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Recent findings in the pathogenesis and treatment of fear and anxiety

Aktualne koncepcje dotyczące patogenezy oraz terapii lęku i strachu

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Abstract

This paper presents a brief overview of current knowledge regarding the neuroscientific and biological background of anxiety and fear. The conceptualisation of the "two-system" framework is described in detail. In terms of terminology, the terms fear and anxiety are limited in this framework to mental states connected with consciously experiencing emotions as opposed to nonconscious autonomic nervous system reactions. The introduced terminology may have practical implications in psychotherapy as people seek help mainly because of subjective experiences of fear and anxiety and the effectiveness of mental health interventions is also evaluated on the basis of experiencing these mental states. The background of developing anxiety disorders is briefly described, emphasising the key role of sympathetic and parasympathetic systems. As nowadays anxiety disorders are prevalent among adolescents and adults, it is necessary to implement interventions preventing development of full-blown disorders in people suffering from excessive or sub-threshold anxiety levels. Acceptance and commitment therapy (ACT) is suggested as the evidence-based prevention model. ACT promotes building psychological flexibility, incorporates mindfulness techniques which enable alteration of the anoetic form of consciousness, and introduces breathing exercises that may stimulate the sympathetic system through the vagus nerve. Thus ACT model as a preventive tool has the implications to bridge the psychological and neuroscientific research and theory with practical usage.

Key words: anxiety, psychopathology, acceptance and commitment therapy.

Streszczenie

Praca przedstawia przegląd aktualnej wiedzy dotyczącej rozumienia neuronaukowego oraz biologicznego podłoża lęku i strachu. Opisano szczegółowo konceptualizację modelu obwodu przetrwania i motywacji obronnej. W modelu tym określenia lęk i strach ograniczone są do stanów umysłowych związanych ze świadomym doświadczaniem emocji, w przeciwieństwie do nieświadomych reakcji autonomicznego układu nerwowego. Wprowadzona terminologia może mieć implikacje kliniczne w psychoterapii, ponieważ ludzie szukają pomocy głównie z powodu subiektywnie odczuwanego lęku i strachu, a efektywność interwencji związanych ze zdrowiem psychicznym jest oceniana na podstawie doświadczania tych stanów umysłowych. Następnie opisano zwięźle podłoże zaburzeń lękowych z położeniem akcentu na kluczową rolę sympatycznej i parasympatycznej części układu nerwowego. Ze względu na rozpowszechnienie zaburzeń lękowych oraz nadmiarowego lęku na poziomie subklinicznym wśród młodzieży i dorosłych zaproponowano zastosowanie profilaktyki w zakresie zdrowia psychicznego zogniskowanej na zapobieganiu zaburzeniom lękowym i związanym ze strachem. Model terapii akceptacji i zaangażowania (*acceptance and commitment therapy* – ACT) jest oddziaływaniem o potwierdzonej naukowo skuteczności. Wspiera on budowanie elastyczności psychologicznej, włącza techniki uważności, które umożliwiają zmianę anoetycznej formy świadomości, oraz wprowadza ćwiczenia oddechowe, które mogą stymulować sympatyczny układ nerwowy poprzez aktywację nerwu błędnego. Z tego powodu model ACT jako narzędzie prewencyjne ma potencjał, by budować pomost między wynikami badań oraz psychologiczną i neuronaukową teorią a jej praktycznym zastosowaniem.

Słowa kluczowe: lęk, psychopatologia, terapia akceptacji i zaangażowania.

Emotions of anxiety and fear – a short introduction

Different cultures have used various medical, religious, philosophical, moral, and social frameworks to characterise anxiety and its disorders. Across centuries and even millenniums the artefacts of culture and arts represented a mental state called anxiety (LeDoux and Pine 2016). It became the axis of the social attention after the second world war. The omnipresence of the anxiety theme in the culture was the consequence of war atrocities, nuclear arming and potentially catastrophic tensions of the cold war. Nowadays, the anxiety has escalated due to the COVID-19 pandemic.

