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Respiratory influence on brain dynamics: the preponderant role of the nasal pathway and deep slow regime.

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ABSTRACT

As a possible body signal influencing brain dynamics, respiration is fundamental for perception, cognition and emotion. The olfactory system has recently acquired its credentials by proving to be crucial in the transmission of respiratory influence on the brain *via* the sensitivity to nasal airflow of its receptor cells. Here, we present recent findings evidencing respiration-related activities in the brain. Then, we review the data explaining why the fact that breathing is *i)* nasal and *ii)* slow and deep is crucial in its ability to stimulate the olfactory system and consequently influence the brain. In conclusion, we propose a possible scenario explaining how this optimal respiratory regime can promote changes in brain dynamics of an olfacto-limbic-respiratory circuit, providing a possibility to induce calm and relaxation by coordinating breathing regime and brain state.

Respiratory influence on neuronal dynamics has been well known for a long time in the olfaction community, being described as a slow rhythm shaping neuronal activity at the different levels of the olfactory pathway (epithelium, bulb, piriform cortex) and neuronal activities (local field potential, spiking discharge, membrane potential). However, such an interest for this slow rhythm was not shared by other domains of neurophysiology probably because the different communities have long remained sealed off from each other. But still more probably such a lack of interest could be explained by the fact that, for a long time, this influence was mainly explored through the prism of odorant stimulations. Consequently, respiratory drive was explained by the rhythmic activation of the olfactory epithelium by odorant molecules entrained at each inhalation, restricting the interest to the olfaction community. As described below, the discovery of the mechano-receptive property of olfactory receptor neurons, and therefore of their sensitivity to airflow, has changed the general viewpoint on the interest of this respiratory signal passing through the olfactory system to influence the rest of the brain.

Respiratory influence on brain dynamics has been explored in non-olfactory areas for about ten years so that, from an overlooked rhythm, breathing rhythm has progressively acquired its credentials. Here we first review recent findings on respiration-entrained activity in the brain. Then, we will attempt to explain why the olfactory nasal route is crucial in the influence of breathing on brain dynamics, and to clarify why slow deep nasal breathing (e.g. slow frequency and high nasal flow rate) is more favorable to induce brain entrainment.

A respiratory drive in the brain

In the olfactory brain. Respiration influence has been described as soon as the first Adrian's work [2]. Already at that time, he described respiration-related oscillations in the olfactory bulb (OB) local field potentials (LFP) in the anesthetized preparation, on which were superimposed higher frequency oscillations in the gamma range and he attributed these induced waves to the velocity of the air through the nose [2, 3]. Then, respiration influence has been described in the activity all along the olfactory pathway. As revealed by electro-olfactogram recordings in the freely breathing anesthetized rat, the olfactory epithelium shows oscillatory responses synchronized to respiration during odor presentation, maximal depolarization of receptor cells occurring at the end of inspiration [21]. Without any odorant stimulation, the activity of individual olfactory sensory neurons also appears respiration-locked, probably reflecting stimulation by airflow [29].

This rhythmic message is then transmitted to the OB where the influence of respiration has been largely described (for review, [11]). The first studies revealed that the unitary discharge of mitral /

tufted cells were phase-locked to the respiratory cycle both in anesthetized [13, 18, 20, 62, 93] and awake rodent [26, 45]. Fewer works describe a slow oscillation in the membrane potential of mitral/tufted cells which phase-locks to respiration [1, 10, 14, 22, 40]. After Adrian [2, 3], Freeman's work [38, 39] reported in the awake rabbit inspiration-locked LFP gamma bursts superimposed on a respiration-related oscillation. Our group largely contributed to the description of the influence of respiration on OB dynamics in the anesthetized rat. Particularly, we showed a powerful temporal structuring of LFP fast rhythms by respiration: odors induce an alternation between gamma oscillations occurring at the end of inspiration and beta oscillations appearing during expiration [12]. At the same time, neuronal assemblies of gamma-synchronized spiking activities emerge during inspiration, alternating with spiking beta-synchronized neuronal assemblies during expiration [18]. The presence of a respiration-related slow oscillation in the membrane potential of these mitral/tufted cells favors the phasing of gamma / beta oscillations expressed in their membrane potential with the gamma / beta oscillations respectively expressed in the network [35]. Interestingly, the slow respiratory rhythm, thanks to the level of activation that it imposes to the OB input, constitutes a real gate system favoring the functioning of the OB in a beta or gamma mode network [24, 27, 36].

