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Review article

Deconstructing arousal into wakeful, autonomic and affective varieties

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ABSTRACT

Arousal plays a central role in a wide variety of phenomena, including wakefulness, autonomic function, affect and emotion. Despite its importance, it remains unclear as to how the neural mechanisms for arousal are organized across them. In this article, we review neuroscience findings for three of the most common origins of arousal: wakeful arousal, autonomic arousal, and affective arousal. Our review makes two overarching points. First, research conducted primarily in non-human animals underscores the importance of several subcortical nuclei that contribute to various sources of arousal, motivating the need for an integrative framework. Thus, we outline an integrative neural reference space as a key first step in developing a more systematic understanding of central nervous system contributions to arousal. Second, there is a translational gap between research on non-human animals, which emphasizes subcortical nuclei, and research on humans using non-invasive neuroimaging techniques, which focuses more on gross anatomical characterizations of cortical (e.g. network architectures including the default mode network) and subcortical structures. We forecast the importance of high-field neuroimaging in bridging this gap to examine how the various networks within the neural reference space for arousal operate across varieties of arousal-related phenomena.

Arousal involves one of the largest and most complex sets of biological changes in the body. It is linked to major daily oscillations in the environment, including light and temperature, and corresponding behavioral activities [e.g. when to be awake, pay attention, search for food, avoid predators, rest and digest, 1]. Despite its centrality to surviving and thriving, research has yet to produce an integrative and generalizable neural model of arousal, for at least two reasons.

First, arousal is a heterogeneous construct [2]. When studying wakeful arousal, researchers focus on the brain regions that are critical for transitioning to wakefulness from sleep (and vice versa), and often use electroencephalography (EEG) de-synchronization as a biomarker of wakefulness [3]. When studying autonomic arousal, the focus is on brain control of (and responses to) peripheral autonomic responses, including changes in heart rate, pupil dilation, and electrodermal responses [4,5]. And in affective arousal, researchers typically study the state of engagement with salient or evocative stimuli [6], often measured through self-reports of felt arousal [e.g. 2,7,8,9].

A second reason we are currently without a general neural model of arousal can be found in the challenge of identifying homologies across species. Research in non-human animals has developed a rich and detailed model of brainstem thalamic and hypothalamic nuclei involved in wakeful arousal, but it remains unclear how this model relates to autonomic and affective arousal. The location of these nuclei is guided by the use of a stereotaxic framework [10, e.g., 11] in part to facilitate lesion and intra-cortical electrode positioning [e.g. 12]; the accuracy of these procedures can be corroborated with histological staining after sacrificing the animals. In contrast, conventional neuroimaging studies in humans have focused on the cortical and larger subcortical correlates of arousal, with less attention paid to smaller subcortical nuclei that are more difficult to localize in humans, such as the small yet complex brainstem and diencephalic structures that are the focus of studies in non-human animals. Most of these nuclei are not clearly visible with

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conventional neuroimaging techniques used on (living) humans. The resolution and contrast needed to resolve the location and build preliminary stereotaxic atlases of these key nuclei are just now being developed using high and ultra-high (e.g. 7 Tesla) field MRI scanners [13–22].

In this paper, we briefly review the neuroanatomic substrates underlying wakeful, autonomic, and affective arousal to reveal their overlapping neural architectures. On the basis of research in non-human animals and humans, we propose a distributed neural reference space for arousal whose nodes combine in different ways to create varieties of arousal. We highlight the importance of recently established high-resolution neuroimaging techniques as a methodology for conducting studies to better examine generalization and differentiation across formulations of arousal and across species. Our review emphasizes the brain regions that prior work suggests are important for arousal, but this does not imply that these areas are uniquely involved in arousal [e.g., 23]. In other words, we describe findings showing that activity in areas such as the amygdala, the cingulate cortex, and the insula, along with the many other areas are all associated with arousal, but these areas may also play a role in other mental phenomena that are not the focus of this article.

1. The neuroanatomic substrate for arousal: findings from studies of non-human animals

A range of findings in non-human animals suggest that there is overlap between neural pathways involved in wakeful, autonomic, and affect arousal. Below, we briefly review some of the main areas involved with respect to wakeful arousal and further note their involvement in autonomic and affective arousal varieties.

1.1. Wakefulness

In the past 68+ years, several brainstem nuclei have been implicated in the maintenance of wakefulness (typically measured as widespread cortical EEG de-synchronization) based on invasive functional studies involving stimulation and recording from neurons directly, lesion studies, and on the basis of whether a nucleus has the ability to widely modulate activity throughout the cerebral cortex. Table 1 lists the nuclei that have been implicated in wakeful arousal. These nuclei have widespread anatomical connections to the cerebral cortex, and/or project to the reticular and intralaminar thalamic nuclei, the hypothalamus, or the basal forebrain, all of which project widely to the cerebral cortex [24].

