

Journal Club

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The Respiratory Modulation of Memory

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Review of Arshamian et al.

Breathing originates in the respiratory pacemaker, the preBötzinger complex (Del Negro et al., 2018). Before each inspiration, this group of brainstem neurons transmits a motor signal to the diaphragm, whose contraction creates a depression in the rib cage that draws air into the lungs through the nose or mouth. During nasal breathing, the airflow activates mechanoreceptors of the olfactory sensory neurons, which generate a breathing-locked rhythmic signal transmitted to the olfactory bulb that is then relayed to the olfactory cortex. This respiratory-entrained rhythm spreads beyond olfactory areas and has been measured in the medial prefrontal cortex (mPFC) and the hippocampus, two areas strongly involved in memory processing (for review, see Tort et al., 2018).

The phase of the slow olfactory reafferent rhythm modulates the amplitude of faster oscillations in neocortical and limbic regions through a well documented process called cross-frequency phase–amplitude coupling (Hyafil et al., 2015). This neural mechanism occurs spontaneously between oscillations of different frequency bands and is thought to support the communication between distant brain

areas. These observations led to the hypothesis that the breathing mode (nose vs mouth) and respiratory phase (inspiration vs expiration) can influence memory performance. Indeed, Zelano et al. (2016) demonstrated that the respiratory phase of nasal breathing modulates the performance of memory encoding and retrieval of visual objects in humans. These effects disappeared when breathing was diverted from the nose to the mouth, highlighting a causal role of the breathing mode.

Building on previous findings, Arshamian et al. (2018) recently investigated the effect of the breathing mode on memory consolidation, the information storage occurring between memory encoding and retrieval. They exposed participants to a set of 12 odors presented one-by-one via a nasal cannula. After this first encoding phase, subjects were randomly assigned to breathe only through the nose or through the mouth for 1 h, during which olfactory memories were consolidated. Subjects were then presented a set of 24 odors (12 targets and 12 new lures) and asked whether each odor had been presented during the initial exposure period. The experiment was repeated in all participants 2 d later using the breathing mode that had not been tested in the first session. This paradigm allowed the authors to measure the effect of the breathing mode on olfactory memory consolidation. A control experiment was also conducted using classical attentional tasks to rule out any potential confounding effect of the

breathing mode on participants' attention. The results demonstrated that nasal breathing increases olfactory memory consolidation. Specifically, the performance in odor recognition improved when participants had breathed through their nose during the consolidation period. In addition, the control experiment did not reveal any effect of the breathing mode on attentional resources, therefore excluding a potential attentional bias. These findings extend the results of Zelano et al. (2016) and suggest that respiratory modulation of memory is a general mechanism spanning multiple sensory modalities (vision, olfaction) and memory processes (encoding, consolidation, and retrieval).

Although brain activity was not monitored in this study, Arshamian et al. (2018) suggest that a specific type of hippocampal oscillations named sharp-wave ripples (SWRs) are involved in their results. These highly synchronized fast oscillations occur in the hippocampal formation during sleep or awake rest periods and are thought to be involved in the replay of past events. After learning, the rate of SWR occurrence transiently increases, and this is associated with memory consolidation (for review, see Joo and Frank, 2018). Animal studies also demonstrated that the suppression of SWRs impairs memory consolidation (Girardeau et al., 2009). In mice, the respiratory phase modulates the occurrence of SWRs (Liu et al., 2017), but the effect disappears if the

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olfactory bulb is inhibited (via bilateral injection of viral vectors), suggesting it depends on the olfactory reafferent rhythm. Because breathing through the mouth does not activate the olfactory reafferent rhythm in humans, Arshamian et al. (2018) argue that the respiratory modulation of SWRs would be abolished during mouth breathing and that this reduced occurrence of SWRs leads to decreased olfactory memory consolidation.