Further away in the olfactory pathway, the piriform cortex has been mainly studied. Respiration-paced oscillations appear in LFP activity [34, 37, 57, 68]. Superimposed on this slow rhythm, as in the OB, are gamma oscillations, locked to the end of inspiration [8, 9, 58]. Spiking discharges of cortical cells have been also shown to exhibit a clear phase-locking with respiration [7, 34, 57, 94]. Litaudon and colleagues [57] confirmed this rhythmicity in both the anterior and posterior piriform cortices but highlighted a difference between these two structures: cells in the anterior part of the piriform cortex phase-lock their spikes with the end of inspiration, while cells in the posterior part phase-lock with either inspiration or expiration. *In vivo* intracellular recordings have demonstrated that membrane potential also exhibit respiration-related slow oscillations [32, 34, 81, 94]. Even if these experiments were performed under anesthesia and under odorant stimulation, they reveal to what extent respiratory rhythm can shape brain activity to the point of modifying its functioning.

Most of the above studies were performed under odorant stimulation, it was thus not surprising to observe a respiration-related activity, sampling of odorant molecules being inspiration-slaved. It was more surprising to observe such an influence in the absence of odorant molecules in the inhaled air [2, 3, 19, 62, 73, 76, 77, 93]. The mechanical activation of the olfactory system by nasal airflow as a cause of this effect was first suggested by Adrian and Ludwig [4]. It was later on debated on whether there was a real mechanical stimulation of the olfactory receptor neurons or an odor pollution of the setup [2, 75, 91, 93]. An elegant fMRI study reported that sniffing without any odorant induces

activation in the olfactory cortex [87]. The authors concluded that sniff-induced activation is related to brain activity induced by the sensation of air flow. Over 50 years later, Grosmaître and colleagues [44] created a little revolution in the olfactory literature by demonstrating that the olfactory sensory neurons were not only responsive to chemicals but also to mechanical stimuli. Indeed, using patch-clamp recordings, they showed responses of olfactory sensory neurons to pressure ejections of a ringer solution. We know today that this mechanical response is mediated through the G protein-coupled odorant receptors and depends on the type of olfactory receptors [23]. This finding was not yet available when [33] published their hypothesis on the “sniffing brain”, where they hypothesized that neocortical slow-waves might be entrained and coordinated by entry of air into the nostrils.

Beyond the olfactory brain. We had to wait another ten years for the first evidence of a respiratory drive in neocortical structures to appear. Indeed, since 2014, several teams have revealed the existence of respiratory modulation of LFP activity beyond olfactory areas (for a recent review, see [31]). Although most of these studies agreed that breathing rhythm could drive brain dynamics, data were often disparate because of several reasons: i) The preparation was different: anesthetized, awake head-fixed, awake freely moving, ii) Respiratory regime was different: sniff, calm, very slow during freezing, iii) Recorded areas were different: more or less rostral, iv) The brain state was different: waking (exploration or rest), sleep (SWS or REM). The main characteristics of all these studies are synthesized in Table 1.

