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Physiological changes in sleep that affect fMRI inference

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Abstract

fMRI relies on a localized cerebral blood flow (CBF) response to changes in cortical neuronal activity. An underappreciated aspect however is its sensitivity to contributions from autonomic physiology that may affect CBF through changes in vascular resistance and blood pressure. As is reviewed here, this is crucial to consider in fMRI studies of sleep, given the close linkage between the regulation of arousal state and autonomic physiology. Typical methods for separating these effects are based on the use of reference signals that may include physiological parameters such as heart rate and respiration; however, the use of time-invariant models may not be adequate due to the possibly changing relationship between reference and fMRI signals with arousal state. In addition, recent research indicates that additional physiological reference signals may be needed to accurately describe changes in systemic physiology, including sympathetic indicators such as finger skin vascular tone and blood pressure.

Introduction

Blood oxygen level dependent (BOLD) fMRI of sleep provides unique opportunities to investigate brain function across a range of arousal states. fMRI relies on the blood flow (hemodynamic) response to local cortical circuit activity (Iadecola 2017), involving the so-called “neurovascular” unit in which arteriolar diameter is controlled by chemical signaling secondary to synaptic activity subserving local computation. Spontaneous and evoked fMRI activity may thus inform on the function and interaction of cortical areas. However, a number of studies have shown that the fMRI signal may also be affected by widespread contributions from fluctuations in autonomic physiology (Birn et al. 2009; Shmueli et al. 2007; van Houdt et al. 2010) or activity of modulatory neurotransmitters. As reviewed in the following, these contributions may vary strongly, and potentially jointly, with arousal state, and thus -- if not modeled -- constitute a serious impediment for the interpretation of fMRI

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studies in general, those of sleep in particular. The main focus of this article will be on the effects of autonomic physiology on the fMRI signal.

Sources contributing to the fMRI signal

It is well recognized that various spurious factors can affect the fMRI signal, including head motion, system drift, and changes in systemic physiology such as heart rate (HR) and respiration (Liu 2016). While the effects of motion and system drift are well understood and can be adequately separated from the signals of interest, physiological effects are more difficult to deal with (Caballero-Gaudes and Reynolds 2017). The way they lead to cerebral blood flow (CBF) (and fMRI) changes, and covary with electro-cortical activity, is incompletely understood, making removal difficult. Fortunately, recent additions to a large body of prior research is starting to clarify this.

In addition to local CBF increases to local cortical activity mediated by the neurovascular unit, CBF increases may be mediated by various other mechanisms that can affect resistance of the central nervous system (CNS) vasculature (Fig. 1) (Hotta 2016; Lecrux and Hamel 2016), typically in a rather widespread manner. These include the action of circulatory vasoactive agents like CO_2 and catecholamines, as well as neurogenic control of vascular tone of the extracortical arteries from vascular innervation originating from sources outside (“extrinsic”) the CNS (Hamel and Ford-Hutchinson 1985). This extrinsic innervation includes sympathetic, parasympathetic, and somatosensory nerves originating from ganglia of the autonomous nervous system (ANS), such as the superior cervical, otic, sphenopalantine, and trigeminal ganglia. Vascular tone may also be affected by the intrinsic (originating from within the CNS) innervation through fibers originating from basal forebrain (BF), raphe nuclei (RN), and locus coeruleus (LC). These (neuro-) modulatory brain regions can affect CBF in a non-local manner indirectly by modulating cortical activity, and possibly directly through direct neurotransmitter release onto endothelial cells (Lecrux and Hamel 2016). A variety of neurotransmitters and neuropeptides is involved in the neurogenic control of CBF, including noradrenaline, serotonin, glutamate, acetylcholine, and GABA. The relative contribution of these neurotransmitters to CBF regulation is not well known, is animal species and possibly arousal state dependent, and varies across brain regions.

Furthermore, CBF may also be affected through changes in blood pressure effected by changes in heart rate and ejection fraction (Shivkumar and Ardell 2016), or changes in tone of the vasculature outside the CNS. Thus, a complexity of regulatory systems exist that allow for various contributions to the fMRI signal that are widespread and potentially obscure the localized response to electro-cortical activity mediated by the neurovascular unit. Because these contributions may depend on arousal state, their influence in fMRI studies of sleep may be particularly difficult to account for.

