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Cortico-limbic circuitry and the airways: Insights from functional neuroimaging of respiratory afferents and efferents

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Abstract

After nearly two decades of active research, functional neuroimaging has demonstrated utility in the identification of cortical, limbic, and paralimbic (cortico-limbic) brain regions involved in respiratory control and respiratory perception. Before the recent boon of human neuroimaging studies, the location of the principal components of respiratory-related cortico-limbic circuitry had been unknown and their function had been poorly understood. Emerging neuroimaging evidence in both healthy and patient populations suggests that cognitive and emotional/affective processing within cortico-limbic circuitry modulates respiratory control and respiratory perception. This paper will review functional neuroimaging studies of respiration with a focus on whole brain investigations of sensorimotor pathways that have identified respiratory-related neural circuitry known to overlap emotional/affective cortico-limbic circuitry. To aid the interpretation of present and future findings, the complexities and challenges underlying neuroimaging methodologies will also be reviewed as applied to the study of respiration physiology.

Keywords

neuroimaging; fMRI; PET; respiration; breathing; dyspnea; motor control; anxiety

1. Introduction

The act of breathing and the perception of breathing impairment are vital homeostatic functions essential to human life. It is widely accepted that brainstem respiratory centers mediate automatic respiratory rhythm (Feldman and Del Negro, 2006); however, the higher motor-cognitive and emotional centers thought to modulate the intrinsic respiratory rhythm as well as mediate the conscious perception of respiratory sensations remain poorly understood. Cortical, limbic and paralimbic sites for respiratory efferent/afferent processing were first identified by pioneering surgical/electrophysiological work in humans and animal models (as reviewed by (Hugelin, 1986)). With an acknowledgement of the ongoing debate over anatomical divisions of limbic vs. paralimbic architectonics (LeDoux, 2000), the integrated brain regions typically involved in motor-cognitive and emotional processing will

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be collectively referred to as “cortico-limbic” circuitry in this review of respiratory neuroimaging.

The last twenty years have witnessed an amazing acceleration and expansion of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) technologies. These technological advances have facilitated the non-invasive, *in vivo* investigation of respiratory-related regional neural activity within cortico-limbic circuitry with spatial resolution on the order of a few millimeters and temporal resolution within fractions of a second. Advanced electroencephalographic event-related potential studies have also contributed to our understanding of cortico-limbic respiratory circuitry but are reviewed elsewhere (Davenport, 2009). Prior to these advances in imaging technology, evidence for respiratory-related activity within cortico-limbic circuitry was largely derived from invasive electrophysiological studies of animals and surgical patients (Foerster, 1936; Kaada and Jasper, 1952; Penfield and Faulk, 1955; Frysinger and Harper, 1990).

The findings from recent PET and fMRI studies reviewed here provide intriguing support for longstanding hypotheses regarding cortico-limbic modulation of respiratory control and respiratory sensation. This circuitry shares remarkable homology with cortico-limbic elements known to mediate cognitive and emotional/affective processing (Dolan, 2000; Cabeza and Kingstone, 2001) as well as primal alarm/threat processing (LeDoux, 2000; Denton, 2005). Recent studies which employed hypothesis-driven experimental paradigms involving cognitive (Evans et al., 2009a) and affective (von Leupoldt et al., 2008) breathing tasks provide preliminary evidence of cortico-limbic modulation of respiratory control and respiratory sensation. In view of the wide-reaching implications regarding this shared circuitry, an integrated neural systems model for cortico-limbic influences on respiratory control and respiratory perception is considered as supported by the literature reviewed (Figure 1).

Our understanding of cortico-limbic circuitry as related to respiratory control and perception should be viewed as a work in progress. Although the identification and function of many of the cortico-limbic elements discussed herein have been validated across imaging modalities and by various experimental designs, several of the recent findings reviewed require replication and should be considered with caution. Scholars within and outside of the field of neuroimaging, as well as the lay press, have voiced growing concern over the persuasive impact of neuroimaging data given its intrinsic vulnerability to Type I Error (Check, 2005; Dolan, 2008; McCabe and Castel, 2008; Poldrack, 2008; Hamilton, 2009). In keeping with this concern, this author is humbled to state that the discipline of respiratory neuroimaging is still in its infancy. The framework provided here is anticipated to serve as a primer on the current knowledge regarding the role of cortico-limbic circuitry in respiratory control and respiratory sensation and also serve as a guide for the interpretation of future findings given the complexities and challenges underlying neuroimaging studies of respiration.

2. Design and analytic considerations for neuroimaging studies of respiration

A. Neuroimaging methods

The majority of neuroimaging studies of respiration have employed blood flow sensitive techniques such as oxygen¹⁵ PET (O-15 PET) and blood oxygenation level dependent fMRI (BOLD-fMRI) to provide indirect measures of neural activity. Arterial spin labeling (ASL) is a relatively new fMRI approach which has only been used in a handful of published respiration studies (e.g., MacIntosh et al., 2008; Pattinson et al., 2009a; Pattinson, 2009b). These techniques are based on the assumption that the magnitude of regional brain activity

at any given time is proportional to the regional blood flow (O-15 PET, ASL-fMRI) or oxygen content (BOLD-fMRI) and each method yields statistical maps that reflect regional brain activity.

The time-course for the respiratory process under study should guide the choice of imaging modality as each method confers an optimized temporal resolution. Typical BOLD-fMRI block designs require rapidly alternating conditions (in the order of seconds) for adequate statistical power with standard analytic approaches. Processes with relatively short inter-trial latencies (e.g., within breath, or breath-by-breath time course) may be best addressed with event-related BOLD-fMRI (Buckner, 1998), although this approach requires further validation and replication (Buckner, 1998; Evans et al., 2009a; Evans et al., 2009b). Processes with relatively long inter-trial latencies, may be best addressed with O-15 PET in which the inherent inter-scan latency is 1.5–2 minutes (secondary to oxygen¹⁵ half-life). However, innovative, non-standard analytic approaches to BOLD-fMRI block designs have been shown to confer adequate power at inter-trial latencies up to 2 minutes (Evans, 2009c). The PET isotope fluorine¹⁸ deoxyglucose (FDG) has a substantially long half-life, which permits the examination of neural activity over a 30 minute period preceding actual image acquisition. Thus, FDG-PET could be used in protocols that involve ambulatory respiratory tasks of long duration, yet few respiratory neuroimaging studies have used FDG-PET (Garakani et al., 2007; Tashiro et al., 2008). ASL-fMRI has also been found to support protocols with significant inter-trial latencies (i.e., minutes to hours) (Wang et al., 2003).

In addition to temporal resolution, there are further considerations regarding advantages and limitations for each neuroimaging method. O-15 PET can provide absolute measures of rCBF and had been considered the “gold standard” method for many years. This quantitative feature can be viewed as a significant advantage over BOLD-fMRI which relies on relative between condition (or group by condition interaction) comparisons. However, with recent advances in MRI technology, ASL-fMRI sequences can now also provide absolute measures of rCBF. Contemporary criticisms of O-15 PET include the radiation risk to subjects, scarcity of research institutions with O-15 capability, and cost (hourly rates are 2–3 times those for fMRI). Furthermore, compared to fMRI, PET confers inferior spatial and temporal resolution. Landmark findings established with O-15 PET for both motor (Ramsay et al., 1993) and sensory (Banzett et al., 2000) respiratory circuits have been replicated and extended with fMRI (Evans et al., 1999; Evans et al., 2002; McKay et al., 2003). Nonetheless, fMRI has limitations, such as physical constraints related to the exclusion of metallic instrumentation and small diameter scanner bores, which can introduce claustrophobic/affective confounds. In addition, fMRI is vulnerable to susceptibility artifacts, common to ventral frontal and medial temporal regions (as reviewed by (Jezzard and Clare, 1999; Merboldt et al., 2001)). fMRI is also particularly vulnerable to confounds related to the respiration itself (considered in detail below).