A respiratory drive has been first described in the hippocampus, where medial septum neurons and CA1 place cells were observed to phase-lock to respiration during slow breathing and sniffing in freely moving rats [90]. Shortly after, Yanovsky and colleagues observed in the hippocampal activity, under urethane anesthesia, a coexistence of theta and respiration-related oscillations in LFP during activated state [97]. This result was in contradiction with those of Viczko and colleagues [92] reporting that respiratory-related oscillations were strictly limited to olfactory structures in the urethane-induced sleep-like slow-wave state. This discrepancy was explained when Lockmann [60] found that respiration-related oscillations are observable in activated hippocampus, whereas absent in deactivated state. Then, respiration-related oscillations were described in the hippocampus of awake head-fixed mice, with the highest amplitude in the dentate gyrus during awake immobility and running [69]. Interestingly, respiration has also been described to influence the timing of hippocampal slow-wave ripples [53, 59]. Then, respiratory drive in a non-olfactory cortical structure was firstly observed in the mice barrel cortex where delta and gamma band oscillations, and spiking discharges appeared correlated with respiratory rhythm in the quietly awake mice [50]. In a recent study refining the anatomy of rodent barrel cortex, a region representing the nose / nostril was found, in which spike activity and LFP were much strongly respiration-locked than whisker/barrel

cortex sites [63]. A respiratory drive has also been recently evidenced the medial prefrontal cortex [6, 53, 55, 66, 100]. Similarly, respiration-related oscillations and spiking discharges were observed in the orbitofrontal, anterior cingulate, infralimbic, and parietal cortices [52, 53, 55]. Interestingly, during slow-wave sleep, UP and DOWN occurrences have been shown to be modulated by respiratory phase [53]. In Human, EEG studies were mainly conducted on the impact of slow breathing on higher frequencies such as theta (4 – 8Hz) and alpha (8 – 12Hz), highlighting increases of alpha and decreases of theta power during slow breathing exercises [42, 78, 98]. However, it has been recently possible to test respiratory related entrainment in human with quality signal close to LFP in animals in a wide range of brain regions with intracranial EEG signal from patients with drug resistant epilepsy. These studies revealed the presence of respiration-related oscillations in the piriform cortex [99] but also in other brain regions with more than 60% of recording sites expressing significant iEEG respiration coherence such as the amygdala, the hippocampus, the insula, primary motor and sensory cortices, as well as frontal regions [48].

Binding local activities between distant areas. Having observed that different brain areas could display a respiration-related oscillation, several groups were then interested in how the breathing rhythm could serve in coupling local activities between distant areas. A series of studies in human [48, 99] and in the awake animal [16, 17, 43, 52, 53, 67, 85, 89, 100] emerged in which the authors observed inter-areal coupling through different brain states. Among these works, Zhong and colleagues [100] showed that brain areas could be coupled in different gamma sub-bands, coupling being provided either through the respiration-entrained rhythm or through theta rhythm. Interestingly, the coupling specificity depends on both brain state and region. During awake immobility in rodents, the respiration-entrained rhythm couples exclusively to a mid-gamma sub-band (80-120 Hz) LFP oscillation in OB, parietal cortex, prefrontal cortex and CA1. Conversely, during exploration, only OB and prelimbic cortex display mid-gamma oscillations coupled with respiration-related oscillation, CA1 and parietal cortex displaying a prominent low (40-80 Hz) / high (120-160 Hz) gamma coupling with theta rhythm. A delta-range coupling between prefrontal cortex and hippocampus supported by respiratory drive has also been evidenced [67]. In a study in freely moving mice, Tort and colleagues [89] reported that LFPs from 15 recorded areas show significant coherence with both respiratory and theta rhythms during REM sleep and exploration. However, the strength of the coherence highlights a power balance between respiratory rhythm and theta in each area, suggesting some areas are more sensitive to theta and others more sensitive to respiratory rhythm. Using whisking and sniffing activities in the rat, Rojas-Libano and colleagues [85] identified rest and exploration states. They found a cross-area modulation of gamma activity in V1, M1 and S1 cortical areas phase-locked to the animal's slow respiratory rhythm (about 2.5 Hz) at rest.

