The common ancestors of anxiety and depression: Comorbidity as a cognitive, behavioural, neural and cellular phenotype, and current evidence for photobiomodulation as a novel treatment.

Gabriel Barg, Ph.D.

Psychophysiology Lab, Neuroscience & Learning Department, Catholic University of Uruguay.

Julia N. Lukacs, M.Sc.

Department of Psychology, Simon Fraser University, Burnaby, BC, CA

Guillermo Perez Algorta, Ph.D.

Division of Health Research, Faculty of Health and Medicine, Lancaster University, UK.

As of June of 2021, the COVID-19 pandemic has threatened the physical and mental health of individuals for over a year. The capacity for resilience both as individuals and as a global community has been and continues to be tested. Billions of people may be experiencing sustained emotional stress. This has been brought about or exacerbated by increased levels of sadness, fear of illness or the death of themselves or loved ones, and hopelessness due to the personal and material losses associated with the pandemic.

Different groups – older adults, healthcare front line workers, and children -- have faced a range of common and specific challenges. Those with pre-existing mental health conditions, such as depression and/or anxiety, are confronting new situations of daily life disruptions, such as longer periods of isolation or lack of access to health support. Preliminary evidence comparing mental health experiences before and after COVID-19 indicates an increase in levels of psychological distress in American adults (1), and adults from the United Kingdom (2).

In the Netherlands, people with more severe chronic mental health problems are reporting more fear of COVID-19, and less coping with the pandemic than people with less severe or no mental health issues (3). However, this same research shows that the relative increase in depressive symptoms, anxiety, worry, and loneliness is greater in people with no or less severe problems than those with more severe or already existing problems, foreshadowing the impact of COVID-19 on mental wellness of the general population.

Now that vaccination programs have been initiated and have shown early signs of success around the world, albeit inequalities between low and high-income countries, the resolution of the acute COVID-19 crisis is within view. Nevertheless, even in high-income countries such as England, first models forecast the impact of COVID-19 on mental health to be long-lasting. It is safe to anticipate significant increments in demand (referrals) of mental

health services over the next years throughout the world. It would be premature to despair, however, as crises are often a time of ample opportunity.

The information we have gleaned from the COVID-19 crisis will allow us, as a field, to examine our conceptualisation of mental health issues, their treatment and limitations, and whether there are new treatments alternatives that require further evaluation. This chapter intends to be a response to this opportunity, where we review epidemiological and clinical data concerning the problem of anxiety and depression comorbidity. This is followed by the description of novel theoretical models of this comorbidity, that integrate psychopathological and neuroscientific evidence in different dimensions: cognition, behaviour, neural circuits and cellular mechanisms. Finally, with a focus on recent key findings on intracellular processes involving the mitochondria shared by anxiety and depression, the last section of the chapter provides a review of the evidence of Photobiomodulation (PBM); a promising non-invasive, low-cost intervention for anxiety and depression.

Evidence on comorbidity: Epidemiological and clinical data

Before COVID-19, the estimated lifetime prevalence of anxiety disorders was between 25% and 29%. For unipolar major depression alone this number was 17% (4). Regarding the prevalence of comorbid depression and anxiety, in the US, 58% of those with lifetime depression also had a lifetime anxiety disorder diagnosis, and for those with MDD in the past 12 month, 51% had an anxiety disorder (5). Data from the same study also showed that 68% of people with secondary depression presented with a primary anxiety disorder (contrasting for example with 19% with primary substance use disorder). The types of anxiety in descending order of frequency observed with depression are, Generalised Anxiety Disorder, panic disorder, and PTSD (6).

Adding to the epidemiological evidence about the co-occurrence of these anxiety disorders and depression, clinical data tell us that first line treatment recommendations for these problems are similar if not identical (e.g. SSRI, CBT). They also share the same challenges regarding treatment response. Current treatments are still suboptimal, resulting in limited remission rate efficiency for depression (approximately 50% in adults) (7), while more than a third of anxiety disorder patients are treatment-resistant (8).

These observations imply that the commonalities between depression and anxiety need special attention. Comparing similarities between mood and anxiety at a cognitive, behavioural, and neurobiological level may elucidate our understanding of their comorbidity. Considering comorbidity in this manner may advance both theoretical conceptualisation and treatment.

