Experimental Physiology – *Review Article*

Breathing rhythms and emotions

Ikuo Homma and Yuri Masaoka

Department of Physiology, Showa University School of Medicine, Tokyo, Japan

Respiration is primarily regulated for metabolic and homeostatic purposes in the brainstem. However, breathing can also change in response to changes in emotions, such as sadness, happiness, anxiety or fear. Final respiratory output is influenced by a complex interaction between the brainstem and higher centres, including the limbic system and cortical structures. Respiration is important in maintaining physiological homeostasis and co-exists with emotions. In this review, we focus on the relationship between respiration and emotions by discussing previous animal and human studies, including studies of olfactory function in relation to respiration and the piriform–amygdala in relation to respiration. In particular, we discuss oscillations of piriform–amygdala complex activity and respiratory rhythm.

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Corresponding author I. Homma: Department of Physiology, Showa University School of Medicine, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142-8555, Japan. Email: ihomma@med.showa-u.ac.jp

Behavioural breathing

Respiratory chest wall movement is performed by the intermittent contraction of inspiratory and expiratory respiratory muscles. Motor commands for the contraction of these muscles are generated in complex neuronal networks in the brain. Various afferent inputs are integrated to produce respiratory rhythm and tidal activity, primarily in response to metabolic demands. The most important inputs for the regulation of breathing involve chemoreceptors that form reflex feedback mechanisms for respiratory motor activities. However, respiratory motor output is also influenced by internal and external environmental changes. This is called behavioural breathing and is generally considered to have a different mechanism from metabolic breathing.

Final motor outputs for breathing are generated by motoneurons in the spinal cord. Descending autonomic (metabolic) and voluntary breathing pathways to spinal motoneurons from higher centres are essentially and functionaly different. The origin of the voluntary control of breathing is in the cerebral cortex; stimulation of the primary motor cortex induces contraction of the diaphragm and intercostal muscles in humans (Gandevia & Rothwell, 1987; Gandevia & Plassman, 1988). This primary motor area has been shown by transcranial magnetic stimulation to coincide with the middle cortex 1 cm posterior to the vertex (Maskill *et al.* 1991). Aminoff & Sears (1971) reported in cats that electrical stimulation of the cerebral cortex at the vertex induces short-latency activation of contralateral motoneurons of the intercostal muscles. Transection of the dorsolateral columns of the spinal cord abolishes responses to electrical stimulation. However, transection does not affect the spontaneous rhythmic activities of the intercostal muscles.

The medulla oblongata and pons comprise the centre for metabolic breathing; this pathway descends along the spinal ventrolateral column as the bulbospinal pathway. The descending tract for autonomic inspiration is located laterally in the ventrolateral column, whereas the tract for expiration is located ventrally. Transection of the tract abolishes autonomic rhythmic breathing but has no effect on responses of the respiratory muscles to cortical stimulation.

Beside these studies that show the different pathways for metabolic and behavioural breathing, studies of Orem and Trotter show the cortical projections to brainstem respiratory neurons (Orem, 1989; Orem & Trotter, 1994), indicating that behavioural influences arising from higher centres modify metabolic breathing patterns.

Autonomic breathing is not only controlled by metabolic demands but also constantly responds to changes in emotions, such as sadness, happiness, anxiety and fear. Final respiratory output involves a complex interaction between the brainstem and higher centres, including the limbic system and cortical structures. It is interesting that respiration, which is important in maintaining physiological homeostasis, and emotions co-exist. In this review, we focus on the relationship between respiration and emotions by discussing previous studies of olfactory function and respiration.

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Emotional breathing in humans

Emotional breathing and the amygdala. Emotions involve physiological changes within the entire body. Animal and human studies have shown the autonomic and behavioural responses during fear and the anxiety state (Davis, 1992). In humans, the relationship between emotions, increases of heart rate and blood pressure have been investigated (Hugdahl, 1995). Relationships between emotions and respiration have shown more rapid breathing during an arousal state (Nyklicek *et al.* 1997; Boiten, 1998). Relationships between emotions and respiratory reactions to natural noises or unpleasant sounds have been explored (Masaoka & Homma, 1997; Gomez & Danuser, 2004). Respiration also changes when subjects look at photographs, which induces emotional changes. Respiration is one of the physiological processes altered by emotions (Boiten *et al.* 1994). In respiratory patterns, respiratory rate is changed dramatically by emotional changes. It can also be emphasized that changes of respiratory rate are related to individuality; Masaoka & Homma (1997) have shown the personality differences in the patterns of breathing during mental stress and physical load. Levels of individual anxiety affect respiratory rate, especially the expiratory time (Masaoka & Homma, 1999). It is fathomable that identical twins breathe in similar ways (Shea *et al.* 1989). Anxiety is regarded as a basic emotion and is associated with defense mechanisms (Öhman, 2000), that is, matter of life or death. Anticipatory anxiety, which has been defined as the time between the warning presentation and stimulation, increases the respiratory rate; this change is not related to changes in O_2 consumption, that is, changes in metabolic demand (Masaoka & Homma, 2001). Thus, respiratory changes in response to anxiety are affected by higher centres related to the emotion. Respiratory rate has also been positively correlated with individual trait anxiety scores (Fig. 1; Masaoka & Homma, 2001).

