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Respiration-coupled rhythms in prefrontal cortex: beyond if, to when, how, and why

Bernat Kocsis[1], **Benjamin R. Pittman-Polletta**[1], and **Alexis Roy**[1]

[1]Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Dear Editor

We are greatful to Lockmann and Tort (2017) and Bagur and Benchenane (2017) for their comments which draw important connections between our results published earlier this year (Roy et al. 2017) and recent research on repiratory-related oscillations (RROs). In our results, we showed a reciprocal relationship between hippocampus (HC) and prefrontal cortex (PFC) in which the well-established theta synchrony promoted by the HC is reciprocated by a unique low-frequency oscillation dominant in PFC local field potential (LFP) recordings. The latter oscillation was consistently detected as a narrow peak in the spectrum of PFC LFP in the 2–5 Hz range, i.e., in the delta band; but this rhythm was markedly different from the well-known wide-band delta rhythmicity, that is, the signature pattern of cortical activity during sleep. We showed in particular that in urethane anesthetized rats the 2–5 Hz rhythm appears not only spontaneously, alternating with wide-band delta, but can also be elicited by electrical stimulation of the reticular arousal system (RPO—nucleus reticularis pontis oralis), i.e., in a controlled experimental paradigm which has been used for decades to study HC theta oscillations (see, e.g., Kittelberger et al. 2012; Ly et al. 2013). In their letter, Lockmann and Tort (2017) suggested that the 2–5 Hz oscillations described in our study might synchronize with the respiratory rhythm (RR), based on a recent flurry of publications describing RROs in the cortical LFP of freely moving and urethane-anesthetized rodents. Importantly, RROs were not directly derived from the respiratory circuits, but rather were conveyed through the olfactory bulb (OB) and eliminated by tracheotomy (Fontanini et al. 2003; Lockmann et al. 2016). In their accompanying comment, Bagur and Benchenane assess the validity of Lockmann and Tort's suggestion, and judging it likely, attempt to integrate our findings on the role of thalamic nucleus reticularis (nRE) in mediating 2–5 Hz PFC-HC coherence with what is known about RROs.

Correspondence to: Bernat Kocsis.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors. All applicable international, national, and institutional guidelines for care and use of animals were followed. All procedures were approved by the Institutional Animal Care and Use Committee of the Beth Israel Deaconass Medical Center.

We have tested Lockmann and Tort's exciting idea on a few rats in the RPO stimulation paradigm, and found that the induced 2–5 Hz rhythm observed in PFC may indeed synchronize with RR; Fig. 1 shows a few examples. However, these preliminary data also indicate that this issue deserves further systematic investigation, as the relationship between RR and the PFC 2–5 Hz rhythm is far from a driver–receiver relationship. The examples in Fig. 1 show epochs of 2–5 Hz oscillations in PFC which are not coupled with higher frequency RR, suggesting that, while RR is ongoing without interruption, its synchronization with intrinsic LFP patterns at similar frequencies in higher brain structures is dynamic. Also shown are examples in which 2–5 Hz oscillations undergo amplitude changes opposite those seen for RR in response to RPO stimulation, suggesting that PFC rhythms are unlikely to be mechanistically generated by incoming respiration-related sensory input. Thus, these examples suggest that the ongoing LFP oscillations at 2–5 Hz in PFC and other brain regions may be mechanistically independent from RR, and furthermore, that the synchrony between RROs and RR may occur dynamically in a behavior-, state-, and task-dependent manner. These observations—as well as recent reports hinting at the potential complexity of the relationships between RR, RROs, and brain function—caution against an overly simplistic interpretation of the role of RROs in brain circuits. By adding this missing information to support the dynamic entrainment of PFC network activity by RR, we thus would like to emphasize the dynamic nature of this coupling in multiple brain structures which may undoubtedly play an important role in the organization of network activity in cognitive processes.

