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Review article

Towards a cognitive neuroscience of self-awareness

H.C. Lou[a,*], J.P. Changeux[b], A. Rosenstand[c]

[a] Center for Integrative Neuroscience, Aarhus University, 8000 Aarhus C, Denmark
[b] Institut Pasteur, 75724 Paris, France
[c] Department of Ophthalmology, Copenhagen University Hospital, Rigshospitalet, Glostrup, Denmark

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ABSTRACT

Self-awareness is a pivotal component of conscious experience. It is correlated with a paralimbic network of medial prefrontal/anterior cingulate and medial parietal/posterior cingulate cortical "hubs" and associated regions.

Electromagnetic and transmitter manipulation have demonstrated that the network is not an epiphenomenon but instrumental in generation of self-awareness. Thus, transcranial magnetic stimulation (TMS) targeting the hubs impedes different aspects of self-awareness with a latency of 160 ms. The network is linked by ~40 Hz oscillations and regulated by dopamine.

The oscillations are generated by rhythmic GABA-ergic inhibitory activity in interneurons with an extraordinarily high metabolic rate. The hubs are richly endowed with interneurons and therefore highly vulnerable to disturbed energy supply. Consequently, deficient paralimbic activity and self-awareness are characteristic features of many disorders with impaired oxygen homeostasis. Such disorders may therefore be treated unconventionally by targeting interneuron function.

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1. Naturalization of self-awareness: its biological function, and how it may be investigated

Self-awareness provides the information essential for conscious self-monitoring (metacognition). Metacognition is a tool for consciously controlling behavior and adjusting our experiences of the world. It is essential for learning by conscious experience, not only within ourselves, but, importantly, also between individuals (Bahrami et al., 2010). Self-awareness is therefore of decisive importance by giving humans an advantage in phylogeny (Fabbro et al., 2015; Lagercrantz and Changeux, 2009; Lou, 2012; Perner and Roessler, 2012). Self-awareness was until quite recently considered off-limits for the natural sciences. More specifically, neurobiological research has shunned the "hard question of how and why consciousness and self-awareness arise from a physical basis", considering it un-accessible with current technology following Chalmers DJ (Chalmers, 1996; Koch, 2009; Lou, 2012; Neafsey, 2009). The difficulties encountered in investigating the biology of self-awareness have been discussed by Zahavi and Roepstorff (2011). They draw attention to the discrepancies between the effort applied to setting up self-awareness experiments and discussing the experimental results, while disregarding the very notion of the concept of self-awareness. More radically, Dretske stresses that there are explanatory challenges related to consciousness per se and puts forward the theory that we never have experiences of ourselves, but only on the contents of consciousness (Mehta and Mashour, 2013).

* Corresponding author.
E-mail addresses: hanslou1@gmail.com (H.C. Lou), Changeux@noos.fr (J.P. Changeux), rosenstand.astrid@gmail.com (A. Rosenstand).