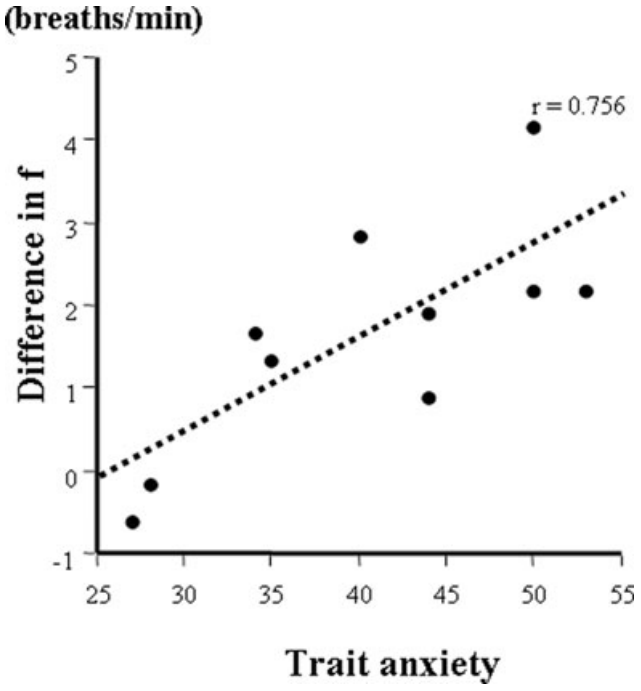

Figure 1. Relationship between respiratory frequencies (f) and individual trait anxiety scores during anticipatory anxiety
All subjects were tested for anxiety levels by using Spielberger's State-Trait anxiety Inventory. A positive correlation between trait scores and increase in respiratory frequency (f) was observed. Reproduced with permission from Masaoka & Homma (2001).

Functional neuroimaging studies have investigated the neuroanatomical correlates of negative emotions of fear and anxiety (Adolph *et al.* 1994; Morris *et al.* 1998). These studies have revealed that the amygdala plays a crucial role for processing these negative emotions. In humans, there are limitations to investigating the link between the amygdala, emotions and respiration. However, recent technology has advanced the study of functional anatomy of the human brain using non-invasive methods of functional brain mapping. Electroencephalogram (EEG) dipole tracing is one method of neuroimaging that can determine neural activation triggered by physiological activities (Homma *et al.* 1994, 2001). If the subjective feeling of anxiety increases the respiratory rate, electrical current sources synchronized with the onset of inspiration during anxiety are present in the limbic areas. From 350 to 400 ms after the onset of inspiration, in the averaged EEG activities triggered at the onset of inspiration, a positive wave is observed in the averaged potentials. This positive wave is referred to as respiration-related anxiety potentials (RAP; Fig. 2). A dipole tracing method that incorporates a scalp–skull–brain head model has estimated the source location of the RAP to be in the right temporal pole, whereas it is in the right temporal pole in subjects with low anxiety and left amygdala in the most anxious subjects (Masaoka & Homma, 2000).

Recently, respiratory-related activities have been estimated in the human brain using functional magnetic resonance imaging (fMRI). Many studies have shown activities in the limbic system. During the sensation of air hunger (an uncomfortable urge to breathe) induced by mechanical ventilation at a low tidal volume, the limbic and paralimbic loci are activated in normal subjects (Evans *et al.* 2002). Respiratory unpleasant sensation, usually described as dyspnoea or breathlessness, depends on the affective state of the subject. Respiratory sensation and changes in respiratory pattern are involved or elicited by anxiety and distress (Wilhelm *et al.* 2001).

Functional anatomical studies of disability of the limbic system have been performed in patients with mediotemporal lobe epilepsy. Lesions of the amygdala impair recognition of a fearful face (Adolph *et al.* 1994). Masaoka *et al.* (2003) have shown that anxiety levels and respiratory rate during anticipatory anxiety are reduced after lesion of the left amygdala in patients who show

foci of epileptic spikes in the left amygdala. Electrical stimulation applied to the amygdala produces emotional responses of fear (Halgren *et al.* 1978). A stimulation study has also been performed in mediotemporal lobe epileptic patients. Direct electrical stimulation of the left amygdala, in a patient with deep electrodes installed to evaluate the location of epileptic spikes, shows a decrease in total respiratory time (Fig. 3). After the test, the subject reported that during stimulation she had experienced the feeling of losing the distinction between herself and an external object and had a fear of losing herself (Masaoka & Homma, 2004).

Harper *et al.* (1984) reported in an animal study that electrical stimulation of the amygdala increases respiratory rate. Electrical stimulation of the amygdala elicits specific signs of fear, which include various autonomic and physiological responses.

Emotion of anxiety. The above studies lead to the question of whether anxiety enhances respiratory rate or vice versa. The centre for these two outputs may be in the limbic system, paticularly in the amygdala. The respiratory-related anxiety potential recorded in EEG activities may be produced in the amygdala or the temporal pole. The temporal pole is included in paralimbic areas involved in evaluation of environmental uncertainty or danger (Reiman *et al.* 1989). If anxiety increases respiratory rate, these areas may be activated before the onset of inspiration. It is assumed that an increase in respiratory rate is caused by unconscious evaluation in the amygdala and that these two activities occur in parallel. Stimulation of the amygdala produces a rapid increase in respiratory rate followed by a feeling of fear and anxiety (Masaoka & Homma, 2004). A period of 350–400 ms of RAR after the onset of inspiration may be required for the conscious representation or labelling of the physiological event. Unconscious activation of the amygdala and an uncertain feeling before labelling may represent emotion, and later an interpretation of the physiological event may represent feeling.