The emotions of fear and anxiety are the legacy of the evolution of our species or can be the result of the processes of learning and socialising (Davidson *et al*. 1994). The emotion of fear is one of the universal emotions experienced by people regardless of origin, race or nationality (Ekman 1984). Although the emotions of fear and anxiety consist of three core elements – physiological arousal, cognitive assessment and behavioural response (Barlow 2002) – they are defined differently. Fear is characterised as an emotion emerging as a response to concrete, dangerous, identifiable objects and situations accompanied by a strong physiological arousal, whereas anxiety is defined as a state of expecting a potential threat, negative event or future danger that may or may not occur (Seligman *et al*. 2003).

Biological perspective

The current emphasis on grounding anxiousness in neurochemistry in many respects echoes the dominant somatic paradigm of nineteenth-century psychiatry that explored how specific biological malfunctions in the nervous system make certain individuals vulnerable to anxiousness. For some leading neuroscientists anxiety is embedded in neural circuits (LeDoux and Pine 2016). Initially, scientists were trying to define the key structure in the central nervous system responsible for regulating the emotional reactions – consecutively the thalamus, hypothalamus (Cannon 1929), hypothalamus with additional anatomical circuits in the forebrain (Papez 1937) and the limbic system (MacLean 1955) were considered to be the brain's centres of emotions. The results of the studies from many laboratories with the application of Pavlovian fear conditioning showed the importance of the amygdala in acquisition and expression of conditioned fear (LeDoux 2000). The amygdala is the key component of the "fear system" as it evaluates the input signals from the sensory nerves. The amygdala is described as a "fear centre" or "the hub of the fear circuit" (LeDoux 1996; Panksepp 2011). It has extensive projections to the prefrontal cortex and receives hippocampal projections (LeDoux 2003). The direct thalamus-amygdala pathway (LeDoux 2003) is thought to be responsible for the innate "fear system" in the mammalian brain. The brain mechanisms involved in the confrontation with the threatening stimuli potentially harmful to the organism create a highly efficient threat-processing circuitry present across mammal species (LeDoux 2003). The innate involuntary reactions that occur in the presence of a threat comprise defensive behaviours (freeze/fight/flight responses, facial expressions, avoidance), reactions from the autonomic nervous system (including changes in heart rate and blood pressure) and responses of neuroendocrine systems (release of hormones). In addition to the quick, evolutionary mechanism of reacting to danger, emotions are also experienced after the nonautomatic, will-initiated process of the cognitive evaluation. The reactions to stimuli and situations can be altered under the influence of our personal experience which is the outcome of differentiated contexts and conditions of our social existence. Through the lifespan, the broad scope of stimuli and situations was associated with the range of stimuli, which from birth were connected with triggering specific emotions. The reactions to these stimuli and situations can be "filtered" through a conscious evaluation. This process enables the possibility of differentiating the scope and intensity of inborn, fixed emotional patterns (Damasio 2013).

A "two systems" framework

LeDoux and Pine (2016) proposed a "two systems" framework of fear and anxiety as opposed to one "fear system" that generates both the physiological and behavioural reactions to threat and the conscious experience of emotion. One system is responsible for generating conscious emotions and mainly involves cortical areas, while the other system largely operates unconsciously and controls behavioural and physiological reactions to threats and mostly comprises subcortical areas with connections with certain cortical regions (Fig. 1).

The authors argue that understanding the distinction of the two systems may improve

