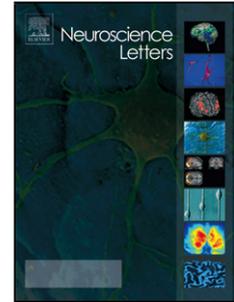


Accepted Manuscript

Title: Deconstructing arousal into wakeful, autonomic and affective varieties

Authors: Ajay B. Satpute, Philip A. Kragel, Lisa Feldman Barrett, Tor D. Wager, Marta Bianciardi



PII: S0304-3940(18)30048-X
DOI: <https://doi.org/10.1016/j.neulet.2018.01.042>
Reference: NSL 33376

To appear in: *Neuroscience Letters*

Received date: 8-7-2017
Revised date: 13-1-2018
Accepted date: 22-1-2018

Please cite this article as: Ajay B.Satpute, Philip A.Kragel, Lisa Feldman Barrett, Tor D.Wager, Marta Bianciardi, Deconstructing arousal into wakeful, autonomic and affective varieties, *Neuroscience Letters* <https://doi.org/10.1016/j.neulet.2018.01.042>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Deconstructing arousal into wakeful, autonomic and affective varieties

Ajay B. Satpute^{1,2}Philip A. Kragel³Lisa Feldman Barrett^{2,4,5}Tor D. Wager³Marta Bianciardi⁴**Affiliations:**¹Departments of Psychology and Neuroscience, Pomona College, Claremont, CA, USA²Department of Psychology, Northeastern University, Boston, MA, USA³Department of Psychology and Neuroscience and the Institute of Cognitive Science, the University of Colorado, Boulder⁴Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA⁵Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA**Corresponding Authors:**

Ajay B. Satpute, email: a.satpute@northeastern.edu, Department of Psychology, Northeastern University, 360 Huntington Ave., Boston, MA 06880, USA. Phone: +1 310 948 5681; Fax: +1 617 373 8714

Marta Bianciardi, email: martab@mgh.harvard.edu, Athinoula A. Martinos Center for Biomedical Imaging Department of Radiology, Massachusetts General Hospital, Building 149, Room 2301, 13th Street, Charlestown, MA 02129, USA. Phone: +1 617 724 1723 ; Fax: +1 617 726 7422

highlights

- We review research on wakeful, autonomic, and affective arousal.
- And we propose an integrated neural reference space for arousal.
- The reference space highlights coordination between brainstem and cortical areas.
- The role of brainstem nuclei in arousal is poorly understood in humans.
- 7T imaging provides new opportunities to examine arousal in humans.

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. 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 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.

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 between 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.

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. serotonergic, 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].

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 monoaminergic 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.

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, 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 animal studies showing the importance of brainstem nuclei, thalamus, hypothalamus, and basal forebrain structures to arousal (Table 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].

Most of these studies implicating the cortical areas are on the basis of correlational findings using human neuroimaging. 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 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].

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, etc., 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) but 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].

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 was more reliably engaged visual and somatosensory affect inductions, different induction modalities appeared 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 EDR 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], and autonomic activity and affective valence [125].

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 Figure 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 circuitry across some varieties of arousal occurs as early on as the NTS and parabrachial complex, and practically at every level of the central nervous system. Our proposed reference space (Figure 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 Figure 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].

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 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 structures 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 0.5-1mm isotropic spatial resolution might not be able to investigate 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 brain stem 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, 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 compliment 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).

ACCEPTED MANUSCRIPT

Figure Captions

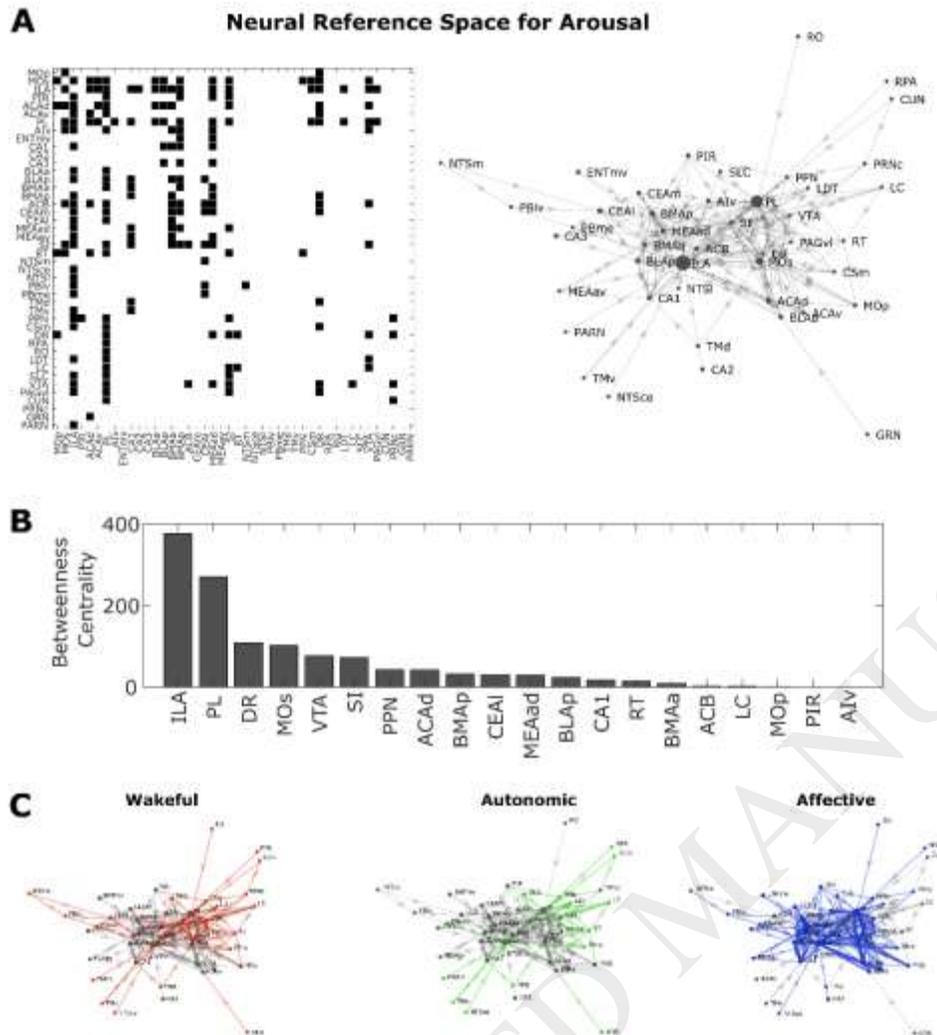


Figure 1. The neural reference space for arousal. **(A)** Left panel indicates connections between brain regions of the arousal reference space (see Table 2 for abbreviations) based on the Brain Architecture Knowledge Management System (BAMS) rat neuroanatomical macroconnectome [148]. The right panel 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 and the lateral part of the superior central nucleus raphe 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. 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 TABLE 1

c [29]; d [150]; e [151]; f [152]; g [153]; h [154];