The search for the key subcortical regions involved in arousal began with the observation that widespread cortical EEG de-synchronization differentiated wakefulness from sleep [25], which subsequently was used as a neural signature for the awake state [3]. Much of the initial work focused on the reticular formation, a collection of nuclei in the brainstem that extends longitudinally from the medulla through the pons to the midbrain, and on nuclei surrounding the reticular formation. Landmark work in the cat by Moruzzi and Magoun [26] found that stimulating nuclei of the meso-pontine (i.e. at the midbrain/pons junction) reticular formation elicited wakefulness, from which the term “ascending reticular activating system” was coined. Consistent with this notion, it was later found that some of the nuclei spanning through the pons and medulla of the reticular formation have the anatomical prerequisites to widely modulate the cerebral cortex via afferents to the thalamus and/or upper brainstem nuclei [see Table 1, 24].

It is now known, however, that many brainstem nuclei surrounding the reticular formation, rather than the reticular formation itself, are more central for generating the widespread modulation of cortical activity associated with the EEG wakefulness state [24,27–29]. The subsequently proposed “diffuse modulatory system” [29] underlying cortical arousal comprises several distinct modulators that are each capable of exerting their influence upon a diffuse set of regions (i.e. modulate neuronal cell properties, such as excitability). These putative neuro-modulators of wakeful arousal are cholinergic and monoaminergic (i.e. serotoninergic, norepinephrinergic and dopaminergic) neuronal cell groups in the brainstem, histaminergic and orexinergic hypothalamic nuclei, and cholinergic nuclei of the basal forebrain [28,30–32] (see Table 1 for a detailed list of arousal neuro-modulators proposed by the non-human animal literature). Note, that today the reticular formation is recognized mainly as a coordination network of brainstem nuclei (for autonomic, postural, oculomotor function) and is not the diffuse modulatory system originally proposed [29].

1.2. Autonomic and affective arousal

Accumulating research on the neural basis of arousal suggests that there is substantial overlap between the brain systems that control wakefulness and those that control autonomic function and affective arousal. The diffuse modulatory system for wakefulness encompasses nuclei that have also been implicated in autonomic and affective arousal [11,24,28,33]. One example is the parabrachial nucleus. Extending beyond the initial focus on cholinergic and monoamingergic nuclei, Fuller et al. [11] found that glutamatergic brainstem cell populations in the parabrachial nuclear complex (and adjacent preoptic area) were also necessary to maintain a waking state in rodents [Table 1, also see 34]. Notably, the parabrachial complex is also important for autonomic function [29,35] and phenomena that involve intense affective arousal such as pain [36,37] and affect [38,39]. For example, in rodents, a large proportion of lamina 1 spinal neurons that are important for pain processing project to the lateral parabrachial complex [40]. From an anatomical perspective, it is reasonable that the parabrachial complex contributes to various types of arousal: It is a major integrative center that receives interoceptive input from the solitary nucleus and intermediate reticular zone, and operates as an interface between these structures and the limbic forebrain [amygdala, hypothalamus, anterior insula, 41]. Integration across varieties of arousal is also present several other nuclei (Table 1), such as the periaqueductal gray [29,35,42,43] and ventral tegmental area [12,44].

Moreover, several limbic structures influence brainstem nuclei involved in wakefulness and sleep [45–47]. For example, the amygdala, while known for its role in affective behaviors [48–50], also plays a key role in the rapid-eye-movement (REM) sleep circuit, and is involved in sleep disorders such as narcolepsy and cataplexy [46,51]. Limbic areas that are typically observed in studies of affective processing [e.g. 31,52,53,54], are also known to influence autonomic function via the hypothalamic-pituitary-adrenocortical (HPA) axis [55]. Research on physical and psychological stressors has implicated multiple brain regions in controlling autonomic arousal, including limbic prefrontal cortex, amygdala, hippocampus (and the ventral subiculum in particular), the bed nucleus of the stria terminalis, the hypothalamus, and multiple brainstem nuclei (see Table 2 for a list). Recent work has utilized optogenetic and pharmacogenetic manipulations to link specific amygdala circuits to affective arousal behaviors [e.g. freezing, anxiety, feeding, and reinforcement learning, as reviewed in, 50].

As we will see in the next section, the overlap in neural pathways involved in between wakeful, autonomic, and affect arousal is also apparent in brain imaging studies of humans.

2. The neuroanatomic substrate for arousal: findings from neuroimaging studies

Studying the functionality of these key brainstem nuclei in humans has been difficult using conventional fMRI. Many of these nuclei are small and in close proximity to other nuclei, making partial volume effects a major limitation. Scanning artifacts, too, can be a larger contributor to noise in brainstem areas. Perhaps because of these concerns, research on the neural basis of arousal in humans has focused mainly on cortical areas and gross subcortical structures. As reviewed below,

Table 1
Brain regions proposed to be involved in wakeful arousal (the Ascending[a] Arousal System[b]).