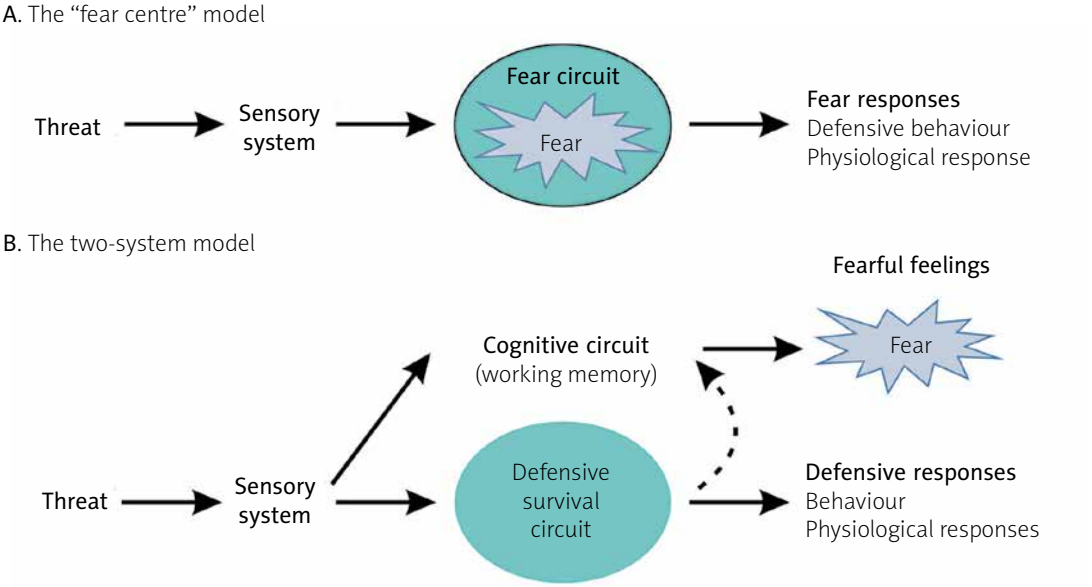

Fig. 1. The traditional "fear centre" view versus the "two-system" view of fear (with permission of Joseph LeDoux)

development of effective pharmaceutical and psychological interventions. In order to precisely tailor further scientific progress, the terminology needs to be redefined. LeDoux and Pine (2016, p. 1083) suggest limiting the definition of such terms as *fear* and *anxiety* to the primary meaning of mental states – "subjective feelings of fear and anxiety" as they are reflected in self-reports. This understanding of fear and anxiety excludes referring to physiological and behavioural responses to threatening stimuli. This distinction may trigger practical implications in psychotherapy as people seek help mainly because of subjective experiences of fear and anxiety. Moreover, the effectiveness of mental health interventions is also evaluated on the basis of experiencing these mental states as opposed to nonconscious autonomic nervous system reactions. The two systems framework introduces such terminology as *defensive circuits* to refer to brain circuits that detect and react to threat stimuli, *defensive behaviours* involving behaviours that occur as a response to threat and *defensive physiological adjustments* to refer to physiological changes accompanying defensive behaviours (LeDoux and Pine 2016). According to recent research, the amygdala's function is detecting and controlling the behavioural and physiological responses to immediate danger while the uncertain threats are processed by the bed nucleus of the stria terminalis (BNST; Walker and Davis 2008; Hammack *et al*. 2015) (Fig. 2).

The neural circuits responsible for subjective emotional states are distinct to defensive circuits. According to some researchers (LeDoux and Pine 2016), the subjective feelings of fear and anxiety depend on the cortical consciousness networks, which are also responsible for other conscious experiences. This higher-order association cortex is engaged in working memory and attention processes. The lower-order information about external stimuli from the defensive system is re-represented in cortical regions, which is the basis of forming the conscious awareness of the non-conscious processing of the threat (D'Esposito and Postle 2015; Damasio and Carvalho 2013). Thus, the subjective feelings of fear and anxiety arise indirectly from the subcortical circuits responsible for brain and body arousal (defensive circuits), which, in turn, influence working memory function (LeDoux and Pine 2016). The "two-system" model enables understanding the role of language in inducing the subjective feelings of fear and anxiety. Language plays a crucial role in experiencing these emotional states without the presence of an immediate or imminent threat in the environment (Forsyth and Eifert 1996). Language skills predispose people to experience imagined danger, which can lead to unremitting excessive anxiety, which in turn may lead to development of a full-blown anxiety disorder.

