Catecholamine function, brain state dynamics, and human cognition

Brink, R.L. van den

1. General introduction

1.1 Introduction

The locus coeruleus (LC) is a small nucleus that is located in the pontine tegmentum, and derives its name (literally meaning 'blue spot') from its color, which is a result of neuromelanin deposits within its cell bodies. The LC projects widely to the forebrain (Figure 1) where it releases norepinephrine (NE; also referred to as noradrenaline) (Aston-Jones et al., 1984; Berridge and Waterhouse, 2003).

Catecholamines such as NE do not have a unitary effect on their target neurons, but instead influence the function of other neurotransmitters, a process that is known known as neuromodulation. By virtue of the LC's wide projection profile and the neuromodulatory properties of NE, the LC-NE system profoundly influences neural firing characteristics and associated cognitive processes (Berridge and Waterhouse, 2003; Aston-Jones and Cohen, 2005; Bouret and Sara, 2005; Yu and Dayan, 2005).

In this introductory chapter, an overview of current findings and accounts pertaining to the LC-NE system and its relationship with 'brain state' (defined further below) and cognition is presented, followed by a summary of the chapters of this dissertation.

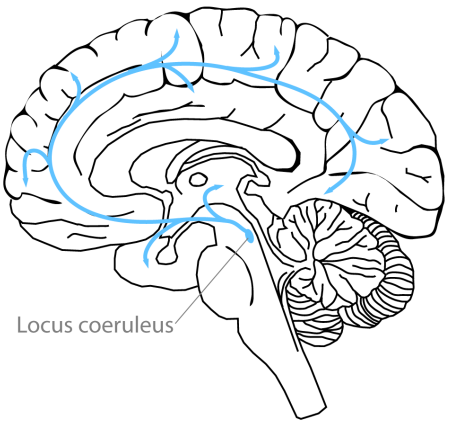

Figure 1. Schematic illustration of the locus ceuruleus and its projections.

1.2 Anatomical overview of the LC-NE system

The LC is situated directly anterior to the fourth ventricle, in the dorsal pons. In the healthy adult brain, the LC contains approximately 35,000 neurons in either hemisphere, which amount to a bilateral nucleus that is roughly the size of a grain of rice (Mouton et al., 1994). Despite its size, the LC sends wide, ascending, projections to the forebrain. For example, major innervation targets of the LC include the amygdala, hippocampus, thalamus, basal ganglia, cerebellum, spinal cord, and all

cortical lobes (Aston-Jones et al., 1984), Consequently, the LC is the dominant source of NE in the central nervous system.

While the projections that emanate from the LC have long been believed to be homogenously distributed across the brain, recent evidence suggests that distinct portions of the LC preferentially innervate select brain areas (Chandler et al., 2014; Schwarz and Luo, 2015; Schwarz et al., 2015). Moreover, recent evidence suggests that the LC does not solely supply the brain with NE, but, but may also release the catecholaminergic neuromodulator dopamine (DA) (Devoto et al., 2004; Kempadoo et al., 2016; Takeuchi et al., 2016). Although this introductory chapter is focused primarily on NE function, it should be noted that NE shares some of its functional properties with DA, such as its effect on neural gain (see below).

1.3 Functional overview of the LC-NE system and theories of LC-NE function in cognition

When released from noradrenergic terminals, NE acts on receptors that can be divided into three major classes: α1, α2, and β. Following release, NE is cleared from the synaptic cleft by the NE transporter (NET). Due to the cortical paucity of DA transporters, NET is also responsible for the reuptake of DA within the cortex. In chapters 3 and 4, NET is blocked pharmacologically in order to causally manipulate catecholamine levels in healthy human participants.

Direct measurements in monkeys have suggested that the LC has two distinct modes of operation (Aston-Jones and Cohen, 2005). In the 'phasic' mode, the LC fires rapidly and transiently in response to salient, novel, or otherwise behaviorally relevant stimuli. During bursts of phasic activity, LC neurons discharge *en masse* in a highly synchronized manner as a consequence of direct electrical coupling between individual neurons of the LC (Ishimatsu and Williams, 1996), although asynchronous firing has also been reported (Totah et al., 2017). Phasic bursts show a close temporal relationship with behavioral responses, suggesting that bursts occur to facilitate internally generated top-down decision processes.