Our group approached this question of binding between areas by analyzing LFP signals from 7 areas in freely moving rats during four brain states, namely exploration (EX), quiet wake (QW), slow-wave sleep (SWS) and rapid-eye movements sleep (REM) [43]. Importantly, even if a significant coherence appeared in all areas and during all states, quiet wake was the only vigilance state during which all the recorded structures can be respiration-driven whatever the respiratory frequency. In a non-published analysis illustrated in Fig.1 , we explored the connectivity between areas during the different brain states, in four rats. Fig.1 B and C left shows respiratory rhythm-mediated connectivity network in low frequency (0.3-15 Hz) LFP. Width of links between structures represents the probability to observe co-occurring respiration-related oscillation (RRo) in both structures. It is obvious that network connectivity is particularly dense during QW, i.e. all areas are interconnected, and this is observed in all the four animals studied. Nonetheless, V1 co-vary rarely with other areas. It is obvious that during EX, while probabilities are globally lower than during QW, network is still robust since each connected pair is observed in all four animals also. On the contrary, during SWS and REM, probabilities are low and many connected pairs are not detected in all animals. Fig.1 B and C right shows mid-gamma (60-90 Hz) synchronization network during episodes of respiration-mediated synchronization. A link between two areas means that cross-area mid-gamma synchronization was significantly modulated by respiratory phase. Width of the link represents mid-gamma modulation index. It shows that, during QW only, the network displays a complete profile, most pairs of areas being connected in several animals. In conclusion, these preliminary results suggest that connectivity between distant brain areas can be supported by respiratory rhythm during both waking states (EX and QW). Conversely, connectivity supported by respiration-mediated mid-gamma synchronization appears only during quiet waking. Respiratory rhythm can thus coordinate local activities of distant areas with different strengths according to the brain state.

Respiratory drive and nasal breathing

All this above cited literature highlights activation of olfactory pathway by nasal airflows as the major route to transmit respiration-related activity to the brain. The effect of nasal airflow has been first approached in the anesthetized rodent in the context of odorant stimulation. Using calcium imaging of olfactory receptor cells terminations in the mouse OB glomeruli, Oka and colleagues [72] showed the glomerular response to odorants was strongly impacted by nasal airflow rate, but differently impacted by airflow frequency according to the physicochemical properties of the odorant molecules. Furthermore, voltage-sensitive dyes glomerular responses display a dual response to odor stimulation: a tonic and a phasic components which are dependent on flow rate and inspiration volume, respectively [30]. The phasic component is respiration-locked. Comparing effects of mechanical vs odorant stimulation on the BOLD and LFP signals of the rat OB, Wu and colleagues [95]

showed that the activity pattern evoked by airflow in the nasal cavity was more broadly distributed than patterns evoked by odors. We reported that OB response to odors was strongly modified by nasal flow rate [24, 25]. A high flow rate improved mitral/tufted cells spike phase-locking to gamma, whereas a low flow rate improved spike phase-locking to beta. Furthermore, gamma oscillations appeared more frequently when odors were delivered with a high nasal flow rate, while beta oscillations were more often induced when odors were delivered with a low flow rate. All these data evidenced that nasal airflow consistently shapes respiration-related activity in the OB. It would therefore not be surprising that respiration-related activity is also modified in non-olfactory structures by changes of nasal airflow.

And in fact, when a respiratory drive began to be observed in non-olfactory structures, several authors suspected the nasal airflow as the source of this drive. They used different methodologies to evidence the nose and its mechanical sensitivity as a leading route to the brain, through the OB. The conclusion is threefold:

- *The effects pass through the olfactory epithelium.* After lesion of the olfactory epithelium by using methimazole, a strong decrease in the OB respiratory-related oscillation has been found [65]. In addition, this treatment also abolishes the respiratory-related oscillation in the prefrontal cortex [5, 53].

- *The nasal airflow is the force transmitting the respiratory rhythm.* A current method used to by-pass nasal airflow in animals while leaving the animal respiration unaltered is the tracheotomy. Tracheotomy decreases the respiratory-locked activity in the hippocampus [97] or the whisker barrel cortex [50]. Nasal airflow can also be by-passed by naris closure. Moberly and colleagues [65] described a decrease of the OB respiratory-related rhythm following naris occlusion as well as a decrease in the coherence between the OB and the prefrontal cortex activity. In humans, the nasal airflow can be by-passed by instructing the subjects to breathe through the mouth. Recording iEEG under nasal or oral breathing, Zelano and colleagues [99] demonstrated that mouth breathing significantly decreases the respiratory-related rhythms in the piriform cortex, amygdala and hippocampus.