The basic emotional circuits

Another theory based on empirical research employing neuroscience evidence to explain the nature of emotions was formulated by Panksepp (1982). The researcher utilised animal brain research to understand the affective state

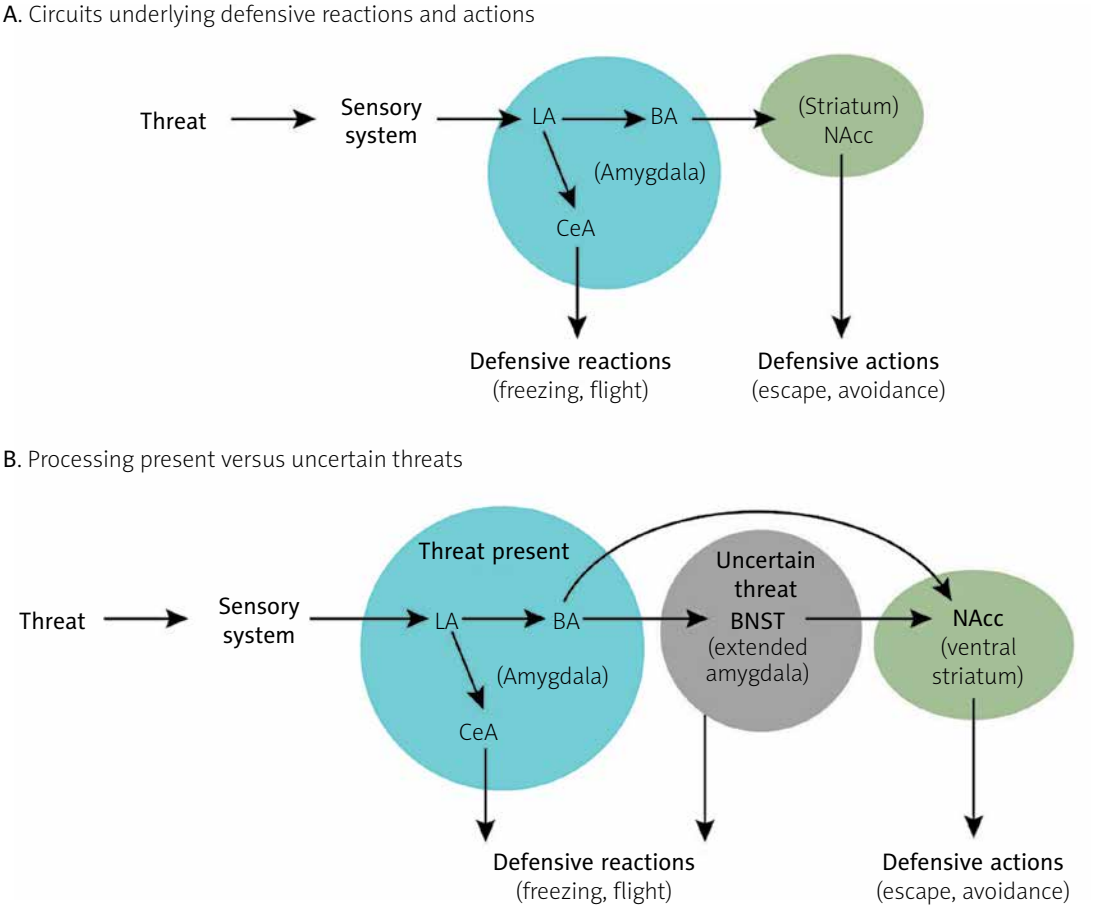

Fig. 2. Neural control of reactions and actions elicited by present versus uncertain threats. LA – lateral amygdala, BA – basal nucleus, CeA – central nucleus of the amygdala, BNST – bed nucleus of the stria terminalis, NAcc – nucleus accumbens (with permission of Joseph LeDoux)