Conversely, in the 'tonic' mode, the LC shows a sustained and regular pattern of firing, without an immediate temporal correspondence between LC discharges and behavioral responses. Across extended periods of time, however, the level of tonic LC activity cofluctuates with task performance, whereby periods of strong tonic activity are marked by distractible behavior, periods of weak tonic activity are marked by under-arousal or sleep, and periods of intermediate tonic activity are marked by (near-) optimal task performance (Aston-Jones and Cohen, 2005). Moreover, the strongest phasic LC activity occurs at time points of intermediate tonic firing.

At the synaptic level, NE can enhance the effect of both excitatory and inhibitory input (Moises et al., 1979; Rogawksi and Aghajanian, 1980). These and other findings have led to the view that NE boosts the efficacy of synaptic interactions between

neurons (Berridge and Waterhouse, 2003), a phenomenon that is known as gain modulation (Aston-Jones and Cohen, 2005). An increase in neural gain results in an increased difference in firing rates between strongly and weakly active neurons (Waterhouse et al., 1998), and consequently yields a system-wide facilitation of signal transmission (Servan-Schreiber et al., 1990; Aston-Jones and Cohen, 2005). In other words, an increase in neural gain does not necessarily modify the likelihood of a single neuron responding to its input, but at the system-level, increased signal propagation emerges and allows dominant neural firing patterns to prevail at the expense of less dominant firing patterns (Servan-Schreiber et al., 1990). The gain-regulating properties of the LC-NE system form a key ingredient of adaptive gain theory (Aston-Jones and Cohen, 2005), which is discussed further below.

In addition to the regulation of neural gain, work done primarily on crustaceans has revealed that NE has the ability to fundamentally reshape the firing properties of the combined set of its target neurons (Marder, 2012; Bargmann and Marder, 2013; Marder et al., 2014). For example, depending on the concentration of NE, the firing pattern in target neurons, and the presence of other neuromodulators, NE can elicit a shift towards rapid, synchronous bursting, or intermittent and asynchronous firing (Marder, 2012; Marder et al., 2014). These findings form the basis of another influential account of LC-NE function, 'network reset' (Bouret and Sara, 2005), also discussed further below.

The study of the LC-NE system in humans has been limited by methodological problems associated with its size and location. Consequently, almost everything we know about its function is based on animal work and computational modeling. Nevertheless there are several major theoretical accounts about how the LC-NE system affects brain state, cognition, and behavior, making it a rare example in cognitive neuroscience where theory outweighs data. The major theoretical accounts regarding LC-NE function will be discussed next.

1.3.1 Adaptive gain theory

In their adaptive gain theory, Aston-Jones and Cohen (2005) propose that the LC-NE system balances the trade-off between exploitation of the current task set and exploration of alternative task sets through NE's effect on neural gain. Because phasic LC activity predominantly occurs only in response to salient or motivationally relevant stimuli, phasic LC activity promotes immediately goal-relevant sensory information at the expense of goal-irrelevant and distracting information, and consequently, fast and accurate behavioral responses to goal-relevant information. Thus, timely bursts of LC activity result in the exploitation of reward from the current task set. Conversely, periods of sustained LC firing (tonic activity) provide a nonspecific and temporally less constrained amplification of incoming sensory information, and thus enable alternative, potentially rewarding, task sets to be explored. Thus, by balancing the trade-off between tonic and phasic activity, the LC

can orchestrate shifts in behavioral strategies in accordance with environmental demands.

1.3.2 The network reset account

The network reset account by Bouret and Sara (2005) describes NE as inducing large-scale neuronal reorganization to promote behavioral adaptation following environmental changes in behavioral requirements. In this context, phasic bursts of LC activity elicit a dynamic reorganization of the LC's target neuronal networks, thereby provoking or facilitating a cognitive shift in task set when such a shift is needed. In contrast to adaptive gain theory, the network reset account proposes that the distractible behavior that accompanies periods of strong tonic LC activation results from inappropriate and repeated cognitive shifts that are a consequence of the sustained and temporally nonspecific characteristics of tonic LC activity. However, in a broader sense, both adaptive gain theory and the network reset account converge on the notion that the LC facilitates goal-directed behavior via adaptation to environmental demands.

1.3.3 Unexpected uncertainty and GANE

In addition to the adaptive gain theory and network reset account discussed above, other accounts exist. The latter, however, will be discussed only briefly here because they are not central to this dissertation.

