Published in final edited form as:
Depress Anxiety. 2013 April ; 30(4): 315–320. doi:10.1002/da.22076.

The breathing conundrum – interoceptive sensitivity and anxiety

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Abstract

Cognitive and affective processing has been the central focus of brain-related functions in psychology and psychiatry for many years. Much less attention has been paid to, what could be considered the primary function of the brain, to regulate the function of the body. Recent developments, which include the conceptualization of interoception as a process consisting of integrating the information coming from the inside of the body in the central nervous system (CNS) and the appreciation that complex emotional processes are fundamentally affected by the processing and regulation of somatic states, have profoundly changed the view of the function and dysfunction of the brain. This review focuses on the relationship between breathing and anxiety. Several anxiety disorders have been associated with altered breathing, perception of breathing and response to manipulations of breathing. Both clinical and experimental research studies are reviewed that relate breathing dysfunctions to anxiety. Altered breathing may be useful as a physiological marker of anxiety as well as a treatment target using interoceptive interventions.

Anxiety and Breathing – The Interoceptive Connection

Anxiety is an emotional state associated with a (a) cognitive component of increased attentional focus on threat to the integrity of the individual [1], (b) a complex sympathetic arousal response [2], and (c) behaviors aimed to avoid stimuli or contexts predictive of threat to the individual [3]. Breathing is one of the most fundamental physiological functions of the human body. Moreover, it is an integral component of interoceptive processing, i.e. the sensing of the physiological condition of the body [4], the representation of this internal state [5] within the context of ongoing activities, and the initiation of motivated action to homeostatically regulate the internal state [6]. Changes in breathing can be both the consequence of an increased level of anxiety (e.g. [7]) as well as the source of threat experienced by the individual, which, in turn, leads to increased anxiety [8]. Thus, assessing breathing might be a useful physiological marker of the level of anxiety but can also serve as an experimental tool to influence anxiety levels. The elucidation of the physiological mechanisms and neural pathways regulating breathing can help to better delineate how an emotional state emerges from the interaction between the body and the brain.

We have recently refined [9] a previously proposed insular model of anxiety [10]. The aim of this model is to integrate emerging neuroanatomy of interoception with a process focused formulation of anxiety to provide a novel heuristic for the development of assessments and interventions. In this model, we considered that anxiety is a result of an increased anticipatory response to the potential of aversive consequences, which manifests itself in enhanced anterior insular cortex processing. Specifically, when anxious individuals receive body signals they cannot easily differentiate between those, which are associated with potential aversive (or pleasant) consequences versus those, which are part of constantly ongoing and fluctuating interceptive afferents. As a consequence, these individuals imbue afferent interoceptive stimuli with motivational significance, i.e. an increased tendency to plan and act upon the reception of this input. Specifically, an internal body signal, e.g. an

inspiratory breathing sensation, is associated with negative valence and linked to belief-based processes, e.g. “I am not getting enough air”, which results in an increased “fight/flight” response and potential withdrawal or avoidance behaviors. As a consequence of this noisy amplification, top-down modulatory brain areas such as the anterior cingulate, dorsolateral prefrontal cortex, and orbitofrontal cortex are engaged constantly to differentially amplify or attenuate signals that are predictive or not predictive of future states, respectively. This relative “overactivity” of cognitive control related brain areas is subjectively experienced as increased production of thoughts and associated beliefs, which provide prediction-enhancing propositions. Practically, these cognitive processes result in “worrying”, which is aimed at providing increased prediction accuracy. This model relies on the notion of “accurate” processing of interoceptive afferents in general and breathing in particular. However, it is unclear at what level inaccurate processing of interoceptive afferents occurs in anxious individuals. This review aims to delineate the current status of knowledge about the physiological and neural pathways of breathing perception to provide a background and potential targets of research as well as opportunities to modulate breathing in order to decrease anxiety

Previous investigations have shown that individuals with anxiety disorders show altered breathing characteristics [11; 12] or altered responses to manipulating breathing [13]. The focus of this review is to provide insights into the physiology of breathing, its underlying neural circuitry, challenge paradigms, and its relation to emotional processing. In particular, the focus is on changes in breathing load, i.e. the degree to which individuals experience breathing resistance during inspiration. Other studies, which will not be reviewed here, have focused primarily on the regulation of carbon dioxide and its contribution to anxiety (e.g. see [14; 15]). The goal is to provide clinicians and researchers with information that can be useful to better understand why breathing is so closely linked to anxiety or to consider modulation of breathing as a mode of treatment and to develop a program of research aimed at better understanding the pathophysiology that relates breathing changes to anxiety.