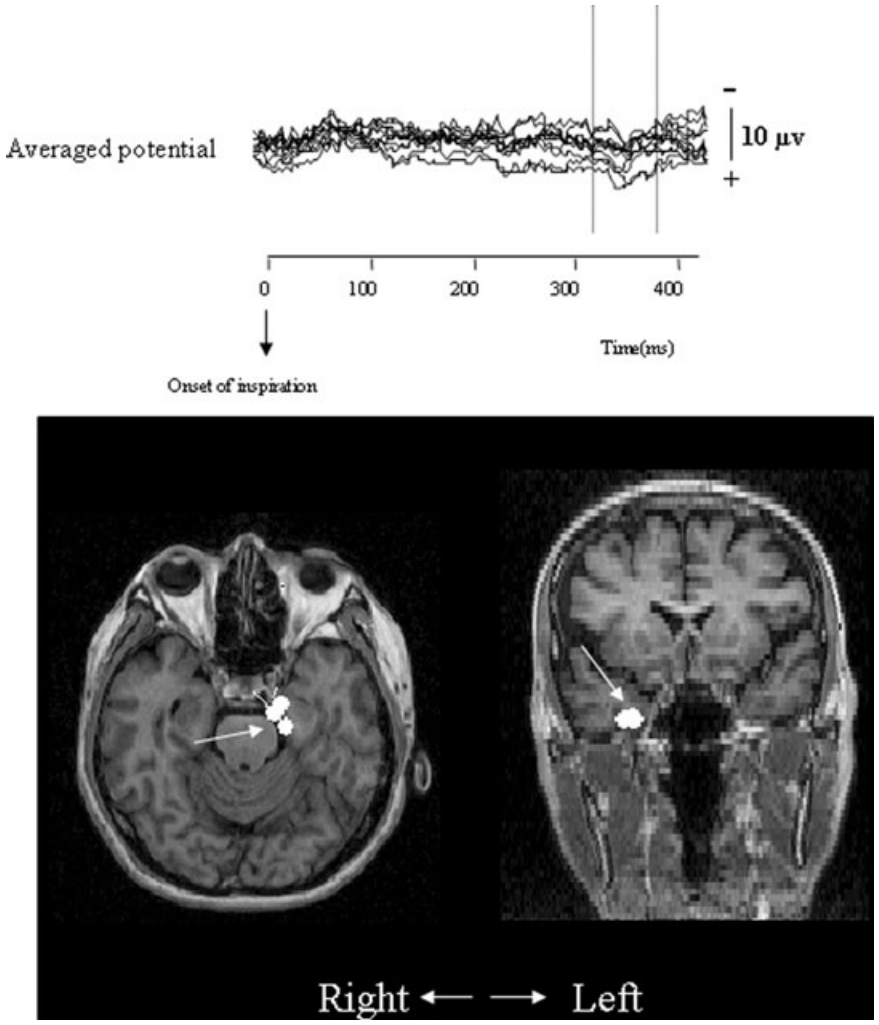

Figure 2. Respiration-related anxiety potentials (RAP) and their source generators
Top panel, EEG; bottom panel, Dipole locations of RAP estimated by a dipole tracing method. The generators of RAP were observed in the right temporal pole in subjects with low anxiety and in the temporal pole and amygdala in the most anxious subjects. Data modified with permission from Masaoka & Homma (2000).

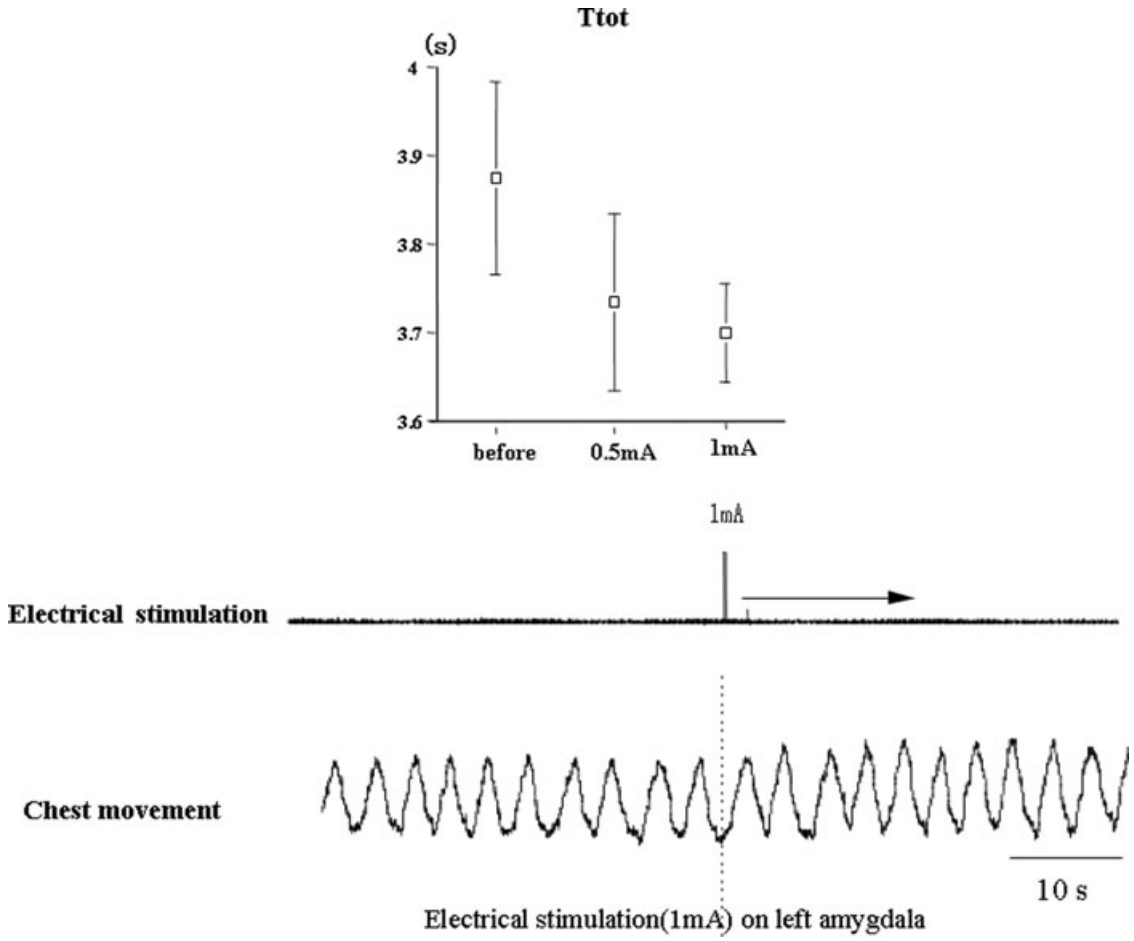

Figure 3. The effect of electrical stimulation of the left amygdala on respiration
Top panel shows total respiratory time (Ttot) during baseline, 0.5 and 1 mA of stimulation. Bottom panel shows chest movement measured with Respitrace transducer during stimulation (1 mA) on left amygdala. Data modified with permission from Masaoka & Homma (2004).