The focus of this paper is on functional neuroimaging studies of respiratory afferents/efferents within cortico-limbic circuitry, yet it is important to also acknowledge structural neuroimaging methods that have provided complementary findings. For instance, diffusion tensor imaging (DTI) provides an index of the number and composition of axons within white matter tracts and voxel-base morphometry (VBM) enables the quantitative assessment of the volume of specific brain structures of interest. Few respiratory studies have used these methods, yet the published structural findings provide complementary support for the integrated cortico-limbic model we consider herein (Kumar et al., 2008; Macey et al., 2008; Pattinson et al., 2009a).

B. Breathing tasks and stimuli

An overarching aim in respiratory neuroimaging is to address the questions of “which” brain regions are involved and “how” these structures mediate function within afferent and efferent respiratory pathways. The isolation of a particular pathway under study serves as a significant challenge in the design of experimental protocols as the existing evidence suggests that these pathways are bidirectional and considerably interconnected. As reviewed below, attempts to isolate predominantly motor respiratory circuitry have been fairly successful yet not without caveats (e.g., breathing to targets engage neural circuits involved in attention, monitoring, and motivation). Attempts to isolate afferent respiratory circuitry on the other hand have been difficult as the integration of afferent (respiratory sensation) and efferent (motor command) signals together with cognitions and affect have been proposed to jointly contribute to the neural processing underlying respiratory perception (Lansing et al., 2009).

Most neuroimaging studies of respiratory sensation have employed stimuli that evoke dyspnea (breathlessness). It is important to appreciate that the general term “dyspnea” subsumes several sensations such as the sense of respiratory work/effort, chest tightness, and air hunger (an uncomfortable urge to breathe) (Lansing et al., 2009). Air hunger has been suggested as the dominant component of dyspnea (Smith et al., 2009) in pulmonary patients, however, air hunger is often experienced by patients in combination with sensations of increased work/effort or chest tightness (Manning and Schwartzstein, 1995). Air hunger is one of the few stimuli used in respiratory neuroimaging studies to actually target one of the primary component sensations of dyspnea (Banzett et al., 2000). Even though respiratory loads have been used (Peiffer et al., 2001; von Leupoldt et al., 2008), a work/effort stimulus of substantial duration has yet to be investigated during imaging. Other stimuli used in respiratory neuroimaging studies have included: hypercapnia (Corfield et al., 1995; Harper et al., 2005), hypoxia (Macey et al., 2005), and breath-hold (Macefield et al., 2006; McKay et al., 2008; Pattinson et al., 2009a; Pattinson, 2009b). Few studies have imposed these stimuli for a sustained duration. Compared to the 3.5 minute air hunger epochs of Banzett et al. (2000), the 15 second breath-holds of McKay et al. (2008) and 24 second epochs of inspiratory load (work/effort) of von Leupoldt et al. (2008) could be viewed as relatively short. Given the variability in subjective reporting of respiratory sensations, the stimuli intended to evoke a given sensation should be well characterized and validated prior to neuroimaging. For example, Banzett and colleagues conducted a series of studies which characterized stimuli that evoke air hunger (Banzett et al., 1989; Banzett et al., 1990; Manning et al., 1992; Banzett et al., 1996; Harty et al., 1996) prior to conducting PET and fMRI studies of air hunger (Banzett et al., 2000; Evans et al., 2002).

C. Considerations for respiratory-related confounds

In contrast to the typical stimuli used in cognitive neuroscience with inert properties relative to the imaging modality (e.g., tactile or visual stimuli), the stimuli typically used in studies of human respiration can serve as confounds that pose significant challenges to neuroimaging (e.g., respiratory loads, hyperpnea, hypercapnia and hypoxia). Respiratory stimuli and associated confounds may not be fully orthogonal to the experimental design and thereby bias or obscure the detection of between-condition differences in regional brain activity.

i. Confounds related to changes in gas tensions—Perhaps the most common and concerning cause of respiratory-related confounds in neuroimaging studies of respiration is task-related changes in arterial gas tensions. For example, hypocapnia causes cerebral vasoconstriction and hypercapnia causes cerebral vasodilatation, both of which serve as

significant confounds to blood flow sensitive techniques such as O-15 PET, BOLD-fMRI, and ASL-fMRI (Ramsay et al., 1993; Posse et al., 2001; MacIntosh et al., 2008).

Experimental protocols designed to avoid task-related changes in arterial gases can minimize the associated confounds. Some studies of respiratory motor control used mechanical ventilation as a passive condition and volitional breathing (targeted to the minute ventilation of the passive condition) as an active, comparison condition and thereby avoided between-condition differences in partial pressure of carbon dioxide (P_{CO_2}) (Colebatch et al., 1991; Ramsay et al., 1993; Evans et al., 1999).

Another strategy is to use a specialized breathing apparatus that minimizes condition-related changes in P_{CO_2} . The contrivance developed by Banzett et al. (2000) employs a dynamic dead-space that maintains nearly constant P_{CO_2} and P_{O_2} within ± 1 mmHg. McKay et al. (2003) used this apparatus to minimize changes in end-tidal gases between conditions of volitional hyperpnea (average tidal volume = 1.3 liters) and resting spontaneous breathing (average tidal volume = 0.5 liters). More recently, computer controlled devices have been designed that utilize either feed-forward (Prisman et al., 2008) or feed-back mechanisms. One rather elaborate computer controlled feed-back apparatus enables independent control of the fraction of inspired O_2 and CO_2 every breath, a process that has been called dynamic end-tidal forcing (DEF) (Wise et al., 2007).

An alternative strategy to contend with changes in gas tensions is to model the anticipated neuroimaging signal change (associated with changes in gas tensions) independent from the condition of interest. Breath-hold studies have employed this strategy, where the non-specific BOLD-fMRI signal changes associated with the rise in P_{CO_2} during the breath-hold were determined from a separate hypercapnic condition of equal magnitude of change in P_{CO_2} to that observed during the breath-hold (McKay et al., 2008; Pattinson et al., 2009a; Pattinson, 2009b). Thus, regional BOLD signal changes reflecting sensorimotor neural activity could then be dissociated from non-specific effects related to hypercapnia during breath-hold.

Despite best efforts to keep gas tensions constant, small breath to breath oscillations in gas tensions are unavoidable in spontaneously breathing subjects even with the most advanced breathing apparatus (e.g., DEF discussed above). Indeed, BOLD-fMRI signal can be modulated by end-tidal P_{CO_2} fluctuations as small as 1 mmHg (Wise et al., 2004). A number of analytic strategies are currently available to correct for these fluctuations. One approach is to model end-tidal P_{CO_2} (acquired during scanning) as a null regressor in BOLD-fMRI analyses (see von Leupoldt et al. (2008), Evans et al. (2009a), Pattinson et al. (2009b)). Another approach is to model the whole brain global signal as a null regressor (Corfield et al., 2001) since the global signal is tightly correlated to P_{CO_2} (Wise et al., 2004; Chang, 2009). This approach has been widely used in BOLD-fMRI studies of respiration (Evans et al., 2002; McKay et al., 2003; McKay et al., 2008; von Leupoldt et al., 2008; Evans et al., 2009a; von Leupoldt et al., 2009a; von Leupoldt et al., 2009b). The global regressor approach is limited by its reliance on the assumption of homogeneity in global signal across the whole brain, though Macey et al. (2004) have refined the global regressor approach by employing voxel-wise time-course models to account for regional variability in global effects. Another caveat to the global regressor approach surrounds its susceptibility to induce Type I Error. Recent empiric studies of connectivity across brain networks have shown the global regressor approach to introduce spurious anti-correlations (de-activations) (Murphy et al., 2009; Van Dijk et al., 2010).