The Sensation of Breathing – From the Periphery to the CNS

The sensation of breathing and its impairment is a complex process that is modulated by both peripheral and central nervous factors. From a peripheral perspective there are at least seven sensory airway receptors, which have been characterized electrophysiological [16] that contribute to the sensation and regulation of breathing. Among these are slowly and rapidly adapting receptors, bronchial and pulmonary C-fiber receptors, high threshold Aδ-receptors, cough receptors and neuroepithelial bodies. This diversity of afferents gives rise to a complex representation of breathing in the brain. Thus, emotions such as anxiety can profoundly influence the subjective experience by amplifying particular afferent sensory components of breathing. On a subjective level, individuals are able to separately assess work of breathing, the degree of breathing coordination, the sense of suffocation, and the sense of struggling for air. Evidence from statistical analyses support the idea that these subjective experiences can be subsumed into two super-ordinated clusters, which have been termed perceived breathing effort and air hunger, both of which contribute to the overall sensation of dyspnea [17]. Thus, even on a basic neurophysiological level breathing is a complex sensation that emerges from the interplay of multiple sensory afferents. The relationship between levels of anxiety and experienced breathing effort or air hunger may be bi-directional. First, genetic or molecular heterogeneity in the afferent breathing pathway may give rise to differential amplification of perceived breathing effort or air hunger, which become associated with increased levels of anxiety. Second, anxiety levels may act to amplify breathing afferents thereby generating a subjective experience of increased breathing effort or air hunger.

In an important review of the neural systems underlying breathing, Davenport [18] has argued that there are two primary cortical pathways, which he has termed the discriminative pathway, which is related to respiratory proprioception, and the affective pathway related to the qualitative assessment of breathing. Whereas the former processes the awareness of the spatial, temporal, and intensity of the breathing sensation, the latter is concerned about the evaluative or emotive aspects of breathing. Not surprising, the discriminative pathway includes the somatosensory cortex, associated thalamic nuclei, and higher order association areas. In comparison, the affective pathway involves the limbic circuitry including the amygdala and the insular cortex as well as thalamic relay nuclei. This circuit contributes to the perception of effort of breathing, interoceptive perception of ventilatory status [18], and is thought to be altered in individuals with high trait anxiety [19; 20] or panic disorder [21]. Finally, this affective dimension of the perception of breathing is particularly vulnerable to emotional influences, irrespective of objective lung function [22]. However, it is unclear whether anxiety in general and pathological anxiety states in particular selectively affects the discriminative or evaluative pathway or whether modulation of these breathing-specific pathways can alter levels of anxiety.

Until recently, investigations of the neural basis of breathing have relied mostly on electroencephalogram (EEG) methodology. The ability of humans to program and control breathing related movements in the EEG is accompanied by a low-amplitude negativity starting approximately 2.5 s before inspiration that is best known as a Bereitschaftspotential (BP). The presence of this BP is considered to be a regulatory marker that is modulated by different inspiratory breathing resistance and is thought to be generated as part of the cortical involvement during ventilatory behavior [23]. Another approach to examine the contributions of the different brain areas on breathing and disruption of breathing is to examine the electrophysiological signature associated with breathing efforts. Respiratory-related evoked potentials (RREP) can be elicited by inspiratory occlusions and have a number of component waves, which can be modulated by voluntary attention, changes in resistance to inspiration and pulmonary disease state [24]. In particular, respiratory sensory gating has been demonstrated with the RREP using different levels of intensities and frequencies of respiratory stimuli [24]. Finally, modulation of these peaks using various experimental approaches can be mapped to differences in respiratory perceptions [25]. Taken together, the electrophysiological studies show that the sensation and regulation of breathing occurs on different levels and can be mapped onto specific ERP signatures.