Respiration and emotion: why are they related?. In various perceptions of sensations that influence or produce emotion, the perception of odours is dependent on respiration; our sense of smell is enhanced by inhalation or inspiration. Olfactory cells have cilia (dendrites) that extend from the cell body into the nasal mucosa. The axons carry impulses from activated olfactory receptors to the olfactory bulb. The olfactory bulb sends signals to the prepiriform and piriform cortex, which include the primary olfactory cortex, anterior olfactory nucleus,

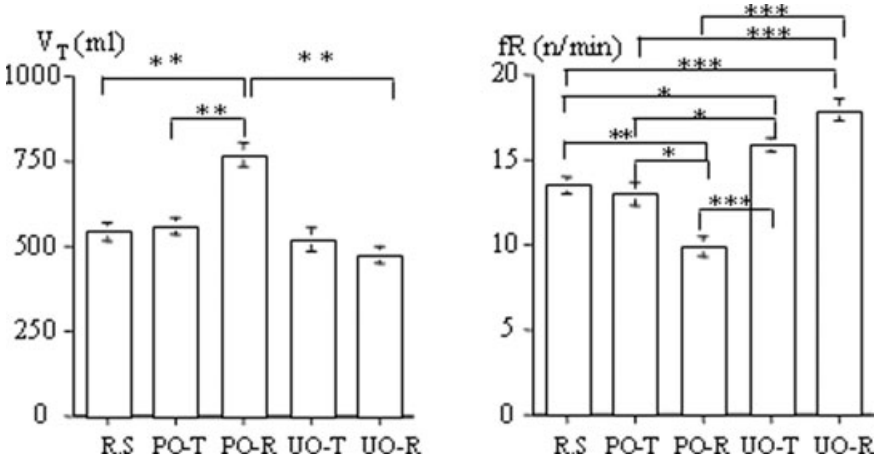

Figure 4. Tidal volume (V_T) and respiratory frequency (fR) during the resting state (RS), pleasant odour-threshold (PO-T), pleasant odour-recognition (PO-R), unpleasant odour-threshold (UO-T) and unpleasant odour-recognition (UO-R)
Statistical differences between the stimuli were judged by Bonferroni tests. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$. Reproduced with permission from Masaoka *et al.* (2005).