- *The respiratory entrainment of the brain passes through the OB.* Another proof that the main pathway for the respiratory drive to different cortical areas is the olfactory system comes from experiments where the OB was removed or pharmacologically inactivated. Indeed, Ito and colleagues [50] demonstrated respiration-locked oscillations in the whisker cortex were significantly reduced (>90%) following a bulbectomy. This effect was also observed in the prefrontal cortex following bilateral bulbectomy [6]. Thanks to cellular labeling and tracing methods, it was demonstrated that the respiratory drive from the OB to the prefrontal cortex can possibly pass through different

olfactory relays: the piriform cortex, dorsal endopiriform nucleus or anterior olfactory area [6, 65]. Finally, inactivating the OB using DREADD also eliminates the relationship between respiration and hippocampal sharp-wave ripples (which occur during the expiration phase; [59]). Using Granger causality method to assess inter-areal connectivity, Nguyen Chi and colleagues [69] revealed that respiration-related oscillation in the hippocampus was caused by the OB.

All these different studies point out for a major role of the nasal airflow and the olfactory pathway in leading the respiratory-related activities throughout the brain. Obviously, a central origin coming from the respiratory centers cannot be excluded, especially for non-olfactory structures [53, 79, 82, 83]. Karalis and Sirota [53], who used methimazole to eliminate inputs from the olfactory epithelium, demonstrated that, while this manipulation abolished the respiratory-related oscillation in the prefrontal cortex, some prefrontal neurons as well thalamic neurons were still modulated by respiration (although to a lesser extent). This observation led the authors to suggest the involvement of a respiratory corollary discharge coming from the brainstem respiratory rhythm generators. Both origins (i.e. olfactory pathway and central respiratory structures) probably work together and are amplified by each other. They may work as a gradient, the respiratory nasal olfactory influence most likely having a strong impact on more anterior structures or the ones directly connected to the OB and the central respiratory structures influencing more strongly the posterior structures. This could explain the antero-posterior gradient influence of nasal breathing observed by Tort and colleagues [89]. Another influence which cannot be ruled out is the one from the trigeminal nerve. Indeed, the trigeminal nerve terminations in the nasal epithelium can be activated airflow temperature and specific odorant molecules (for review, see [49]). In any case, these central and trigeminal influences are probably minor regarding the strong olfactory impact.

Respiratory drive and slow deep breathing

If breathing-related air pressure into the nose is the main source of respiratory drive in the brain, then one can expect variations in air movements to induce different effects in the brain. It is what has been explored in different studies in the anesthetized rodent, using a double tracheotomized preparation with artificial sniff paradigm, allowing an independent control of nasal airflow. By independently varying frequency and flow rate of the circulating air in the nasal cavity, we evidenced in the rat that an increase in airflow frequency decreased the amplitude of odor-evoked LFP and respiration-related spiking discharges activities, which was offset by an increase in peak flowrate [24, 25, 30].

This trade-off effect between flowrate and frequency was further confirmed in the awake animal, outside of any context of odorant stimulation [43]. Indeed, analyzing respiration-related oscillation in

the LFP activity of a large brain network, we observed that neither a deep inspiration alone (high inspiratory flow rate) nor a long inspiration alone (slow respiratory frequency) was sufficient to drive non-olfactory areas. Brain entrainment is allowed by an “optimal” respiratory regime, consisting in a deep (around 20 mL/sec) and long (around 0.15 s) inspiration. The further away the respiratory regime is from this optimal regime, the less respiration-driven brain areas are. This is well illustrated by **Fig.2** representing the probability to observe a respiratory-related oscillation as a function of inspiration depth / duration ratio. While almost any regime is able to independently drive one brain area (see the large range of yellow to green pixels), only a restricted range of regimes is able to entrain simultaneously all the six areas. Interestingly, the optimal respiratory regime entraining simultaneously the different brain areas is the one corresponding to the QW state (see orange outline). We brought evidence that respiratory drive on brain structures mainly depends on the respiratory regime rather than the brain state. Indeed, using a 5% CO₂ enriched air, we modified the respiratory regime without altering brain state [43]. Under such condition, where peak flowrate and frequency increased, the most striking result was the emergence of respiration-related oscillations in all recorded areas during the SWS state, where they did not appear under normal breathing regime condition. We concluded that the emergence of respiration-related oscillations is probably due to respiratory pattern rather than the brain state itself. It is worthwhile to compare our results with those of Hammer and colleagues [46] showing, in the mice posterior parietal cortex, that the respiration-related theta-gamma coupling is maximal at breathing frequencies of 4–6 Hz. Indeed, it is likely that this range of respiratory frequencies could correspond to the inspiration depth / duration ratio we reported as optimal for respiratory drive in rats. Similarly, we think that the powerful respiration-related oscillations observed in the prefrontal cortex during freezing behavior is probably related to the fact that respiration presents the optimal characteristics to drive the OB during this condition [5, 65].