The cognitive dimension

At a cognitive level, different hypotheses involving higher-order cognitive schemes for processing information have been proposed. One classic proposal comes from Beck (9), which suggested that anxiety disorders are characterized by vulnerability schemes, while mood disorders would be characterized by schemes of self-depreciation. *Schemes*, as defined by Beck are internally stored representations of stimuli, ideas, or experiences, capable of controlling information processing systems (10). The cognitive similarities between depression and anxiety are observed at basic, automatic levels of processing, rather than at content levels. In these automatic levels, shared cognitive biases have been found, especially in attention and memory.

People experiencing anxiety tend to allocate more attentional resources to threatening stimuli, ignoring non-threatening stimuli. This observation has been replicated in diverse populations using different experimental paradigms, such as emotional stroop, dot probe, and flanker tasks (11, 12). A similar type of processing has been observed in people experiencing

depression, where the ability to disengage from negative stimuli to allocate resources in the environment is compromised (13) (14).

Attentional disengagement is a key coping mechanism to counter negative or threatening situations. COVID-19 is an example of a real-world test of attentional disengagement capacity, as social networks and media are constantly offering information about disease, danger and loss. In fact, to respond to this challenging situation, one of the recommendations during the lockdowns was to "take breaks from the news" to facilitate people disengaging from negative events and focus on other things (15).

Similar shared mechanisms have also been identified regarding memory in anxiety and depression (16). For example, selective retrieval of negative information is a maintenance factor of worry and depressed mood (17). People recognize items related to experiences (familiarity) but have trouble retrieving the contextual information related to that element (recollection). In the context of COVID-19, selective retrieval may occur when watching news related to the pandemic. Familiarity is demonstrated when people later remember precise verbatim information only (e.g. number of deaths per day), instead of contextual details (recollection).

From an adaptive point of view, however, the recovery of contextual cues (e.g. information about location and time, sanitary conditions) may be considered a better resource to cope with challenges such as COVID-19. An individual that recalls only familiarity-based specific experiences reinforces the feeling of having seen something negative, but is unable to recollect specific details of past news to palliate negative experiences. This selective retrieval in favour of familiarity (versus recollection) impairs coping and promotes generalization of fear (18). In anxiety, the familiarity bias is evidenced when the anxious subject recognizes negative stimuli with accuracy but might have difficulty recovering contextual information,

necessary to effectively cope with the situation. Consequently, they develop increasing avoidance of such stimuli. In depression, this bias towards familiarity manifests in the overgeneralization of autobiographical memory, preventing a reality-based correction of global negative self-referent thoughts (19).

In summary, both anxiety and depression manifest memory biases, in their faulty retrieval of items without contextual information. The difference between the posited processes in both conditions is that familiarity recognition is oriented toward future stimuli in anxiety and overgeneralization is oriented towards the past stimuli in depression (20). These basic cognitive biases in attention and memory, constitute some of the basis of common clinical observations of repetitive negative thinking in people with anxiety (worry, "what if?") and depression (rumination, "why?") (21).

The behavioural domain

At a behavioural level, the inhibition of functional behaviour is characteristic of anxiety and depression. In the former case, inhibition is linked to the avoidance of stimuli, while in the latter it is due to a lack of motivation (22, 23). These two aspects of inhibition have been explained through two propositions of cognitive functioning: by the action of a behavioural inhibition system (24), and by the withdrawal-approach complex (25).

Excessive activation of the behavioural inhibition system, triggered by increased punishment or the absence of reward expectations, has often been observed in anxiety and depression (26, 27). The functions impaired in people experiencing depression and anxiety extend to the capacity to stop ongoing behaviours to avoid harm, and the search for other adaptive goals. Attention needs to be biased towards negative information to recognize negative feedback and stop an ongoing action. Furthermore, to ensure that new goals are

associated with positive outcomes in personal experience, memory retrieval must also be biased toward negative content to screen any potential negative outcomes.