Acknowledgements

This work was supported by the following sources of funding: National Institutes of Health (NIH) National Cancer Institute U01 CA193632; NIH National Institute for Biomedical Imaging and Bioengineering K01 EB019474. National Institute on Deafness and other Communication Disorders R21 DC015888.

References

- [1] P. Sterling, S. Laughlin, Principles of neural design, MIT Press, 2015.
- [2] L.F. Barrett, E. Bliss-Moreau, Affect as a Psychological Primitive, *Advances in Experimental Social Psychology* 41 (2009) 167-218.
- [3] J. Siegel, Brain mechanisms that control sleep and waking, *Naturwissenschaften* 91 (2004) 355-365.
- [4] J.I. Lacey, The evaluation of autonomic responses: Toward a general solution, *Ann. N. Y. Acad. Sci.* 67 (1956) 125-163.
- [5] W.B. Cannon, Bodily changes in pain, hunger, fear and rage, (1929).
- [6] J. Panksepp, *Affective neuroscience: The foundations of human and animal emotions.*, Oxford University Press, New York, 1998.
- [7] P.J. Lang, M.M. Bradley, J.R. Fitzsimmons, B.N. Cuthbert, J.D. Scott, B. Moulder, V. Nangia, Emotional arousal and activation of the visual cortex: an fMRI analysis, *Psychophysiology* 35 (1998) 199-210.
- [8] J.A. Russell, A circumplex model of affect, *J. Pers. Soc. Psychol.* 39 (1980) 1161-1178.
- [9] M.S. Yik, J.A. Russell, L.F. Barrett, Structure of self-reported current affect: Integration and beyond, *J. Pers. Soc. Psychol.* 77 (1999) 600.
- [10] G. Paxinos, C. Watson, *The rat brain in stereotaxic coordinates.*, Academic Press, San Diego, CA, USA, 1998.
- [11] P. Fuller, D. Sherman, N.P. Pedersen, C.B. Saper, J. Lu, Reassessment of the structural basis of the ascending arousal system, *J. Comp. Neurol.* 519 (2011) 933-956.
- [12] A. Eban-Rothschild, G. Rothschild, W.J. Giardino, J.R. Jones, L. de Lecea, VTA dopaminergic neurons regulate ethologically relevant sleep-wake behaviors, *Nat. Neurosci.* 19 (2016) 1356.
- [13] M. Bianciardi, N. Toschi, B.L. Edlow, C. Eichner, K. Setsompop, J.R. Polimeni, E. Brown, H.C. Kinney, B.R. Rosen, L.L. Wald, Towards an in vivo neuroimaging template of human brainstem nuclei of the ascending arousal, autonomic and motor systems, *Brain connectivity* (2015).
- [14] M. Bianciardi, C. Strong, N. Toschi, B.L. Edlow, B. Fischl, E.N. Brown, B.R. Rosen, L.L. Wald, A probabilistic template of human mesopontine tegmental nuclei from in vivo 7 T MRI, *Neuroimage* (2017).
- [15] M.C. Keuken, P.-L. Bazin, L. Crown, J. Hootsmans, A. Laufer, C. Müller-Axt, R. Sier, E. van der Putten, A. Schäfer, R. Turner, Quantifying inter-individual anatomical variability in the subcortex using 7T structural MRI, *Neuroimage* 94 (2014) 40-46.
- [16] L. Zrinzo, L.V. Zrinzo, S. Tisch, P.D. Limousin, T.A. Yousry, F. Afshar, M.I. Hariz, Stereotactic localization of the human pedunclopontine nucleus: atlas-based coordinates and validation of a magnetic resonance imaging protocol for direct localization, *Brain* 131 (2008) 1588-1598.
- [17] R. Chowdhury, C. Lambert, R.J. Dolan, E. Düzel, Parcellation of the human substantia nigra based on anatomical connectivity to the striatum, *Neuroimage* 81 (2013) 191-198.
- [18] D.H. Kwon, J.M. Kim, S.H. Oh, H.J. Jeong, S.Y. Park, E.S. Oh, J.G. Chi, Y.B. Kim, B.S. Jeon, Z.H. Cho, Seven-tesla magnetic resonance images of the substantia nigra in Parkinson disease, *Ann. Neurol.* 71 (2012) 267-277.