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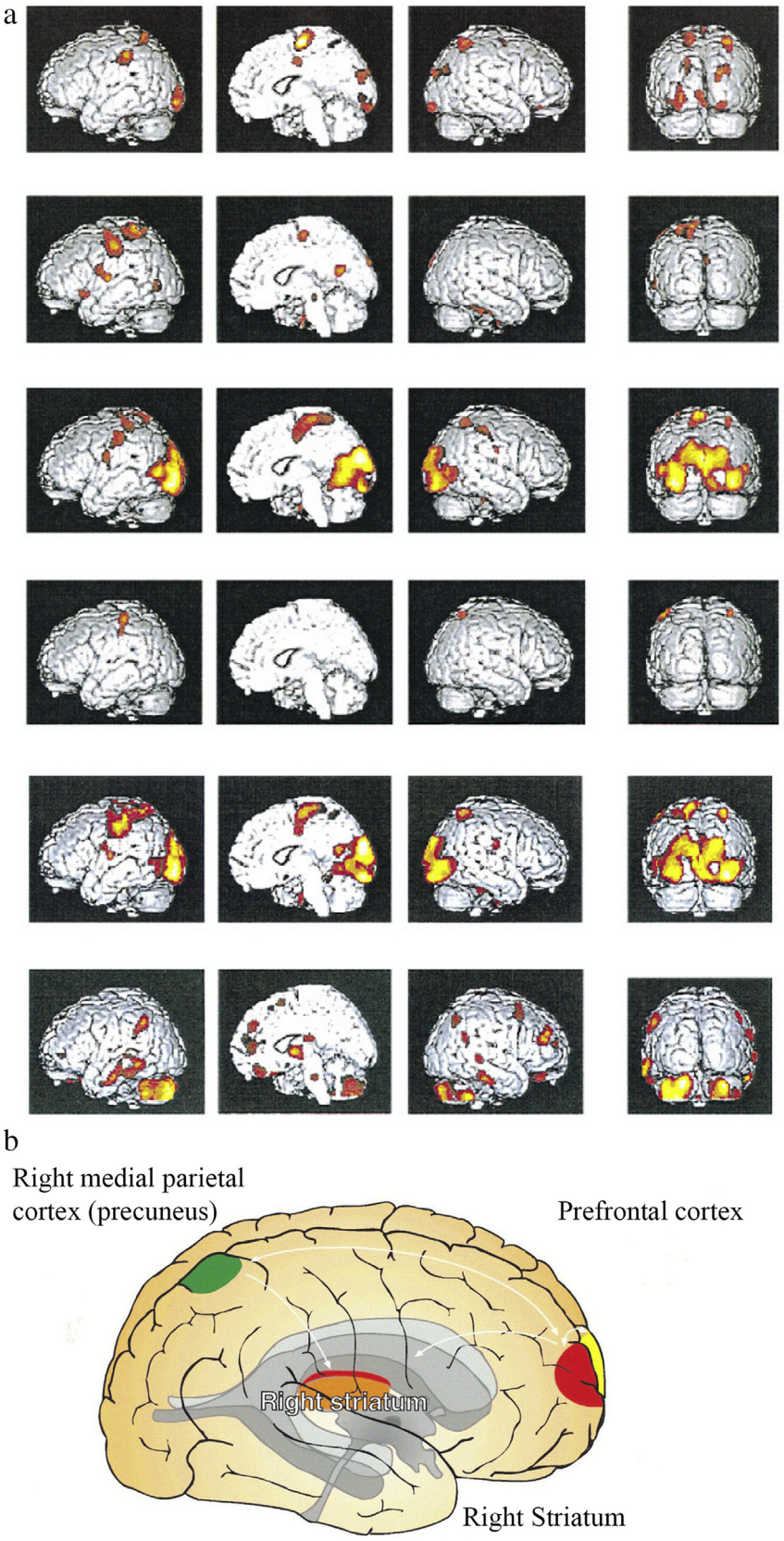

Fig. 1. Cerebral activation patterns vary with shifting contents of consciousness. All conscious states are linked to activity in a medial paralimbic network. (a)The four upper rows represent cerebral blood flow patterns measured with ^{15}O—H_2O-PET during yoga nidra meditation on weight of own body part (upper row) abstract perception of joy (second row) visual imagery of landscape (third row), and symbolic representation of self (lower row) with permission (Lou et al., 1999). (b) The right medial parietal cortex (precuneus), prefrontal cortex, and right striatum are activated in all meditative states and in the control state (Lou and Kjaer, 2005) (with permission).