During the COVID-19 health crisis, a recent study corroborated the impact of behavioural inhibition system activation. Specifically, young adults with a stable pattern of excessive activation of the behavioural inhibition system in childhood (measured using behavioural observations of children's response to novel toys and interactions with unfamiliar adults) had problems with worry regulation in adolescence and developed more anxiety symptoms during the pandemic (28). Broadly (beyond COVID-19), this kind of worry dysregulation has been considered a developmental pathway to depression in youth (29).

The neurobiological domain

At a neurobiological level, people with high trait anxiety [a phenotype associated with anxiety and mood disorders risk (30)], tend to present enhanced activation of the amygdala in response to emotional stimuli, mainly in the basolateral area. In addition, concomitant hyper-reactivity of the hypothalamic–pituitary–adrenal (HPA) axis, present in individuals with high trait anxiety, potentiates a "fight or flight" physiological response to not only negative stimuli, but also neutral stimuli perceived as threatening (31).

Individuals with high trait anxiety may also show disruptions between the amygdala and other brain regions. For example, it has been proposed that the prefrontal cortex may have limited capacity to downregulate hyperactivation of the amygdala caused by negative stimuli, and the integration of contextual information via hippocampal connections may be compromised and restricted. Evidence on these processes was assessed and summarised in a recent meta-analysis of 226 fMRI studies with people with both anxiety and mood disorders (32). Three right-sided clusters of hypoactivation were identified centred in the inferior prefrontal cortex/insula, the inferior parietal lobule and the putamen while the dorsal anterior

cingulate cortex, the left amygdala/parahippocampal gyrus and the left thalamus were hyperactivated across the reviewed studies.

In sum, when individuals with high trait anxiety are exposed to major stressful life events, the hyper-reactivity of the amygdala to threats is strengthened and reinforced by a loop of sympathetic activation produced by HPA dysfunction (30).

Meanwhile, attention and memory bias are consolidated in a mood-congruent bias, oriented to negative thoughts. Intense negative affect would activate the behavioural inhibition system, and interfere with higher order cognitive processes, such as executive functions, social cognition and learning. Behavioural and neurophysiological changes reinforce each other, for the better or the worse.

The person experiencing intense negative affect and cognitive biases about their own abilities will avoid interactions with other individuals, decreasing social reinforcement. The lack of motivation for social interactions could lead to learned helplessness (33). According to the tripartite model (22, 23), the prevalence of each dimension of the process [distress, low positive affect (anhedonia) and/or physiological hyperarousal] will determine the development of anxiety problems (i.e. worry, hyper-arousal) (34) (28), mood problems (loss of motivation), or a combination of both, comorbidity (35).

The cellular domain – mitochondrial function

Several single nucleotide polymorphisms (SNPs) associated with the serotonergic, dopaminergic and GABAergic system have been associated with trait anxiety. These SNPs are posted to act through the modification of proteins that alter behavioural outcomes, such as reactivity to emotional stimuli (36, 37). These findings have informed the development and refinement of pharmacological interventions where monoamine depletion plays a role as a mechanistic model. However, the delay observed between pharmacological action and

clinical relief (e.g. antidepressants act within minutes to hours of administration, contrasting with the alleviation of symptoms that usually happens after two weeks of chronic administration), unveil the presence of a more complex pathogenic model. In fact, new ideas have been proposed about the role of the downstream cascade resulting from cellular events and adaptive brain processes beyond monoamine transmission as an underlying element shared by anxiety and depression (38, 39). In particular, mitochondrial function has been linked to the pathophysiology and treatment of these problems (40).

The complex intracellular cascades upregulated in stress-related conditions such as anxiety and depression may be associated with mitochondrial capacity for resilience to sustain resources and provide stability at a cellular level (41). For example, elevated levels of glucocorticoids can compromise cellular energy capacity and facilitate neurotoxicity (40, 42, 43). Also, downregulation of BDNF during stress (44), and disruptions in the regulation of intracellular calcium --a critical mediator of apoptosis-- can generate reactive oxygen species (ROS) via the electron transport chain (45).