Brain region involved in maintaing wakefulness	Main neurotransmitter/ neuromodulator Involved	Name originally given to the arousal system	Other Function
Brainstem			
Mesopontine reticular formation nuclei [26]: - Mesencephalic reticular formation - Cuneiform nucleus - Pontine reticular nucleus, oral part	Glutamate	Ascending reticular activating system	Coordination of autonomic/motor/sensory brainstem nuclei [29]
Pontomedullary reticular formation nuclei [24]: - Pontine reticular nucleus, caudal part - Gigantocellular reticular nucleus - Parvicellular reticular nucleus - Subnucleus reticularis dorsalis	Serotonin, Adrenaline, Norepinephrine	Ascending reticular activating system	Coordination of autonomic/motor/sensory brainstem nuclei [29]
Mesopontine tegmental nuclei [24,27,28]: - Pedunculotegmental nucleus - Laterodorsal tegmental nucleus	Acetylcholine	Diffuse neuromodulatory system	Locomotor, Limbic [29]
Raphe nuclei [24,27,28]: - Median raphe - Dorsal raphe - Raphe pallidus - Raphe obscurus	Serotonin	Diffuse neuromodulatory system	Nociception, Limbic, Temperature regulation, Blood pressure control, Memory, Motor [29]
Locus coeruleus [24,27,28]	Norepinephrine	Diffuse neuromodulatory system	Autonomic, Attention, Memory, Motivation [29]
Ventral tegmental area [12,24,44]	Dopamine	Diffuse neuromodulatory system	Attention, Memory, Reward, Drug abuse, Motivation [29]
Parabrachial nuclei [11,33,27,28]	Glutamate	–	Autonomic, Limbic, Viscerosensory [29]
Subcoeruleus area [11,28]	Glutamate	–	Limbic, Motor [29]
Periaqueductal gray, ventrolateral part [24,28]	Dopamine	–	Autonomic, Limbic [29]
Solitary nucleus [24]	Glutamate	–	Viscerosensory, Autonomic [29]
Hypothalamus			
- Tuberomamillary nucleus [27,28]	Histamine	–	Limbic, Learning, Memory, Temperature regulation, Endocrine homeostasis [150]
- Lateral hypothalamus [27,28]	Orexin	–	Feeding behavior, Temperature regulation, Nociception, Reward [151]
Thalamus			
- Thalamic reticular nuclei [24]	GABA	–	Modulation of thalamic nuclei [152]
- Intralaminar thalamic nuclei [24] (centromedian, parafascicular, centrolateral)	Glutamate	–	Nociception, Motor [153]
Basal forebrain			
- Nucleus accumbens, nucleus basalis, diagonal band of Broca [24,27]	Acetylcholine	–	Memory, Attention [154]

[a] "Ascending" refers to the fact that several pathways of this system involve ascending fibers from the brainstem, hypothalamus, thalamus and basal forebrain to the cortex.
[b] Note that we only list brain regions that are thought to directly increase arousal (e.g. level of wakefulness, responsiveness to stimuli). In addition, arousal could also be increased by inhibiting sleep promoting brainstem (e.g lateral pontine tegmentum) and hypothalamic (ventrolateral preoptic nucleus) nuclei. For a review of sleep promoting regions and their involvement in sleep state switching see [28].

neuroimaging studies of humans suggest that areas of the default mode network (discussed below) and limbic areas participating in a "salience network" play a role in wakeful, autonomic, and affective arousal (Table 2). A handful of more recent studies have also begun to replicate findings from studies of non-human animals (Table 1) showing the importance of brainstem nuclei, thalamus, hypothalamus, and basal forebrain structures to arousal.

2.1. Wakeful arousal

Wakefulness has primarily been examined using a combination of EEG coupled with MRI or PET techniques. Findings from these studies highlight the importance of the thalamus but also wide-spread changes in the engagement and functional architecture of large-scale cortical networks, such as the default mode network [DMN, which includes prominent nodes in the precuneus and the anterior medial prefrontal cortex, among other areas, 56,57]. Using a behavioral measure of decreasing wakefulness based on eyelid closing and EEG, Chang et al. [58] found that in non-human primates, decreased wakefulness was associated with a combination of increased thalamic activity and reduced cortical activity with particularly reliable decreases in the DMN. Other studies examined how functional connectivity (i.e. correlations in functional activity between brain regions over time) change during sleep v. wakefulness. In humans, functional connectivity between the thalamus and the DMN was reduced during sleep [59]. In a large sample study examining a combination of EEG and fMRI in humans [60], reduced connectivity was observed during sleep among nodes in the DMN [also see, 61], and also the frontoparietal network. Using a combination of PET-fMRI and anesthesia-induced unconsciousness, glucose metabolism and cerebral blood flow significantly decreased in DMN but also frontoparietal networks in unconscious v. awake states [62]. DMN areas also showed reduced functional connectivity with the thalamus during unconsciousness [62].