In addition to these regressor methods, recent studies have acquired both BOLD- and ASL-fMRI images during conditions that change arterial gas tensions. Thus condition-related

changes in both global and regional CBF can be quantified and incorporated into analytic models to account for confounding effects of CBF changes on the BOLD signal (MacIntosh, 2008; Pattinson, 2009b).

ii. Confounds related to respiratory movement—All neuroimaging techniques are vulnerable to confounds related to gross head movement. Respiratory stimuli (e.g., resistive loads) or changes in respiration (e.g., hyperpnea) can result in head movement within and/or movement in/out of the imaging plane. Both Type I and Type II errors may be encountered with task-related movement. BOLD-fMRI is exquisitely sensitive to movement related artifacts (Birn et al., 1998; Andersson et al., 2001). Notably, subtle movement of the lung and chest-wall during the respiratory cycle can induce shifts in the magnetic field (Birn et al., 2006; Harvey, 2008; Birn et al., 2009). Within-subject image realignment is a standard pre-processing step that aligns the series of images acquired from a given subject (Friston et al., 1995; Friston et al., 2007), thereby correcting for gross head movement prior to performing statistical tests on the data. To further correct for the effects of movement-related variance that persist after pre-processing, the realignment parameters (calculated during the realignment procedure) can be included as null regressors in BOLD-fMRI analyses (Evans et al., 2009a). This approach has been shown to enhance neural signal detection (Lund et al., 2005), particularly in subcortical structures (Friston et al., 1996). However, this approach is highly conservative, given its vulnerability to the Type II error (e.g., may exclude regional imaging signal driven by respiratory-related neural activity that correlate with movement). Other methods employ peripheral measures (e.g., chest expansion via “respiratory belt” systems) to model respiratory movement such as retrospective correction of physiological motion effects (RETROICOR) (Glover et al., 2000; Harvey, 2008) and respiration volume per time (RVT) (Birn et al., 2006). Similar to the global regressor method, these methods incorporate the confounding signals into image analyses as null regressors.

Given this background, the question arises regarding which method for addressing respiratory confounds may be superior. This question may be best addressed by considering the specific respiratory conditions an investigator uses to test a given hypothesis. Examples of these methods are provided within the discussion of empirical findings in the following sections of this paper. Few studies have systematically evaluated these methods in a quantitative manner (see Van Dijk et al., 2010). There is some evidence to suggest RVT could potentially be used as a proxy for P_{CO_2} to model the variance in BOLD signal due to breathing. Chang et al. (2009) demonstrated respiratory motion (as modeled by RVT) to be well correlated with breath-by-breath fluctuations in P_{CO_2} in the eucapnic range. Moreover, spatio-temporal variance in the BOLD signal has been well characterized by both RVT and P_{CO_2} when modeled separately (Chang, 2009). On the other hand, there is substantial support for using the global regressor to account for variance in BOLD signal under various respiratory conditions (i.e., rest, volitional breathing maneuvers, hypercapnia, hypoxia, etc.) (Corfield et al., 2001; Birn et al., 2006; Van Dijk et al., 2010; McKay et al., 2010). However, as noted above, findings of anti-correlation (de-activation) must be interpreted with caution in analyses that use the global regressor (Murphy et al., 2009; Van Dijk et al., 2010).

D. Neuroimaging Analyses

Great care and strong *a priori* hypotheses are required in performing neuroimaging analyses as neuroimaging statistics are complex, based on many assumptions, and have several different approaches with no one optimal approach (Marchini and Presanis, 2004; Friston et al., 2007). Two general approaches to data analysis have been used in neuroimaging studies of respiration: (1) voxel-wise searches (e.g., statistical parametric mapping (SPM)) and (2)

region of interest (ROI) based searches, sometimes referred to as small volume correction (SVC). Voxel-wise SPM approaches implement statistical comparisons across the whole brain. SPM approaches convey several advantages over ROI-based approaches, particularly when combined with *a priori* hypotheses and appropriately conservative significance thresholds (thereby reducing Type I errors). ROI approaches involve testing one or more specific brain regions of interest and analyzing data in only those regions. ROI approaches are particularly vulnerable to Type II errors, since effects in regions other than those driven by *a priori* hypotheses may be neglected, and effects within sub-territories of a given ROI may be overlooked due to dilution that occurs from averaging across the entire ROI.

ROI approaches have enjoyed increasing use in respiratory neuroimaging studies as investigators have begun to attribute *a priori* confidence to certain regions within the cortico-limbic circuitry (e.g., Maldjian et al., 2003; Eickhoff et al., 2006; von Leupoldt et al., 2008; von Leupoldt et al., 2009b). ROIs may be defined by coordinates from prior studies or by probabilistic atlases (Tzourio-Mazonyer et al., 2002; Maldjian et al., 2003; Eickhoff et al., 2006) or by the structural or functional data from the subjects under study (Nieto-Castanon et al., 2003). In addition to the SVC capabilities mentioned above, ROIs can also be used to ascertain functional specificity for a given region. Specifically, raw data may be extracted from a ROI to demonstrate the time course and/or magnitude of neuroimaging signals for a given condition (see <http://marsbar.sourceforge.net/>) (e.g., Harper et al., 2005; Macey et al., 2005). Like all approaches to neuroimaging analysis, ROI approaches have their caveats, criticisms, and cautions (Poldrack, 2007; Mitsis et al., 2008). Importantly, in contrast to voxel-wise SPM approaches, ROI approaches have not yet undergone systematic, rigorous validity testing. Another important consideration is the risk for reification that can occur when the data extracted from a ROI in a particular data set is used to make further inferences about the same data set, leading to over-interpretation of extended findings (a process aptly referred to as “double-dipping”) (Poldrack, 2007; Kriegeskorte et al., 2009).

Further considerations are required when performing group and between group analyses. The majority of PET and early fMRI respiratory studies used “fixed-effect” analytic models that are based on the assumption that the condition-related effects for each individual make an equivalent or fixed contribution to observed group effects. More recent respiratory neuroimaging studies have used “random-effect” analytic models that account for random within-subject and between-subject (intersession) effects. This is particularly important in fMRI studies where inter-session inconsistencies of BOLD signal are common (Friston et al., 2007). Random-effect analytic models permit formal inferences to be made about the population from which the study sample was drawn. However, compared to fixed effect models, random effect models confer reduced sensitivity due to fewer degrees of freedom (Lazar et al., 2002).

Another approach to group data is the “conjunction” or “main effects of condition” analytic model. Conjunction analyses are statistical tests that determine the probability of regional effects being in common among two (or more) different conditions (e.g., regional effect X occurs in condition A *and* condition B). Interpretive caution is required particularly when a conjunction analysis is found to be non-significant. Notably, an erroneous conjunction inference can be made in the case where the magnitude of regional effect X is observed to significantly differ between conditions A and B, yet regional effect X would be considered as statistically significant in independent analyses of condition A *and* condition B (Nichols et al., 2005). It is therefore informative to report such independent findings as they may strengthen or weaken the overall interpretation of the findings. Each of the approaches to neuroimaging analysis has strengths and weaknesses, which should be considered in interpreting the findings in the respiratory neuroimaging literature.

3. Neuroimaging studies of respiratory efferents and volitional motor control

Pioneering O-15 PET studies by researchers at the Charing Cross Hospital, London UK, heralded the first maps of respiratory efferents localized to the motor cortex (Colebatch et al., 1991; Ramsay et al., 1993). In their first study, Colebatch et al. (1991) measured rCBF in healthy subjects during conditions of passive mechanical ventilation and active voluntary targeted hyperpnea at similar minute ventilation, minimizing potential P_{CO_2} confounds. The active condition of hyperpnea was associated with increased rCBF bilaterally in the primary motor cortex and supplementary motor area (SMA) near midline. Increased rCBF in premotor and cerebellar regions was also observed during the active inspiratory condition. Using a similar O-15 PET protocol, a separate cohort of subjects was studied by Ramsay et al. (1993) during conditions of active inspiration and active expiration compared to a condition of mechanical ventilation. The findings of respiratory-related increased rCBF within motor cortical, SMA, pre-motor and cerebellar regions were replicated. As an extension to the previous study, increased rCBF was also observed within the thalamus for both active breathing conditions.