These are examples of mitochondrial function affected by glucocorticoids and other stress mediators. However, it is notable that stress hormone glucocorticoids are produced and metabolized by mitochondria, determining the magnitude of stress response, and regulating the cellular homeostasis during response to stress. Mitochondria may be at the core of the mechanisms of stress adaptation and regulation (46). Mitochondrial function is fundamental for neuronal growth and sprouting, synaptic transmission, neuronal plasticity, and connectivity, supporting complex cognitive and behavioural functions that are common to anxiety and depression (46) (47).

Unsurprisingly, new treatments informed by the role of mitochondria have been developed to target varied medical conditions. Well-known limitations with current mental

health treatments, such as side effects of pharmacological treatments (48), or lack of access to evidence based psychological interventions, have stimulated new treatment alternatives informed by these mechanistic models. Photobiomodulation (PBM), an intervention based on light as energy to support biological changes is one example of a recent mechanism-targeting intervention. The next section offers an introduction to photobiomodulation, and summarizes preliminary findings of studies with non-responsive groups of patients suffering from mood and anxiety problems.

Photobiomodulation. A new light in treatment options?

With appropriate wavelengths and light dosing parameters, all eukaryotic cells and tissues should be responsive to photobiomodulation via mitochondria (49-51). Two mechanisms have been proposed to explain this mitochondrial response and the production of ATP. The most popular model refers to the absorption of the photons by cytochrome c oxidase (CCO), leading to high levels of ATP (52). A second novel model (53), suggests that PBM target the interfacial water layer (IWL) viscosity on hydrophilic surfaces, associated with ATP level restoration. In this model, the target for photons absorbed by cells will be H2O molecules constituting the IWL on intracellular surfaces, whose physical properties can be modulated by light.

To reach its target, the photons need to cross barriers, and different strategies are under evaluation to obtain better stimulation of different brain areas (54). In transcranial PBM (t-PBM), the most prevalent modality, the light must cross tissues and the skull to reach the cortex, and it is estimated that near infrared radiation (NIR) coming from Low-Level Lasers or Light-Emitting Diodes (LED) has a penetration rate of 2%-3% at target prefrontal cortex regions (50). This small percentage fluence (or energy density) on the human brain has been considered equivalent to the energy density capable of inducing neurological benefits in

animal model studies (55). Furthermore, different studies are currently testing different parameters such as irradiation wavelengths, continuous or pulse patterns to enhance penetration [for a review relevant to mental health see (56)].

Photobiomodulation for anxious and depressive symptomatology

Few pioneer animal studies showed positive clinical results for treatment of anxiety and depression problems with t-BPM (57) (58). These results have been replicated by Eshaghi et al. (59), where they delivered t-PBM using animal (mice) models of anxiety and depression (chronic restraint stress). The research indicated noticeable improvement in behavioural results, decreased serum cortisol levels, increased serotonin and decreased nitric oxide concentrations in the Pre Frontal Cortex and Hippocampus.

Caldieraro and Cassano (2019) conducted a systematic review, indicating the growth of literature on PBM in humans (50). In 2009, Schiffer et al. (60) conducted a within-subjects pilot study, and found that single-session t-PBM (four times four minutes, randomized NIR/sham, at 810 nm) delivered at electrode sites F3 and F4 (on the forehead, bilaterally targeting the dorsolateral prefrontal cortex) led to remission [assessed using the Hamilton Depression Rating Scale (HAM-D)] in six of ten patients. Nine of these ten patients had comorbid anxiety, and they found remission in seven of ten subjects for anxiety [using the Hamilton Anxiety Rating Scale (HAM-A)]. Greatest changes were observed at the two-week mark.

Of note, two randomised clinical trials of t-PBM and two randomised clinical trials of low-intensity laser acupuncture have been conducted. Adjunctive t-PBM (at 1064 nm) to Attention Bias Modification (ABM) treatment for elevated depressive symptoms (n=51) at right and left (bilateral) forehead locations demonstrated that t-PBM enhanced improvements. However, this was specific to right stimulation (not left), and there were no significant

differences due solely to t-PBM (61). These results may be expected given the additive nature of the therapy.

In non-adjunctive trials, Cassano et al. (62) utilized t-PBM (823 nm) to test efficacy in MDD treatment. Twenty-one participants were randomized to a sham or experimental condition and received bilateral stimulation to the forehead. The PBM condition yielded a greater decrease in scores than the sham condition on the HAM-D, and response to treatment was higher in the active treatment condition than the sham condition (50% and 27% respectively).