The Bayesian theory outlined by Yu and Dayan (2005) proposes that NE signals unforeseen changes in task demands. This 'unexpected uncertainty' reflects changes in environmental parameters that require an appropriate modification of predictions about the environment, and therefore a change in behavior. In this sense, prolonged heightened NE release prompts behavioral adaptation, akin to the heightened exploration resulting from increased tonic activity in adaptive gain theory. Moreover, the theory by Yu and Dayan (2005) proposes that NE functions (partially) antagonistically with another neuromodulator, acetylcholine, which in this framework signals known uncertainty about task contingencies.

Another, more recent, and neurobiologically based account (Mather et al., 2015) proposes that the LC-NE system promotes neural representations of goal-relevant information through the 'ignition' of local hotspots with locally concentrated pockets of the neurotransmitter glutamate. In this 'glutamate amplifies noradrenergic effects' (GANE) account, high-priority perceptual representations are favored over low-priority representations through the synergetic action of glutamate and phasically released NE.

The accounts outlined above broadly converge on the notion that NE prompts behavioral adaptation to the demands of the environment. Where these accounts differ lies mostly in how NE is proposed to orchestrate such behavioral adaptation

neurally. As discussed below, sensory information that informs an agent of the state of the environment is not processed neurally as a linear function of the stimulus, but instead interacts with ongoing, intrinsic, neural activity. Resent research indicates that NE may play a critical role in shaping the state of intrinsic neural activity and its interplay with external sensory information, offering new insights into the neural mechanisms by which LC-NE system dynamically regulates behavior.

1.4 The junction between brain state, neuromodulation, and cognition

Brain activity does not simply follow from external (sensory) input, but instead arises from a nonlinear interaction between sensory input and spontaneous - internally generated - brain activity (Luczak et al., 2009; Harris and Thiele, 2011). The state of such spontaneous activity, and the way it shapes cortical responses to sensory input, fluctuates dynamically over time.

A well-known example of fluctuations in dynamic brain state is the sleep-wake cycle. In the deep stages of sleep, neural activity alternates rhythmically between mass-synchronized spiking and near-complete quintessence. These low-frequency fluctuations form a stark contrast with the cortical state that is seen during alert wakefulness, in which neurons fire predominantly asynchronously (Pace-Schott and Hobson, 2002). More recently, less prominent fluctuations between such synchronous and asynchronous cortical firing states have been shown to occur within periods of wakefulness as well (Crochet and Petersen, 2006; Greenberg et al., 2008; Poulet and Petersen, 2008). The membrane potential of cortical neurons and their responsivity to input covary with fluctuations in cortical state (Zagha et al., 2013), leading to the view that the brain's repertoire of possible activity states – the joint set of parameters that are subject to rapid variation, such as gamma power, spiking correlation, and intracellular potentials – is determined by the brain's dynamic state (Okun and Lampl, 2008; Luczak et al., 2009; Harris and Thiele, 2011).

The ability to select and respond to the appropriate sensory information while ignoring irrelevant sensory information, known as top-down attention, shows similar neural characteristics as the desynchronized cortical state. In addition to the near-complete absence of neural and behavioral responsivity to sensory input during sleep, fluctuations in cortical state during wakefulness determine responsivity of cortical neurons to relevant sensory input (Reimer et al., 2014; McGinley et al., 2015b) as well as an animal's ability to respond appropriately to such input (McGinley et al., 2015a). Specifically, local desynchronization in neural population activity co-occurs with better signal detection performance at the behavioral level (McGinley et al., 2015a). Accordingly, attention to task-relevant stimuli has been proposed to rely on similar neural mechanisms as global cortical state change (Harris and Thiele, 2011).

Interestingly, the activity of the LC-NE system fluctuates as a function of brain state. For instance, the transition from wakefulness to the onset of sleep is marked by a progressive reduction of LC firing that continues until near-complete silence during paradoxical sleep (Aston-Jones and Bloom, 1981). Moreover, rapid changes in cortical activity state that occur during wakefulness co-occur with NE release within the cortex (Reimer et al., 2016), and with fluctuations in pupil diameter (Reimer et al., 2014). Fluctuations in pupil diameter in turn co-vary with activity in the LC (Aston-Jones and Cohen, 2005; Murphy et al., 2014b; Varazzani et al., 2015; Joshi et al., 2016). As mentioned earlier, the changes in brain state that accompany changes in pupil diameter and cortical NE release also co-vary with behavioral signal detection performance (McGinley et al., 2015a). Moreover, the magnitude of the pupil-linked attentional orienting response predicts the degree of behavioral adaptation following performance errors (Murphy et al., 2016).