To clarify our perspective, it is worth noting that the issues at hand are reminiscent of the debate that took place in the field of central autonomic regulation over 30 years ago (Gebber and Barman 1977). Unlike RR, the cardiac rhythm is generated in the periphery by the sinus node; the heart keeps beating after being removed from the body. Yet, the nervous output through sympathetic efferents to the heart and the widely distributed system of vasoconstrictors shows strong cardiac rhythmicity. At first, this rhythmicity was attributed solely to entrainment of these outputs by the baroreceptor feedback. Only when it was found that sympathetic nerve activity remains rhythmic after barodenervation (Gebber and Barman 1981), was it realized that the cardiac rhythm (heart beat) does not simply drive the sympathetic circuits. Instead, brainstem sympathetic networks have the capacity to generate intrinsic oscillations at frequencies overlapping with the cardiac rhythm. Thus, this brain network responsible for controlling a rhythmic peripheral system developed to produce a pattern of activity that could be easily and dynamically entrained by periodic (inhibitory baroreceptor) input from that rhythmic peripheral system (Gebber et al. 1990).

The OB, the first station relaying RR to other brain structures, has similar characteristics. While its activity in tracheotomized rats is no longer entrained by RR, the OB continues to generate intrinsic oscillations at frequencies similar to RR, although with lower amplitude and reduced regularity (Fontanini et al. 2003). These oscillations remained synchronized to field potentials and pyramidal neuron membrane potentials in the cortex even after removing RR input. This finding led Fontanini to the conclusion that "in freely breathing rats, … slow oscillations in the OB, cortex, and sensory input from respiration are certainly interacting with an intrinsic tendency for olfactory structures to oscillate" (Fontanini et al. 2003; Bower 1995).

The analogy between cardiac-related sympathetic oscillations and RRO is limited, of course; RR is of neural origin but the primary goal of the neuroal activity entrained by this rhythm in PFC, HC, and other areas is unlikely to be the control of respiration. Just as OB integrates different inputs, including RR, theta (Tort et al. 2017), and others into its own emerging activity, higher brain structures integrate a variety of inputs to perform their own function. Thus, when RRO appears in a non-respiratory neural circuit, as indicated now by solid evidence (see (Lockmann and Tort 2017) for references), it is expected to be utilized and transformed as an important component of the activity generated by that circuit, which is tuned to perform the functions specific to that circuit. This involves behavior- and task-dependent “de novo” re-generation of RR-synchronized oscillations (Tort et al. 2017) in certain specific behaviors and tasks but not in others. The question is what these networks are using RR synchrony for—as well as when, how, and why.

Several important reports (Tort et al. 2017; Biskamp et al. 2017; Zhong et al. 2017) which appeared recently after our publication (Roy et al. 2017) further support and clarify this interpretation. As explained by Tort et al. (2017) “local generation of an oscillation is typically inferred by bipolar recordings, current source density analysis, or modulation of unit activity in the recorded region”. This group used multi-site recordings to detect RROs in freely moving mice in 15 widespread cortical regions, including PFC, insula, parietal and visual cortices, as well as in HC, entorhinal cortex and subcortical structures such as the medio-dorsal thalamus and amygdala. In many of these structures, the local origin of RROs has been shown by current source density analysis [e.g., in HC (Lockmann et al. 2016)] or rhythmic modulation of spiking [e.g., in PFC, HC (Biskamp et al. 2017; Zhong et al. 2017)]. Tort et al. argue that as neocortical circuits are known to generate “genuine delta oscillations”, it is less likely “that all delta-frequency activity in the cortex would be due to respiration” (Tort et al. 2017). When present, however, “RR-coupled oscillations represent a global brain rhythm” which “provide a mechanism for binding different networks and neuronal ensembles into a common regime, and thus fulfill similar behavioral and cognitive functions as other rhythms in the same frequency domain” (Tort et al. 2017).