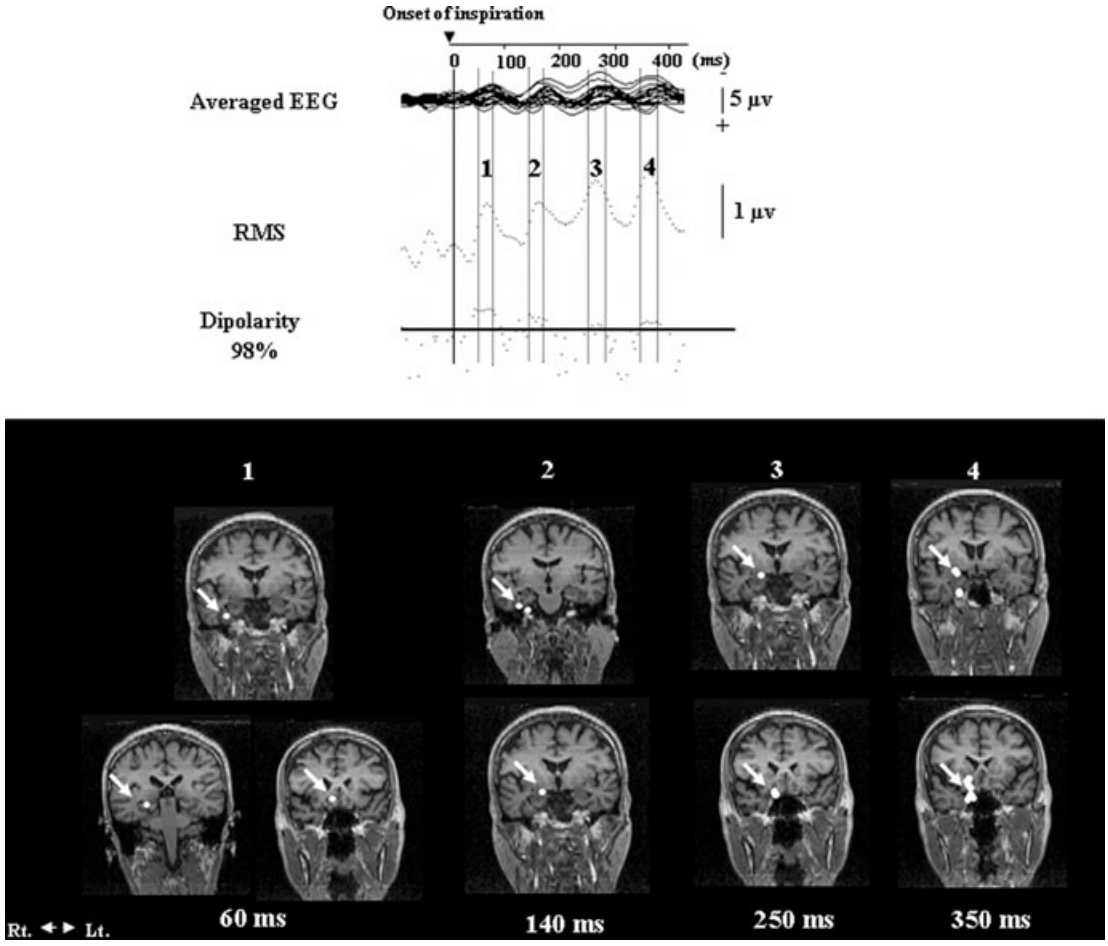

Figure 5. Inspiration phase-locked α-band oscillation (I-α) and source generators of I-α estimated by a dipole tracing method during unpleasant odour recognition
Dipoles were estimated in accordance with time after inspiration onset and were superimposed on a subject's coronal MRI sections (lower panel). RMS; mean absolute potentials recorded from 19 electrodes. Reproduced with permission from Masaoka *et al.* (2005).

amygdaloid nucleus, olfactory tubercle and entorhinal cortex (Rolls, 2001). Olfactory information ascends directly to limbic areas and is not relayed through the thalamus, so that each breath activates these areas directly. Direct stimulation of the olfactory limbic areas unconsciously alters the respiratory pattern. Unpleasant odours increase respiratory rate and induce rapid shallow breathing, and pleasant odours induce deep breathing (Fig. 4; Masaoka *et al.* 2005). It is interesting to note that the respiratory rate increases even before subjects discern whether a smell is unpleasant. It is likely that physiological outputs respond more rapidly than cognition (LeDoux, 1998).

Positron emission tomography (PET) and fMRI studies have revealed olfactory-related brain regions that are related to higher-order olfactory processing, such as discrimination (Rolls *et al.* 2003) and emotion (Royet *et al.* 2000) in humans. Electroencelphalography studies with the advantage of temporal resolution have also shown that during inspiration three to four negative and positive

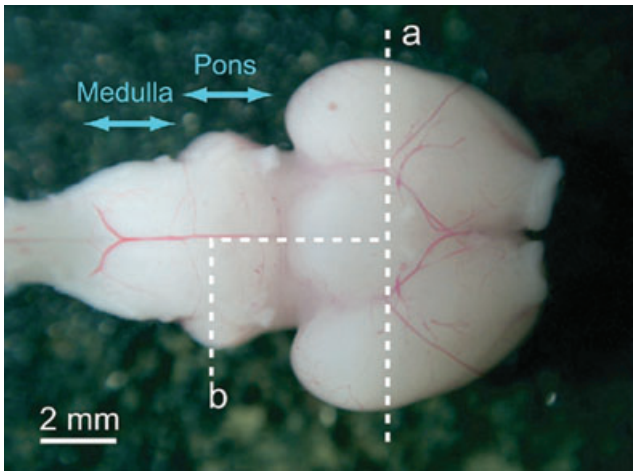

Figure 6. Ventral view of the limbic brainstem–spinal cord preparation
Preparations were transected rostrally at a level slightly caudal to bregma (dotted line 'a'), and half of the brain rostral to the pons was removed (dotted line 'b'). Reproduced with permission from Onimaru & Homma (2007).

waves can be observed, and the waves are phase-locked to inspiration (Masaoka *et al.* 2005). These waveforms, referred to as inspiration phase-locked α-band oscillation (I-α), are not observed during the expiratory phase or during breathing of normal air. The EEG dipole tracing method has estimated the location of source generators of I-α to the entorhinal cortex, amygdala, hippocampus and orbitofrontal cortex (Fig. 5). At 300–400 ms, the dipole converges most in the orbitofrontal cortex. At this time, recognition and identification of the odour occurs after the evaluation in the olfactory limbic areas (Masaoka *et al.* 2005).

Slow-wave oscillations and respiration

Slow-wave oscillations. Neurons and neuronal networks produce various rhythms in the brain, and activities are synchronized and desynchronized with each other. Synchronized neuronal rhythms are associated with