The above indicates that cortical state, noradrenergic neuromodulation, and cognitive processes such as attention, are tightly intertwined. It is this junction that forms the central theme of this dissertation. Below, an overview of the chapters of this dissertation is presented, and each chapter is discussed within the context of brain state, neuromodulation, cognition, or a combination of these sub-themes.

1.5 An overview of the current dissertation

1.5.1 Chapter 2: Post-Error Slowing as a Consequence of Disturbed Low-Frequency Oscillatory Phase Entrainment

One of the most ubiquitous findings across reaction time (RT) tasks is that RTs slow down on trials following errors (Rabbitt, 1966; Laming, 1979). This phenomenon is known as post-error slowing (PES) and occurs across various task conditions and response modalities (Gehring and Fenscik, 2001b; Ridderinkhof, 2002; Endrass et al., 2005; Cavanagh et al., 2009a; Cohen et al., 2009; Dudschig and Jentzsch, 2009; Jentzsch and Dudschig, 2009; Eichele et al., 2010). PES has been suggested to reflect the strategic adjustment of behavior (Botvinick et al., 2001; Dutilh et al., 2012a) as well as a detrimental processing interference caused by the error (Jentzsch and Dudschig, 2009; Notebaert et al., 2009).

As discussed in the previous section, brain state influences our ability to select and respond to relevant sensory information. One line of literature suggests that, under conditions of rhythmic stimulus presentation, our brain may dynamically adjust its activity state in order to actively anticipate incoming stimuli by rhythmically aligning neural oscillations to the stimulus stream (Lakatos et al., 2008; Schroeder and Lakatos, 2009; Saleh et al., 2010; Stefanics et al., 2010b; Besle et al., 2011a; Henry and Obleser, 2012). Such ‘entrainment’ ensures that goal-relevant sensory

information is processed in the optimal neural context, and thus facilitates appropriate behavioral responses.

In chapter 2 of this dissertation, we test the novel hypothesis that PES may reflect a temporary perturbation of the entrained state. To test this hypothesis, we measured oscillatory EEG dynamics while human subjects performed a demanding discrimination task under time pressure. We show that brain state actively adjusts to the stimulus presentation rhythm by entraining low-frequency neuronal oscillations, and that the phase of these oscillations at stimulus onset predicts the speed of responding. Importantly, we show that entrainment is disrupted following errors, and that the degree of phase disturbance is closely related to the degree of PES on the subsequent trial.

Our results are consistent with the orienting account of PES, which proposes that errors, by virtue of being surprising events, result in the temporary reorientation of attention away from the current task, and as a consequence, longer RTs on the following trial (Notebaert et al., 2009). Interestingly, the LC-NE system is known to fire phasically in response to salient and surprising events, and theoretical accounts exist that link PES to the LC-NE system (Cohen et al., 2000; Nunez Castellar et al., 2010). Moreover, and in line with the concept of an orienting response, phasic NE release has also been proposed to act as a neural interrupt signal, whereby unexpected events (e.g., errors) lead to a reset and reorganization in target neuronal networks, and subsequent behavioral adaptation (Bouret and Sara, 2005; Dayan and Yu, 2006). We speculate that it is possible that the entrained brain state and consequent mode of behavioral responding are disrupted by an error-evoked orienting response in the LC-NE system (Nieuwenhuis et al., 2010; Nunez Castellar et al., 2010; Ullsperger et al., 2010). An orienting response (or interrupt signal) may aid task performance at longer intervals between errors and subsequent trials by facilitating the appropriate adjustment of behavior (Murphy et al., 2016).