While Tort et al. (2017) analyzed theta states of REM sleep and waking exploration, Biskamp et al. primarily focused on RR coupling in non-theta states during the tail suspension test. They suggest that this activity “contributes to the processing of multimodal information streams that reach the PFC from cortical and subcortical brain areas” and proposed that it “may support the synthesis of multimodal information content as a basis of decision-making and execution of certain behaviors” (Biskamp et al. 2017), i.e., the primary function of PFC. They regard RROs as part of the family of sub-theta frequency activity patterns which emerge in different behaviors—including anxiety and working memory—and which may or may not synchronize with RR, depending on state. Although direct evidence will require simultaneous RR recordings, Biskamp et al. speculate that whereas the 4 Hz rhythm accompanying fear-induced freezing (Karalis et al. 2016; Dejean et al. 2016) may synchronize with RR, the 4 Hz rhythm pacing neuronal assemblies in the PFC, HC, and even in the dopaminergic ventral tegmental area in a spatial working memory paradigm requiring bidirectional PFC–HC communication (Fujisawa and Buzsaki 2011) is unlikely to couple with RR, as the RR frequency is highly variable in this memory task. Even if this 4 Hz rhythm turns out to synchronize with RR (as predicted in (Tort et al. 2017)), the precise

timing of its appearance—limited to a specific phase of a specific cognitive task—and its precise localization—limited to specific subsets of neurons predicting the turn choices of the rat—would indicate that at the time this task is executed RRO becomes an integral component of the emergent PFC network activity. The goal of our experiments (Roy et al. 2017) was to study the mechanism of PFC–HC coupling in using a reduced, behavior-independent preparation, to test "the idea that the theta and 4 Hz oscillations may serve as parallel channels of communication in opposite directions between the HC and the PFC" and "to hopefully generate further investigations" as Bagur and Benchenane (2017) correctly infer. These investigations might indeed benefit from including respiratory recordings to test whether, how, and when PFC takes advantage of the global RRO, manifest in a number of task-relevant brain structures.

The possibility that RRO-frequency oscillations may be endogenously generated simultaneously in multiple brain structures, and dynamically and selectively synchronized with RR only during certain states or to meet certain task demands, expands the possible interpretations of RRO coherence between brain regions. Once RR becomes integrated into PFC 2–5 Hz activity, RROs may be broadcast further to networks functionally connected to PFC. Many of these connections are reciprocal and thus the RR is not just relayed to the next structure, as a soccer ball, but may become part of the interplay between these structures. Many cortical oscillations are in fact thalamo-cortical, just as theta is not solely hippocampal but rather septo-hippocampal with rhythmic drives in both directions between HC and subcortical structures (Kang et al. 2017; Kocsis and Kaminski 2006). The thalamic nucleus reuniens (nRE) has reciprocal connections with the PFC as well as with HC (Vertes et al. 2015). We have shown in (Roy et al. 2017) using RPO stimulations in urethane anesthetized rats that nRE plays an important role in synchronizing and transmitting the 2–5 Hz rhythm but much less in synchronizing and transmitting theta between PFC and HC. Besides these core findings supported by both partial correlation analysis and pharmacological nRE suppression, the mechanisms generating 2–5 Hz oscillations in these three structures remain unknown. In (Roy et al. 2017), we summarized several observations requiring further investigations and presented an alternative model [Fig. 7b in (Roy et al. 2017)] in which the oscillation is generated by a thalamocortical network rather than being relayed from PFC through nRE. Furthermore, as explained by Bagur and Benchenane (2017), a simple direct relay of RR by PFC to HC also does not fit the existing nRE-to-HC anatomical connections heavily targeting the CA1 region and the primary RR current source density in the dentate gyrus. They offer a hypothetical model and a "different form of explanation than that of anatomical relay between structures" in which the role of nRE is to control the responsiveness of PFC and HC circuits to the common RR input. Investigations with parallel RR recording will be required to find the right model describing how low-frequency coupling of rhythmic networks are contributing to task-dependent information transfer between PFC and HC. The mechanisms of participation of nRE may be quite complex. It was shown recently (Kafetzopoulos et al. 2017) in freely moving rats that nRE lesion reduced PFC–HC coherence without affecting PFC and HC LFP power, and had anti-depressive effects, as measured in the forced swim test and the chronic mild stress model of depressive behavior in rodents. It was thus proposed that reduced PFC–HC coherence was an important factor contributing to nRE's impact on the overall brain connectome in chronic