In an additional O-15 neuroimaging study, the Charing Cross Hospital investigators tested the hypothesis that increased respiratory force would evoke increased neural activity and corresponding increased rCBF within the previously identified elements of respiratory motor circuitry (Fink et al., 1996). Scans acquired during graded conditions of inspiratory load were contrasted with conditions of passive mechanical ventilation and unloaded spontaneous ventilation. This study further extended the previous findings observed during hyperpnea as significant increases in rCBF were reported with increasing respiratory force in the superior motor cortex, SMA, and premotor area. Moreover, additional brain regions were detected with incremental force, in particular: the prefrontal cortex, inferolateral sensorimotor cortex, basal ganglia, midbrain, and cerebellar vermis. The authors concluded that increases in inspiratory muscle force indeed results in greater motor cortical activity as well as the additional recruitment of subcortical regions associated with motor control.

The O-15 PET studies of Colebatch et al. (1991), Ramsay et al. (1993), and Fink et al. (1996) were all carefully designed to optimize visualization of regional volitional respiratory-motor neural activity (via changes in rCBF). Taken together, the birth of “respiratory neuroimaging” as a field may be attributed to these nascent O-15 PET studies. However, the findings from these studies should be considered in balance with a few limitations. Although the use of passive mechanical ventilation as a control condition in these studies was critical to minimizing cerebrovascular imaging confounds due to task-related changes in P_{CO_2} , mechanical ventilation induces confounds related to (1) upper airway positive pressure and (2) the cognitive requirement for subjects to relax their airway, chest wall, and diaphragm. Lastly, these studies were constrained to the spatio-temporal limitations of O-15 PET noted above (Section 2A, “Neuroimaging Methods”).

In an effort to further replicate and extend the early O-15 PET findings, Evans et al. (1999) conducted the first three-dimensional BOLD-fMRI study of volitional breathing at 1.5 Tesla. BOLD signal was acquired during conditions of passive mechanical ventilation and active voluntary targeted hyperpnea, where minute ventilation and P_{CO_2} were similar between conditions. Compared to the passive condition, BOLD signal in the active hyperpneic condition was greater in the sensorimotor cortex, premotor cortex, and SMA with stereotactic coordinates comparable to the early O-15 PET findings. Additional loci were identified within the prefrontal cortex and basal ganglia. The fMRI modality provided enhanced temporal and spatial resolution compared to the earlier O-15 PET studies. However, compared to more recent BOLD-fMRI studies conducted with higher magnetic

field strength and expanded field of view, this study was limited in its sensitivity and brain coverage (i.e., limited field of view precluded visualization of the cerebellum and brainstem).

A subsequent 2 Tesla BOLD fMRI study by McKay et al. (2003) provided the first *in vivo* evidence of simultaneous cortical and brainstem activity during volitional hyperpnea in humans. In contrast to previous studies of hyperpnea, resting spontaneous breathing was used as the passive condition in place of mechanical ventilation. The specialized breathing contrivance discussed earlier (Banzett et al., 2000) maintained nearly constant P_{CO_2} (± 2 mmHg) despite dynamic, threefold increases in ventilation from resting spontaneous breathing to active hyperpnea. This study design also minimized the potential confounds noted above related to mechanical ventilation. During hyperpneic periods, BOLD-fMRI signal increases were observed within the sensorimotor cortex, SMA basal ganglia, thalamus, cerebellum, premotor and prefrontal cortices. Upon small volume correction, an additional loci was identified in midline superior dorsal medulla, likely representing task-related neural activity within the nucleus of the solitary tract (NTS) or the nucleus ambiguus. The medullary finding was thought to represent excitatory or inhibitory activity from either motor cortical efferents or from pulmonary vagal afferents. Despite the uncertainty surrounding functional significance, this study emphasized the potential for *in vivo* fMRI assessments of respiratory-related neural activity in the human brainstem. Indeed, subsequent methodological advances (see Harvey et al., 2008) have facilitated enhanced sensitivity and specificity in brainstem imaging (e.g., Pattinson et al., 2009a).

In summary, the findings from neuroimaging studies of volitional motor control of breathing converge to define a cortico-striatal-bulbar-cerebellar circuitry (Table 1, Figure 1). Despite the noted caveats for individual studies, findings localized to the sensorimotor cortex, cerebellum, supplementary motor and premotor areas have been common across most neuroimaging studies of motor control. Those neuroimaging studies with increased sensitivity (e.g., fMRI, increased force during PET) identified additional respiratory motor activity within the basal ganglia, thalamus, and prefrontal cortices.

4. Neuroimaging studies of respiratory afferents and sensory perception (dyspnea)

Until very recently, the principal cortico-limbic components of human respiratory afferent pathways had been largely unknown, mainly due to the lack of useful animal models or relevant clinical lesion studies. The majority of neuroimaging studies that have formally investigated respiratory perception have focused on dyspnea and accordingly, these studies will serve as the focus here. As noted above in Section 2B “Breathing tasks and stimuli,” the general term “dyspnea” subsumes several distinct sensations such as the sense of respiratory work/effort, chest tightness, and air hunger (Lansing et al., 2009). It is quite likely that these different dyspnea sensations may have distinct cortico-limbic representation; however, studies designed to explore this possibility have yet to be published. Thus far, there have been few hypothesis-driven neuroimaging studies specifically designed to investigate dyspnea circuitry. Most dyspnea imaging studies have used either air hunger, respiratory loads (work/effort) or hypercapnic stimuli.

Early evidence for cortico-limbic involvement in respiratory perception was provided by an O-15 PET study of hypercapnic-stimulated breathing versus eucapnic passive mechanical ventilation (Corfield et al., 1995). After correction for between-condition differences in global CBF (modeled as a null regressor via ANCOVA), the hypercapnic condition was associated with increased rCBF localized to the midbrain, cerebellar vermis, and cortico-limbic regions, namely the hypothalamus, thalamus, hippocampal/parahippocampal,

fusiform gyri, anterior cingulate, insular and prefrontal cortices. Interestingly, there was no evidence of increased rCBF in the primary motor cortex or SMA, suggesting a lack of motor cortical involvement during the increased ventilatory drive associated with hypercapnia. It should be underscored that this study was not explicitly designed to dissociate sensory from motor neural processes related to the hypercapnic condition, nor to examine dyspnea in isolation. Notably, respiratory sensations for the hypercapnic condition were characterized (e.g., “urge to breathe” and “work/effort”) retrospectively during a supplementary study conducted outside the scanner. The interpretation of these findings can be held with one final caution related to the use of the global null regressor. The temporal resolution of O-15 PET (combined with the study design) precluded the dissociation of inhomogeneous regional vascular responses to hypercapnia from neural responses related to respiratory sensation and ventilatory drive.