The involvement of cortical areas in wakeful arousal in humans is mainly based on correlational evidence from neuroimaging studies. It is important to note that in studies of comatose patients, brainstem lesions (rather than more diffuse cortical damage) seems to be the necessary component for producing complete loss of wakefulness at least in comatose states [63]. Nevertheless, consistent across the studies reviewed above is the involvement of DMN and DMN-thalamus connectivity during arousal, and potentially other large-scale functional networks like the frontoparietal network. Few neuroimaging studies have examined how these cortically oriented networks relate with the small brainstem nuclei that have been the focus of non-human animals with respect to sleep and wakefulness. However, at least in resting fMRI, some emerging work is examining how brainstem nuclei functionally

Table 2
Integrative reference neural space of arousal.

Brain region	Acronym	W.A.	Au.A.	Aff.A.
Brainstem:				
mesencephalic reticular nucleus	MRN			
cuneiform nucleus	CUN			
pontine reticular nucleus, caudal part	PRNc			
gigantocellular reticular nucleus	GRN			
parvicellular reticular nucleus	PARN			
medullary reticular nucleus, dorsal part	MDRNd			
pedunculopontine ("pedunculotegmental") nucleus	PPN			
laterodorsal tegmental nucleus	LDT			
superior central nucleus ("median") raphé, lateral part	CSl			
superior central nucleus ("median") raphé, medial part	CSm			
dorsal nucleus raphé	DR			
nucleus raphé pallidus	RPA			
nucleus raphé obscurus	RO			
locus coeruleus	LC			
ventral tegmental area	VTA			
parabrachial nucleus, ventral lateral part	PBlv			
parabrachial nucleus, external medial part	PBme			
subcoeruleus nucleus	SLC			
periaqueductal gray, ventrolateral division	PAGvl			
nucleus of the solitary tract, central part	NTSce			
nucleus of the solitary tract, lateral part	NTSl			
nucleus of the solitary tract, medial part	NTSm			
Hypothalamus:				
tuberomammillary nucleus, dorsal part	TMd			
tuberomammillary nucleus, ventral part	TMv			
lateral hypothalamic area	LHA			
Thalamus:				
reticular nucleus	RT			
intralaminar nuclei	ILM			
Basal forebrain:				
nucleus accumbens	ACB			
substantia innominata	SI			
diagonal band of Broca	db			
Other subcortical areas:				
basolateral nucleus amygdala, anterior part	BLAa			
basolateral nucleus amygdala, posterior part	BLAp			
basomedial nucleus amygdala, anterior part	BMAa			
basomedial nucleus amygdala, posterior part	BMAp			
central nucleus amygdala, medial part	CEAm	*		
central nucleus amygdala, lateral part	CEAl	*		
medial nucleus amygdala, anterodorsal part	MEAad			
medial nucleus amygdala, anteroventral part	MEAav			
field CA1 hippocampus	CA1			
field CA2 hippocampus	CA2			
field CA3 hippocampus	CA3			
Cortical areas:				
entorhinal area, medial part, ventral zone	ENTmv			
piriform area	PIR			
agranular insular area, ventral part	AIv			
anterior cingulate area, dorsal part	ACAd			
anterior cingulate area, ventral part	ACAv			
infralimbic area	ILA			
prelimbic area	PL			
primary motor area	MOp			
secondary motor areas	MOs			
posterior cingulate cortex	PCC			
precuneus	PCUN			
medial prefrontal cortex	mPFC			

Note: The table lists a set of neural nodes that have been generally implicated in wakeful arousal (W.A.), autonomic arousal (Au.A.), and affective arousal. (Aff. A.), as pooled across several references [23,24,27–29,35,49,50,55,71,77,149–151,155–163]. We note that the table is primarily a schematic representation of an integrative neural reference space for arousal. Fig. 1 provides a graph representation of the above set of regions to illustrate how nodes may form functional networks that give rise to different varieties of arousal. Much work remains to be done to determine the precise role of many of these nodes across varieties of arousal. *For example, the amygdala is involved in sleep (REM sleep atonia), yet not strictly in promoting and maintaining wakefulness.

integrate with large-scale networks. For example, using seed based connectivity, seeds placed in areas of the brainstem that correspond with portions of the raphe nuclei show functional connectivity with the DMN [64]. Of note, the so-called "salience" network, or limbic regions [which includes the anterior cingulate cortex and insula, and amygdala, among other regions, 65], also shows functional connectivity with portions of the thalamus and brain stem areas. These functional connectivity findings parallel structural connections with areas involved in wakeful arousal and autonomic function including the hypothalamus, thalamus, and brainstem nuclei [66,67].