Current approaches for distinguishing contributions to fMRI signals

Due to the multitude of potential processes contributing to the fMRI signal, separation of desired and undesired contributions to the fMRI signal is a difficult problem and somewhat

dependent on the goal of the study. If one is specifically interested in local neural activity, one would want to remove all contributions that do not involve the neurovascular unit, including systemic (autonomic) physiology and any direct effects on CBF from the intrinsic vascular innervation. Currently, this question is not fully resolved and still an area of active investigation.

Existing approaches for reducing systemic physiological effects are typically pragmatic and involve regressing out from the fMRI voxel time-series references signal(s) that reflect the effects one may wish to remove, including a global (brain-averaged) signal, signal from a reference region in white matter or cerebrospinal fluid (CSF), or signals that reflect fluctuations in heart rate (Shmueli et al. 2007) and/or respiratory flow rate (respiratory volume per unit time, or RVT) (Birn, Murphy, and Bandettini 2008). The rationale of these approaches is that the contribution of systemic physiology to the fMRI signal depends linearly on the reference signals with gains that are stationary (constant over the experiment). In the following, we will see that this may not be generally true. In addition, there are several other factors that may compromise the effectiveness and appropriateness of this strategy.

One issue is that global systemic effects may covary with neuronal effects (Scholvinck et al. 2010; Turchi et al. 2018), which then get (partially) eliminated with the removal approach. For example, joint changes in cortical excitability (and activity) and systemic physiology may result from changes in arousal state. Alternatively, changes in systemic physiology may be effectuated by neural activity in (sub-) cortical regions (Cechetto 2014; Silvani et al. 2016) (Fig. 2). Depending on the goal of the study, removal of the fMRI correlate with the aforementioned physiological regressors may not be desirable. Furthermore, variations in systemic physiology relevant for the fMRI may not be adequately described by just HR and RVT regressors (van Houdt et al. 2010).

For example, the mechanisms by which fMRI depends on HR and RVT are indirect and not well known. RVT generally assumes a close relationship with arterial CO_2, which then affects BOLD through flow changes mediated by arterial and local (intracortical) vasodilatory mechanisms. The existence of this mechanism has been demonstrated in animals (Atkinson, Anderson, and Sundt 1990; Hoiland et al. 2016), and fMRI based human CO_2 reactivity measurements are consistent with this (Chang and Glover 2009; Liu et al. 2017). However, as will be discussed in the next section, there are alternative ways by which CO_2 (and thus RVT) can affect CBF (and thus fMRI) with potentially different spatio-temporal characteristics. Specifically, O_2- and CO_2-dependent brainstem mechanisms exist that can control cortical vascular tone through extrinsic vascular innervation. A successful removal strategy will need to take the various mechanisms into account as their relative contribution may vary across arousal states.

Potential contribution of vascular innervation to CBF regulation in human

While underappreciated in the fMRI literature, the notion of a neurogenic contribution to CBF regulation through extrinsic and intrinsic vascular innervation (originating from the ANS and within the CNS respectively) is supported by substantial anatomical and functional

evidence. Numerous studies have reported the presence of perivascular nerves supported by various neurotransmitters, including dopamine, serotonin, acetylcholine, and GABA (for review see (Foote and Morrison 1987; Hamel and Ford-Hutchinson 1985; Larsen and Waters 2018).

Functional studies have reported CBF changes in response to stimulation of the intrinsic innervation from various neuromodulatory centers including BF, RN, and LC. Vasoactive responses have been reported (Lecrux and Hamel 2016), sometimes without accompanying changes in electro-cortical activity (e.g., (Underwood et al. 1995)). Using pharmacologic manipulation of cholinergic and serotonergic activity, recent studies have shown changes in fMRI activity patterns (Hahn et al. 2012; Shah et al. 2016). Clearly, CBF changes orchestrated from a coordinating brain region, either with or without changes in cortical activity, complicate the interpretation of the fMRI signal in terms of cortico-cortical communication.