Subsequently, three O-15 PET studies of dyspnea were published in five reports from the period 2000–2001 (Banzett et al., 2000; Brannan et al., 2001; Liotti et al., 2001; Parsons et al., 2001; Peiffer et al., 2001). Using mechanical ventilation under a constant hypercapnic background, Banzett et al. (2000a) provoked air hunger (>60% of scale) in healthy subjects during 3.5 minute epochs of low tidal volume (~0.6 liters), alternating with relief epochs of high tidal volume (~1.2 liters). Increased rCBF during air hunger epochs was localized to the anterior insula/operculum (bilaterally), SMA, thalamus and basal ganglia. Peiffer et al. (2001) studied healthy subjects during loaded breathing. Comparison of the high load condition (~50% of scale) to the unloaded condition demonstrated increased rCBF in the right anterior insula/operculum, SMA, left dorsolateral prefrontal cortex (DLPFC), pons, cerebellar vermis and cerebellar hemispheres. In a three-paper series Brannan et al. (2001), Liotti et al. (2001), and Parsons et al. (2001) reported on differential rCBF effects observed in healthy subjects during various breathing challenges. Most notably, widespread increases in cerebellar and cortico-limbic rCBF was reported in a contrast of hyperoxic-hypercapnia ($P_{CO_2} > 60$ mmHg, ~90% inspired O_2) versus hyperoxic resting breathing (Table 1). Taken together, these early O-15 PET studies of dyspnea used experimental paradigms that varied significantly, yet the findings of the studies converge to reveal a common limbic/paralimbic circuitry during laboratory induced dyspnea.

More recently, fMRI has been used in studies of respiratory perception. Using a constant P_{CO_2} air hunger protocol similar to the one used by Banzett et al. (2000a), but with shorter, 42-second air hunger epochs, Evans et al. (2002) studied healthy subjects with BOLD-fMRI at 2 Tesla. Voxel-wise SPM analyses were performed in which subjective air hunger ratings, acquired every breath, served as the primary independent regressor and the global BOLD signal served as a null regressor. The findings from this first fMRI study of air hunger replicated and extended those reported in the preceding PET study of Banzett et al. (2000a). Specifically, air hunger was correlated with BOLD signal increases in the anterior insula/operculum (bilaterally), SMA, thalamus, and basal ganglia. Additional findings were localized to the bilateral DLPFC, anterior cingulate cortex (ACC), amygdala, cerebellar hemispheres and cerebellar vermis. Limitations of this study include a transient air hunger stimulus (i.e., not steady-state, compared to Banzett et al. (2000a)), and an analytic method that was incapable of dissociating the neural activity related to dyspnea perception from the neural activity related to subjects' rating their dyspnea.

Evans (2009c) recently presented work in progress in which BOLD-fMRI time-courses were extracted from cortico-limbic functional ROIs (amygdala, anterior insula and ACC) in a separate cohort of healthy subjects during 90 second steady-state epochs of air hunger alternating with epochs of relief. The BOLD-fMRI time-course data were observed to mirror the time-course of subjective reports of air hunger and relief (maximal response within 30 seconds). The findings suggest that recent O-15 PET studies of dyspnea relief (e.g., Peiffer

et al. (2008) may not have adequate temporal resolution to fully characterize the neural dynamics underlying changes in respiratory sensation.

Von Leupoldt and colleagues have conducted several fMRI studies (3 Tesla) using brief inspiratory loads (von Leupoldt et al., 2008, 2009a; von Leupoldt et al., 2009b) (Table 1). In one study, von Leupoldt et al. (2008), employed 24-second inspiratory loads (dyspnea reported as 52% of scale) during simultaneous presentation of various affective visual stimuli (scenes previously validated to evoke either positive or negative emotions). Subjective intensity ratings of “increased work and effort of breathing” were similar between different visual stimuli conditions. In contrast to intensity ratings, dyspnea unpleasantness ratings were reported as significantly greater during negative than positive visual stimuli. Differential BOLD-fMRI signal was reported in the amygdala and the anterior insula upon a condition interaction analysis (loaded-negative > unloaded-negative $\times$ loaded-positive > unloaded-positive) after statistical correction for small volume. The authors concluded that the amygdala and insula modulated unpleasantness of perceived dyspnea. This conclusion draws on translations from the field of affective neuroscience (LeDoux, 2000; Lang and Davis, 2006; Etkin and Wager, 2007) yet is incompletely supported by the data. The effect seen on dyspnea unpleasantness ratings is non-specific as are the effects observed in the insula and amygdala which could simply be attributed to attention bias toward the negative visual stimuli irrespective of dyspnea perception. Notably, the amygdala is known to respond to overt as well as subliminal visual threats (Morris et al., 1998; Whalen et al., 1998). The findings of von Leupoldt et al. (2008) are nonetheless intriguing and beckon studies with definitive, falsifiable hypotheses to further define the intersection of affective processing and dyspnea perception.

Overall, the insular cortex has been the most consistently reported structure across all the reviewed studies of sensory perception (Table 1). The amygdala, ACC, SMA, DLPFC, thalamus, cerebellar hemispheres, and cerebellar vermis have also been frequently implicated in these studies suggesting a distributed cortico-limbic-cerebellar circuitry to mediate respiratory sensation. The inferior-lateral motor cortex was uniquely activated during inspiratory load stimuli, presumably due to recruitment of upper airway musculature during loads. However, the superior motor cortex, known to drive volitional breathing, failed to demonstrate significant activity during any studies of provocative sensory stimuli.

5. Complementary neuroimaging studies of sensorimotor respiratory circuitry

A. Studies of combined sensorimotor networks

Neural activity across multimodal networks is likely to influence even resting spontaneous breathing as cognitive and emotional demands are thought to modulate the intrinsic brainstem respiratory rhythm (Shea et al., 1987; Shea, 1996; Boiten, 1998). Using a novel event-related BOLD-fMRI approach at 1.5 Tesla, Evans et al. (2009a) demonstrated synchronized respiratory related neural activity with each breath across a distributed cortico-limbic-bulbar circuit during resting spontaneous breathing. Notably, breath-by-breath neural activity was observed at every level of the brainstem, midbrain, dorsal rostral pons (Kölliker-Fuse/parabrachial nuclei/locus ceruleus (KF/PB/LC)) and medulla (NTS or nucleus ambiguus). In addition, the imposition of a cognitive task (random number generation) produced an expected increased breathing rate (8% greater than baseline) accompanied by significant modulation of neuronal activity within the cortico-limbic-bulbar circuitry, localized to the inferior ventral pontine raphe, amygdala and anterior cingulate cortex. The reported findings are quite extraordinary; however, they should be considered balanced by certain caveats. Although several of the identified regions met stringent

statistical criteria, some regions (e.g., brainstem loci) only met statistical significance after small volume correction. The event-related, breath-by-breath analytic method used strikes a fine balance between dissociating BOLD signal representing respiratory neural activity from BOLD signal related to artifacts induced by respiration itself (see above, Section 2C “Considerations for respiratory-related confounds”). Nevertheless, the reported findings garnered confirmatory support by two independent analyses; one that used a global null regressor and one that used a P_{CO_2} null regressor. Interestingly, the same data set was subjected to additional analyses that demonstrated the global regressor method to be as effective as other methods (i.e. RVT described by Birn et al., (2006)) in removing respiratory related BOLD signal artifacts (Van Dijk et al., 2010). Further validity of the event-related, breath-by-breath analytic method has been conferred by comparable findings obtained when the method has been performed on other BOLD-fMRI data sets (e.g., Evans et al. (2009b)).

As noted earlier in Section 2B “Breathing task and stimuli,” and highlighted in the preceding example, certain respiratory stimuli may evoke sensory, motor, cognitive and also affective neural activity. Recent studies of cough, breath-hold and hypercapnia have been faced with the challenge of dissociating multi-modal neural activity. For example, Mazzone et al. (2007) administered aerosolized capsaicin at doses below cough threshold, to induce an “urge to cough” during BOLD-fMRI (3 Tesla). Compared to placebo (saline) trials, capsaicin trials were associated with robust bilateral activation of the insular cortex and widespread activation of sensorimotor regions within cortico-limbic-cerebellar circuitry. Interestingly, the motor cortex, SMA and ACC were the only regions where the magnitude of fMRI-BOLD signal was significantly correlated with subjective urge to cough ratings (based on BOLD-fMRI signal extracted from functionally defined ROIs for the contrast of capsaicin > saline). The authors acknowledge the inability to dissociate sensory, motor and cognitive processes and speculated the observed SMA and ACC activity reflected inhibition of the cough reflex.