2.2. Autonomic arousal

As in the research on non-human animals, the neural basis of autonomic nervous system (ANS) arousal [i.e., increases in heart rate, electrodermal response, [68,69,70] suggests that there is substantial overlap between the brain systems that control wakefulness and those that control ANS arousal. Beissner and colleagues [71] conducted a comprehensive meta-analysis of dozens of functional neuroimaging studies that examine the relationship between brain activity and autonomic changes. These studies typically induce changes in autonomic function using stress inducing tasks, such as physical challenge [e.g. squeezing a pressure bulb, 72,73] and mental challenge [e.g. cognitive and social performance tasks completed under pressure, 72,74]. The primary areas that reliably relate with autonomic change include nodes in the DMN (the anterior medial prefrontal cortex, medial orbitofrontal cortex, precuneus, angular gyrus), nodes of the salience network (the insula and cingulate cortex), and subcortically, the amygdala, hippocampus, thalamus, and brainstem areas near the PAG.

Recent work on systems-level characterization of cardiovascular arousal and skin conductance in a social stress task has shown that they have: (a) distributed neurophysiological bases that include DMN areas (ventrolateral and medial prefrontal cortex, angular gyrus), limbic areas (insula and cingulate cortex), and subcortical areas (including hippocampus, thalamus, and cerebellum); (b) that across physiological channels, these bases overlap in DMN areas (ventromedial prefrontal cortex, lateral orbitofrontal cortex, temporoparietal junction, among others) and also the thalamus and brainstem areas (covering the locus coeruleus and PAG); and (c) also differentiable bases, indicating that different autonomic output channels reflect activation of different central processes [75]. Activity in cingulate and insular cortices is also often associated with interoception, which involves the awareness of changes in ANS [23,73,76–78]. Damage to some of these areas, such as the orbitofrontal/ventromedial prefrontal cortex and amygdala can cause impairments in autonomic response [e.g. 79,80–82]. Recent connectivity work using resting fMRI data has shown that brainstem nuclei participate in networks shared with limbic and paralimbic structures [23,64].

2.3. Affective arousal

Affective arousal, which is also associated with interoception [83], is considered a property of consciousness that accompanies every waking moment of life [84]. The subjective experience of arousal is experimentally manipulated by presenting participants with evocative stimuli [e.g. images of spiders, victims of injury, etc. that are well-normed for how much subjective arousal and pleasantness/unpleasantness is experienced upon view them, 85] and comparing their neural response to when they are presented with neutral stimuli [7,86–88]. These studies routinely implicate an ensemble of cortical and subcortical areas that have also been implicated in wakefulness and autonomic function. As shown by meta-analyses of now hundreds of such studies, frequently activated brain regions include portions of the default mode network (e.g. anterior medial prefrontal cortex, portions of ventrolateral prefrontal cortex) and the salience network (e.g. the anterior cingulate cortex, insula, amygdala, hypothalamus) [see meta-analyses by, 88,89], as well as brainstem regions [90,91]. Using more fine-grained techniques, high resolution neuroimaging has specifically confirmed the involvement of the periaqueductal gray [92], and invasive intracranial recordings [93] and stimulation studies in humans [94] implicate the subthalamic nucleus [95].

Many of the salience network areas are differentially engaged depending on the sensory modality driving the affective experience [96]. For example, the anterior cingulate is more reliably engaged by visual and somatosensory affect inductions, different induction modalities appear to target different portions of the insula, and the amygdala, too, shows greater reliability of activation depending on the sensory modality [96,97]. The distribution of activity within the insula and cingulate cortices appears to carry a combination of modality general and modality specific representations with respect to affective arousal [98,99].

Intriguingly, early sensory cortical areas, too, show reliably greater activity when processing affective stimuli [see meta-analyses by, 96,100, also, 101,102,103]. For example, occipital cortex exhibits greater activity when participants are viewing affectively arousing natural scene images [7,87], including valence-neutral, high arousal images [86,104] compared to when viewing low arousal images or control stimuli with similar amounts of visual information. Distributed activity in early sensory areas is informative for classifying arousal [99,105,and also pleasure/displeasure,106,107,108]. Even in experimental contexts that do not manipulate affect, activity in early sensory cortices is modulated by multimodal inputs depending in part on informational value [e.g., 109,110,111]. This suggests that the modulation of early sensory areas by affect may also depend on the informational value of affect.

The above sections foreground exemplary studies of arousal using EEG measurements for wakeful arousal, measurements such as heart rate and electrodermal response for autonomic arousal, and subjective experience reports for affective arousal. However, these measurements are also not isolated from one another. EEG measurements of wakeful arousal (including oscillatory waves that are commonly used in sleep and wakefulness research) also relate with affective valence and autonomic function [112] including heart rate variability [113–115]. The subjective experience of arousal routinely correlates with measures of autonomic arousal [83,116–118], and readily incorporates states of sleep and wakefulness alongside emotions into a now widely used "affective circumplex" model [119]. In fact, a small but growing body of research explicitly investigates how one variety of arousal relates to the others, hypothesizing and demonstrating relationships between neural activity during sleep, affective arousal, and emotion [120–122], sleep and autonomic activity [123,124], as well as autonomic activity and affective valence [125].