- [19] R.A. Menke, S. Jbabdi, K.L. Miller, P.M. Matthews, M. Zarei, Connectivity-based segmentation of the substantia nigra in human and its implications in Parkinson's disease, *Neuroimage* 52 (2010) 1175-1180.
- [20] S. Mori, K. Oishi, A.V. Faria, White matter atlases based on diffusion tensor imaging, *Curr. Opin. Neurol.* 22 (2009) 362.
- [21] M. Sasaki, E. Shibata, K. Tohyama, J. Takahashi, K. Otsuka, K. Tsuchiya, S. Takahashi, S. Ehara, Y. Terayama, A. Sakai, Neuromelanin magnetic resonance imaging of locus ceruleus and substantia nigra in Parkinson's disease, *Neuroreport* 17 (2006) 1215-1218.
- [22] N.I. Keren, C.T. Lozar, K.C. Harris, P.S. Morgan, M.A. Eckert, In vivo mapping of the human locus coeruleus, *Neuroimage* 47 (2009) 1261-1267.
- [23] I. Kleckner, J. Zhang, A. Touroutoglou, L. Chanes, C. Xia, W.K. Simmons, K. Quigley, B. Dickerson, L. Barrett, Evidence for a large-scale brain system supporting allostasis and interoception in humans, *bioRxiv* (2017) 098970.
- [24] J. Parvizi, A. Damasio, Consciousness and the brainstem, *Cognition* 79 (2001) 135-160.
- [25] H. Berger, Über das elektroencephalogramm des menschen, *Eur. Arch. Psychiatry Clin. Neurosci.* 87 (1929) 527-570.
- [26] G. Moruzzi, H.W. Magoun, Brain stem reticular formation and activation of the EEG, *Electroencephalogr. Clin. Neurophysiol.* 1 (1949) 455-473.
- [27] C.B. Saper, T.C. Chou, T.E. Scammell, The sleep switch: hypothalamic control of sleep and wakefulness, *Trends Neurosci.* 24 (2001) 726-731.
- [28] C.B. Saper, P.M. Fuller, N.P. Pedersen, J. Lu, T.E. Scammell, Sleep state switching, *Neuron* 68 (2010) 1023-1042.
- [29] J. Olszewski, D. Baxter, *Cytoarchitecture of the human brainstem.*, S. Karger by JB Lippincott Company, Philadelphia and Montreal, North America, 1954.
- [30] C.W. Berridge, Noradrenergic modulation of arousal, *Brain research reviews* 58 (2008) 1-17.
- [31] R. Hernandez-Peon, G. Chavez-Ibarra, P. Morgane, C. Timo-Iaria, Limbic cholinergic pathways involved in sleep and emotional behavior, *Exp. Neurol.* 8 (1963) 93-111.
- [32] T.W. Robbins, B.J. Everitt, *Arousal systems and attention*, (1995).
- [33] M.H. Munk, P.R. Roelfsema, P. Konig, A.K. Engel, W. Singer, Role of reticular activation in the modulation of intracortical synchronization, *Science* 272 (1996) 271.
- [34] D. Martelli, D. Stanic, M. Dutschmann, The emerging role of the parabrachial complex in the generation of wakefulness drive and its implication for respiratory control, *Respir Physiol Neurobiol* 188 (2013) 318-323.
- [35] G. Paxinos, X.-F. Huang, G. Sengul, C. Watson, *Organization of brainstem nuclei. The Human Nervous System*, Elsevier Academic Press, Amsterdam, 2012, pp. 260-327.
- [36] C. Gauriau, J.F. Bernard, Pain pathways and parabrachial circuits in the rat, *Exp. Physiol.* 87 (2002) 251-258.
- [37] J. Brooks, I. Tracey, REVIEW: From nociception to pain perception: imaging the spinal and supraspinal pathways, *J. Anat.* 207 (2005) 19-33.
- [38] S. Han, M.T. Soleiman, M.E. Soden, L.S. Zweifel, R.D. Palmiter, Elucidating an affective pain circuit that creates a threat memory, *Cell* 162 (2015) 363-374.
- [39] M. Sato, M. Ito, M. Nagase, Y.K. Sugimura, Y. Takahashi, A.M. Watabe, F. Kato, The lateral parabrachial nucleus is actively involved in the acquisition of fear memory in mice, *Molecular brain* 8 (2015) 22.
- [40] A.J. Todd, Neuronal circuitry for pain processing in the dorsal horn., *Nat Rev Neuro* 11 (2010) 823-836.
- [41] J.M. Braz, M.A. Nassar, J.N. Wood, A.I. Basbaum, Parallel "pain" pathways arise from subpopulations of primary afferent nociceptor, *Neuron* 47 (2005) 787-793.
- [42] R. Bandler, M.T. Shipley, Columnar organization in the midbrain periaqueductal gray: modules for emotional expression?, *Trends Neurosci.* 17 (1994) 379-389.
- [43] M.M. Behbehani, Functional characteristics of the midbrain periaqueductal gray, *Prog. Neurobiol.* 46 (1995) 575-605.
- [44] J.M. Monti, H. Jantos, The roles of dopamine and serotonin, and of their receptors, in regulating sleep and waking, *Prog. Brain Res.* 172 (2008) 625-646.
- [45] T.W. Vanderah, D.J. Gould, *Nolte's the human brain: an introduction to its functional anatomy*, Elsevier, Philadelphia, PA, USA, 2015.