1.5.2 Chapter 3: Catecholaminergic Neuromodulation Shapes Intrinsic MRI Functional Connectivity in the Human Brain

Spontaneously generated, ongoing, brain activity is correlated across brain regions (Biswal et al., 1995; Leopold et al., 2003; Fox and Raichle, 2007; Hiltunen et al., 2014). Moreover, the global structure of correlated activity changes dynamically with alterations in conscious state (Barttfeld et al., 2015) and task conditions (Nir et al., 2006; Sepulcre et al., 2010). In chapter 3 of this dissertation, we test the hypothesis that fluctuations in the strength of these intrinsic correlations are induced by the LC-NE system (Leopold et al., 2003; Drew et al., 2008; Schölvinck et al., 2010). Using a double-blind placebo-controlled cross-over design, we pharmacologically increase synaptic NE and DA levels by administering atomoxetine, a selective NET blocker, and examine the effects on the strength and spatial structure of 'resting-state' MRI functional connectivity.

As discussed earlier in this introductory chapter, NE increases neural gain, and as a result facilitates brain-wide signal transmission (Servan-Schreiber et al., 1990; Berridge and Waterhouse, 2003; Aston-Jones and Cohen, 2005). Computational modeling has indicated that such an increase in signal transmission should result in a brain-wide increase in the strength of both positively and negatively correlated activity, and the degree of clustering of that activity (Eldar et al., 2013). Eldar et al. (2013) accordingly showed that increased pupil diameter is indeed accompanied by such an increase in the strength of connectivity and clustering. Based on these findings, we predicted that the administration of atomoxetine should increase the strength and clustering of connectivity. Moreover, given the putative spatial aselectivity of the LC-NE system, we expected that an atomoxetine-induced increase in connectivity should be homogenous across the brain.

However, in contrast to an atomoxetine-induced increase in the strength of connectivity, we show that atomoxetine *reduced* the strength of inter-regional correlations across three levels of spatial organization. Furthermore, this modulatory effect on intrinsic correlations exhibited a substantial degree of spatial specificity: the decrease in functional connectivity showed an anterior-posterior gradient in the cortex, depended on the strength of baseline functional connectivity, and was strongest for connections between regions belonging to distinct intrinsic connectivity networks.

Our findings are the first to show that neuromodulation shapes the topography of intrinsic correlations in the human brain in a spatially specific manner. The unexpected reduction of the strength of connectivity indicates that neuromodulation may shape intrinsic correlations in a brain state-dependent manner, which dovetails with positron emission tomography findings (Coull et al., 1999) and theoretical proposals (Mather et al., 2015), but is difficult to account for by a global modulation of neural gain alone. Moreover, spatial specificity in the effect of atomoxetine on intrinsic correlations may be explained by recent findings that the projection profile of the LC-NE system is more heterogeneous than once thought (Chandler et al., 2014; Schwarz and Luo, 2015; Schwarz et al., 2015), and by the heterogeneous distribution of noradrenergic receptors (e.g. α2) across the cortex (Zilles and Amunts, 2009; Nahimi et al., 2015).

1.5.3 Chapter 4: Catecholamines Modulate Intrinsic Long-range Correlations in the Human Brain

In chapter 4, we test a prediction from the network reset account (Bouret and Sara, 2005): an increase in NE should lead to a reorganization of brain functional networks. To do so, we reanalyzed the dataset used in chapter 3: a double-blind placebo-controlled cross-over design in which we pharmacologically increase synaptic NE and DA levels by administering the selective NET blocker atomoxetine. We applied two complementary analysis approaches to examine the effect of NE on fine-grained

patterns of intrinsic functional connectivity patterns: 'dual regression' and 'spatial mode decomposition'. As opposed to chapter 3, in chapter 4 we examine if atomoxetine results in changes to the spatial structure (topology) of intrinsic fMRI correlations rather than a modulation of their strength alone.

Both analysis approaches provided converging evidence for an atomoxetine-related reduction in correlations between distributed brain regions, specifically sensory and motor-related networks. Additionally, spatial mode decomposition revealed a shift in dominance from left to right-lateralized frontoparietal network cofluctuations. Importantly, the pre-dominant effect of atomoxetine was a quantitative change to correlations within existing functional networks that left the spatial structure of these networks intact, rather than a reconfiguration of network topology.

Our findings are consistent with earlier work on primates (Guedj et al., 2016) which demonstrated similar connectivity atomoxetine-induced reductions in sensory and motor-related networks. However, we demonstrate that such reductions can be quantitative in nature, rather than necessarily stemming from a topological reconfiguration of network structure as would be predicted by the network reset account (Bouret and Sara, 2005). We conclude that catecholamines modulate dynamic changes in the strength of intrinsic inter-regional correlations, which may serve to coordinate flexible modulations of network interactions in order to facilitate goal-directed behavior.