3. Toward an integrated framework for the neural basis of arousal

To accommodate the variety of findings above across research areas of arousal requires outlining an integrative neural reference space for arousal (see Table 2, and Fig. 1) consisting of a set of neuroanatomic structures, neurotransmitter systems, and connectivity among these neural components which are the physical ingredients that constitute arousal in its various formulations (wakeful, arousal, affective), but are separable in terms of their weighted contributions and functional interactions (i.e., their recipes). As Saper [126] notes, integration in the neural circuity across some varieties of arousal occurs as early on as in the solitary nucleus (medulla) and parabrachial complex (pons), and practically at every level of the central nervous system. Our proposed reference space (Fig. 1A) builds from the neural basis of wakeful arousal (as shown in Table 1), and broadens it to include other brain regions that are also affiliated with autonomic-related changes in arousal and affective arousal (Table 2). These include nuclei of the diffuse neuromodulatory system, brainstem reticular nuclei, autonomic nuclei, limbic and paralimbic structures, and sensory-systems. The state

of the neural reference space for arousal is captured by the functional activity and connectivity of these nodes, which in turn relates to the quality of arousal that emerges. This is illustrated in Fig. 1B, in which we show the subset of nodes that we hypothesize as being active during three different states of arousal (wakeful, autonomic, affective).

The neural reference space and its states might be thought of as dynamic recipes for various formulations of arousal, but does not, in and of itself, reveal the mechanisms that govern the time-dependent dynamic interactions between its nodes. One possibility is that functional interactions are described well by the concept of allostasis [1] in which activity in brainstem areas is modulated by predictions of future visceromotor fluctuations sent from limbic and paralimbic circuitry [23,127–131]. Allostatic demands also occur along different time scales, corresponding with tonic changes in neuronal activity (i.e. states such as wakefulness vs. sleep) and phasic changes in neuronal activity (i.e. transient fluctuations during wakefulness, vigilance, or as triggered by unexpected stimuli with allostatic relevance, such as evocative images and sounds). Notably, orthogonal tonic and phasic activity modes of the locus coeruleus recorded in monkeys have been associated respectively to disengagement from a task and increased task performance [132].

4. Potential of ultra-high-field neuroimaging to more fully probe the neural reference space for arousal in humans

Exploring this neural reference space for arousal requires the ability to measure activity simultaneously in both cortical and small subcortical areas across a variety of arousal inducing situations, *in vivo*. Recent advances in human neuroimaging technology (ultra-high field −i.e. 7 Tesla- scanners) and methods [e.g. simultaneous multi-slice imaging, 133] enable researchers to concurrently investigate *in vivo* cortical and subcortical arousal mechanisms with enhanced spatial and temporal resolution (i.e. enhanced precision and speed). These technological developments may provide a pathway to address several gaps in our understanding of the neural architecture for arousal including: i) the structural organization of brainstem nuclei and connectivity pathways in humans, ii) how functional activity in these nuclei combine with activity in other subcortical and cortical areas to dynamic states in a neural reference space for arousal, and iii) how these “recipes” produce various instances of arousal with the properties of wakefulness, ANS activity, and affect (individually or in combination). Ultra-high field 7 Tesla scanning techniques may also provide further insight on how nuclei or networks affiliated with specific neurotransmitter systems play a role in arousal [for reviews of that literature, see 134,135].

Progress in *in vivo* human studies of arousal has been mainly limited by the scarce knowledge of the location of brainstem, thalamic, and hypothalamic nuclei in conventional neuro-images, the limited ability to precisely and directly record behavioral/electro-physiological signatures of arousal from these small regions located deeply in the brain, and the presence of confounds in low-frequency signals, which especially provide limited means of evaluating wakeful arousal. Many of these limitations may be overcome by using ultra-high field strength (≥7 Tesla) imaging to localize and atlas subcortical nuclei in humans. A remarkable feature of the human brainstem is its high density of gray matter nuclei. The brainstem is slightly larger than a human thumb, yet about 170 brainstem nuclei have been identified by ex vivo work [35], and the nuclei count reaches about 300 if the nuclei substructures are counted separately. We estimate that the location of less than 10% of brainstem nuclei has been mapped in vivo by structural neuro-imaging techniques [13–22]. This is in line with recent work, which estimates that over 90% of the subcortical annotations are missing from human MRI atlases [136].