- [46] J.J. Fraigne, Z.A. Torontali, M.B. Snow, J.H. Peever, REM sleep at its core—circuits, neurotransmitters, and pathophysiology, *Frontiers in neurology* 6 (2015) 123.
- [47] A. Venkatraman, B.L. Edlow, M.H. Immordino-Yang, The Brainstem in Emotion: A Review, *Frontiers in neuroanatomy* 11 (2017).
- [48] M. Davis, The role of the amygdala in fear and anxiety, *Annu. Rev. Neurosci.* 15 (1992) 353-375.
- [49] E.A. Murray, The amygdala, reward and emotion, *Trends in cognitive sciences* 11 (2007) 489-497.
- [50] P.H. Janak, K.M. Tye, From circuits to behaviour in the amygdala, *Nature* 517 (2015) 284-292.
- [51] M. Liu, C. Blanco-Centurion, R.R. Konadhode, L. Luan, P.J. Shiromani, Orexin gene transfer into the amygdala suppresses both spontaneous and emotion-induced cataplexy in orexin-knockout mice, *Eur. J. Neurosci.* (2016).
- [52] J.E. LeDoux, Emotion circuits in the brain, *Annu. Rev. Neurosci.* 23 (2000) 155-184.
- [53] J. Panksepp, The basic emotional circuits of mammalian brains: do animals have affective lives?, *Neurosci. Biobehav. Rev.* 35 (2011) 1791-1804.
- [54] P.D. Maclean, Some psychiatric implications of physiological studies on frontotemporal portion of limbic system (visceral brain), *Electroencephalogr. Clin. Neurophysiol.* 4 (1952) 407-418.
- [55] Y.M. Ulrich-Lai, J.P. Herman, Neural regulation of endocrine and autonomic stress responses, *Nature reviews. Neuroscience* 10 (2009) 397-409.
- [56] M.E. Raichle, A.M. MacLeod, A.Z. Snyder, W.J. Powers, D.A. Gusnard, G.L. Shulman, A default mode of brain function, *Proc. Natl. Acad. Sci. U. S. A.* 98 (2001) 676-682.
- [57] M.D. Greicius, B. Krasnow, A.L. Reiss, V. Menon, Functional connectivity in the resting brain: a network analysis of the default mode hypothesis, *Proc. Natl. Acad. Sci. U. S. A.* 100 (2003) 253-258.
- [58] C. Chang, D.A. Leopold, M.L. Schölvinck, H. Mandelkow, D. Picchioni, X. Liu, Q.Y. Frank, J.N. Turchi, J.H. Duyn, Tracking brain arousal fluctuations with fMRI, *Proceedings of the National Academy of Sciences* (2016) 201520613.
- [59] D. Picchioni, M.L. Pixa, M. Fukunaga, W.S. Carr, S.G. Horovitz, A.R. Braun, J.H. Duyn, Decreased connectivity between the thalamus and the neocortex during human nonrapid eye movement sleep, *Sleep* 37 (2014) 387-397.
- [60] E. Tagliazucchi, F. von Wegner, A. Morzelewski, V. Brodbeck, K. Jahnke, H. Laufs, Breakdown of long-range temporal dependence in default mode and attention networks during deep sleep, *Proceedings of the National Academy of Sciences* 110 (2013) 15419-15424.
- [61] S.G. Horovitz, A.R. Braun, W.S. Carr, D. Picchioni, T.J. Balkin, M. Fukunaga, J.H. Duyn, Decoupling of the brain's default mode network during deep sleep, *Proc. Natl. Acad. Sci. U. S. A.* 106 (2009) 11376-11381.
- [62] O. Akeju, M.L. Loggia, C. Catana, K.J. Pavone, R. Vazquez, J. Rhee, V.C. Ramirez, D.B. Chonde, D. Izquierdo-Garcia, G. Arabasz, Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness, *Elife* 3 (2014) e04499.
- [63] W.I. Rosenblum, Immediate, irreversible, posttraumatic coma: a review indicating that bilateral brainstem injury rather than widespread hemispheric damage is essential for its production, *J. Neuropathol. Exp. Neurol.* 74 (2015) 198-202.
- [64] K.-J. Bär, F. de la Cruz, A. Schumann, S. Koehler, H. Sauer, H. Critchley, G. Wagner, Functional connectivity and network analysis of midbrain and brainstem nuclei, *Neuroimage* 134 (2016) 53-63.
- [65] W.W. Seeley, V. Menon, A.F. Schatzberg, J. Keller, G.H. Glover, H. Kenna, A.L. Reiss, M.D. Greicius, Dissociable intrinsic connectivity networks for salience processing and executive control, *J. Neurosci.* 27 (2007) 2349-2356.
- [66] D. Ongur, A.T. Ferry, J.L. Price, Architectonic subdivision of the human orbital and medial prefrontal cortex, *J. Comp. Neurol.* 460 (2003) 425-449.
- [67] H. Barbas, Flow of information for emotions through temporal and orbitofrontal pathways, *J. Anat.* 211 (2007) 237-249.
- [68] J.T. Cacioppo, L.G. Tassinary, G. Berntson, *Handbook of psychophysiology*, Cambridge University Press, 2007.
- [69] G.G. Berntson, J.T. Cacioppo, K.S. Quigley, Autonomic determinism: the modes of autonomic control, the doctrine of autonomic space, and the laws of autonomic constraint, *Psychol. Rev.* 98 (1991) 459.
- [70] W.B. Mendes, Assessing autonomic nervous system activity, *Methods in social neuroscience* (2009) 118-147.

- [71] F. Beissner, K. Meissner, K.-J. Bär, V. Napadow, The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function, *J. Neurosci.* 33 (2013) 10503-10511.
- [72] H.D. Critchley, D. Corfield, M. Chandler, C. Mathias, R.J. Dolan, Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans, *The Journal of physiology* 523 (2000) 259-270.
- [73] O. Pollatos, R. Schandry, D.P. Auer, C. Kaufmann, Brain structures mediating cardiovascular arousal and interoceptive awareness, *Brain Res.* 1141 (2007) 178-187.
- [74] A.P. Allen, P.J. Kennedy, J.F. Cryan, T.G. Dinan, G. Clarke, Biological and psychological markers of stress in humans: focus on the Trier Social Stress Test, *Neurosci. Biobehav. Rev.* 38 (2014) 94-124.
- [75] H. Eisenbarth, L.J. Chang, T.D. Wager, Multivariate brain prediction of heart rate and skin conductance responses to social threat, *J. Neurosci.* 36 (2016) 11987-11998.
- [76] N.I. Eisenberger, M.D. Lieberman, A.B. Satpute, Personality from a controlled processing perspective: an fMRI study of neuroticism, extraversion, and self-consciousness, *Cognitive, affective & behavioral neuroscience* 5 (2005) 169-181.
- [77] H.D. Critchley, S. Wiens, P. Rotshtein, A. Ohman, R.J. Dolan, Neural systems supporting interoceptive awareness, *Nat. Neurosci.* 7 (2004) 189-195.
- [78] A.R. Damasio, The somatic marker hypothesis and the possible functions of the prefrontal cortex, *Philos T Roy Soc B* 351 (1996) 1413-1420.
- [79] H. Klüver, P.C. Bucy, "Psychic blindness" and other symptoms following bilateral temporal lobectomy in Rhesus monkeys, *Am. J. Physiol.* 119 (1937) 352-353.
- [80] H. Damasio, T. Grabowski, R. Frank, A.M. Galaburda, A.R. Damasio, The return of Phineas Gage: clues about the brain from the skull of a famous patient, *Science* 264 (1994) 1102-1105.
- [81] R. Adolphs, D. Tranel, A.R. Damasio, The human amygdala in social judgment, *Nature* 393 (1998) 470-474.
- [82] J.S. Feinstein, Lesion studies of human emotion and feeling, *Curr. Opin. Neurobiol.* 23 (2013) 304-309.
- [83] L.F. Barrett, K.S. Quigley, E. Bliss-Moreau, K.R. Aronson, Interoceptive sensitivity and self-reports of emotional experience, *J. Pers. Soc. Psychol.* 87 (2004) 684-697.
- [84] W.M. Wundt, *Grundriss der psychologie*, A. Kröner, Berlin, Germany, 1913.
- [85] P.J. Lang, M.M. Bradley, B.N. Cuthbert, International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8., University of Florida, Gainesville, FL, 2008.
- [86] R.D. Lane, P.M. Chua, R.J. Dolan, Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures, *Neuropsychologia* 37 (1999) 989-997.
- [87] D. Sabatinelli, E.E. Fortune, Q. Li, A. Siddiqui, C. Krafft, W.T. Oliver, S. Beck, J. Jeffries, Emotional perception: meta-analyses of face and natural scene processing, *Neuroimage* 54 (2011) 2524-2533.
- [88] K.A. Lindquist, A.B. Satpute, T.D. Wager, J. Weber, L.F. Barrett, The Brain Basis of Positive and Negative Affect: Evidence from a Meta-Analysis of the Human Neuroimaging Literature, *Cereb. Cortex* 26 (2016) 1910-1922.
- [89] K.L. Phan, T. Wager, S.F. Taylor, I. Liberzon, Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI, *Neuroimage* 16 (2002) 331-348.
- [90] J.T. Buhle, H. Kober, K.N. Ochsner, P. Mende-Siedlecki, J. Weber, B.L. Hughes, E. Kross, L.Y. Atlas, K. McRae, T.D. Wager, Common representation of pain and negative emotion in the midbrain periaqueductal gray, *Social cognitive and affective neuroscience* (2012).
- [91] H. Kober, L.F. Barrett, J. Joseph, E. Bliss-Moreau, K. Lindquist, T.D. Wager, Functional grouping and cortical-subcortical interactions in emotion: a meta-analysis of neuroimaging studies, *Neuroimage* 42 (2008) 998-1031.
- [92] A.B. Satpute, T.D. Wager, J. Cohen-Adad, M. Bianciardi, J.K. Choi, J. Buhle, L.L. Wald, L.F. Barrett, Identification of discrete functional subregions in the human periaqueductal grey., *Proc. Natl. Acad. Sci. U. S. A.* 110 (2013) 17101-17106.
- [93] T. Sieger, T. Serranová, F. Růžička, P. Vostatek, J. Wild, D. Šťastná, C. Bonnet, D. Novák, E. Růžička, D. Urgošík, Distinct populations of neurons respond to emotional valence and arousal in the human subthalamic nucleus, *Proceedings of the National Academy of Sciences* 112 (2015) 3116-3121.
- [94] S.A. Guillory, K.A. Bujarski, Exploring emotions using invasive methods: review of 60 years of human intracranial electrophysiology, *Social cognitive and affective neuroscience* (2014) nsu002.