of emotions. In his view, the primary-process (unconditioned, instinctual) aspects of brain organisation is the basis for secondary-processes (learning) and tertiary processes related to higher cognitive processes. The behavioural brain research (Panksepp 1982) demonstrated that emotions arise from hard-wired neural circuits in the visceral-limbic brain. These circuits developed early in mammalian brain evolution and are similar in humans and other mammals. They are called basic-emotion command systems and are responsible for adjusting the behavioural and physiological response to major classes of environmental demands. These systems presumably control and are controlled by various higher forms of conscious "awareness" – they substantially interact with higher cognitive brain areas (Panksepp 2011). In the revised version of the emotional systems, Panksepp (2011) distinguished seven partially overlapping systems, at least two of which are connected with fear and anxiety: the FEAR/Anxiety System and the Separation Distress PANIC System. The Fear/Anxiety System is responsible for generating the unconditional affective state of fear and is connected with avoiding or escaping from threats. The neural substrates of this system consist of medial and basolateral regions of the amygdala, anterior and medial hypothalamus and dorsal periaqueductal grey matter (PAG) in the midbrain and adjacent tegmental fields (Panksepp *et al*. 2011). The FEAR/Anxiety System circuit starts in the amygdala, descends through the hypothalamus to the PAG to trigger the state of anxiety or fear. The main substrates that operate in this system are amino-acid glutamate, diazepam-binding inhibitor (DBI) and corticotropin releasing factor (CRF; Panksepp *et al*. 2011). The aim of the Separation Distress PANIC System is for offspring to signal the need for care and to obtain it. This system is also activated during human sadness. The brain regions constituting the PANIC system include the anterior cingulate cortex, the BNST (bed nucleus of the stria terminalis), dorsal medial hypothalamus, the preoptic area, the ventral tegmental area (VTA), and PAG. The neurotransmitters and neuromodulators of this system are opioids,

prolactin, oxytocin, corticoliberin, and glutamic acid (Panksepp 2011).

Anxiety – the psychopathological perspective

The term *neurosis* was first used three centuries ago in 1777 by William Cullen (Cierpiałkowska 2015) to characterise the symptoms indicating the functional disorder of an organ in which any structural changes were found. Later the definition expanded to embrace the whole range of symptoms that occurred as a consequence of the real or expected experience of powerful psychological or physical danger or threat (Cierpiałkowska 2015). Fear and anxiety fulfil the adaptive role by signalizing the approaching danger and they are followed by important defensive reactions: freeze, fight or flight (LeDoux 2017). Excessive anxiety, though disproportional to the actual threat, can be the predisposing factor in developing many mental disorders. The symptoms of anxiety may be more or less noticeable in individuals and include: cognitive, emotional, physiological and behavioural aspects (Cierpiałkowska 2015). The cognitive aspect of anxiety is connected with anticipation of a non-specific or less probable threat, frequent or excessive worry, or poor concentration. When a person cannot identify the direct object triggering anxiety, he or she becomes hypervigilant, focusing on finding the precise source of danger. A wide body of research shows attentional bias towards threat-related stimuli across anxiety disorders. The content of the biases is specific to particular disorders depending on the personal past history and learning experience (Craske *et al*. 2009). The emotional aspect of anxiety is connected with the subjective feeling of being in danger. The valence of the emotion is negative. Sometimes the feeling is not recognized by the person, but instead constant tension and unpleasant arousal is experienced. The physiological aspect of anxiety is connected with the function of the sympathetic nervous system. The autonomic nervous systems comprises two subsections: the sympathetic and parasympathetic systems that are responsible for controlling the energy levels. When the amygdala sends a distress signal, the hypothalamus activates the sympathetic nervous system, which in turn prepares the body for action. The sympathetic system functions even when the threat is not processed consciously yet. In the situation of proximate danger, the autonomic nerves send signals to adrenal glands which pump the hormone epinephrine (adrenaline) into the bloodstream. Epinephrine circulation causes physiological changes in the whole body including a higher heart rate and blood pressure, enabling more blood to be pumped into the muscles and other vital organs in order to prepare the body for action. The person breathes more rapidly and extra oxygen is provided to the brain, which increases alertness. Blood, rich in glucose and fats released from storage sites to the bloodstream, is circulated to the arms and legs. The parasympathetic nervous system is responsible for dampening the stress response and bringing the body into balance. However, the sympathetic nervous system can malfunction, which can cause constant alertness and the feeling of tension and anxiety. If the situation continues, it can lead to a permanent anxiety response and put a person at risk of developing full symptoms of anxiety disorder. The key part of the parasympathetic system – the vagus nerve (Porges 2001) – has recently received much scientific attention due to its connections with breathing and the possibility of soothing the stress response. The behavioural aspect of anxiety is connected with readiness for action. As fear and anxiety cause three different types of behaviour – freeze, fight or flight (avoidance) – fear is associated with fighting or freezing in response to an immediate threat, while anxiety results in avoidant behaviours such as procrastination, difficulty in making decisions and social withdrawal (Seligman *et al*. 2005).