Difficulty in localizing brainstem nuclei in conventional (e.g. 3 Tesla) imaging can be ascribed to the deep location of the brainstem (resulting in a lower MRI sensitivity compared to the cortex), the small size of brainstem nuclei, and − for most nuclei − the diminished gray-white matter contrast (e.g. relaxivity-based) compared to the cortex. Promisingly, technological advances in neuroimaging (ultra-high field −e.g. 7 Tesla– scanners, phase-array receive coils) and/or multi-contrast approaches using novel (e.g. diffusion-based, proton density, magnetization transfer) MRI contrasts for brainstem nuclei delineation have shown progress in brainstem nuclei delineation and atlasing [13,14,16,21,22]. These approaches suggest that delineation of small (volume greater or equal to 15 mm^3) brainstem nuclei (including nuclei of the ascending arousal and autonomic system) can be achieved using an about 1mm-isotropic resolution MRI with adequate sensitivity and contrast. By a preliminary inspection of the brainstem nuclei size [35], we foresee that the use of multi-contrast MRI with currently achievable 0.5-1mm-isotropic resolution might enable the delineation of at least one third of the brainstem nuclei described in *ex vivo* human brainstem atlases. *In vivo* brainstem nuclei atlasing will thus greatly benefit from the tailoring of current MRI contrast or the development of novel MRI contrast for *in vivo* brainstem nuclei delineation. We and others have created *in vivo* probabilistic atlases of several brainstem nuclei involved in arousal, including the locus coeruleus [22], as well as the dorsal/median/paramedian raphe, the pedunculotegmental nucleus, and the periaqueductal gray, raphe magnus cuneiform nucleus, and pontis oralis nuclei [13,14]. These atlases can be used to map the nuclei location in healthy subjects and patients (i.e. by coregistering conventional −e.g. 3 Tesla- MRI to the brainstem atlas space), and investigate arousal mechanisms, connectivity pathways (“connectomes”) and spatiotemporal dynamics within the arousal matrix in the living and behaving human brain. A comprehensive atlas of brainstem nuclei of the ascending arousal system would be a critical step towards the identification of the key nodes and pathways that are necessary to maintain a waking state in living humans and to promptly respond to affective stimuli. Such an atlas would also bring new insight in the understanding the possible redundancy or hierarchy of the multitude of channels assumed to be involved in arousal.

There are some general limitations in the use of ultra-high field MRI and fMRI to examine subcortical circuits. The contribution of physiological (e.g. respiration, heartbeat, brain motion) noise [137] and the presence of field inhomogeneities (both related to static magnetic field and to radiofrequency wavelength effects, [138,139] increase with the field strength. These effects need to be properly characterized [138,140,141] to be able to fully exploit the improvements in detection sensitivity, contrast and spatial resolution of ultra-high field MRI [142], and to abide to statistical fMRI assumptions [143]. Finally, a 0.5–1 mm isotropic spatial resolution MRI might not enable the investigation of the anatomy and function of some arousal brainstem nuclei and subnuclei that have a columnar shape and small cross-sectional area (e.g. the raphe obscurus has an in plane linear size of about 100–200 μm and extends rostro-caudally for more than 1 cm). Thus, further technological development might be needed to fully investigate in living humans the neural reference space for arousal and its dynamic mechanisms.

Despite these limitations, recent in vivo ultra-high resolution neuroimaging studies have been used successfully to examine functional activity and functional connectivity in brainstem nuclei. For instance, using submillimeter resolution, Satpute et al. [92] localized functional activity to distinct subregions of the periaqueductal gray that correlated with the presentation of images known to evoke affective arousal, and Sclocco et al. [144] examined how brainstem nuclei relate with painful stimuli. Bianciardi et al. [145] and Edlow et al. [146] delineated respectively a functional and a structural connectome of several brainstem nuclei involved in arousal and allostasis. Future high-resolution 7 Tesla MRI and EEG/MRI studies might bring clarity to arousal mechanisms in living humans by combining the resolution to identify subcortical/brainstem nuclei and by providing the means to examine cortical-brainstem connectivity.

Finally, ultra-high field imaging has the potential to improve the robustness and generalization of research findings across species,