McKay et al. (2008) used BOLD-fMRI at 2 Tesla to identify the neural circuits underlying respiratory motor inhibition during 15 second breath-holds at resting expiratory lung volume. In line with the findings of Mazzone et al. (2007), motor cortical, SMA and ACC activation was observed during the brief breath-holds. However, activation was also reported in other regions likely involved in motor inhibition: dorsal rostral pons (KF/PB/LC), inferior ventral pons, thalamus and basal ganglia. In addition, breath-hold related activation of the bilateral insular cortex, amygdala and prefrontal cortex was also noted and suggested to mediate the subjects’ sensory experience, as all subjects reported “a need for more air.” However, this implication is somewhat speculative since subjective reports were only acquired in debriefings after the scans (not simultaneously during the scans). The interpretation of this study is also limited by the use of small volume correction in the brainstem.

Pattinson et al. (2009b) adapted the protocol of McKay et al. (2008) to include breath-hold conditions with and without the opioid drug, remifentanyl, in order to test the hypothesis that low-dose remifentanyl (1.0 ng/ml infusion) would preferentially down-regulate sensory affective regions but have no significant effect on volitional motor regions. Both BOLD and ASL fMRI data were acquired at 3 Tesla. Voxel-wise SPM image analyses incorporated measures of CBF (via ASL data) as null regressors to account for potential vascular confounds associated with remifentanyl infusion. The findings were consistent with the stated hypotheses, as remifentanyl during breath-hold resulted in attenuated fMRI-BOLD signal within sensory/affective (inhibitory) circuitry (the insula, operculum, DLPFC, ACC, cerebellum). Low-dose remifentanyl had no significant effect on breath-hold induced activation in motor circuitry (the motor cortex, basal ganglia).

Lastly, hypercapnia and hypoxia pose a special challenge to isolating efferent from afferent neural responses. For example, hypercapnia, as discussed earlier, can evoke sensations of dyspnea (urge to breathe, work and effort) and has been associated with widespread limbic/paralimbic and thalamic activity (in the absence of motor cortical activity) (Corfield et al., 1995; Brannan et al., 2001). McKay et al. (2010) recently employed a novel BOLD-fMRI (2 Tesla) paradigm consisting of brief (45 second) periods of isoxic-hypercapnia (mean P_{CO_2} = 48mm Hg), hypoxic-isocapnia (mean P_{O_2} = 54mm Hg) and hypoxic-hypercapnia (mean P_{O_2} = 56mm Hg, mean P_{CO_2} = 47mm Hg) in an attempt to isolate the neural circuits driving chemo-stimulated increases in ventilation without intentionally inducing dyspnea. Here the global regressor method was used to control for respiratory confounds related to task-related changes in arterial gases. Post-scan debriefing revealed that nearly all subjects (8 out of 9) experienced an increased awareness of their breathing but not strong dyspnea (contrast to the studies of (Banzett et al., 2000; Liotti et al., 2001; Evans et al., 2002)). Chemo-stimulated increases in ventilation were associated with bilateral BOLD signal increases within the medulla (NTS, or nucleus ambiguus), pons (KF/PB/LC) and midbrain (red nuclei) as well as the thalamus, basal ganglia, cerebellum, cingulate, frontal operculum and precuneus. The authors concluded that spontaneous chemo-stimulated increases in ventilation are mediated by a network of brainstem respiratory nuclei in coordination with subcortical and higher centers (specifically, the cingulate, operculum and precuneus). Interestingly, cortico-limbic regions typically active during dyspnea (e.g., DLPFC, anterior insula and amygdala) failed to reach significance in this study designed to produce chemo-stimulated increases in ventilation in the absence of significant dyspnea. It is important to note that the reported imaging findings are the result of a main effects of condition analysis (i.e., conjunction, see Section D “Neuroimaging Analyses”) and correspond to only those regions with common activity across the three different conditions (isoxic-hypercapnia, hypoxic-isocapnia, and hypoxic-hypercapnia). Since the study design and analyses did not permit independent or between-condition comparisons of the individual conditions of chemo-stimulated ventilatory drive, the interpretation of the findings is duly limited.

Pattinson et al. (2009a) examined the brainstem and thalamus during brief (11–120 second) periods of very mild hypercapnia (2–4 mmHg above each subject’s baseline) with an optimized BOLD-fMRI approach (i.e., 2.5mm thin coronal-oblique slices at 3 Tesla). A volume corrected, voxel-wise search restricted to brainstem and thalamus revealed hypercapnic induced ventilatory changes associated with regional foci of increased BOLD signal. Specifically, increased BOLD signal was localized within the anteroventral, ventral posterolateral and ventrolateral thalamic nuclei, as well as the dorsal medulla (NTS or nucleus ambiguus), inferior ventral pontine raphe, dorsal rostral pons (KF/PB/LC).

This overview of studies of combined sensorimotor networks highlights the difficulty in dissociating motor from sensory functionality. However, the consistent localization of NTS, KF/PB/LC, and ventral pontine raphe in recent fMRI studies of breathing (McKay et al., 2003; Macefield et al., 2006; McKay et al., 2008; Evans et al., 2009a; Pattinson et al., 2009a; Pattinson, 2009b) is intriguing and encourages future studies to further elucidate the sensorimotor functions of the human brainstem.

B. Functional studies in patient populations

Functional abnormalities within essential elements of cortico-limbic and bulbar-cerebellar circuitry have been reported in patients with congenital central hypoventilation syndrome (CCHS), obstructive sleep apnea (OSA) and asthma (Macey et al., 2004; Harper et al., 2005; Macey et al., 2005; von Leupoldt et al., 2009b). Structural abnormalities have also been reported in CCHS and OSA (Kumar et al., 2008; Macey et al., 2008). The neuroimaging studies of CCHS patients are of particular interest as these individuals have diminished perception and ventilatory response to hypercapnia and hypoxia, yet preserved volitional

respiratory motor output (Shea et al., 1993; American, 1999). Harper et al. (2005) and Macey et al. (2004b, 2005) used hypercapnic (5% inspired CO₂), hypoxic (15% inspired O₂) and volitional forced expiratory challenges to differentiate neural responses between CCHS and healthy control (HC) cohorts in a series of BOLD-fMRI studies. These studies employed voxel-wise SPM and ROI time-course analyses. A global regressor method (Macey et al., 2004a) was used to account for task-related changes in arterial gases. Across the studies, between-group responses were quite varied with respect to brain region, laterality and relative BOLD signal magnitude and time-course. However, differential BOLD signal responses were localized to regions previously implicated in respiratory motor control (e.g., midbrain, pons, medulla, thalamus, basal ganglia and cerebellum) as well as limbic regions (e.g., amygdala, hippocampus). Notably, the BOLD-fMRI signal in the insular cortex of the CCHS patients was significantly less during respiratory challenges compared to the control subjects.

Patients with panic disorder (PD) are another interesting population to consider in regard to sensorimotor and affective processing of respiratory stimuli. Despite findings of normal ventilatory response to hypercapnia and hypoxia (Papp et al., 1997; Katzman et al., 2002), PD patients have been shown to consistently demonstrate exaggerated anxiety responses to provocative respiratory stimuli (Abelson et al., 1996; Rassovsky and Kushner, 2003). Garakani et al. (2007) measured regional glucose uptake via FDG-PET in PD patients and healthy control subjects during challenge with doxapram, a potent respiratory stimulant with demonstrated efficacy to provoke panic attacks in PD patients. Compared to healthy controls, PD patients demonstrated exaggerated regional glucose uptake in the amygdala, insula, ACC and basal ganglia, but decreased glucose uptake in the DLPFC during doxapram challenge.