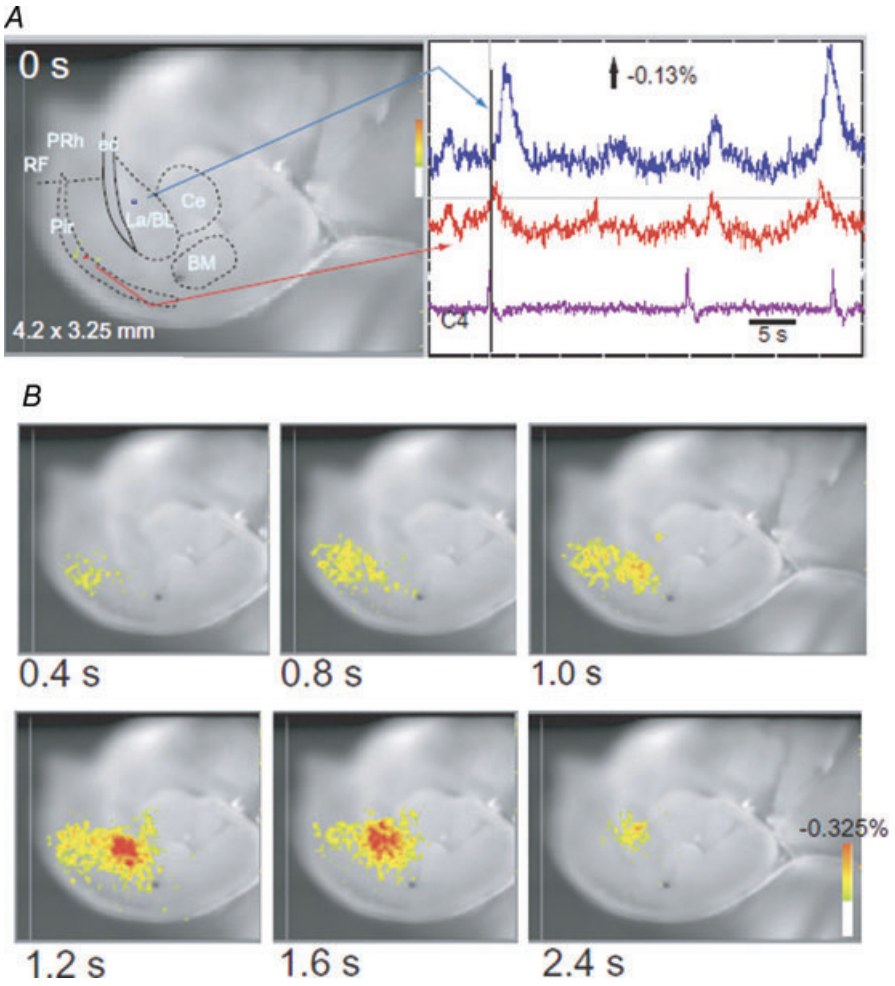

Figure 7. Optical recordings of spontaneous activity in the rostral cut surface of the limbic brainstem–spinal cord preparation
A, left, optical image of the cut surface of the piriform–amygdala region at the time of burst initiation in the piriform cortex (dark vertical bar in right panel). Abbreviations: BM, basomedial amygdaloid nucleus; Ce, central amygdaloid nucleus; ec, external capsule; La/BL, lateral and basolateral amygdaloid nucleus; Pir, piriform cortex; PRh, perirhinal cortex; and RF, rhinal fissure. Right, fluorescence changes at the two locations indicated in the left panel: blue, dorsal part of the lateral amygdala; red, piriform cortex. Upward deflection (calibration arrow) denotes a decrease of fluorescence intensity (i.e. depolarization) and corresponds to red in the pseudocolour calibration. The fluorescence change is expressed as the ratio (per cent, fractional change) of fluorescence intensity to that of the reference image. The C4 trace represents inspiratory activity of the C4 ventral root. Although this recording appears to show occasional coactivation of C4 and piriform–amygdala activity, statistical analysis was required to show significance. *B*, spatiotemporal pattern of the spontaneous burst activity. Numeric values at the bottom left of each image denote time (in seconds) after burst initiation in the piriform cortex (time 0 in *A*). Propagated activity terminated in the dorsal part of the lateral amygdala. Reproduced with permission from Onimaru & Homma (2007).

functions or behaviours, but a detailed characterization of these associations except for breathing rhythm has yet to be reported. In the human brain, rhythmic neuronal activity can be observed by EEG. Oscillations appear as alterations in amplitude or frequency and are synchronized broadly or locally and temporally. The origin of EEG potential wave oscillations is generally believed to be in the thalamocortical networks, and oscillations can be classified into fast waves with frequencies >1.5 Hz and slow waves with frequencies <1.5 Hz. Fast oscillations show low amplitude and are observed during awake or rapid eye movement (REM) sleep. Slow oscillations show high amplitude during non-REM slow-wave sleep and while under general anaesthesia (Steriade, 2000). During deep sleep, inhibition of synaptic transmission arises in thalamocortical neurons, blocking communication between the thalamus and the neocortex. Slow oscillation remains after thalamectomy and therefore is produced in the neocortex (Steriade *et al.* 1993). Slow depolarization and hyperpolarization are alternately repeated in neuronal networks of the neocortex in the absence of sensory afferents (Timofeev & Steriade, 1996). During deep sleep, the brain is isolated from environmental stimuli, and sensory coding via the thalamus is absent (Averbeck & Lee, 2004). Sanchez-Vives & McCormick (2000) showed in neocortex slice experiments that a slow oscillation with a frequency of 0.1–0.5 Hz arises in response to an excitatory interaction of pyramidal neurons which propagates to the neocortex. The functional significance of this oscillation is unclear; it has generally been believed that this slow oscillation is related to the process of attention or memory (Engel *et al.* 2001; Ward, 2003). Slow oscillations during