- [95] J. Péron, S. Frühholz, M. Vérin, D. Grandjean, Subthalamic nucleus: A key structure for emotional component synchronization in humans, *Neurosci. Biobehav. Rev.* 37 (2013) 358-373.
- [96] A.B. Satpute, J. Kang, K.C. Bickart, T. Wager, L.F. Barrett, Involvement of sensory regions in affective experience: A meta-analysis, *Frontiers in psychology* 6 (2015) 1860.
- [97] S.G. Costafreda, M.J. Brammer, A.S. David, C.H.Y. Fu, Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies, *Brain research reviews* 58 (2008) 57-70.
- [98] C. Corradi-Dell'Acqua, A. Tusche, P. Vuilleumier, T. Singer, Cross-modal representations of first-hand and vicarious pain, disgust and fairness in insular and cingulate cortex, *Nature communications* 7 (2016).
- [99] L.J. Chang, P.J. Gianaros, S.B. Manuck, A. Krishnan, T.D. Wager, A Sensitive and Specific Neural Signature for Picture-Induced Negative Affect, *PLoS Biol* 13 (2015) e1002180.
- [100] D.J. Hayes, G. Northoff, Identifying a network of brain regions involved in aversion-related processing: a cross-species translational investigation, *Front Integr Neurosci* 5 (2011) 49.
- [101] S. Francis, E.T. Rolls, R. Bowtell, F. McGlone, J. O'Doherty, A. Browning, S. Clare, E. Smith, The representation of pleasant touch in the brain and its relationship with taste and olfactory areas, *Neuroreport* 10 (1999) 453-459.
- [102] J.-P. Royet, D. Zald, R. Versace, N. Costes, F. Lavenne, O. Koenig, R. Gervais, Emotional responses to pleasant and unpleasant olfactory, visual, and auditory stimuli: a positron emission tomography study, *J. Neurosci.* 20 (2000) 7752-7759.
- [103] B. Wicker, C. Keysers, J. Plailly, J.-P. Royet, V. Gallese, G. Rizzolatti, Both of Us Disgusted in< i> My</i> Insula: The Common Neural Basis of Seeing and Feeling Disgust, *Neuron* 40 (2003) 655-664.
- [104] J. Mourao-Miranda, E. Volchan, J. Moll, R. de Oliveira-Souza, L. Oliveira, I. Bramati, R. Gattass, L. Pessoa, Contributions of stimulus valence and arousal to visual activation during emotional perception, *Neuroimage* 20 (2003) 1955-1963.
- [105] L.B. Baucom, D.H. Wedell, J. Wang, D.N. Blitzer, S.V. Shinkareva, Decoding the neural representation of affective states, *Neuroimage* 59 (2012) 718-727.
- [106] V. Gazzola, M.L. Spezio, J.A. Etzel, F. Castelli, R. Adolphs, C. Keysers, Primary somatosensory cortex discriminates affective significance in social touch, *Proceedings of the National Academy of Sciences* 109 (2012) E1657-E1666.
- [107] L. Ceravolo, S. Frühholz, D. Grandjean, Proximal vocal threat recruits the right voice-sensitive auditory cortex, *Social cognitive and affective neuroscience* (2016) nsw004.
- [108] S.V. Shinkareva, J. Wang, J. Kim, M.J. Facciani, L.B. Baucom, D.H. Wedell, Representations of modality-specific affective processing for visual and auditory stimuli derived from functional magnetic resonance imaging data, *Hum. Brain Mapp.* 35 (2014) 3558-3568.
- [109] S. Werner, U. Noppeney, Distinct functional contributions of primary sensory and association areas to audiovisual integration in object categorization, *J. Neurosci.* 30 (2010) 2662-2675.
- [110] E. Budinger, P. Heil, A. Hess, H. Scheich, Multisensory processing via early cortical stages: connections of the primary auditory cortical field with other sensory systems, *Neuroscience* 143 (2006) 1065-1083.
- [111] A. Pooresmaeili, T.H. FitzGerald, D.R. Bach, U. Toelch, F. Ostendorf, R.J. Dolan, Cross-modal effects of value on perceptual acuity and stimulus encoding, *Proceedings of the National Academy of Sciences* 111 (2014) 15244-15249.
- [112] G.G. Knyazev, EEG delta oscillations as a correlate of basic homeostatic and motivational processes, *Neurosci. Biobehav. Rev.* 36 (2012) 677-695.
- [113] C.C. Yang, C.-W. Lai, H.Y. Lai, T.B. Kuo, Relationship between electroencephalogram slow-wave magnitude and heart rate variability during sleep in humans, *Neurosci. Lett.* 329 (2002) 213-216.
- [114] T.B. Kuo, C.C. Yang, Scatterplot analysis of EEG slow-wave magnitude and heart rate variability: an integrative exploration of cerebral cortical and autonomic functions, *Sleep* 27 (2004) 648-656.
- [115] F. Jurysta, P. Van De Borne, P.-F. Migeotte, M. Dumont, J.-P. Lanquart, J.-P. Degaute, P. Linkowski, A study of the dynamic interactions between sleep EEG and heart rate variability in healthy young men, *Clin. Neurophysiol.* 114 (2003) 2146-2155.
- [116] R.W. Levenson, *Autonomic nervous system differences among emotions*. SAGE Publications Sage CA: Los Angeles, CA, 1992.