In addition to CBF changes elicited by intrinsic vascular innervation, substantial evidence exists for a contribution of extrinsic innervation originating from sympathetic and parasympathetic systems to blood-flow regulation (Hernandez-Perez, Raichle, and Stone 1975; Boysen, Dragon, and Talman 2009; Heistad, Marcus, and Gross 1978; Talman et al. 2007; Hamner et al. 2010; Zhang et al. 2002; Sandor 1999; ter Laan et al. 2013; Brassard, Tymko, and Ainslie 2017). Importantly, recent work has shown widespread correlation of fMRI with peripheral vascular tone as measured from finger skin (van Houdt et al. 2010; Özbay et al. 2018) using photoplethysmography (Shelley 2007). The fact that finger skin vascular tone is actively regulated by the sympathetic system thus would suggest a sympathetic contribution to fMRI signal. This is relevant for sleep, as sympathetic activity varies with arousal state. In fact, a recent study (Özbay et al. 2019) found joint changes peripheral vascular tone (as measured with photoplethysmography) and widespread fMRI signal to occur with EEG K-complexes during non-REM stage 2 sleep, previously associated with sympathetic activity triggered by sub-cortical arousal (Ackner and Pampiglione 1957). The general conditions under which this occurs, and the associated physiological mechanisms, are not clear due to the complex overlap of brainstem regions that mediate arousal and affect systemic physiology (Silvani et al. 2015; Benarroch 2018) (Fig. 3).

Variation of systemic effects across arousal states

The study of sleep with fMRI is challenging as the contribution of systemic (neurogenic and non-neurogenic) sources to the fMRI signal may vary with arousal state (Fig. 4). Thus, when comparing fMRI activity patterns between arousal states, modeling of systemic contributions requires special attention.

As we have seen above, fMRI may be sensitive to various aspects of autonomic physiology and neurotransmitter activity and both of these are known to vary dramatically during sleep (Benarroch 2018). For example, physiological aspects such as HR, respiration rate, and respiration depth are known to undergo changes during sleep. Their variability in the 0–0.1 Hz frequency band relevant for the fMRI signal typically is relatively high during wake, light sleep, and REM sleep and relatively low during deep sleep (Bonnet and Arand 1997;

Tobaldini et al. 2013; Gutierrez et al. 2016). In addition, known changes in CO_2 reactivity (Meadows et al. 2003; Klingelhöfer 2012) and baroreflex sensitivity during sleep may change the level and way by which HR and respiration affect the fMRI signal during various arousal states (Benarroch 2019; Silvani et al. 2016). For example, the effect of arousal on CBF has been shown to vary with sleep state (Bangash et al. 2008).

Together with the autonomic changes, a major change with arousal state is the influence of the various neurotransmitters that modulate neural activity and affect CBF from brain regions such as BF, LC, and RN. Because of the close integration of these modulatory centers with regions affecting autonomic physiology (Fig. 3), autonomic and modulatory activity often jointly change with arousal state. Generally speaking, aminergic neurotransmitter levels reduce with increasing sleep depth, while REM sleep is associated with strong fluctuations in cholinergic activity (Saper, Scammell, and Lu 2005; Jones in press) (Fig. 4). It is unclear if this cholinergic activity affects CBF in a manner proportional to the strongly varying neuronal activity levels associated with this sleep stage. Either way, like the autonomic changes, these modulatory influences are likely to similarly confound the interpretation of fMRI correlations patterns in terms of cortico-cortical communication.

Lastly, as indicated above, the prevalence of sympathetic activity is highly dependent on arousal state (Fig. 4). During wakefulness, sympathetic activity varies with the level of alertness and attention and episodic increases can be elicited by a wide range of physiological, sensory, and cognitive stimuli. In fact, widespread fMRI signal changes have been observed with momentary increases in pupil diameter, associated with sympathetic activation during alerting stimuli (Yellin, Berkovich-Ohana, and Malach 2015; Schneider et al. 2016). Changes in sympathetic activity, indexed by skin conductance, have also been observed with arousal-inducing stimulation and tied to fMRI signal changes (Fan et al. 2012; Henderson et al. 2012). Consistent with this are the large-scale changes in fMRI signal seen with spontaneous eye closure (Chang et al. 2016; Wang et al. 2016). However, the mechanisms underlying the covariation between arousal, sympathetic activity, and fMRI signal under these conditions is not clear and may include local neurovascular control as well as involving effects from intrinsic and extrinsic vascular innervation.