stress, along with other factors including stress-induced deficits of neuroplasticity, such as dendritic atrophy and spine loss in the PFC (Kafetzopoulos et al. 2017). Regardless of mechanism, given the selective and task-dependent entrainment of PFC ensemble activity to RR, the simultaneous selective enhancement of RROs in HC by nRE may mediate task-dependent information flow from PFC to HC.

That RROs in higher brain networks do not represent a “contamination” by respiration but rather an activity pattern integral to the information processing in these structures is further underscored by the fact that they act similar to “normal” slow LFP rhythms, taking part in behavior- and task-dependent interactions within an oscillatory hierarchy of brain activity. Modulation of high frequency oscillations by slow rhythms has been proposed as a powerful mechanism of neural processing (Tort et al. 2009). RROs were recently found to modulate local beta rhythms in the OB and HC (Lockmann et al. 2017) and gamma rhythms in several higher brain structures (Biskamp et al. 2017; Zhong et al. 2017). Zhong et al. (2017) specifically tested low-frequency modulation of gamma activity in OB, PFC, parietal cortex, and HC and found region- and behavior-dependent modulation of different gamma bands, i.e., modulation of 40–80 Hz gamma by theta and of 80–120 Hz gamma by RROs, “indicative of selective local computations in the respective networks” (Zhong et al. 2017). In theta states, RRO gamma modulation was observed in OB and PFC simultaneously with theta modulation in HC and parietal cortex. In non-theta states (immobility), theta modulation switched to RRO modulation in HC and parietal cortex, as well. The authors proposed (Zhong et al. 2017) that “not only theta but also RR constitutes a global brain signal … and play[s] a role in coordinating network communication across distant regions”. Interestingly, theta–gamma coupling in the PFC was state-dependent, i.e., “on” during waking but “off” during REM sleep, a strong theta state. Coupling of fast rhythms by 2–5 Hz/delta/RROs is most likely also state-, and task-dependent, i.e., not “on” all the time even though respiration never stops. A shift between theta and 2–5 Hz/delta cross-frequency coupling can also be elicited by pharmacological interventions. Theta modulation of gamma amplitude was replaced by delta modulation after dopamine release into the PFC (Andino-Pavlovsky et al. 2017). Similar shifts between theta and delta modulation of the amplitude of high frequency oscillations (120–160 Hz; Hunt et al. 2006) have been observed following administration of psychoactive drugs mimicking cognitive deficits in schizophrenia, such as subunit-specific NMDA receptor blockers (Pittman-Polletta et al. 2017). Indeed, it may be worth revisiting reports, implicating the impairment of slow oscillations in psychiatric diseases from the perspective of RROs. Theta impairment is prominent in these disorders, and in some of them a direct connection with respiration would be more likely [e.g., anxiety, (Adhikari et al. 2010)] than in others [e.g., schizophrenia, (Pittman-Polletta et al. 2015)].

In conclusion, we congratulate the laboratories of Jurij Brankack and Adriano Tort for their major contribution to our understanding of RR-synchronized oscillations in widely distributed brain networks. We specifically wanted to mention their recent reports (Tort et al. 2017; Zhong et al. 2017) published this year in which this new global rhythm receives an interpretation we fully agree with. This interpretation goes beyond the simplistic view of RR as a source of “contamination” of LFP recordings or as an afferent input determining the activity of cortical and subcortical networks, to safely avoid the misconception that these circuits are passively “driven” by respiration. Rather, RROs are seen to result from intrinsic

resonances in neuronal population activity, dynamically recruited by a widespread network of brain regions to meet task demands and support state-specific information processing and communication—an interpretation unfortunately missing from Lockmann and Tort and Bagur and Benchenane's comments.