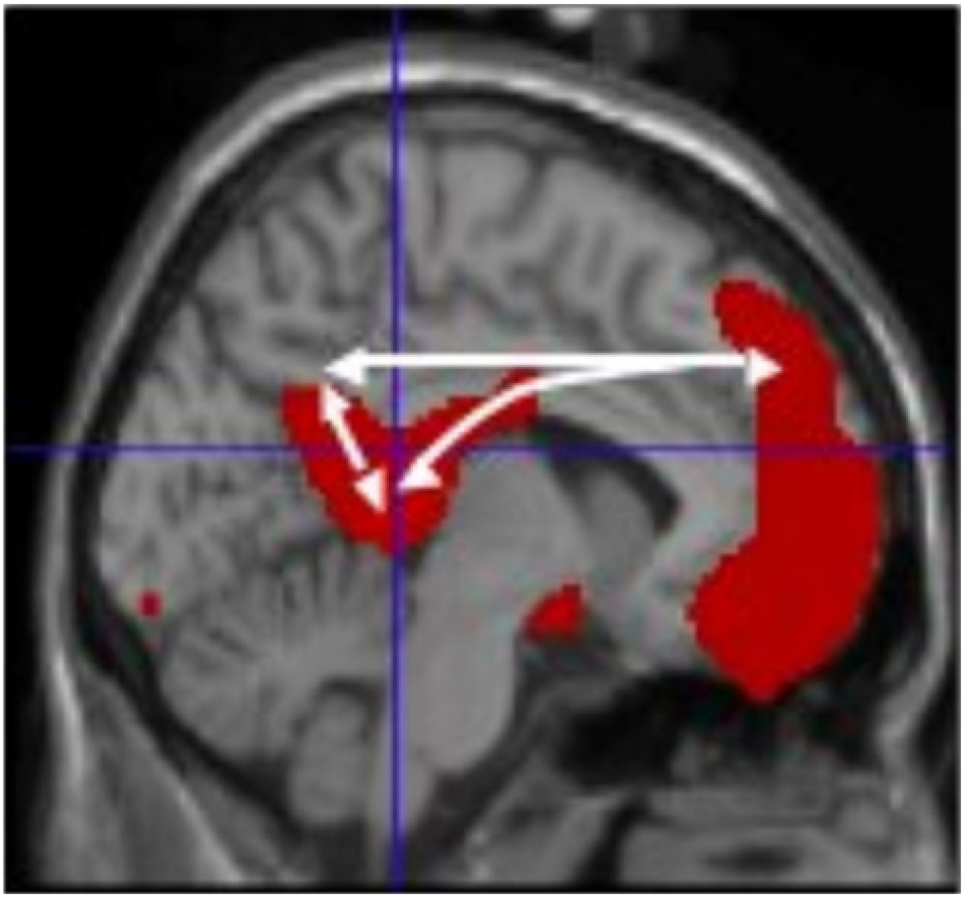

Fig. 2. The paralimbic network in narrative self-awareness. Retrieval of previous judgment of oneself activates a paralimbic network of medial prefrontal/anterior cingulate (anterior "hub") and medial parietal/posterior cingulate cortices (posterior hub), together with thalamus (Changeux and Lou, 2011) (with permission).

In contrast, Damasio (2000); Gallagher (2000), following Wittgenstein and the phenomenologists, claim that we are self-aware whenever we are conscious. Consequently, attempts at separating the notions of "self-awareness" and "familiarity" may seem futile (*e.g.* Kapitan, 1999). Accordingly, self-awareness is an indispensible part of our experience of the world, whether it is minimal self-awareness (pre-reflective, with an automatic sense of ownership of the experience), or narrative self-awareness, extended in time by retrieval of personal memories and thereby allowing predictions of the future (Ingvar, 1985). Minimal self-awareness may be investigated using rapidly presented visual stimuli of varying duration (Weiskrantz et al., 1995), and by first person *vs* third person perspective (Vogeley et al., 2004). Narrative, extended, self-awareness may be investigated using retrieval of episodic memory of previous judgments. Both minimal self-awareness and narrative self-awareness may be ranked according to degree of self-reference (Craik et al., 1999). This approach has allowed recent research to surpass earlier limitations and gives us insights into the biological origin and function of self-awareness, and how its impediment in disease may account for major disorders in conscious regulation, with consequences for treatment and prevention.

2. The paralimbic network associated with self-awareness

Shifting cerebral activation patterns occur with changing contents of consciousness during "mind wandering", both during yoga nidra meditation and in the normal resting conscious state. This was documented already in 1999 using H_2O^{15}-positron tomography (PET) (Lou et al., 1999). In spite of the variability, a set of medial paralimbic regions were continuously active, including medial and lateral prefrontal cortex, the right medial parietal cortex, and right striatum (Kjaer and Lou, 2000; Kjaer et al., 2001) (Fig. 1a and b). Following this discovery, it was proposed that the medial prefrontal and parietal regions constitute a self-referential core of changing conscious experiences according to Damasioís and Gallagherís concept. It is consistent with the assumption that self-awareness is an integral function of all conscious experiences, binding conscious experiences together into a single construct with a sense of unity of consciousness (Kjaer et al., 2001; Kjaer et al., 2002a,b; Lou et al., 2005).

During the following years a number of experimental approaches characterized a neural correlate of self-awareness more fully. The early studies were done primarily with the ^{15}O—H_2O PET method, which is still considered a gold standard for examining the distribution of activity in the brain. For practical reasons, most recent studies have used functional magnetic imaging (fMRI). They have given results comparable to the early PET-studies, in spite of relying on more complex, and disputed, physiological principles (Mechelli et al., 2001; Zaldivar et al., 2014). Different levels of complexity and different levels of representational processes have been examined. In spite of applying different methodologies on the different aspects of self-awareness, like verbal, spatial, emotional, and facial, these experiments showed converging evidence for medial prefrontal/anterior cingulate and parietal/posterior cingulate paralimbic regions being correlated with self- awareness (Fig. 2). On this basis it was concluded that the medial paralimbic network is a common neural signature for self-awareness (Newen and Vogeley, 2003). The idea has been supported by a large meta-analysis by