During stage 1 and 2 non-REM sleep, a generally low sympathetic tone and high parasympathetic tone is punctuated by brief (seconds long) sympathetic increases associated with the occurrence of EEG K-complexes (Halász 1993; Colrain 2005). In part, these increases are thought to be part of a so-called “fight or flight” or “orienting” response (Johnson and Lubin 1967; Pampiglione and Ackner 1958). With increasing sleep depth, the rate of these episodic sympathetic surges decreases and is near zero during slow-wave sleep. During REM sleep, the typically strong variations in sympathetic activity that occur may be in part associated with both cortical activity and the strong heart rate and respiratory variations occurring in this sleep stage (Aserinsky and Kleitman 1953; Oudiette et al. 2018).

Summarized, the contributions from autonomic physiology to the fMRI signal can vary across arousal states and affect its relationship with (electro-) physiological regressors. Any strategy aimed at separating these effects from fMRI signal reflecting local cortical processing and cortico-cortical communication will need to take this into account, and as of

yet have not been developed. Incomplete removal makes comparison of fMRI activity patterns across arousal state difficult and prone to misinterpretation.

Interrelationships between various brain and physiological signals

The dependence of the dynamics of the systemic physiology on arousal state can in part be explained by the strong anatomical overlap between the system components that mediate arousal, modulate neural activity, and regulate systemic physiology (Benarroch 2018; Silvani et al. 2015) (Fig. 2). For example, the various neuronal cell groups in LC have been shown to have the capability to jointly modulate breathing, arousal state, and neural activity subserving sensory processing (Yackle et al. 2017). Furthermore, many of the interactions between the various system components can vary in direction and strength, complicating causal interpretation and the understanding of their effect on fMRI.

For example, sympathetic activity is frequently generated in close association with respiratory activity (Moreira and Mulkey 2015; Guyenet and Bayliss 2015). Increases in sympathetic activity are typically associated with a biphasic heart rate change, but this is dependent on parasympathetic tone (which is in turn dependent on arousal state). As a result, the relationship between physiological parameters such as HR, RVT, end-tidal CO_2, blood pressure, pupil diameter, and peripheral vascular tone is generally arousal state dependent, as is their relationship with the fMRI signal (Chang et al. 2018). This complicates the ability to isolate specifically the component of fMRI signal relating to local neurovascular coupling.

The overlap between the neural substrates controlling arousal state and systemic physiology also results in a possible covariation between the electrophysiological hallmarks of arousal and alertness on one hand, and systemic physiology one the other. For example, K-complexes, signatures of subcortical arousal, are associated with sympathetic activity and respiratory changes (Roth, Shaw, and Green 1956; Poole 1961), whereas the alertness and arousal changes associated with EEG alpha band activity may also modulate sympathetic activity. In fact, recent work reported a covariation between EEG alpha band activity, RVT, and the fMRI signal (Yuan et al. 2013). The pontine regions that mediate ponto-geniculo-occipital waves during phasic REM sleep may also be responsible for the strong respiratory variations seen during this sleep stage (Krieger et al. 1990; Sforza et al. 1990). Taken together, these possible associations between the electrophysiological signals and systemic physiology indicate that care has to be taken when interpreting EEG-fMRI correlations as reflecting local cortical processing (Jahnke et al. 2012; Laufs et al. 2006; Dang-Vu et al. 2008), as they in part may be mediated by secondary, non-neuronal mechanisms.