Taken together, the neuroimaging findings in patients with impaired chemosensitivity (CCHS) and exaggerated emotional responses to respiratory stimuli (PD) inform the model of distributed cortico-limbic and bulbar-cerebellar circuitry presented below (Figure 1).

6. Working model for respiratory sensorimotor neural circuitry

Even though the field of respiratory neuroimaging may be viewed as in its early stages, the convergence of findings to date prompts the consideration of a working cortico-limbic model for respiratory sensorimotor circuitry. The model as depicted in Figure 1 should be taken as a preliminary gross graphical summary of human respiratory neural circuitry, based exclusively on consistent cortico-limbic findings across functional neuroimaging studies of respiration. The model considers a Motor Division that carries respiratory efferents responsible for volitional motor control, a Sensory Division that carries respiratory afferents responsible for sensory perception, and regions that share overlap between the two distinct divisions.

A. Motor Division

The motor division of the model proposed here is simplified, focusing on (a) the cortico-spinal circuitry identified by neuroimaging studies of volitional control of breathing, and (b) the bulbo-spinal circuitry identified by neuroimaging studies of chemo-reflex control of breathing. The cortico-limbic circuitry thought to mediate emotional and behavioral modulation of breathing (Garakani et al., 2007; Evans et al., 2009a), requires replication and further evidence prior to its formal integration into the model.

Converging lines of evidence strongly suggest the orchestration of voluntary breathing to occur within the cortico-spinal circuitry. Motor cortical and SMA findings have been common to all neuroimaging studies with hypotheses related to the volitional control of

breathing (Ramsay et al., 1993; Evans et al., 1999; McKay et al., 2003) (color coded in blue and purple; Figure 1, Table 1), and these findings are in line with an established motor control literature (Lemon, 1993; Passingham, 1993). Notably, the motor cortical neuroimaging findings are consistent with locations previously associated with diaphragmatic contraction during electrical stimulation (Foerster, 1936) and transcranial magnetic stimulation (Maskill et al., 1991). The SMA is well situated to mediate its established role in coordinating self initiated movement as it lies immediately anterior to the motor cortex, with strong motor cortical, pre-motor, basal ganglia and brainstem connections (Frackowiak et al., 1997; Schmahmann et al., 2004; Nachev et al., 2008; Passingham, 1993; Hanakawa et al., 2008; Nachev et al., 2008).

The basal ganglia, thalamus and cerebellum have also been common findings in neuroimaging studies of volitional breathing (Ramsay et al., 1993; Evans et al., 1999; McKay et al., 2003; Macefield et al., 2006; Evans et al., 2009a; Pattinson et al., 2009a; Pattinson, 2009b) (color coded in purple; Figure 1, Table 1), and are well known to be strongly interconnected motor structures (Houk and Wise, 1995; Ramnani, 2006). Each of these regions is known to have direct projections to the brainstem and each has been implicated in respiratory control (Radna and MacLean, 1981; Hugelin, 1986; Cechetto, 1987; Chen et al., 1992; Harper, 2002; Xu and Frazier, 2002; Ito and Craig, 2008; Lois et al., 2009). It is important to also consider that the basal ganglia, thalamus and cerebellum have known sensory function and have been implicated in studies of respiratory sensation (reviewed above and discussed in the next section).

The bulbo-spinal circuitry has been established as essential for the homeostatic, chemo-reflex control of breathing in the service of maintaining arterial gases to meet metabolic requirements (Feldman and Del Negro, 2006; Nattie and Li, 2009). The findings of Pattinson et al. (2009a) and McKay et al. (2010) point to coordinated ponto-medullary reflex responses to hypercapnia and hypoxia. The bulbo-spinal circuitry likely also facilitates volitional control and emotional modulation of breathing via cortico-spinal and cortico-limbic interactions (McKay et al., 2003; Evans et al., 2009a). Bulbo-spinal lesions that spare cortico-spinal circuitry impair chemo-reflex breathing yet leave the voluntary control of breathing intact, suggesting these circuits to be functionally distinct (Severinghaus and Mitchell, 1962; Nathan, 1963). And aberrant bulbar activity in CCHS patients during hypercapnic and hypoxic challenges (Harper et al., 2005; Macey et al., 2005) provide further *in vivo* support for the importance of bulbo-spinal circuitry in the chemo-reflex control of breathing.

Respiratory neuroimaging findings within the brainstem have been limited by the challenges surrounding spatial resolution and field of view. Common respiratory-motor brainstem findings have included: the dorsal medulla likely representing the NTS, the ventral pons in proximity of the reticular and raphe nuclei, the dorsolateral pons in proximity to KF/PB nuclei and LC and the midbrain (McKay et al., 2003; Macefield et al., 2006; Evans et al., 2009a; Pattinson et al., 2009a; Pattinson, 2009b). These regions share anatomical and functional connectivity with each other as well as other important brainstem respiratory centers that have yet to be consistently identified by functional imaging (e.g. ventral respiratory group, pre-Bötzinger complex) (Rybak et al., 2004; Song and Poon, 2004; Kubin et al., 2006).

In summary, the motor division of the proposed model for respiratory sensorimotor neural circuitry comprises the motor cortex, SMA, basal ganglia, thalamus, cerebellum and brainstem (Table 1, Figure 1). Given the established motor functionality of these structures it follows that the overt hyperpneic tasks employed by the reviewed neuroimaging studies of volitional breathing would necessarily recruit distributed activity across the cortico-spinal

circuitry. As only limited neuroimaging findings of respiratory motor processes related to bulbo-spinal and cortico-limbic circuitry are available, the full characterization of these circuits await future studies.

B. Sensory Division

Given the scope of this paper, the sensory division of the model will be addressed in the context of dyspnea, appreciating the fact that there are numerous respiratory sensations that may not evoke dyspnea (Table 1, Figure 1). The model conceptualizes the perception of dyspnea sensation to arise from the integration of a complex array of neural activity across respiratory sensorimotor networks (e.g., shared elements of the motor division, brainstem chemoreceptors, peripheral chemoreceptors, pulmonary stretch receptors, chest wall mechanoreceptors, etc).

The primary elements of the model's sensory division include the primary and secondary sensory cortices, insular cortex and associated operculum, ACC, amygdala, DLPFC, and cerebellar vermis. These regions have been consistently implicated in neuroimaging studies of respiratory sensation (color coded in red; Figure 1, Table 1) and found noncontributory to studies of volitional motor control. The insula and associated operculum are posited as the central elements in the sensory division responsible for respiratory interoception given the insula's known role in sensing of internal state/physiologic homeostasis (Craig, 2002;Denton, 2005). There are heavy reciprocal connections between the insula, amygdala, ACC and brainstem respiratory centers (Mesulam and Mufson, 1982;Mufson and Mesulam, 1982;Augustine, 1996;Gaytan and Pasaro, 1998;Hanamori et al., 1998;Shi and Cassell, 1998;Vertes, 2004;Tsumori et al., 2006). Noted as important to breath awareness in meditative practices (Lazar et al., 2005;Evans et al., 2009b) the insula has also been the most consistently implicated structure in patient populations known to have diminished respiratory sensations (e.g., CCHS, OSA, asthmatics) (Harper et al., 2005;Macey et al., 2005;Macey et al., 2006;von Leupoldt et al., 2009b). The other primary structures in the sensory division (i.e., amygdala, ACC) are suggested to coordinate with the insula in the modulation of attentional and affective experience of respiratory stimuli based on their arousal and valence characteristics. This proposal is supported by the repeated identification of the amygdala and ACC in studies of fear, anxiety, emotional reactivity and general arousal (LeDoux, 2000;Critchley et al., 2002;Mayberg, 2003;Phan et al., 2004;Lang and Davis, 2006;Paulus and Stein, 2006;Etkin and Wager, 2007;Milad, 2007).