- [117] P.J. Lang, M.K. Greenwald, M.M. Bradley, A.O. Hamm, Looking at pictures: Affective, facial, visceral, and behavioral reactions, *Psychophysiology* 30 (1993) 261-273.
- [118] R.M. Stern, W.J. Ray, K.S. Quigley, *Psychophysiological recording*, Oxford University Press, USA, 2001.
- [119] J.A. Russell, L.F. Barrett, Core affect, prototypical emotional episodes, and other things called emotion: dissecting the elephant, *J. Pers. Soc. Psychol.* 76 (1999) 805.
- [120] S.-S. Yoo, N. Gujar, P. Hu, F.A. Jolesz, M.P. Walker, The human emotional brain without sleep—a prefrontal amygdala disconnect, *Curr. Biol.* 17 (2007) R877-R878.
- [121] P. Hu, M. Stylos-Allan, M.P. Walker, Sleep facilitates consolidation of emotional declarative memory, *Psychol Sci* 17 (2006) 891-898.
- [122] M.P. Walker, E. van Der Helm, Overnight therapy? The role of sleep in emotional brain processing, *Psychol. Bull.* 135 (2009) 731.
- [123] F. Snyder, J.A. Hobson, D.F. Morrison, F. Goldfrank, Changes in respiration, heart rate, and systolic blood pressure in human sleep, *J. Appl. Physiol.* 19 (1964) 417-422.
- [124] A. Bunde, S. Havlin, J.W. Kantelhardt, T. Penzel, J.-H. Peter, K. Voigt, Correlated and uncorrelated regions in heart-rate fluctuations during sleep, *Physical Review Letters* 85 (2000) 3736.
- [125] S. Schachter, The interaction of cognitive and physiological determinants of emotional state, *Advances in experimental social psychology* 1 (1964) 49-80.
- [126] C.B. Saper, The central autonomic nervous system: conscious visceral perception and autonomic pattern generation, *Annu. Rev. Neurosci.* 25 (2002) 433-469.
- [127] L.F. Barrett, The theory of constructed emotion: An active inference account of interoception and categorization, *Social cognitive and affective neuroscience* (2016) nsw154.
- [128] L.F. Barrett, W.K. Simmons, Interoceptive predictions in the brain, *Nat Rev Neuro* 16 (2015).
- [129] L. Chanes, L.F. Barrett, Redefining the role of limbic areas in cortical processing, *Trends in cognitive sciences* 20 (2016) 96-106.
- [130] M. Roy, D. Shohamy, N. Daw, M. Jepma, G.E. Wimmer, T.D. Wager, Representation of aversive prediction errors in the human periaqueductal gray, *Nat. Neurosci.* 17 (2014) 1607-1612.
- [131] A.K. Seth, K. Suzuki, H.D. Critchley, An interoceptive predictive coding model of conscious presence, *Frontiers in psychology* 2 (2012) 395.
- [132] G. Aston-Jones, J.D. Cohen, Adaptive gain and the role of the locus coeruleus–norepinephrine system in optimal performance, *J. Comp. Neurol.* 493 (2005) 99-110.
- [133] K. Setsompop, B.A. Gagoski, J.R. Polimeni, T. Witzel, V.J. Wedeen, L.L. Wald, Blipped-controlled aliasing in parallel imaging for simultaneous multislice echo planar imaging with reduced g-factor penalty, *Magn. Reson. Med.* 67 (2012) 1210-1224.
- [134] M. Mather, D. Clewett, M. Sakaki, C.W. Harley, Norepinephrine ignites local hot spots of neuronal excitation: how arousal amplifies selectivity in perception and memory, *Behav. Brain Sci.* (2015) 1-100.
- [135] N.P. Franks, General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal, *Nature reviews. Neuroscience* 9 (2008) 370.
- [136] B.U. Forstmann, G. de Hollander, L. van Maanen, A. Alkemade, M.C. Keuken, Towards a mechanistic understanding of the human subcortex, *Nat Rev Neuro* 18 (2017) 57-65.
- [137] C. Triantafyllou, R.D. Hoge, G. Krueger, C.J. Wiggins, A. Potthast, G.C. Wiggins, L.L. Wald, Comparison of physiological noise at 1.5 T, 3 T and 7 T and optimization of fMRI acquisition parameters, *Neuroimage* 26 (2005) 243-250.
- [138] J.H. Duyn, The future of ultra-high field MRI and fMRI for study of the human brain, *Neuroimage* 62 (2012) 1241-1248.
- [139] K. Uğurbil, J. Xu, E.J. Auerbach, S. Moeller, A.T. Vu, J.M. Duarte-Carvajalino, C. Lenglet, X. Wu, S. Schmitter, P.F. Van de Moortele, Pushing spatial and temporal resolution for functional and diffusion MRI in the Human Connectome Project, *Neuroimage* 80 (2013) 80-104.
- [140] M. Bianciardi, M. Fukunaga, P. van Gelderen, S.G. Horowitz, J.A. de Zwart, K. Shmueli, J.H. Duyn, Sources of functional magnetic resonance imaging signal fluctuations in the human brain at rest: a 7 T study, *Magn. Reson. Imaging* 27 (2009) 1019-1029.
- [141] F. De Martino, F. Esposito, P.-F. van de Moortele, N. Harel, E. Formisano, R. Goebel, K. Uğurbil, E. Yacoub, Whole brain high-resolution functional imaging at ultra high magnetic fields: an application to the analysis of resting state networks, *Neuroimage* 57 (2011) 1031-1044.