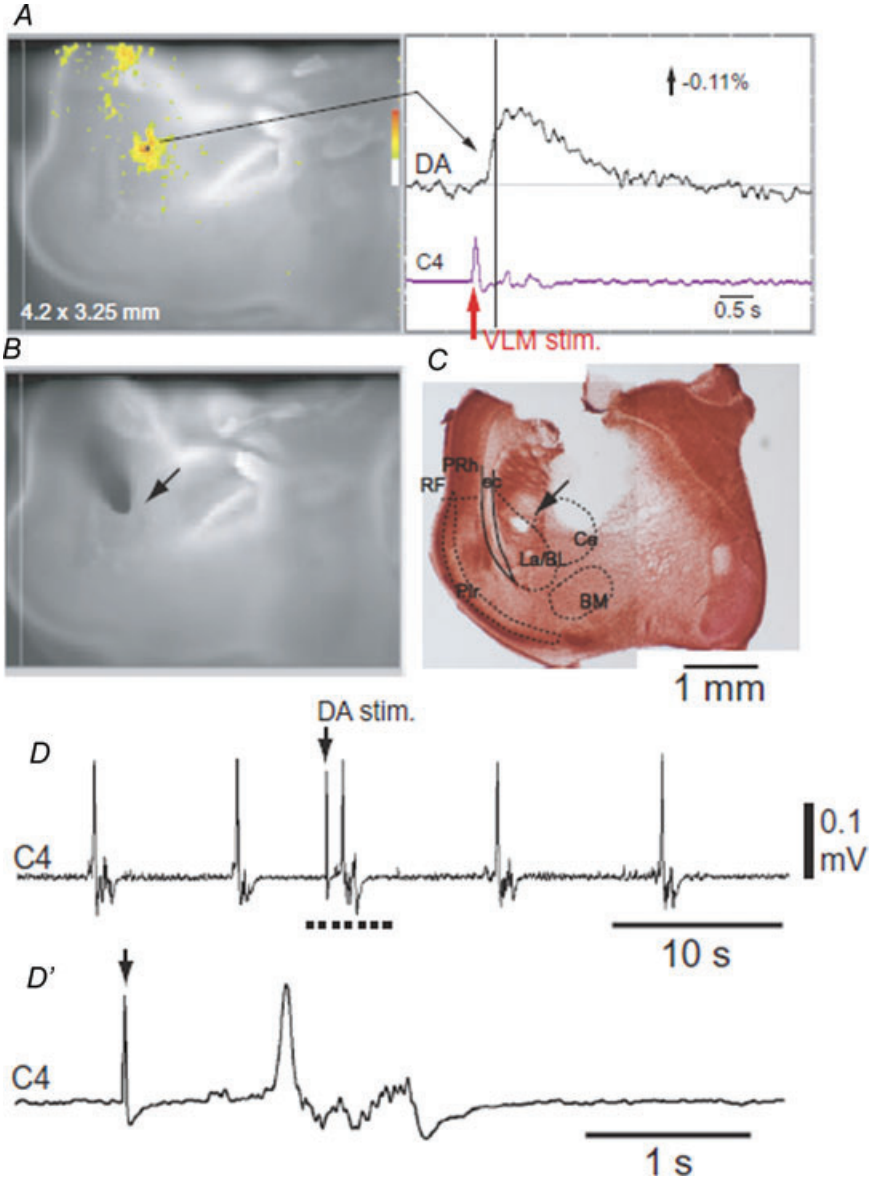

Figure 8. Effects of electrical stimulation of the VLM (*A*) and dorsal amygdala (DA; *B–D*)
A, activity in the DA induced by stimulation of the VLM. Left, optical image of the cut surface of the piriform–amygdala region at the time point of the dark vertical bar in the right panel. There is a focal fluorescence change in the DA. Red arrow (VLM stim.) indicates timing of stimulation. The C4 trace represents inspiratory activity of the C4 ventral root. *B*, position of the stimulation electrode (arrow) in the dorsal amygdala. *C*, histological section of the cut surface. Arrow indicates the position of the stimulation electrode. Abbreviations: BM, basomedial amygdaloid nucleus; Ce, central amygdaloid nucleus; ec, external capsule; La/BL, lateral and basolateral amygdaloid nucleus; Pir, piriform cortex; PRh, perirhinal cortex; and RF, rhinal fissure. *D*, effects of stimulation of the DA (in *B*) on C4 inspiratory activity. *D'*, faster sweep representation for the time period indicated by the dotted line in *D*. Arrows (DA stim.) indicate stimulation artifact. Note that the stimulation induced a premature C4 inspiratory burst within 1 s. Reproduced with permission from Onimaru & Homma (2007).

slow-wave sleep are thought to consolidate synapses (Sejnowski & Destexhe, 2000; Steriade & Timofeev, 2003).

The origins of slow oscillations in the neocortex are of interest. Electroencephalography studies with 256 channels in humans have indicated that the distribution of slow oscillation potentials on the scalp is not uniform and is localized exclusively in the orbitofrontal area of the prefrontal cortex and conducted to the anteroposterior area (Massimini *et al.* 2004). Cerebral blood flow also decreases in this area during non-REM sleep (Braun *et al.* 1997).

Slow oscillation in the limbic system. Slow oscillations have been recorded in pyramidal cells in the neocortex in both *in vitro* and *in vivo* animal experiments; they have also been recorded in the perirhinal cortex and showed a good correlation with those recorded in the lateral amygdala in ketamine–xylazine-anaesthetized cats (Collins *et al.* 2001). Lesion experiments have indicated that the perirhinal cortex and the amygdala cortex are associated with memory encoding (Buckley & Gaffan, 1998). Slow oscillations with frequencies <1 Hz have been recorded in other neocortices as well (Lledo *et al.* 2005; Buonviso *et al.* 2006). Fontanini *et al.* (2003) examined slow oscillations in the olfactory system, paticularly in the olfactory bulb and piriform cortex, in ketamine–xylazine-anaesthetized rats and reported a strong relationship between the occurrence and timing of slow oscillations and on-going sensory input resulting from respiration; they concluded that there is a strong relationship between the timing of respiration and brain rhythm. The piriform cortex is part of the paleocortex, which is the primitive, common cortex among species. Olfactory information is a major emotional input in animals. Primates engage in rapid sensing of environmental danger, identification of food and recognition of sex differences; this is performed via the olfactory system and enhances the immediacy of responses to impending events. Fontanini *et al.* (2003) suggested that the fundamental neuronal architecture of the cerebral cortex was first evolved in the context of the olfactory system and was adapted for uses in other sensory systems via evolutionary development of the neocortex.