Future directions, outstanding questions, and current recommendations

One of the key areas needing to be addressed by future research is the mechanistic understanding of how the changes in autonomic physiology during sleep affect the fMRI signal. Current approaches for removing systemic physiological effects typically use regressors based on physiological parameters such as HR and RVT, fMRI signals from reference regions in the brain (e.g., white matter, CSF, or global brain signal), or independent components based on the spatio-temporal properties of the components

(Glasser et al. 2018). However, because of the poorly understood nature of these signal contributions, and potential non-stationarity and non-linearity between physiological regressors and the fMRI signal, these approaches are unlikely to be adequate across the varying physiological states that occur during the sleep-wake cycle.

For example, a global brain signal regressor may not purely reflect systemic physiology but also contain a contribution from cortical activity, and this contribution may vary across arousal states. As a result, its removal may have varying effectivity (and accuracy) across arousal states, complicating any inference about arousal state dependent changes in neural activity patterns. Similarly, an incomplete mechanistic understanding of the effects of systemic physiology on the fMRI signal compromises the use of physiological regressors. In this regard, an important question is how vascular CO_2 changes lead to changes in CBF. To what extent are CBF changes mediated by local (intracortical) CO_2 changes versus central chemo-sensing and neurogenic control? What are the spatio-temporal characteristics of each of these mechanisms? How do they change across the various sleep stages? As of yet, these questions have not been fully answered.

A second area of future research concerns the general question to what extent can fMRI signal patterns be interpreted as reflecting cortico-cortical communication in so called “functional networks.” During both sleep and wake, rapid fluctuations in blood flow may occur that are mediated by intrinsic and extrinsic vascular innervation and reflect changes in systemic physiology and influence from neuromodulatory centers such as LC, RN, and BF (McGinley et al. 2015; Lecrux and Hamel 2016). These do not reflect cortico-cortical communication but can affect interpretation of the fMRI signal in terms of network function. This has special relevance for sleep studies, as these effects will strongly depend on arousal state. For example, a popular method to study the latter is to determine the fMRI signal correlation between two brain regions and take this as a measure of their “functional connectivity” (van den Heuvel and Hulshoff Pol 2010). Obviously, the presence of large scale autonomic or neuromodulatory effects will affect this measure, and because these effects vary with sleep stage, this will make comparison of functional connectivity pattern across sleep states difficult. It may be possible to use fMRI signals from neuromodulatory regions together with physiological regressors to isolate signals that specifically reflect local cortical activity or cortico-cortical interactions, but this will require additional research.

Clearly, a more mechanistic understanding is needed. Nonetheless, current recommendations are needed for the sleep neuroimager interested in local neural activity. It is recommended that sleep fMRI studies should at a minimum use nuisance regressors that model physiological noise (Horovitz et al. 2009; Shmueli et al. 2007). These regressors should include signals reflecting cardiac and respiratory cycles (Glover, Li, and Ress 2000), their rates, as well as respiratory depth (Birn, Murphy, and Bandettini 2008). In place of cardiac rate, peripheral vascular tone as measured by finger photoplethysmography may be used because both of these measures reflect sympathetic activation (Özbay et al. 2018). Alternatively, use of a whole-brain nuisance regressor may be required. The comparison of multiple preprocessing approaches may also be useful for testing for the robustness of an effect purported to be related to local neural activity.

Conclusion

FMRI has unique potential to study changes in cortical activity and cortico-cortical functional connectivity over the sleep-wake cycle. As such, it may inform about the mechanistic underpinning of sleep regulation, the nature and relevance of spontaneous activity patterns to specific sleep states and consciousness levels, and changes in neuromodulatory activity with sleep states. However, there are various overlapping signal sources whose contributions as of yet are poorly understood and difficult to eliminate. Ongoing research is starting to catalogue and reveal these additional sources and their mechanistic underpinnings, which is helping efforts to differentiate them.

