by a shift from positive to negative affect, including an increase in sadness, anger and frustration [1, 2].

Interestingly, while in some individuals this negative emotional state becomes dominant and enduring, in others it seems to be resolved relatively quickly [2]. These two alternative responses can have enormous effects on psychological and physiological wellbeing, playing a key role in how future stressful life events are engaged and how subsequent tasks are performed [3, 4].

How the brain copes with negative emotions during stressful conditions: Examples from sports

The ability to cope with negative affect significantly affects performance during challenging conditions. In a study on 70 expert athletes where verbal reports on the ability to focus while under pressure were gathered, it was found that participants mostly focused on worries and external factors [5]. This, supports the notion that **affective states influence performance** by their immediate effects on attentional processes [6] and that a negative emotional state is more likely associated with **rumination and threat states**, when compared to a positive state [7].

The **disruptive effects of threat states and rumination on performance** have been demonstrated across a wide range of contexts [8], which suggests that improvements in performance must be facilitated by a change of affect valence, from negative to positive.

Interestingly, a study on cyclists found that purposeful attention was improved and that negative thoughts were reduced after participants took part to a program of mindfulness meditation, suggesting that pessimistic thinking may also interfere with performance under stress and, most importantly, that the disruptive effects of anxiety on performance can be reduced by training aimed at changing the thinking style from negative to positive [9].

Altogether, these findings suggest that **resilience to stress and performance improvement** under stressful conditions can be facilitated by targeted interventions and that psychological wellbeing can be facilitated by changes in specific neural network activity and their functional inter-connectivity, occurring through the modulation of the underpinning neurochemical/electrophy-siological mechanisms.

Affective recovery and prefrontal asymmetry

The evidence indicating a strong link between negative thinking, anxiety and reduced performance under stress, suggests that resilient individuals exhibit the ability to recover after failure, recruiting resources that facilitate a favourable physiological/psychological state, hence reducing the likelihood for performance decrements.

Affective recovery, i.e. the recovery from altered activity in the affective system, is key to determining our affective style, which is determined by multiple factors that altogether shape how we process emotions, including the magnitude of the average response, latency to peak, threshold to respond and the average duration of a response [10].

In this context, research employing electroencephalogram (EEG) has produced a number of key biomarkers of affective processing that have attracted growing interest from clinicians and mental health practitioners. One of the most discussed is **prefrontal asymmetry (PFA)**[11, 12]. which is found in normal subjects and indicates a difference in alpha frequency band (8-13 Hz) activity between the left and right prefrontal cortex [13].

The PFA metric has been shown to be **sensitive to variations in affective processing** and to predict trait-like affective tendencies [14, 15]. It has also been proposed that PFA is linked to both affective valence (negative or positive) and motivation [16], with several studies indicating an association between higher relative left hemispheric activity, approach (positive) motivation [17, 18], positive affect [19, 20] and lower vulnerability to negative stimuli [20-22].

Other research indicates that higher relative PFA in the left-hemisphere is associated with the ability to adapt to challenges [23, 24] in line with the proposed role of PFA [25] in determining vulnerability to develop depression. Hence, rather than correlating with a certain emotional state, **PFA indicates a propensity to modulate a certain state**.

The theta/beta ratio as measure of attentional control under stress

In addition to the role of PFA in the modulation of affect during challenging environmental conditions, there is also evidence that the ratio between low frequency (theta, 4-8 Hz) and high frequency (beta, 12-30 Hz) EEG activity at rest reflects the ability to control/selectively direct attention under stress [26].

It has been proposed that interindividual variance of the **theta/beta ratio at rest** could reflect different predispositions to responding to environmental challenges. In particular, it has been suggested that the theta/ beta ratio provides a metric of attentional control and as such it might be a useful biomarker in the evaluation of **cognitive performance anxiety**.

Increased theta/beta ratio has also been shown to predict the deleterious effects of **acute psychosocial stress on state attentional control** [27]. Importantly, it has been reported that psychopharmacological treatment with noradrenaline or dopamine agonists normalizes the theta/beta ratio [28, 29], further supporting the idea that this measure reflects the prefrontal regulation of attentional control and suggesting that **changes in this ratio should be evaluated and monitored to inform pharmacotherapy**.

Other research indicates that increased slow wave/fast wave ratios may reflect **reduced motivation** or **reward sensitivity** [29], **risk taking** and **impulsiveness** [29, 30].

Together, these findings suggest that increased theta/beta ratio may reflect anomalies in the control of attention and behavior inhibition processes, which rely on the prefrontal cortex.

The role of theta/beta ratio in mind wandering

Like worry, mind wandering is associated with the emergence of task-unrelated negative affect and to distracting thoughts [31]. It has been suggested that mind wandering can play a role in psychological processes like prospection and future planning [32, 33], creativity [34] and coping with negative affect [35].