There is a wide range of factors that may predispose to developing anxiety disorders including biological (genes, disrupted modulation of the nervous system, physical condition), psychological (personality traits, life experience, stress) or social (attachment style, environment, social support) or a combination of them (Strelau and Doliński 2015). Experiencing excessive fear and anxiety mobilises strong defensive reactions inappropriate to the actual situation, bringing about suffering, emotional pain, persistent worry, irritability, sense of threat, helplessness and the sense of limited activity in different domains of life (Cierpiałkowska 2015). The symptoms become persistent and intrusive. People suffering from a severe form of anxiety experience the sense of being overwhelmed by their condition, which interferes with maintaining their daily routines. They have sleep disturbances and find it difficult to relax. Anxiety or fear-related disorders specified in ICD-11 include inter alia generalised anxiety disorder, panic disorder, social anxiety disorder, separation anxiety disorder, substance-induced anxiety disorder,

organic anxiety disorder, and dream anxiety disorder (WHO 2021). The clinical picture of these disorders is distinctive and complex; nevertheless, some of the characteristics remain common, including: raised sensitivity to threat, avoidance behaviours, persistent and repetitive thoughts and physiological arousal (Wolitzky-Taylor *et al*. 2010). In phobia learning, what is threatening can predispose a person to focus fear and anxiety on some particular objects or events. In response to external or internal cues in learned (conditioned) anxiety, the organism prepares to deal with expected threat through conditioned defensive behaviour such as escape or avoidance. A person rapidly develops acute sensitivity and vigilance to newly acquired phobic cues (Barlow 2002).

The data indicate that anxiety disorders are prevalent among adults and adolescents (Kessler *et al*. 2012; Witlox *et al*. 2021), and suggest that these disorders are almost as common as depression (Fukukawa *et al*. 2004; Gum and Cheavens 2008).

Anxiety disorders – prevention and treatment

In recent years the destructive influence of the COVID-19 pandemic on mental health and well-being around the world has been accumulating (McCracken *et al*. 2021). Thus, there is an urgent need to foster understanding of the underpinnings of anxiety and fear-related disorders and implement preventive programmes and interventions which aim to lower early or sub-threshold manifestations of symptoms (Fani Marvasti and Stafford 2012). The training should target both excessive symptoms of anxiety and supporting mental well-being (Bohlmeijer and Westerhof 2021). There is circumstantial evidence for the effectiveness of a wide range of treatment protocols based on cognitive behavioural therapy (CBT) in different anxiety disorders (Sánchez-Meca *et al*. 2010; Kaczkurkin and Foa 2015). CBT is a time-limited, present-oriented approach to psychotherapy fostering the patient's cognitive and behavioural competencies in order to facilitate adaptive functioning (Beck 1993). In CBT treatment of anxiety, the exposure is a central component. Other techniques include cognitive restructuring, relaxation and stress reduction methods, role playing and behavioural experiments. Recently, a substantial number of randomised control trials have confirmed the mindfulness-based approaches to be efficacious concerning anxiety disorders (Hofmann & Gómez 2017). These treatment models comprise mindfulness-based stress reduction and mindfulness-based cognitive therapy.