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Highlights

- fMRI is sensitive to contributions from variations in autonomic physiology
- These affect fMRI through changes in vascular resistance and blood pressure
- The neural substrates controlling autonomic physiology and arousal overlap strongly
- This makes the analysis and interpretation of fMRI studies of sleep particularly challenging
- Developing improved mechanistic understanding of systemic effects on fMRI is critical

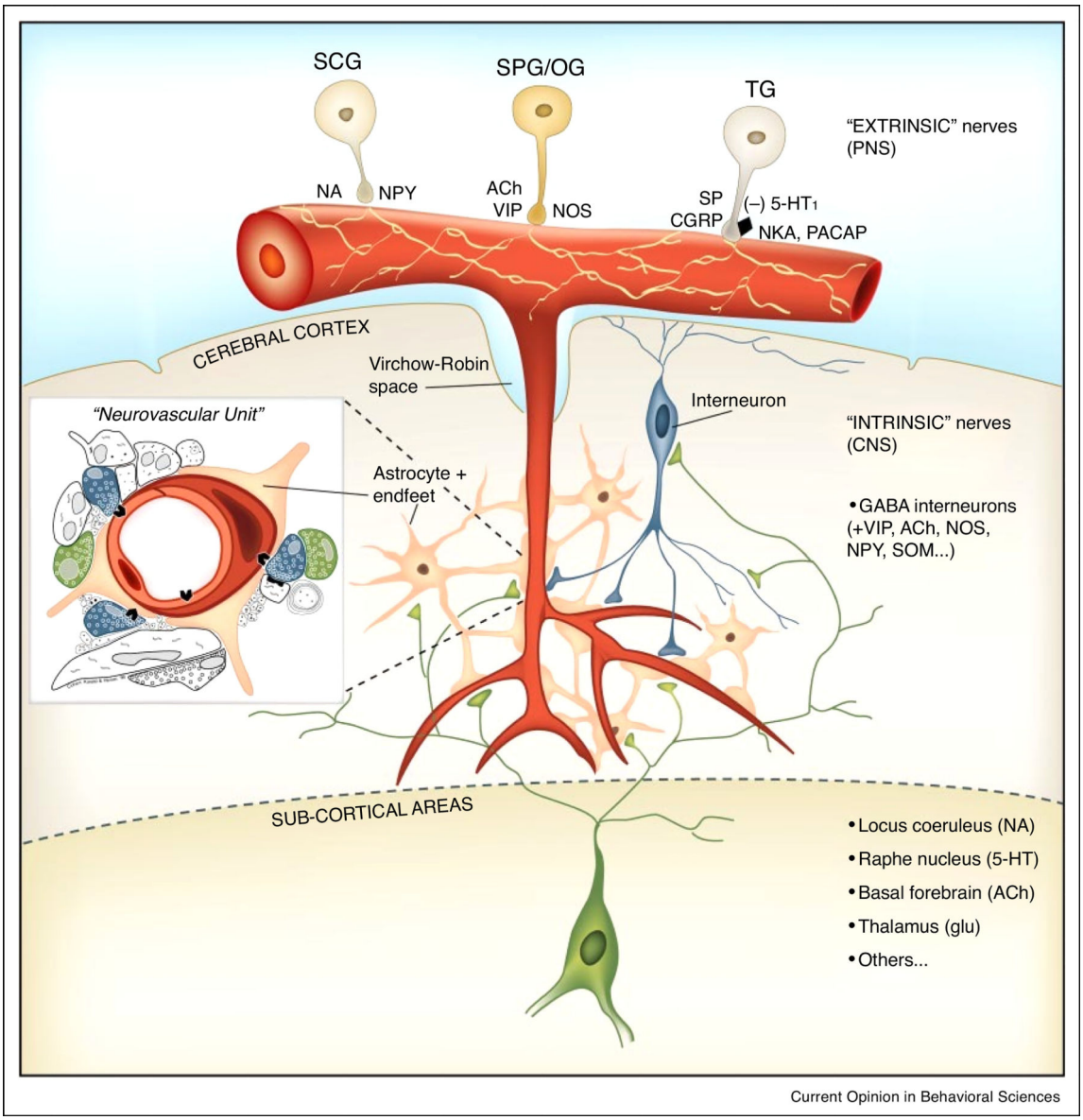

Fig. 1.