In summary, brain dynamics can be influenced by breathing provided that olfactory epithelium is sufficiently activated thanks to an optimal trade-off between inspiration depth and duration. Importantly, under this regime condition, brain areas in a large scale network can synchronize their activity regarding to the respiratory rhythm. This could be a consequence of the calming effect of controlled slow and deep breathing observed during meditative states [61]. In parallel, the beneficial effects slow deep breathing on stress and anxiety largely rely on modifications of autonomous nervous system activity such as a shift from sympathetic dominance toward a net increase in parasympathetic tone (for review, see [71]). These effects are not our point and will not be discussed below. Conversely, we tempt to propose how nasal slow deep breathing could promote a calm state through influence on brain dynamics, particularly in olfacto-limbic-respiratory circuits.

Nasal slow deep breathing and relaxation: a hypothesis

- *First step: an optimal breathing regime allowing airflow to strongly activate the olfactory epithelium*

We posit that nasal breathing with a peculiar regime, consisting in deep and long inhalation, is both necessary and sufficient to drive the rodent brain and change the dynamics. The equivalent for the human brain is probably the slow deep breathing regime which accompanies relaxation or meditative states [51, 74]. We will qualify as “optimal regime” such a respiratory regime.

- *Second step: activation of the olfacto-limbic circuit*

Already in 1998, mechanical stimulation of the olfactory epithelium by air was shown to induce activation in the piriform, entorhinal and parahippocampal regions and also in a small portion of the orbitofrontal cortex [87]. More interestingly, it has been shown that stimulation of the nasal mucosa with periodical odorless airflow at a frequency of 0.05 Hz, reproducing a 8 seconds-long inspiration, with a constant pressure of 1.1 bar, completely independent of the subject’s breathing, results in important changes in oscillatory activity in the limbic system and the DMN structures, with a particular involvement of mPFC and OFC along with the perception of having experienced an altered state of consciousness [80]. Thus, it seems that, provided that the olfactory epithelium is stimulated enough by airflow (optimal regime), it is not even necessary that airflow is synchronized with the central breathing to influence brain activity. In this view, it is noteworthy that, in comatose patients, puffing air into the nasal cavity, at a frequency range similar to regular respiration, increases the connectivity between DMN regions (particularly cingulate cortex, mPFC, insula) in the gamma frequency range [86]. Importantly, mPFC and OFC are densely connected with the different amygdala nuclei [15, 54] which also receive direct projections from the OB and/or piriform cortex (for review, see [64, 88]). Therefore, amygdala is probably recruited by air-induced olfactory pathway stimulation.

- *Third step: amygdala influences respiratory centers*

The limbic system is a central region in the modulation of breathing, amygdala nuclei and respiratory regions being reciprocally connected [41]. Influence of amygdala on breathing has been evidenced in electrical stimulation experiences: electrical stimulation of the amygdala increases respiratory rate in animals [47] or reproduces apnea in human [28, 56, 84]. Furthermore, apnea appears in epileptic patients when the seizure extends to the amygdala [28, 70]. Hence, recruited by nasal airflow stimulation, amygdala nuclei could in turn influence respiratory regime.