Acceptance and commitment therapy model

Promising preventive and treatment interventions are offered by the integrative acceptance and commitment therapy (ACT; Hayes *et al*. 2006) model as it addresses both anxiety symptoms and enhanced well-being. ACT fosters advancing psychological capacities helpful in building psychological flexibility (PF). ACT interweaves principles of mindfulness and acceptance with treatment techniques adopted from behavioural therapy and experiential psychotherapy (Hayes *et al*. 2006). From the ACT perspective, psychopathology derives from the manner in which language and cognition interact with ongoing events that hinder flexible persisting or changing behaviour in accordance with long-term values (Hayes *et al*. 2006). ACT defines this kind of *psychological inflexibility* as a consequence of weak or unhelpful contextual regulation over language processes (Hayes *et al*. 2006). The psychological inflexibility, described also as rigidity or lack of contextual flexibility, is described as a vulnerability factor for developing psychopathology and a signal characteristic of many disorders (Kashdan and Rottenberg 2010). A growing body of research shows that anxiety disorders are connected with psychological inflexibility, particularly as far as a reduced and stereotyped repertoire of behavioural responses to fear and anxiety is concerned (Kashdan and Rottenberg 2010). The empirical research shows that the skill of focused and flexible paying attention can be learned and that the methods of developing acceptance and mindfulness may significantly stimulate the basic attentional processes (Hayes *et al*. 2013). Some mindfulness techniques based on old Eastern traditions involve paying attention to breathing, which is regulated automatically. It can also be regulated by through conscious control over the quantity of inhaled breath and the speed of breathing. Conscious control over breathing is possible via interaction between the function of executive control of the neocortex and neurons regulating breathing in the spinal cord and in the medulla oblongata (Urfy and Suarez 2014). When people are stressed, the sympathetic nervous system dominates (Porges 2001). Mindful breathing in a slow, steady way stimulates the vagus nerve and, as a consequence, the parasympathetic nervous system becomes

more active, toning the stress reaction (Porges 2001). Control of breathing may help in calming anxiety (Zeidan *et al*. 2014). It is considered that mindful focus on somatosensory experience of breathing results in specific improvements to core processes of attentional control. These processes constitute core mechanisms of working memory and are central to the hypothesis of the self-free working memory enhancing disengagement from excessive fear and anxiety (LeDoux 2017). It is commonly thought that consciousness is a higher brain function and can be defined as the capacity to be aware of the external environment and reflect upon the inner experiences. Tulving (2002) differentiated three forms of consciousness: anoetic (forms of experience other than thinking, which may be emotionally intense without being "known"), noetic (forms of consciousness connected with thinking, which are linked to exteroceptive perception and cognition) and autonoetic (abstract forms of perceptions and cognitions, which enable conscious states of awareness and facilitate reflection upon experience through episodic memories and fantasies). People struggling with excessive worry or anxiety tend to allocate their attention to threatening stimuli and worry about possible future events. As the emotions of fear and anxiety are states of anoetic consciousness concerning the self, the working memory processes are focused on the content of conscious experience (images, thoughts, feelings) fostering building self-narrative (LeDoux 2017). During meditation and mindfulness training in ACT working memory processes are deployed to prevent the inflow of information and allow the mind to be present in the here and now, non-judgementally and free of ongoing self-narrative. While meditation and mindfulness control neural networks of working memory, the self-free mind would not experience fear or anxiety in terms of personal meaning. Thus the anoetic form of consciousness may be modified through disengaging working memory from continuously being self-absorbed through the practice of meditation and mindfulness (LeDoux 2017).

Summing up, ACT-based interventions have potential to prevent excessive anxiety through different pathways: by practising breathing exercises which stimulate the vagus nerve and calm the nervous system; by implementing meditation and mindfulness which can modify the anoetic form of consciousness; and by training psychological skills fostering developing PF.

According to ACT building greater PF results in better health and well-being, despite ongoing experiencing of difficult and painful personal events (Kashdan and Rottenberg 2010). ACT-based interventions might provide people with a buffer against detrimental impacts of the pandemic and everyday anxiety and fear-inducing challenges (Kashdan *et al*. 2020; Dawson and Golijani-Moghaddam 2020; McCracken *et al*. 2021).

Disclosure

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