Consistent with the notion that anxiety plays an important role in the perception of breathing, von Leupoldt and colleagues [8] found that whereas low anxious individuals showed the expected pattern of reduced magnitudes of later RREP components P2 and P3 during the unpleasant compared to the neutral affective context higher anxious individuals showed greater magnitudes of P2 and P3 during the unpleasant compared to the neutral affective context. In comparison, earlier components of the RREP (Nf, P1, N1) were not affected by anxiety. During an anticipatory anxiety situation, high trait anxiety relative to low trait anxiety individuals showed an increase in flow of breathing and a decreased expiration time [26] but greater tidal volume increases [27]. Similarly, anticipatory threat cues can elicited significant startle potentiation, enhanced skin conductance, heightened corrugator EMG changes, and pronounced “fear bradycardia” consistent with defensive activation in the context of threatened respiratory dysfunction, which are enhanced in high trait anxious individuals [28]. Others have reported an altered temporal pattern of breathing consisting of an increased variability and unpredictability in panic disorder patients [21], which was significantly attenuated after treatment with a serotonin-specific reuptake inhibitor [29]. This underlying respiratory vulnerability in PD seems to constitute a subtle, unstable trait, which may be subject to significant environmental modulation [30]. There also appears to be a relationship between breathing patterns as indexed by breath holding

duration and level of avoidance symptoms in patients with Post-Traumatic Stress Disorder. Specifically, lower breath-holding duration was associated with greater PTSD Avoidance symptom severity [31]. Finally, subjects a specific phobia of fear of flying were more accurate in detecting the loads, thereby indicating higher interoceptive awareness [32]. Together, these findings support the idea that EEG-derived measures of breathing and breathing manipulations may be useful to characterize individuals with anxiety disorders. However, little is known whether these can serve as a physiological marker of fluctuations of severity of predictors of outcomes to interventions.

Resistive Loads – An Experimental Approach to Measure Breathing Changes in Anxiety

Manipulating breathing opens the possibility for both assessing the significance of specific physiological pathways in anxiety and as a technique to intervene in order to lower anxiety levels. Resistive load, i.e. restricted inspiration, was first introduced by Lopata [33] and Gottfried [34], is an airflow-dependent load [35] and a simple but powerful experimental approach to induce an altered interoceptive state. In contrast to expiratory breathing load which affects $C0_2$ [33], inspiratory breathing load results in stable, unchanged carbon dioxide levels [36]. Inspiratory breathing loads can be used to examine experienced breathing effort and generate respiratory-related evoked potentials with several peaks that indicate the transition from an early sensory component to a later cognitive aspect [37-40]. Moreover, resistive loads generate pre-motor potentials that reflect the involvement of higher cortical motor areas [41], they decrease systolic blood pressure [42], they differ for males and females [43], they are perceived less intense in older individuals [44], they generate load-dependent increases of unpleasantness [45], and the subjective effects can be modified by attentional distractions [46]. Thus, inspiratory breathing load provides a powerful experimental approach to examine the relationship between breathing as a form of interoceptive processing and anxiety.

Not surprisingly, there are significant inter-individual differences in breathing load perception and load-related processing. Interestingly, individuals who report relatively more breathing-related symptoms were less accurate when reporting different loads than low symptom reporters [47]. Consistent with the idea that reduced accuracy may accompany pulmonary pathology is the finding that children with life-threatening asthma are at risk of life-threatening asthma attacks, in part because it requires a greater change in resistance above their baseline resistance before they sense an increased mechanical load [48]. Tiller and colleagues [13] found that contrary their initial hypothesis that there may be a heightened sensitivity to respiratory stimuli in patients with anxiety disorder, sensitivity may actually be blunted. These authors concluded that anxious patients do not perceive changes in respiratory proprioceptive stimuli in a normal fashion but only after substantial deviations from homeostasis. The abrupt change in their perceptions following substantial deviations may then be perceived as increased anxiety “out of the blue” and responded to as such, as there is no basis to appropriately ascribe the altered perceptions. This contrasts with the situation for normal subjects, who readily perceive proprioceptive changes and adapt and respond to them gradually as they occur. Others have reported that levels of individual anxiety affect respiratory rate, especially the expiratory time [49] and that the amount of perspiration response, i.e. breathing habituation and sweating, and state anxiety scores may reflect altered homeostatic adjustment mechanisms [49]. The notion of attenuated sensitivity to different loads is consistent with our extended insular model of anxiety [9]. Specifically, an increased “noisy” input of interoceptive afferents due to indiscriminate amplifications of these signals would make it difficult for the individual to differentiate between different loads. As a consequence, attenuated discriminability of interoceptive afferents results in