- *Last step: influence of the respiratory regime on behavior and brain state*

A key element in our rationale is that the respiratory regime can act on the state of arousal. This was nicely shown in mice [96] where the authors succeeded in isolating a small sub-group of neurons in the pre-Bötzinger complex, a central nucleus in respiratory rhythmogenesis. These neurons project to the locus coeruleus, which through its diffuse projections to the entire cortex, promotes the awake state. Showing that inhibition of these neurons induces a calm state in the mice, this study reveals that respiratory centers can control higher-order brain structures associated with behavioral arousal. This breathing corollary signal would thus serve to coordinate the brain state with the breathing pattern, explaining why a slow deep breathing accompanies relaxed state. Interestingly, the central nucleus of the amygdala being connected with autonomic system centers [88], this could explain why the heart rate and the spontaneous respiratory rate decreased when a regular mechanical airflow is imposed to nasal epithelium [95]

Finally, being optimal for activating mechano-sensitivity of olfactory receptor cells, slow deep nasal breathing promotes changes in brain dynamics of an olfacto-limbic-respiratory circuit, providing a possibility to induce calm and relaxation by coordinating breathing regime and brain state.

Figure captions

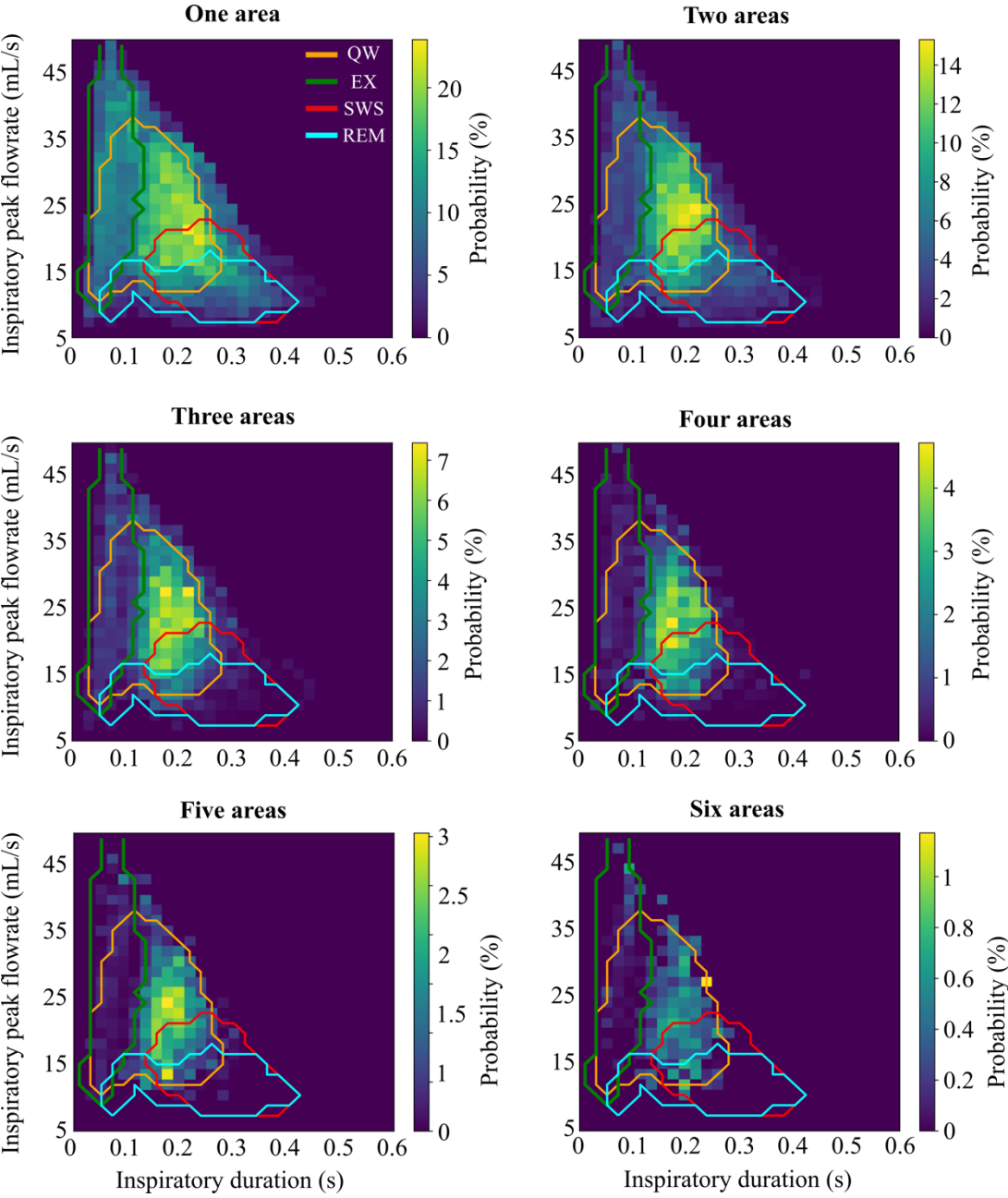
Fig.1 *Respiratory rhythm can bind most areas in low and high frequency bands during quiet waking*