Importantly, mind wandering can be a state of reduced working memory/attentional control [36, 37], and can increase the risk for performance errors [38]. On the other hand, working memory training has been shown to decrease the frontal theta/beta ratio [39] and a theta-based brain stimulation protocol that has been shown to increase working memory could decrease the theta/beta ratio in frontal and central head regions, while increasing flexible rule learning in motivated decision making [40].

Quantitative EEG (QEEG) has emerged over the last few decades as a reliable tool to be used for diagnostic clarification in mental illness.

How can frontal/prefrontal asymmetries and altered theta/beta ratios be reliably measured?

While standard EEG can be useful to record electrical activity that underpins underlying cortical brain activity, **quantitative EEG (QEEG)** has emerged over the last few decades as a reliable tool to be used for diagnostic clarification in mental illness. QEEG allows to measure brain activity through the scalp applying sophisticated mathematical and statistical analysis to compare recordings to a normative database (hundreds of scans from healthy individuals grouped by sex and age). Both the EEG and QEEG can offer valuable information about real-time brain activity, however QEEG allows to plot brain maps showing where non-normative activity exists.

The American Academy of Neurology (AAN) and the American Clinical Neurophysiology Society (ACNS) support the use of quantitative EEG (QEEG) in combination with clinical EEG for the detection of brain activity anomalies in multiple psychiatric conditions [41]. In particular, QEEG has been shown to be a useful tool in the evaluation of cognitive and emotional disorders showing the ability to reveal subtle changes in interhemispheric asymmetries, even in the absence of severe functional or structural alteration [42].

Targeting frontal and prefrontal asymmetry and altered theta/beta ratio in individuals with impaired attentional control

Pharmacotherapy

Given the key role of the cholinergic system in mediating attentional functions, the administration of cholinergic agonists has been proposed for the treatment of reduced attentional control. Collectively, research supports the use of cholinergic drugs, particularly agonists targeting $\alpha 4\beta 2^*$ nicotinic acetylcholine receptors [43].

There is also evidence that dopaminergic agonists (e.g., methylphenidate) can decrease the theta/beta ratio in patients with attentional control deficits, through an increase in beta rather than theta activity [36].

However, our understanding of the underpinning neurochemical mechanisms of attentional control is still underdeveloped and the modulatory effects on either frontal asymmetry or the theta/beta ratio still needs to be fully determined.

Cognitive remediation

While accumulating research supports the use of cognitive remediation strategies in the treatment of attention impairment associated to stress, precise clinical outcomes are often not observed following their administration.

More research is needed to define efficacy protocols before these interventions can be proposed as treatment strategies. More generally, prospective studies should determine a) how to achieve long-term improvements in the control of negative intrusive thoughts, (b) what neural mechanisms are more likely to be targeted by these interventions and (c) what inter-individual differences can influence treatment outcome [44].

Neurofeedback Training

Neurofeedback training or simply **neurofeedback** is a learning-based, non-invasive intervention that allows to differentially modulate EEG activity, targeting specific frequencies and head regions [1].

Accumulating evidence has shown the ability of neurofeedback training to improve clinical symptoms is a variety of neurological and psychological disorders [2], and also enhance performance in sports, arts and other areas [3, 4].

In healthy subjects, neurofeedback has been shown to decrease the theta/beta ratio in frontal, central and occipital regions [45]. Research supports the use of **neurofeedback training in the treatment of depression and anxiety**, as a standalone intervention or in combination with other treatment strategies (most typically pharmacotherapy and/or psychotherapy), and new protocols that target both **alpha symmetry and the frontal theta/beta ratio** hold promise in the treatment of **anxiety symptoms** [46, 47].

Other research further supports the use of theta/beta training neurofeedback protocols indicating that the reduction of anxiety symptoms and increased sustained attention correlated with decreases in salivary cortisol, a measurable product of anxious states and reliable biomarker of hypothalamic-pituitary-adrenal (HPA) axis activity [48].

Transcranial alternating current stimulation (tACS)

In recent years, the application of weak oscillatory currents on the head has shown to have beneficial effects on cognitive functions [49]. For example, application of current in the theta or beta range over the frontal cortex can reduce the theta/beta ratio and support learning [50]. However, these effects can be accompanied by reduced risk taking, suggesting behavioural inhibition.

Altogether, the application of tACS as a treatment of attentional control deficits still needs research as its beneficial effects on behavior and performance are still unclear.

Conclusions

During stressful conditions, reduced emotional wellbeing can derive from the disruption of normal coping strategies. This can result in reduced motivation and poorer performance, although interindividual differences in vulnerability should be taken into account.

Recovery can be facilitated through the redirection of attention from negative to positive affect. This can be achieved through the non-invasive modulation of precise markers of brain activity.

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