Several secondary elements of the model's sensory division share significant overlap with elements of the motor division, namely the SMA, basal ganglia, thalamus and cerebellar hemispheres (color coded in purple; Figure 1, Table 1). The coordinated recruitment of these elements together with the DLPFC is suggested to mediate inhibition or suppression of desired behaviors (e.g., taking a breath to end a breath-hold) during respiratory challenges that require subjects' task compliance (McKay et al., (2008); Pattinson et al., (2009b).

To sum up, the sensory division of the proposed model for respiratory sensorimotor neural circuitry is comprised of primary and secondary elements. The insula and supporting primary structures (i.e., ACC, amygdala) mediate the integration of interoceptive, valence, and arousal processing to dyspnea stimuli. Interaction between the DLPFC and secondary sensory structures, namely the SMA, cerebellum, facilitate inhibitory processing to aversive respiratory stimuli/tasks.

7. Conclusion

Prior to neuroimaging, the knowledge regarding respiratory control and respiratory sensation within cortico-limbic circuitry was poorly understood. Now the convergence of PET and

fMRI data strongly suggests the volitional control of breathing to be mediated by coordinated network activity within motor cortical, SMA, cerebellar and subcortical regions. A similar convergence of data provides strong support for the sensation of dyspnea to be mediated by network activity within cortico-limbic structures, specifically the anterior insula, ACC, and amygdala. The replication of findings across imaging modalities and experimental paradigms is rather impressive and calls for consideration of the integrated sensorimotor neural circuit model proposed here. As we approach the twenty year anniversary of the first neuroimaging study of respiratory neural circuitry (Colebatch et al., 1991), much has been learned. Indeed, our understanding of respiratory control and sensory perception within cortico-limbic circuitry has been enhanced by the recent evidence for distributed brainstem and cortico-limbic responses to modest changes in arterial gases (Pattinson et al., 2009a; McKay et al., 2010) and short breath-holds (McKay et al., 2008; Pattinson, 2009b), together with preliminary evidence for respiratory-related cortico-limbic modulation during cognitive/emotional tasks (von Leupoldt et al., 2008; Evans et al., 2009a) and during opioid drug administration (Pattinson, 2009b). Nevertheless, many questions remain to be addressed. Emotional, cognitive and pharmacologic influences over respiratory motor output and respiratory sensation remain quite vague despite the level of sophistication employed in the recent respiratory neuroimaging studies. If the field of respiratory neuroimaging continues along its current trajectory it is quite possible that many remaining questions surrounding emotional and cognitive influences over respiratory control and sensation may be addressed in the next twenty years of neuroimaging research! For now, it is hoped that the highlighted empirical findings and presentation of the sensorimotor model will provide an essential framework for basic understanding of the afferent and efferent neural elements within cortico-limbic circuitry.

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Figure 1.

Proposed cortico-limbic model for respiratory sensorimotor integration. Regional color-coding follows the same scheme presented in Table 1: blue, predominant motor functionality; red, predominant sensory functionality; purple, mixed sensorimotor functionality. Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; KF/PB, Kölliker–Fuse/parabrachial nuclei; LC, locus ceruleus; NTS, nucleus tract of solitarius; PAG, periaqueductal grey; SMA supplementary motor area.

Table 1

Summary of regional findings from whole brain neuroimaging studies of respiratory efferent/afferent pathways published in the period 1991 to 2010. Regional color-coding follows the same scheme presented in Figure 1: blue, predominant motor functionality; red, predominant sensory functionality; purple, mixed sensorimotor functionality. Studies are listed in descending order of publication for each functional category.

Study	Contrast		superior motor	inferior-lateral motor	pre-motor	pons	medulla	SMA	thalamus	basal ganglia	cerebellar hemispheres	cerebellar vermis	DLPFC	insula	frontal operculum	ACC	amygdala	hippocampus	midbrain
Studies of volitional motor control																			
Colebatch et al., 1991	hyperpnea vs. mechanical ventilation		✓		✓			✓			✓								
Ramsay et al., 1993a	hyperpnea vs. mechanical ventilation		✓	✓	✓			✓	✓		✓								
Fink et al., 1996	inspiratory load vs. mechanical ventilation		✓	✓	✓			✓	✓	✓		✓							✓
Evans et al., 1999	hyperpnea vs. mechanical ventilation			✓										✓					
McKay et al., 2003	hyperpnea vs. spontaneous ventilation		✓	✓	✓		✓	✓	✓	✓	✓								
Studies of sensory perception (dyspnea)																			
Corfield et al., 1995	hypercapnia	dyspnea intensity							✓			✓	✓	✓		✓		✓	✓
Banzett et al., 2000a	air hunger	65%						✓	✓	✓				✓	✓				
Peiffer et al., 2001	inspiratory/expiratory load	52%						✓			✓	✓	✓	✓	✓				
Brannan et al., 2001**	hypercapnia	73%				✓			✓	✓				✓		✓		✓	
Parsons et al., 2001**	hypercapnia	73%									✓	✓							
Evans et al., 2002	air hunger	50%						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
von Leupoldt et al., 2008	inspiratory load + affective visual stimuli	52%		✓				✓	✓					✓	✓		✓		

Study	Contrast		superior motor	inferior-lateral motor	pre-motor	pons	medulla	SMA	thalamus	basal ganglia	cerebellar hemispheres	cerebellar vermis	DLPFC	insula	frontal operculum	ACC	amygdala	hippocampus	midbrain
von Leupoldt et al., 2009a	inspiratory load vs. thermal pain	NR		✓				✓	✓					✓	✓	✓	✓		
Studies of combined sensorimotor function																			
Macefield et al., 2006	breath-hold						✓				✓	✓	✓	✓		✓			
Mazzone et al., 2007	urge to cough		✓	✓	✓			✓			✓		✓		✓	✓			
McKay et al., 2008	breath-hold			✓	✓		✓	✓	✓				✓	✓		✓	✓		✓
Evans et al., 2009a	spontaneous breathing				✓				✓					✓		✓			
Pattinson et al., 2009b	breath-hold			✓					✓		✓*		✓*	✓*	✓*	✓*			
McKay et al., 2010	hypercapnia + hypoxia				✓		✓	✓	✓	✓	✓			✓	✓	✓			✓
Studies of patients vs. healthy controls																			
Macey et al., 2004b	forced expiratory load, CCHS vs. HC					>			✓	✓	✓			✓		✓	✓	✓	^
Harper et al., 2005	hypercapnia, CCHS vs. HC					>	✓		^	^	✓			✓			✓	^	^
Macey et al., 2005	hypoxia, CCHS vs. HC					>			^	✓	>	>		✓			^	✓	
Macey et al., 2006	inspiratory load, OSA vs. HC							✓	^	✓	✓	✓		✓				✓	
Garakani et al., 2007	doxapram PD vs. HC								^	^			✓	^		^			^
von Leupoldt et al., 2009b	inspiratory load, AST vs. HC													✓					

For clarity, only the most significant findings of regional brain activation (n.b., some studies reported de-activations) are presented for each study, indicated by a check-mark (✓). Only primary between-group findings are presented for studies that investigated patient and control cohorts. Greater than (>) or less than (<) symbols indicate significant regional differences using the order convention of patient group, followed by control group. The reader is referred to the text and original publications for details related to laterality and stereotactic localization.

* Asterisk indicates regions down regulated by remifentanyl (see (Patinson, 2009b).

** Double asterisk indicates that the study findings are distributed across several publications; reported findings in the table reflect the cited study.

Abbreviations: ACC, anterior cingulate cortex; AST, asthma; CCHS, congenital central hypoventilation syndrome; DLPFC, dorsolateral prefrontal cortex; HC, healthy control; NR, not reported; OSA, obstructive sleep apnea; PD, panic disorder; SMA supplementary motor area.