increased uncertainty about the actual interoceptive state, which is proposed to result in greater compensatory cognitive activity to reduce this uncertainty.

The relationship between manipulated breathing and various forms of conditioning is an important but yet under-developed line of research [50]. Similar to the affective assessment of visual and auditory stimuli, interoceptive responses to breathing load are organized to a certain degree along the dimensions of valence and arousal and represent a homeostatic balance between metabolic activity and affective arousal [51]. Thus, inspiratory breathing loads themselves can be viewed as an aversive interoceptive stimulus, which evoke affective reactions comparable or stronger than those evoked by the emotional pictures [52]. More recently, this cue-related activation has been extended to startle potentiation [53]. Taken together, similar to exteroceptive stimuli, interoceptive stimuli such as increased breathing load can be subject to conditioning. For example [54], cues signaling breathing may be difficult resulted in significant startle potentiation, enhanced skin conductance, heightened corrugator EMG changes, and pronounced “fear bradycardia” consistent with defensive activation in the context of threatened respiratory dysfunction. These data indicate that anticipating respiratory resistance activates defensive responding, which may mediate symptomatology in patients with panic and other anxiety disorders. Increased breathing rate can also affect the affective evaluation of visual stimuli sensations yielding increased autonomic arousal [55]. Finally, interoceptive fear conditioning (IFC) to an interoceptive and exteroceptive conditional stimulus (CS) with a severe respiratory load applied for 30s as the unconditional stimulus (US) resulted in a CS-load associated larger startle blinks and a smaller decrease in respiratory rate and tidal volume. In comparison, a CS-picture evoked an increase in tidal volume and self-reported fear [50]. Therefore, breathing modulation via inspiratory loads is associated with the similar neural and behavioral plasticity that occurs with other exteroceptive stimuli. However, there are no studies examining differential conditioning of breathing loads in anxiety versus comparison populations.

Although modulating breathing has long been considered an important therapeutic intervention for anxiety, surprisingly little is known about (a) the effect of interoceptively-based interventions on breathing or (b) how modulating breathing affect levels of anxiety. In a recent study, Vlemincs and colleagues showed that worry is characterized by decreased respiratory stability and flexibility whereas mindfulness seem to have countering effects these parameters [56]. For example, a mindfulness-based stress-reduction program [57] had a significant effect on breathing patterns during exercise [57]. It has been well-established that mindfulness approaches have profoundly beneficial effects for anxiety [58], yet we are only beginning to examine how these approaches work on a neurophysiological [59] and molecular level. Future studies will need to examine whether the response to loaded breathing can be used as a biomarker for the degree of anxiety severity or could be a treatment target to reduce the interoceptive sensitivity of anxious individuals.

Conclusion

The physiology and neurobiology of breathing is a rapidly progressing field that provides an experimental scaffold to study the biological basis of how the body and the brain interact. More importantly, the experimental tools available enable one to begin to delineate how specific emotions emerge as a consequence of the body brain interaction. There are some intriguing initial findings of altered breathing perception, different breathing patterns, and changes in the neural signature related to breathing in individuals with high anxiety or anxiety disorders. However, much work needs to be done to better delineate the direction of the relationship between breathing and anxiety as well as to evaluate how brain systems respond to the modulation of breathing as a powerful intervention to attenuate levels of anxiety. A deeper understanding of anxiety and associated disorder can emerge from

investigating the molecular characteristics of peripheral lung receptors to the influence of controlled breathing during mindfulness.

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