Finally, we feel a responsibility to address several statements in (Lockmann and Tort 2017) which appear to stem from a misunderstanding of our data that requires correction. This comment was based on a relatively small subset of experiments ($n = 4$) from a study of RROs in HC (Lockmann et al. 2016) with parallel PFC recordings. While this study also used urethane-anesthetized rats, it otherwise employed quite different approaches from ours, analyzing spontaneous activity rather than testing oscillations by controlled, dosed RPO stimulation. These points of misunderstanding are as follows: (1) Lockmann and Tort disputed the label we used for the PFC rhythm (2–5 Hz oscillation), saying "… at the highest stimulation intensity the peak frequency was ~ 4 Hz [Fig. 3d in (Roy et al. 2017)]". In fact, the correct reading of our Fig. 3d is in agreement with the term of 2–5 Hz, as it shows group averages (4.27 and 3.69 for two groups of rats) and standard errors, indicating dispersion of data in individual experiments (0.65 and 0.30, the latter corresponding to 1.15 standard deviation, i.e., setting the maxima of the frequency ranges to 4.92 and 4.84 Hz). (2) Lockmann and Tort also pointed out that in Fig. 1d (Roy et al. 2017) we demonstrate an "oscillation around 2 Hz, closer to the ~ 1.5 Hz in (Lockmann et al. 2016)". The correct reading of this figure, however, is that there is no narrow band oscillation in the inactive state; power is rather widely distributed in the delta band, up to 4 Hz. Indeed, in their original article, Lockman et al. (2016) argue that in this state there is no RRO in the PFC, confirming prior findings by Viczko et al. (2014). Thus, our finding is in agreement with their original report but not with their comment (Lockmann and Tort 2017). (3) We note further that the ~ 1.5 Hz oscillation of the comment (Lockmann and Tort 2017) was consistently labelled as "< 1.5 Hz" in the original reports (Lockmann et al. 2016), reporting occasional transient peaks on tail pinch up to 2–2.2 Hz [Fig. 3 of (Lockmann et al. 2016)] which is different from our sample, in which RR was rarely below 2 Hz [similar to other studies, e.g., 2.14 Hz in (Viczko et al. 2014)]. RPO stimulation-induced PFC rhythm was, however, always > 2 Hz [see Fig. 3d in (Roy et al. 2017)]. (4) Lockmann and Tort also recommended using the term SO instead of wide-band delta. In (Roy et al. 2017), LFPs were not specifically tested for slow oscillations (SOs) associated with up-and-down state transitions; the wide-band activity Lockmann and Tort call SO in their comment [Fig. 1c in (Lockmann and Tort 2017)] is far from conclusive regarding the presence of this rhythm. It is also not clear how the two sharp spectral peaks in their Fig. 1b correspond to the clearly wide band spectra in the corresponding time–frequency plots in Fig. 1a. The term wide-band delta is used in thousands of papers. For clarity, we would like to quote the characterization of LFP spectra of segments rich in SO by Viczko et al. (2014): "LFP from neocortical and hippocampal sites showed more broadband characteristics … with the largest peak corresponding to the SO … between 1 and 1.5 Hz."