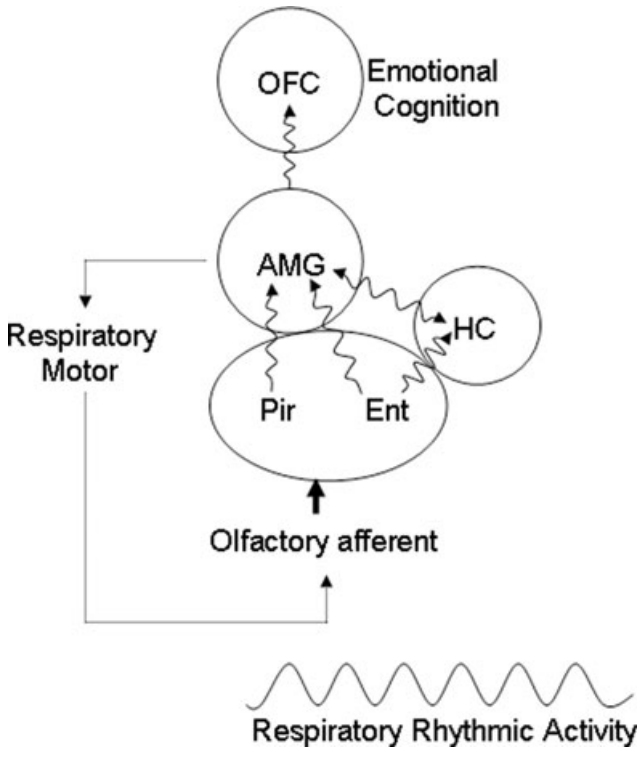

Figure 9. Schematic representation of connections of orbitofrontal cortex (OFC), amygdala (AMG), piriform cortex (Pir), entohinal cortex (Ent) and hippocampus (HC) with respiratory rhythm

Low-frequency oscillations have also been recorded in the frontal cortex in slices of the neonatal immature rat cortex (Peinado, 2000; Calderon *et al.* 2003). The evolution in neonates of the piriform cortex to the frontal neocortex is unclear, but an early close relationship between olfaction and the forebrain has been demonstrated (Aboitiz *et al.* 2003). Slow oscillations have been recorded in the entorhinal and perirhinal cortices in newborn rats (Garashuk *et al.* 2000). Oscillatory waves induced by a calcium influx regulate long-distance wiring in the immature cortex by promoting synchronized neuronal development over large cortical areas (Garashuk *et al.* 2000). Recent *in vivo* experiments have shown slow intervals of recurrent calcium transients in the temporal and parietal cortices of newborn mice (Adelsberger *et al.* 2005).

Onimaru & Homma (2007) reported an origin of the slow wave and its propagation in a limbic brainstem–spinal cord preparation in newborn rats. This preparation is an intermediate between an *in vitro* and *in vivo* preparation. The brainstem–spinal cord preparation was first developed by Suzue (1984) and is currently used worldwide. The preparation allows simultaneous recordings of spinal motor output and neural activities in the brainstem. Unlike the slice preparation, the brainstem–spinal cord preparation can identify neurons from the motor output. Characteristics of various respiratory neurons, in particular pre-inspiratory (pre-I) neurons in the medulla, have been examined with this preparation (Ballani *et al.* 1999). The primary area of respiratory rhythm generation has also been shown optically with the use of a voltage-dependent dye (Onimaru & Homma, 2003).

Activations of the limbic and paralimbic systems, including the piriform cortex, amygdala and hippocampus, can be detected at the rostral surface of coronal sections of the limbic brainstem–spinal cord preparation. This preparation is appropriate for

the examination of characteristics of limbic system neurons (Fig. 6). Spontaneous rhythmic activity has been reported in the piriform cortex and amygdala in the limbic brainstem–spinal cord preparation. Optical signals appear initially in the piriform cortex and propagate mediolaterally to terminate in the lateral amygdala (Onimaru & Homma, 2007). The piriform–limbic system rhythmic activity is associated with inspiratory activity of the C4 ventral root (Fig. 7). Rhythmic activity remains after complete separation of higher brain regions from the lower brainstem by sectioning at the level of the pons, but rhythmic activity is independent of C4 inspiratory activity. Electrical stimulation applied to this region induces a C4 inspiratory burst; and stimulation applied to the ventrolateral medulla (VLM), where the brainstem respiratory rhythm generator exists, induces an excitatory response in the dorsal amygdala complex (Fig. 8). Neurons in the amygdala complex are connected reciprocally with respiratory regions in the medulla and pons (Fulwiler & Saper, 1984; Yasui *et al.* 2004). Data obtained by Onimaru & Homma (2007) suggest that the spontaneous oscillatory activity initiated in the piriform–amygdala complex is associated with respiratory activity in the medulla. This connection is not always close functionally, but the piriform–amygdala complex may control respiratory rhythm when it is activated by an odorant or during various emotions.

The piriform–amygdala complex. This system may connect functionally with the olfactory system. The amygdala and entorhinal cortex receive inputs directly from the olfactory bulb and inputs indirectly from the piriform cortex (Harberly & Price, 1978; McDonald, 1998). Two routes have been identified by stimulation of the olfactory nerve. One is the route from the piriform cortex to the amygdala cortex via the medial pathway, and the other is from the entorhinal cortex to the amygdala cortex via the lateral pathway (Kajiwara *et al.* 2007). The olfactory–amygdala route is considered to be associated with fear in animals (Phillips & Ledoux, 1992; LeDoux, 2000). Almost all sensory modalities, including auditory, visual and somatosensory, are associated with fear. Sensory information produces fear behaviours via activation of the central nucleus of the amygdala, the hypothalamus and the brainstem (LeDoux, 2000).

Results of animal studies of olfactory centres and amygdala activation have similarities to studies in humans. Odour perception and odour-induced emotions are dependent on inspiration. Therefore, it is not surprising that respiratory rhythms are closely associated with emotions. The piriform cortex may produce rhythms, and the piriform–amygdala complex may alter respiratory rhythm in response to qualitative changes in emotions. The entorhinal cortex may also be necessary in this system, as shown in our human experiments. Reciprocal connections between the entorhinal cortex and the amygdala have been identified in animal experiments. This system may be involved not only in odour stimulation but also in various emotional states (Fig. 9). Breathing and emotion are linked with meditation, especially in East Asia (Fontanini & Bower, 2006). Breathing and emotion are also linked with culture. Homma *et al.* (2006) have shown in actors of Japanese traditional 'Noh' drama that the internal expression of the mind is generated in the amygdala with breathing rhythm.

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