The team of Quah-Smith et al. [(63) , n=30]; [(64), n=47] took a different approach and tested acupuncture points as targets for laser therapy on limbs and trunks (primary depression acupoints) over up to 12 sessions over eight weeks. The researchers found significant antidepressant effects in both samples.

While these studies are smaller and may leave something to be desired in terms of sample size, a team of researchers in Russia (65, 66) have conducted a series of larger (n =180 and n = 79) open studies using a combination of red and NIR intravenously and transcutaneously. The first study included a treatment group who accepted PBM as an add-on to pharmacological treatments, resulting in significant decrease in HAM-D and HAM-A scores (as compared to non-randomized controls). The second compared outcomes in individuals with MDD, BD or mixed diagnoses and notably reported a 23% rate of relapse in study participants as compared to 50% in non-randomized, non-blinded controls.

These results in large part focused on depression [with the exception of (60) and (66)], but case studies in other mood and anxiety disorders corroborate results. One elderly individual saw a 50% improvement in symptoms of anxiety while using intranasal PBM and t-PBM as an adjunctive treatment to pharmaceutical treatment for MDD with anxious distress

(67). Four patients with BD diagnoses who used bilateral t-PBM to address anhedonia residuals also saw improvements in their condition (68).

Overall, PBM is an example of a novel intervention for treatment of mood and anxiety disorders that is simple and cost-effective, with few apparent side effects (50). Several clinical trials (NCT02959307, NCT02898233, and NCT03420456) have been registered, and results should hopefully be forthcoming.

Conclusions and future directions

The COVID-19 pandemic is testing our response capacity to address pre-existing and new global mental health issues, in particular prevalent ones such as the comorbidity of anxiety and depression. Different types of health measures are needed, from public health initiatives to novel clinical interventions for those experiencing pervasive negative experiences related with anxiety and depression.

PBM may be a promising treatment option that is easily deployable, low cost, and potentially effective as a complement to traditional evidence-based approaches. Through targeting basic cellular processes, PBM generates a positive cascade in the nervous system, improving regulation of behaviour, affect and cognition. Moreover, some evidence shows a general neuro-protective effect of PBM. Enhancement of learning and memory have been observed in preliminary studies with people with Alzheimer, dementia, stroke and healthy subjects (69).

This evidence highlights a general improvement of pre-frontal cortex functioning (the most frequent sites in anxiety and depression studies where LED are applied are F3 and F4 positions in the 10-20 international system), as an important mediator for the behavioural effects of PBM therapy. The pre-frontal cortex has an important role orienting basic cognitive processes (attention, memory) and emotion regulation. In that sense, PBM can potentiate traditional pharmacological and psychotherapeutic interventions. Ongoing clinical trials will

advance our knowledge about PBM, including the time-to-effects of metabolic changes, and should deepen our understanding of these changes using multimodal neuroscience approaches.

For example, magnetic resonance imaging (MRI) can be used to describe functional changes in blood flow (BOLD signal in functional MRI or even functional near-infrared spectroscopy-fNIRS) and identify cellular biochemical mechanisms (magnetic resonance spectroscopy). At a clinical level, combining PBM with electroencephalography (EEG) could be an excellent avenue for monitoring changes in cortical activity. Moreover, in a set-up for evoked-related potentials, experimental tasks could be used to test specific cognitive effects of PBM. Photo stimulation and EEG sensors could be integrated in the same device, at a reasonable cost and with high temporal resolution.

In conclusion, this chapter demonstrates that reviewing important characteristics of the comorbidity of depression and anxiety in the cognitive, behavioural, and neurobiological domains may unearth commonalities pertinent to the improvement of care. This is demonstrated through the comorbidity in neurobiological (mitochondrial) functioning and its cognitive and behavioural correlates, which lend credence to the transdiagnostic treatments such as PBM. This novel treatment may be both appropriate and promising in targeting of shared mechanisms, particularly essential in a post-pandemic world with an increased demand for mental health services.

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