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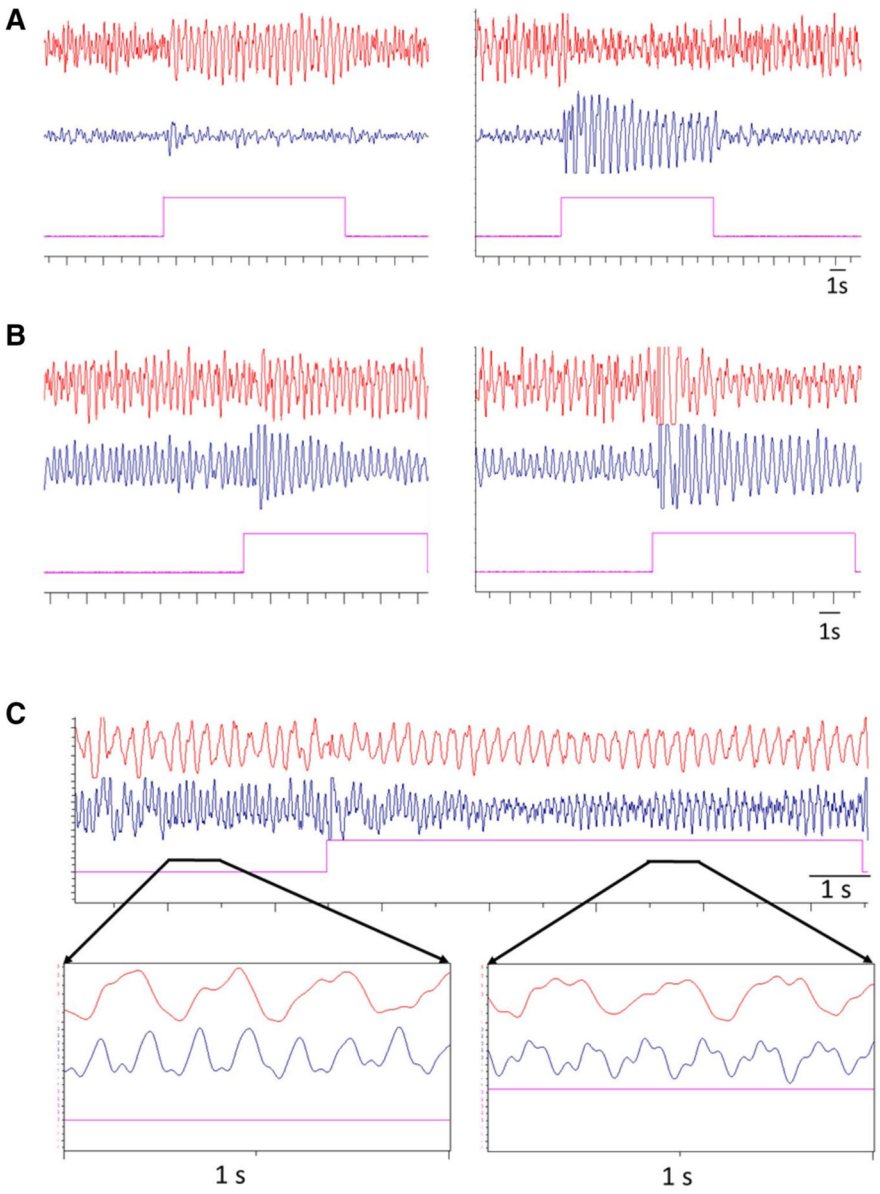

Fig. 1.

Respiratory rhythm and PFC 2–5 Hz LFP induced by RPO stimulation. These traces are examples from two rats, only intended as illustration and preliminary data and not as report on a systematic investigation. **a** and **b** Synchronized oscillations in PFC LFP (red) and respiration (blue) induced by low and high (left and right, respectively) intensity RPO stimulation (purple marker). RPO stimulation was applied on the background of shallow (**a**) and deep breathing (**b**). Note opposite changes in the amplitude of PFC 2–5 Hz rhythm (Roy et al. 2017) and respiration indicating that the 2–5 Hz rhythm in PFC synchronized with respiratory rhythm was unlikely imposed mechanistically by the sensory signal detecting respiration. **c** Example of RPO stimulation induced 2–5 Hz PFC rhythm (~ 3.5 Hz) which

did not couple with fast respiration (6–7 Hz) either in spontaneous recording or during RPO stimulation. Bottom, 1 s segments enlarged from spontaneous and RPO stimulated state