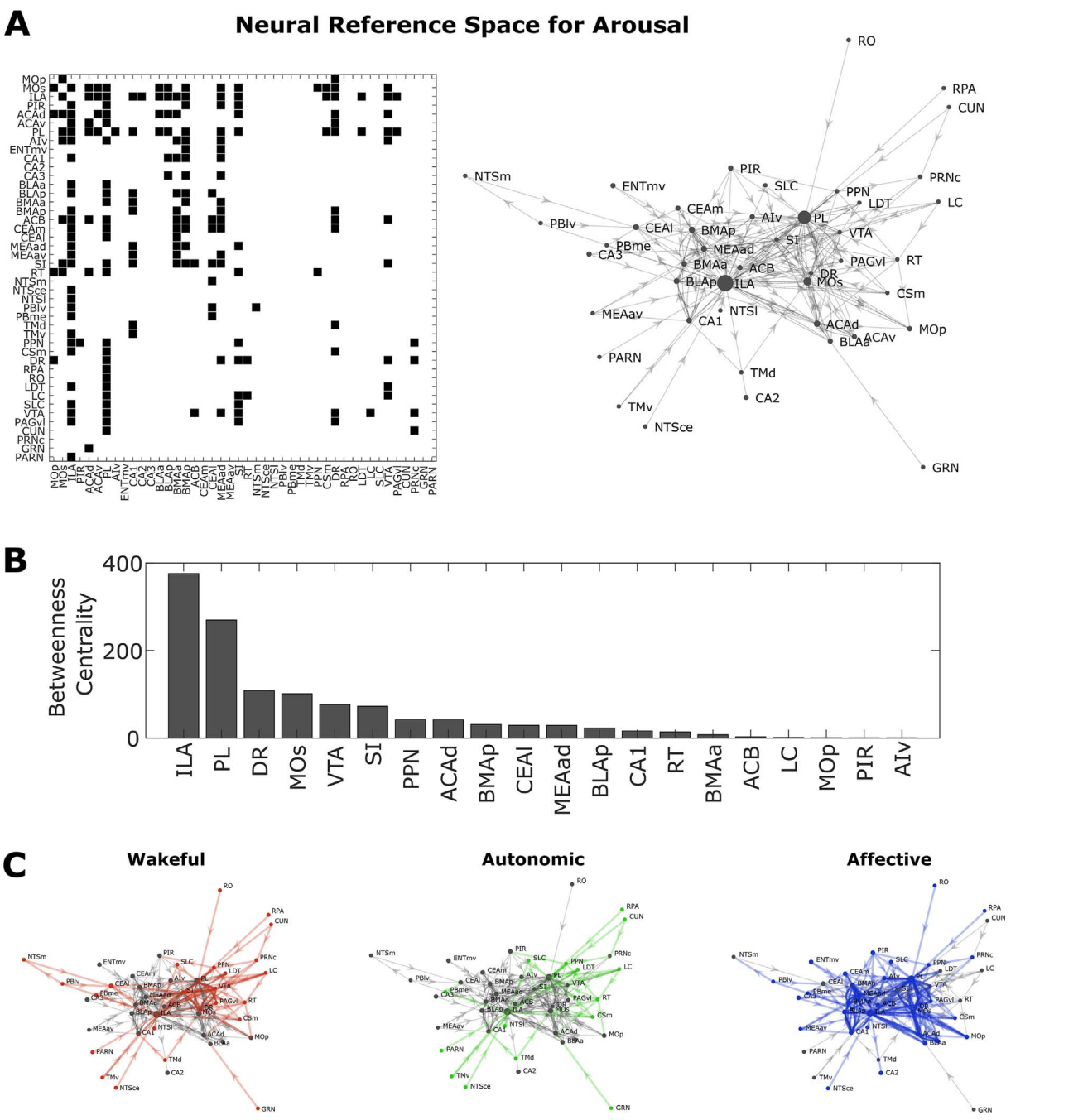

Fig. 1. The neural reference space for arousal. (A) Left panel indicates connections between brain regions of the arousal reference space (see Table 2 for abbreviations) based on the Brain Architecture Knowledge Management System (BAMS) rat neuroanatomical macroconnectome [148]. The right panel depicts these structural connections as a network using a force-directed layout, where more connected regions are placed near each other. Node (i.e. circle) size is based on the betweenness-centrality (i.e. the number of shortest paths from all vertices to all others that pass through that node). Regions with high values of betweenness centrality, such as ILA (BC = 376) and PL (BC = 270), link many different cortical, subcortical, and brainstem areas. These two regions have a larger influence on the network than other regions (e.g., the next highest region is dorsal raphe nucleus, BC = 108). The direction of each connection is indicated with an arrow, based on observations in the animal literature. Regions are identified based on Swanson's nomenclature [149]. Note that the medullary reticular nucleus, the lateral part of the superior central nucleus raphe, the posterior cingulate cortex, the precuneus, and the medial prefrontal cortex are excluded because their connections are absent in the macroconnectome data. (B) Bar plot of betweenness centrality for the top 20 nodes in the network. (C) Visualization of the neural reference space during instances of wakeful, autonomic, and affective arousal. The figure on the left with lines colored in red (in the online version) depicts a model of the functional configuration of the neural reference space for arousal during wakeful arousal, and so forth for the figure in the middle for autonomic arousal, and the figure on the right for affective arousal. These networks provide a preliminary, conceptual sense for how varieties of arousal are formulated in the integrated space. The connections are weighted on the basis of information in Table 2. Increased activation of nodes (colored circles) and heightened connectivity (colored thick lines) serve to differentiate the three forms of arousal (red, green, blue color respectively for wakeful, autonomic and affective arousal). This account proposes that the strength of activity and connectivity are differentially altered during different types of arousal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

particularly for issues that are of interest to humans. Invasive studies in non-human animals have examined in much detail the subcortical circuitry involved in various forms of arousal. Ultra-high field neuroimaging may complement this work by examining dynamic activity in these circuits in the whole brain *in vivo*, and how they coalesce or dissociate during different stages or varieties of arousal. Few other techniques offer the promise of examining whole-brain functional connectivity between subcortical and cortical circuitry. In humans, ultra-high field

imaging may further address how well this circuitry, which has been largely defined from studies in non-human animals, generalizes to arousal-related circuitry in human thereby providing validation for work in non-human animals. It may also produce unique insights into the subjective experience of arousal, and studying how the various features of arousal relate to mental health, physical health [147], and intervening biological processes of interest (e.g. inflammation and immune system challenge).

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