Neurogenic control of CBF involving extrinsic and intrinsic innervation (reproduced from (Hamel 2006)). In addition to control of intraparenchymal vascular resistance by an intraparenchymal neurovascular unit containing a neuron-glia network, two other mechanisms of CBF control may exist that rely on vascular innervation from extra-parenchymal sources. The extrinsic innervation involves extra-parenchymal vasculature and is controlled from ganglia of the peripheral nervous system (PNS), including superior cervical, superior palantine, otic, and trigeminal ganglia. The intrinsic innervation involves the parenchymal vasculature and Is controlled from sub-cortical (neuro-) modulatory regions.

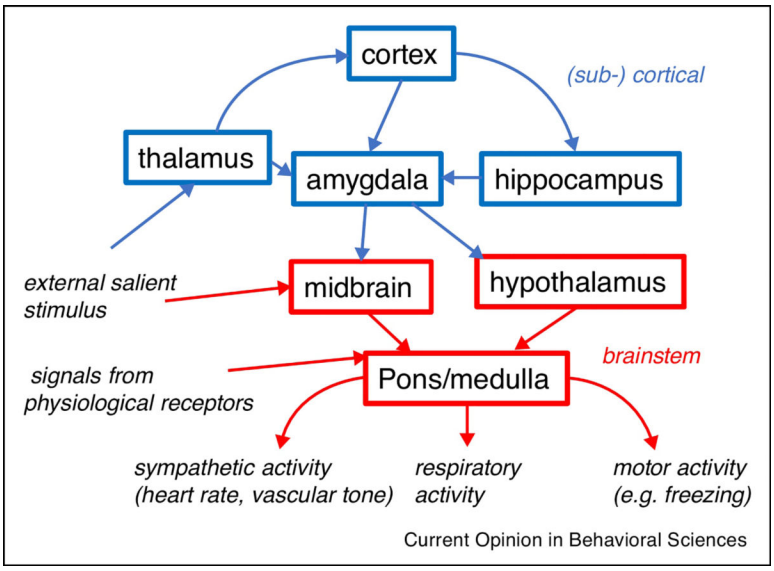

Fig. 2.

Pathways involved in the regulation of systemic physiology (modified from (Dampney 2016)). Various sensory and physiological stimuli can affect cardiovascular and respiratory activity through pathways that can include or bypass (sub-) cortical regions. During sleep, sensory stimuli and signals from receptors sensing various physiological parameters (e.g., arterial pressure, O_2 and CO_2 concentration) typically affect systemic physiology without involving the (sub-) cortex.