1.5.4 Chapter 5: Pupil Diameter Tracks Lapses of Attention

Sustained attention, our ability to continuously monitor and respond to goal-relevant sensory information, is limited. Studies on the relationship between lapses of attention and psychophysiological markers of attentional state, such as pupil diameter, have yielded contradicting results. Adaptive gain theory (Aston-Jones and Cohen, 2005) predicts that baseline pupil diameter should show an inverted-U shaped relationship with attentional performance, whereby most lapses of attention occur in both periods where the pupil is relatively large, and where it is relatively small. In chapter 5, we test this prediction directly. Moreover, we explore additional markers of attentional state, based partially on recent research that showed a close relationship between the derivative of pupil diameter and brain state and attentional performance (Reimer et al., 2014; McGinley et al., 2015a).

We investigate the relationship between tonic fluctuations in pupil diameter and performance on a demanding sustained attention task. We found robust linear relationships between baseline pupil diameter and several measures of task performance, suggesting that attentional lapses tended to occur when pupil diameter was small. However, these observations were primarily driven by the joint effects of time-on-task on baseline pupil diameter and task performance. The linear relationships disappeared when we statistically controlled for time-on-task effects and were replaced by consistent inverted U-shaped relationships between baseline pupil

diameter and each of the task performance measures, such that most false alarms and the longest and most variable response times occurred when pupil diameter was both relatively small and large.

Finally, we observed strong linear relationships between the temporal derivative of pupil diameter and task performance measures, which were largely independent of time-on-task. Our results help to reconcile contradicting findings in the literature on pupil-linked changes in attentional state, and are consistent with the adaptive gain theory of LC-NE function. Moreover, our results suggest that the derivative of baseline pupil diameter is a potentially useful psychophysiological marker that could be used in the on-line prediction and prevention of attentional lapses.

1.5.5 Chapter 6: Task-free Spectral EEG Dynamics Track and Predict Patient Recovery From Severe Acquired Brain Injury

As previously discussed, our ability to process and respond to sensory information is dependent on the dynamic brain state. One prominent example in which brain state is fundamentally altered is that of disorders of consciousness resulting from brain injury. Some of these patients develop signs of awareness, while other patients remain in a state of unresponsiveness (Jennett and Plum, 1972; Laureys et al., 2004). At the neural level, the pathophysiological signatures of disorders of consciousness are reminiscent of hypoactivity in the LC-NE system that occurs during sleep or under-arousal, and concurrent mass-synchronization of cortical neurons. As shown in chapters 3 and 4 of this dissertation, brain activity that is synchronized across cortical areas in the absence of sensory input is susceptible to noradrenergic neuromodulation. In chapter 6 of this dissertation, we explore if the state (quantified as amplitude and connectivity) of such synchronized cortical activity in the absence of sensory input can be used to track and predict the level of awareness of patients with disorders of consciousness and their respective level of recovery. We analyze an existing dataset of patients who participated in an ‘Early Intensive Neurorehabilitation Programme’ (Eilander et al., 2005; Wijnen et al., 2007).

We show that compared to healthy control participants, patients showed a general ‘slowing down’ of cortical rhythms, whereby low-frequency (synchronized) cortical states are relatively dominant. Moreover, across the course of their recovery, patients exhibit nonlinear frequency band-specific changes in spectral amplitude and connectivity metrics, and these changes align well with the metrics’ frequency band-specific diagnostic value. Remarkably, connectivity during a single task-free EEG measurement could predict the level of patient recovery approximately 3 months later with 75% accuracy.

Our findings show that amplitude and connectivity metrics of spectral brain state track patient recovery in a longitudinal fashion, and that these metrics are robust pathophysiological markers that can be used for the automated diagnosis and prognosis of disorders of consciousness. These metrics can be acquired

inexpensively at bedside, and are fully independent of the patient's neurocognitive abilities, which offers substantial improvements on existing methodologies. Lastly, our findings tentatively suggest that the relative preservation of ascending and recurrent interactions between the cortex and subcortical nuclei (speculatively, the thalamus or ascending arousal systems such as the LC), putatively responsible for desynchronized cortical states (Schiff, 2010; Schiff et al., 2014), may predict the later reemergence of awareness. Thus, our findings shed new light on the pathophysiological brain state-related processes that underlie disorders of consciousness.