A) Raw LFP traces from aPCX (black) and mPFC (grey), and the respiratory signal (green). This dataset collects simultaneous LFP recordings from 6 brain areas (medial prefrontal cortex (mPFC), anterior piriform cortex (aPCX), primary somatosensory cortex (S1), primary visual cortex (V1), CA1 and dentate gyrus (DG)), and respiration. **B) Summarized methods** for constructing graphs in C. B Left) Step by step method for quantification of RRo co-occurrence in low frequency (0.3-15 Hz) LFP. ① LFP low pass (0.3-15 Hz) filtering ② RRo detection respiratory cycle by cycle in each area individually. ③ Quantification of RRo co-occurrence for each pair of areas and each brain state. ④ Probabilities averaging (n=4 rats). B Right) Step by step method for quantification of gamma (55-100 Hz) synchronization during RRo co-occurrence. Only periods associated with RRo were analyzed. ① LFP band-pass (55-100 Hz) filtering. ② Extraction of instantaneous LFP phase. Phase difference was obtained by subtraction. Stability of the phase difference (blue trace) was assessed as follows: mean vector of the phase difference signal was computed using sliding windows of 37.5 ms. The longest the vector, the more stable the phase difference (blue trace). ③ Stability of the phase difference averaged across respiratory cycles. ④ Quantification of the respiratory modulation: the mean vector of the respiratory cycle-averaged stability was computed. Length of this vector represents a respiratory modulation index; the longest, the strongest the modulation is. Length was computed and was statistically compared with surrogates. ⑤ Respiratory modulation index averaging. **C) Binding between the 6 areas network across brain states.** B Left) Width of black links between areas represents the mean RRo co-occurrence probability \pm sem (grey). B Right) Width of black links between areas represents the mean respiratory modulation index \pm sem (grey). Number of averaged animals is indicated on the link.

Fig.2: *Respiration-driven networks are favored by respiratory pattern characteristics of quiet waking state.*

The brain state-dependent variability of respiratory pattern was tracked with inspiratory peak flowrate and duration, these two respiratory parameters being the best suited to differentiate the respiratory regimes [43]. For each network size (from one to six areas), the probability to observe a respiration-driven network is represented as a function of the inspiratory peak flowrate and duration. For a given bin of inspiratory peak flowrate and duration, this probability represents the number of respiratory cycles during which N areas displayed simultaneously Respiration-Related oscillations (RRo) divided by the number of respiratory cycles in the bin. Each map is the average of data from 4 animals. In all animals, the 6 recorded areas were medial prefrontal cortex (mPFC), anterior piriform cortex (aPCX), primary somatosensory cortex (barrel field, S1), primary visual cortex (V1), CA1 and dentate gyrus (DG). Probabilities are color-coded. Each map has its own scale. Orange, green, red and cyan curves represent the median distribution of respiratory cycles associated to quiet waking (QW), exploration (EX), slow wave sleep (SWS) and rapid-eye movements sleep (REM) respectively.

Figure2



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