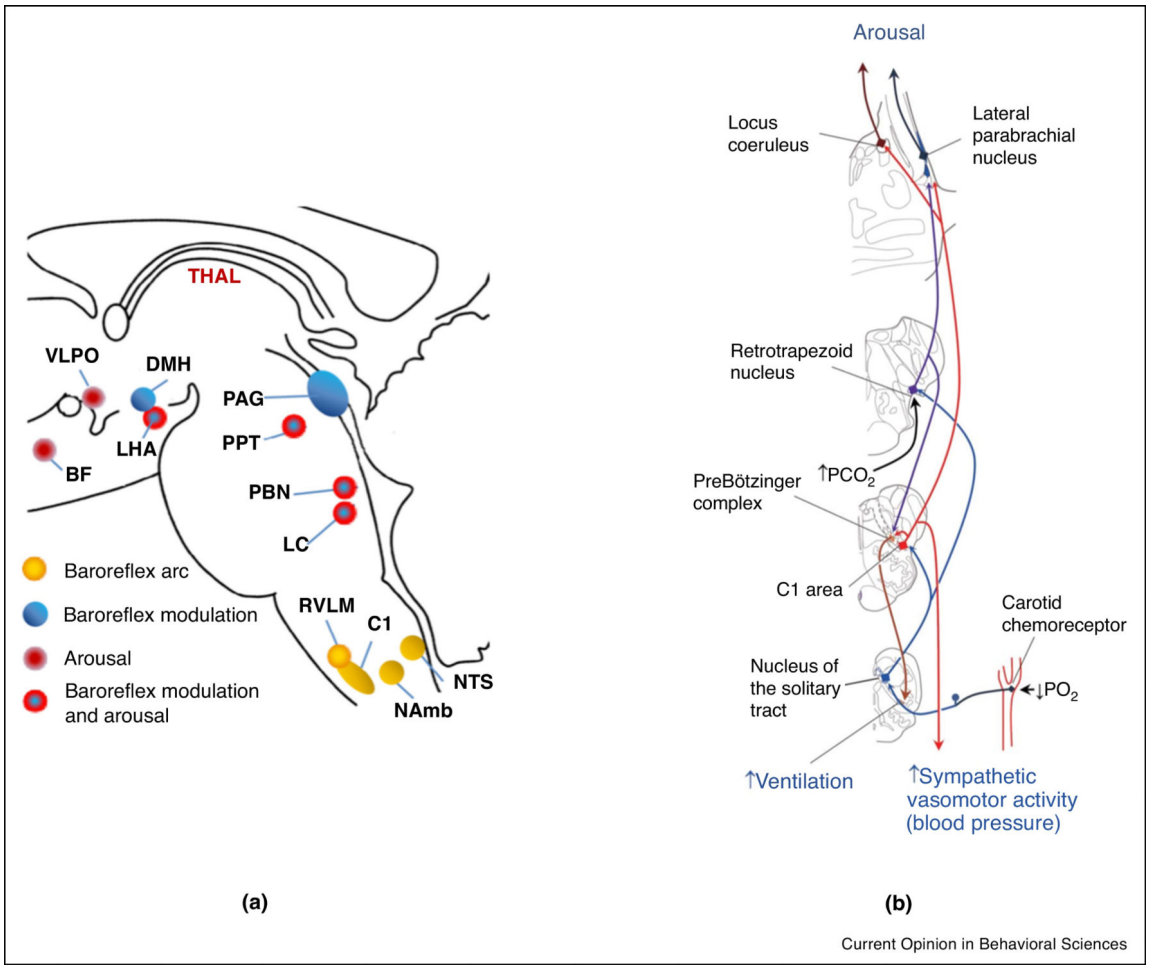

Fig. 3.

Dual role of brain areas in both arousal and autonomic physiology.

a. Joint effects on baroreflex modulation and arousal (reproduced from (Silvani et al. 2015)). In lower brain and brainstem, Locus Coeruleus (LC), Parabrachial Nucleus, Pendunculopontine Tegmental Nucleus (PPT), Raphe Ncleus (RN), and Lateral Hypothalamic Area (LHA) all have dual roles in both arousal and baroreflex modulation. Other relevant regions: Ventrolateral Preoptic Nucleus (VLPO), Basal Forebrain (BF), Dorsomedial Nucleus of the Hypothalamus (DMH), Lateral Hypothalamic Area (LHA), Periaqueductal Grey (PAG), Rostral Ventrolateral Medulla (RVLM), Cell group of adrenergic respiratory neurons in RVLM (C1), Nucleus Ambiguous (NAmb), Nucleus Tractur Solitarius (NTS).

b. Example of joint arousal and systemic (cardiovascular and respiratory) response to hypercapnic or hypoxic stimuli (reproduced from (Benarroch 2018)).

	Alert Wake	N1/2	N3	REM
Acetylcholine	+	-	--	+
Norepinephrine Serotonin	+	-	--	---
Sympathetic/ Parasympathetic balance	symp	symp/para	para	symp
RVT variability, HR variability (<0.1HZ)	+	+	-	++
Head motion	+	+	-	+/-**
Mean CBF	+	+/-*	-	+
FMRI GS	+	++	-	++

*: Cerebral blood flow might increase and also decrease during light sleep.
**: Skeletal muscles are paralyzed during REM, but motion may result from respiratory fluctuations

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Fig. 4.

Physiological changes across arousal states. Towards increasing sleep depth, there is a reduction in neurotransmitter activity from modulatory brain centers, an increased parasympathetic dominance, a reduction in head motion, and a reduction in baseline CBF. During N1/N2 sleep, there is an increase in fMRI global signal due to fluctuations in the balance between parasympathetic and sympathetic activity. FMRI global signal is also high during REM sleep, likely because of strong fluctuations in neural activity, as well as high respiratory variability.