- [142] R. Sladky, P. Baldinger, G.S. Kranz, J. Trostl, A. Hoflich, R. Lanzenberger, E. Moser, C. Windischberger, High-resolution functional MRI of the human amygdala at 7 T, *Eur. J. Radiol.* 82 (2013) 728-733.
- [143] X. Yang, M.J. Holmes, A.T. Newton, V.L. Morgan, B.A. Landman, A Comparison of Distributional Considerations with Statistical Analysis of Resting State fMRI at 3T and 7T, *Proceedings of SPIE--the International Society for Optical Engineering* 8314 (2012).
- [144] R. Sclocco, F. Beissner, G. Desbordes, J.R. Polimeni, L.L. Wald, N.W. Kettner, J. Kim, R.G. Garcia, V. Renvall, A.M. Bianchi, Neuroimaging brainstem circuitry supporting cardiovagal response to pain: a combined heart rate variability/ultrahigh-field (7 T) functional magnetic resonance imaging study, *Phil. Trans. R. Soc. A* 374 (2016) 20150189.
- [145] M. Bianciardi, N. Toschi, C. Eichner, J.R. Polimeni, K. Setsompop, E.N. Brown, M.S. Hämäläinen, B.R. Rosen, L.L. Wald, In vivo functional connectome of human brainstem nuclei of the ascending arousal, autonomic, and motor systems by high spatial resolution 7-Tesla fMRI, *Magnetic Resonance Materials in Physics, Biology and Medicine* 29 (2016) 451-462.
- [146] B.L. Edlow, J.A. McNab, T. Witzel, H.C. Kinney, The structural connectome of the human central homeostatic network, *Brain connectivity* 6 (2016) 187-200.
- [147] E.K. Sloan, J.P. Capitanio, R.P. Tarara, S.P. Mendoza, W.A. Mason, S.W. Cole, Social stress enhances sympathetic innervation of primate lymph nodes: mechanisms and implications for viral pathogenesis, *J. Neurosci.* 27 (2007) 8857-8865.
- [148] M. Bota, H.-W. Dong, L.W. Swanson, Combining collation and annotation efforts toward completion of the rat and mouse connectomes in BAMS, *Frontiers in neuroinformatics* 6 (2012).
- [149] L.W. Swanson, *Brain maps III: structure of the rat brain: an atlas with printed and electronic templates for data, models, and schematics*, Gulf Professional Publishing, 2004.
- [150] H. Haas, P. Panula, The role of histamine and the tuberomammillary nucleus in the nervous system, *Nat Rev Neuro* 4 (2003) 121-130.
- [151] J. Li, Z. Hu, L. Lecea, The hypocretins/orexins: integrators of multiple physiological functions, *Br. J. Pharmacol.* 171 (2014) 332-350.
- [152] D. Pinault, The thalamic reticular nucleus: structure, function and concept, *Brain Research Reviews* 46 (2004) 1-31.
- [153] A. Morel, M. Magnin, D. Jeanmonod, Multiarchitectonic and stereotactic atlas of the human thalamus, *J. Comp. Neurol.* 387 (1997) 588-630.
- [154] I. Villano, A. Messina, A. Valenzano, F. Moscatelli, T. Esposito, V. Monda, M. Esposito, F. Precenzano, M. Carotenuto, A. Viggiano, Basal forebrain cholinergic system and orexin neurons: effects on attention, *Frontiers in behavioral neuroscience* 11 (2017).
- [155] D. Bzdok, A.R. Laird, K. Zilles, P.T. Fox, S.B. Eickhoff, An investigation of the structural, connectional, and functional subspecialization in the human amygdala, *Hum. Brain Mapp.* 34 (2013) 3247-3266.
- [156] L.W. Swanson, G.D. Petrovich, What is the amygdala?, *Trends Neurosci.* 21 (1998) 323-331.
- [157] J.D. Green, A.A. Arduini, Hippocampal electrical activity in arousal, *J. Neurophysiol.* 17 (1954) 533-557.
- [158] K.H. Pribram, D. McGuinness, Arousal, activation, and effort in the control of attention, *Psychol. Rev.* 82 (1975) 116.
- [159] E.J. Mufson, M.M. Mesulam, Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum, *J. Comp. Neurol.* 212 (1982) 23-37.
- [160] A. Craig, Interoception: the sense of the physiological condition of the body, *Curr. Opin. Neurobiol.* 13 (2003) 500-505.
- [161] A. Damasio, G.B. Carvalho, The nature of feelings: evolutionary and neurobiological origins, *Nat Rev Neuro* 14 (2013) 143-152.
- [162] J.T. Coull, Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology, *Prog. Neurobiol.* 55 (1998) 343-361.
- [163] C.M. Laine, K.M. Spitler, C.P. Mosher, K.M. Gothard, Behavioral triggers of skin conductance responses and their neural correlates in the primate amygdala, *J. Neurophysiol.* 101 (2009) 1749-1754.