Intracerebral recordings in epileptic patients shed further light on this hypothesis. The olfactory reafferent rhythm has been shown to modulate faster human hippocampal oscillations in the delta frequency band (0.5–4 Hz; Zelano et al., 2016). Moreover, in humans at rest or asleep, the occurrence of SWRs is phase-locked to the hippocampal delta activity (Axmacher et al., 2008). Thus, during nasal, but not mouth breathing, the delta waves might enable the respiratory modulation of SWRs. In addition, delta oscillations have been shown to mediate the hippocampo-mPFC dialogue underlying memory consolidation in the human brain during both wakefulness and sleep (Euston et al., 2012; Mitra et al., 2016). Altogether, through its cross-frequency coupling with the delta waves, the olfactory reafferent rhythm could modulate both the occurrence of SWRs and the hippocampo-cortical dialogue involved in memory consolidation (Buzsáki, 1996). Therefore, reductions in delta-wave modulation during mouth breathing might contribute to the reduced memory consolidation in the experiments by Arshamian et al. (2018).

Beyond the well documented olfactory reafferent rhythm (Tort et al., 2018), a recent study by Karalis and Sirota (2018) suggests the existence of a respiratory modulation pathway that is independent of the breathing mode and might also modulate memory consolidation. Like Arshamian et al. (2018); Karalis and Sirota (2018) investigated the effect of breathing on memory consolidation, but using a fear conditioning paradigm in mice. They measured the respiratory entrainment of neural activity in several brain regions, including the mPFC and the hippocampus, through multiple single-neuron recordings. After pharmacological olfactory deafferentation (enabling a selective removal of the olfactory mechanoreceptors inputs), the respiratory modulation of mPFC oscillations disappeared, thus replicating previous findings (Tort et al., 2018). Yet, in apparent contradiction with the results reported by Liu et al. (2017),

the pharmacological intervention left the respiratory modulation of SWR occurrence intact. This difference might be related to the fact that the animals did not engage in a learning task in Liu et al. (2017) (see Girardeau et al., 2014) or that the experimental methods used for the olfactory inhibition were different (pharmacological vs viral interventions). But Karalis and Sirota (2018) conclude that the continued influence of respiration on SWRs after olfactory deafferentation reveals the presence of another respiratory modulation pathway, distinct from the olfactory reafferent rhythm. Thus, they suggest that brain activity is modulated by a dual mechanism of respiratory entrainment. They hypothesize that with each inspiration, the preBöttinger complex sends an ascending “respiratory corollary discharge” to the brain, which is a copy of the descending motor signal transmitted to the diaphragm. This corollary signal modulates brain activity in both breathing modes, acting alone during mouth breathing and jointly with the olfactory reafferent rhythm during nasal breathing. Although this neural mechanism would not explain, on its own, the difference in memory performance between nasal and mouth breathing measured by Arshamian et al. (2018), its potential contribution to the consolidation process in both breathing modes should not be excluded.

Although the neuroanatomical substrates of the corollary discharge remain to be identified, Karalis and Sirota (2018) suggest that a potential pathway is projections from the preBöttinger to the locus ceruleus (LC), the principal site of noradrenergic synthesis in the brain. The role of this nucleus in memory and arousal is well documented (Sara, 2009, 2015). The LC projects to the hippocampus and its noradrenergic inputs are thought to modulate SWR occurrence (Hansen, 2017). Moreover, Yackle et al. (2017) recently discovered a subpopulation of preBöttinger neurons that project directly to the LC and regulate the level of arousal in mice. With each inspiration, this neuronal subpopulation transmits a phase-locked excitatory input to the LC. According to the authors, this noradrenergic excitation might also be influenced by the breathing frequency and regularity.

Further research is required to confirm the presence of the respiratory corollary discharge in humans as well as its neuroanatomical substrates. However, a strong argument in favor of its evolutionary preservation is provided by a recent article from Perl et al. (2019), who report respi-

ratory modulation of cognition in humans independent of breathing mode. To investigate the potential role of the preBöttinger complex-LC pathway, researchers must measure the activity of the LC when investigating the effect of breathing on cognitive tasks. Because pupillary dilatation is a reliable indirect marker of LC activity (Murphy et al., 2014), this is achievable at low cost using an eye tracker. In addition to the phase (inspiration vs expiration) and mode (nasal vs mouth), the effect of breathing rate (slow vs fast) and regularity (predictable vs erratic) on the pupil size should be explored (Yackle et al., 2017). Altogether, the recent results discussed in this *Journal Club* highlight the scientific opportunity to unite the respiratory and noradrenergic modulation of brain rhythms into a common research framework.

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