Figure Caption

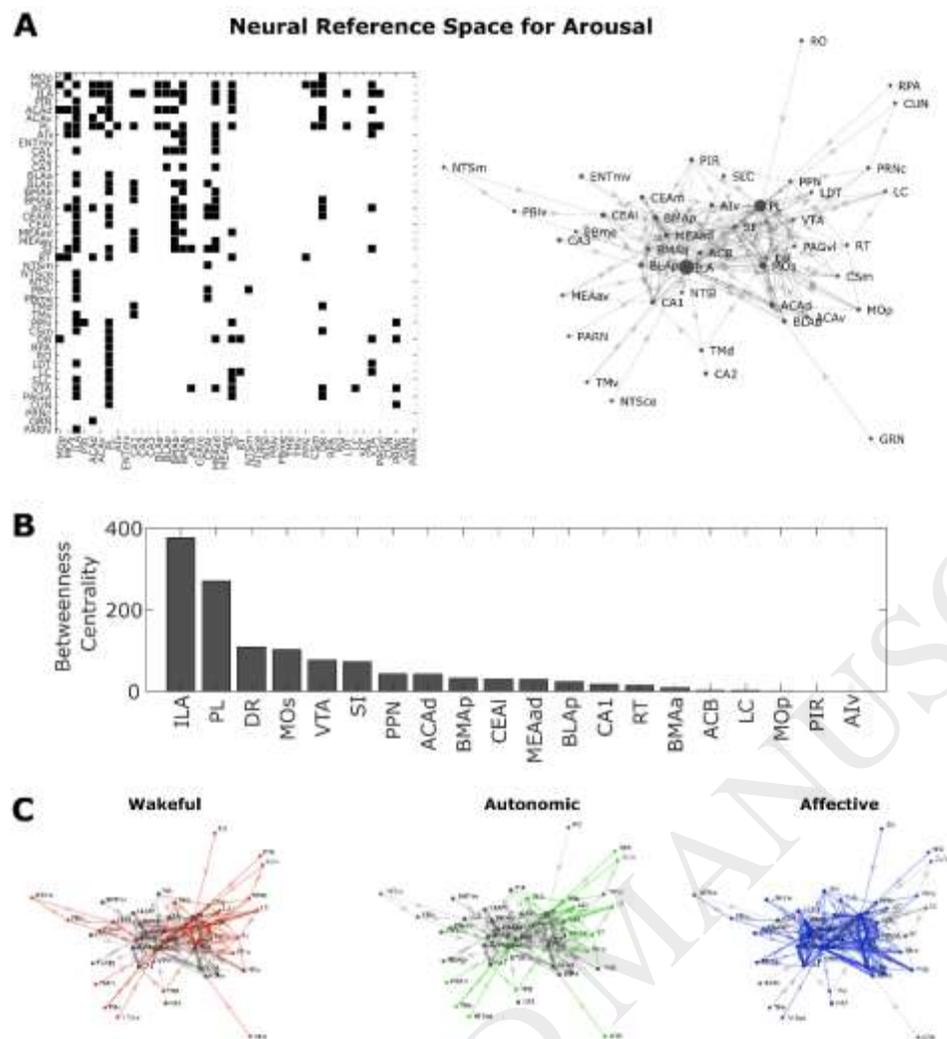


Fig-1

TABLE 1: Brain regions proposed to be involved in wakeful arousal (the Ascending^a Arousal System^b)

Brain region involved in maintaining wakefulness	Main neurotransmitter/neuromodulator or 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	-	Ascending reticular activating system	Coordination of autonomic/motor/sensory brainstem nuclei ^c
Pontomedullary reticular formation nuclei [24]: - Pontine reticular nucleus, caudal part - Gigantocellular reticular nucleus - Parvocellular reticular nucleus - Subnucleus reticularis dorsalis	Serotonin Adrenaline Norepinephrine	Ascending reticular activating system	Coordination of autonomic/motor/sensory brainstem nuclei ^c
Mesopontine tegmental nuclei [24,27-28]: - Pedunculotegmental nucleus - Laterodorsal tegmental nucleus	Acetylcholine	Diffuse neuromodulatory system	Locomotor, Limbic ^c
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 ^c
Locus coeruleus [24,27-28]	Norepinephrine	Diffuse neuromodulatory system	Autonomic, Attention, Memory, Motivation ^c
Ventral tegmental area [12, 24, 44]	Dopamine	Diffuse neuromodulatory system	Attention, Memory, Reward, Drug abuse, Motivation ^c
Parabrachial nuclei [11,33,27,28]	Glutamate	-	Autonomic, Limbic, Viscerosensory ^c
Subcoeruleus area [11,28]	Glutamate	-	Limbic, Motor ^c

Periaqueductal gray, ventrolateral part [24,28]	Dopamine	-	Autonomic, Limbic ^c
Solitary nucleus [24]	-	-	Viscerosensory ^c Autonomic
<u>Hypothalamus:</u>			
- Tuberomamillary nucleus [27,28]	Histamine	-	Limbic, Learning, Memory, Temperature regulation Endocrine homeostasis ^d
- Lateral hypothalamus [27,28]	Orexin	-	Feeding behavior, Temperature regulation, Nociception, Reward ^e
<u>Thalamus:</u>			
- Thalamic reticular nuclei [24]	GABA	-	Modulation of thalamic nuclei ^f
- Intralaminar thalamic nuclei [24] (centromedian, parafascicular, centrolateral)	Glutamate	-	Nociception, Motor ^g
<u>Basal forebrain:</u>			
- Nucleus accumbens, nucleus basalis, diagonal band of Broca [24,27]	Acetylcholine	-	Memory, Attention ^h

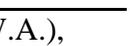
^a "Ascending" refers to the fact that several pathways of this system involve ascending fibers from the brainstem, hypothalamus, thalamus and basal forebrain to the cortex.

^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].

^c [29]; ^d [150]; ^e [151]; ^f [152]; ^g [153]; ^h [154];

TABLE 2: Integrative reference neural space of arousal

Brain region	Acronym	W.A.	Au.A.	Aff.A.
<u>Brainstem:</u>				
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	█		
pedunclopontine ("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	█	█	
<u>Hypothalamus:</u>				
tuberomammillary nucleus hypothalamus, dorsal part	TMd	█	█	█
tuberomammillary nucleus hypothalamus, ventral part	TMv	█	█	█
lateral hypothalamic area	LHA	█	█	█
<u>Thalamus:</u>				
reticular nucleus thalamus	RT	█		█

intralaminar nuclei thalamus	ILM	
<u>Basal forebrain:</u>		
nucleus accumbens, basal forebrain	ACB	
substantia innominata, basal forebrain	SI	
diagonal band of Broca, basal forebrain	db	
basolateral nucleus amygdala, anterior part	BLAa	
basolateral nucleus amygdala, posterior part	BLAp	
basomedial nucleus amygdala, anterior part	BMAa	
basomedial nucleus amygdala, posterior part	BMAp	
<u>Other subcortical areas:</u>		
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	
<u>Cortical areas:</u>		
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	

Note. The table lists a set of neural nodes that that 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. Figure 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.