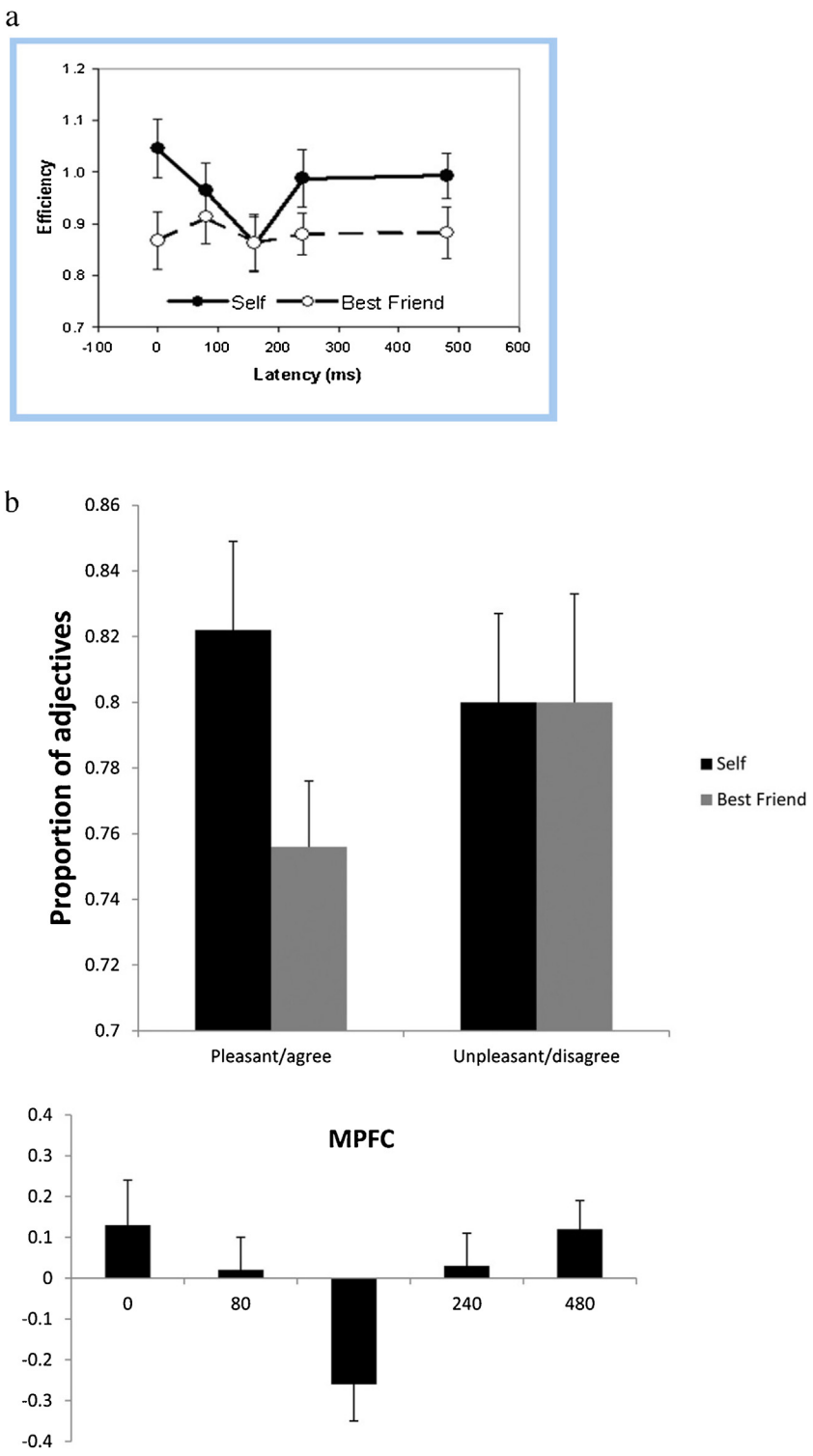

Fig. 3. Causality of paralimbic network evidenced by TMS. Transcranial magnetic stimulation (TMS) targeting medial parietal/posterior cingulate region impairs accuracy and reaction time for identifying previous judgment of self (adjectives) *vs* other ("best friend") (a), Lou et al., 2004), with maximal effect at a latency of 160 ms. In (b), preference for allocating positively rated adjectives to one-self rather than best friend is selectively impaired with TMS targeting the medial prefrontal cortex (Luber et al., 2012). The results demonstrate that the two widely separated regions of self-awareness processing "ignite" simultaneous at a latency of 160 ms.

Northoff et al. of self-related activation, studied mainly by functional magnetic resonance imaging (Northoff et al., 2006).

The ontogeny of narrative, extended, self-awareness occurs concomitantly with the development of the paralimbic network: The newborn has a proprioceptive sense of its own body and readily imitates gestures and facial expression essential for social bonding and anticipation of emotional reactions of other people. The infant is probably aware only of events in the present time, while the adult capacity to put these sensations into a time perspective has to await later development (Lagercrantz and Changeux, 2009; Legrain et al., 2011). This shift takes place together with a change in dominance

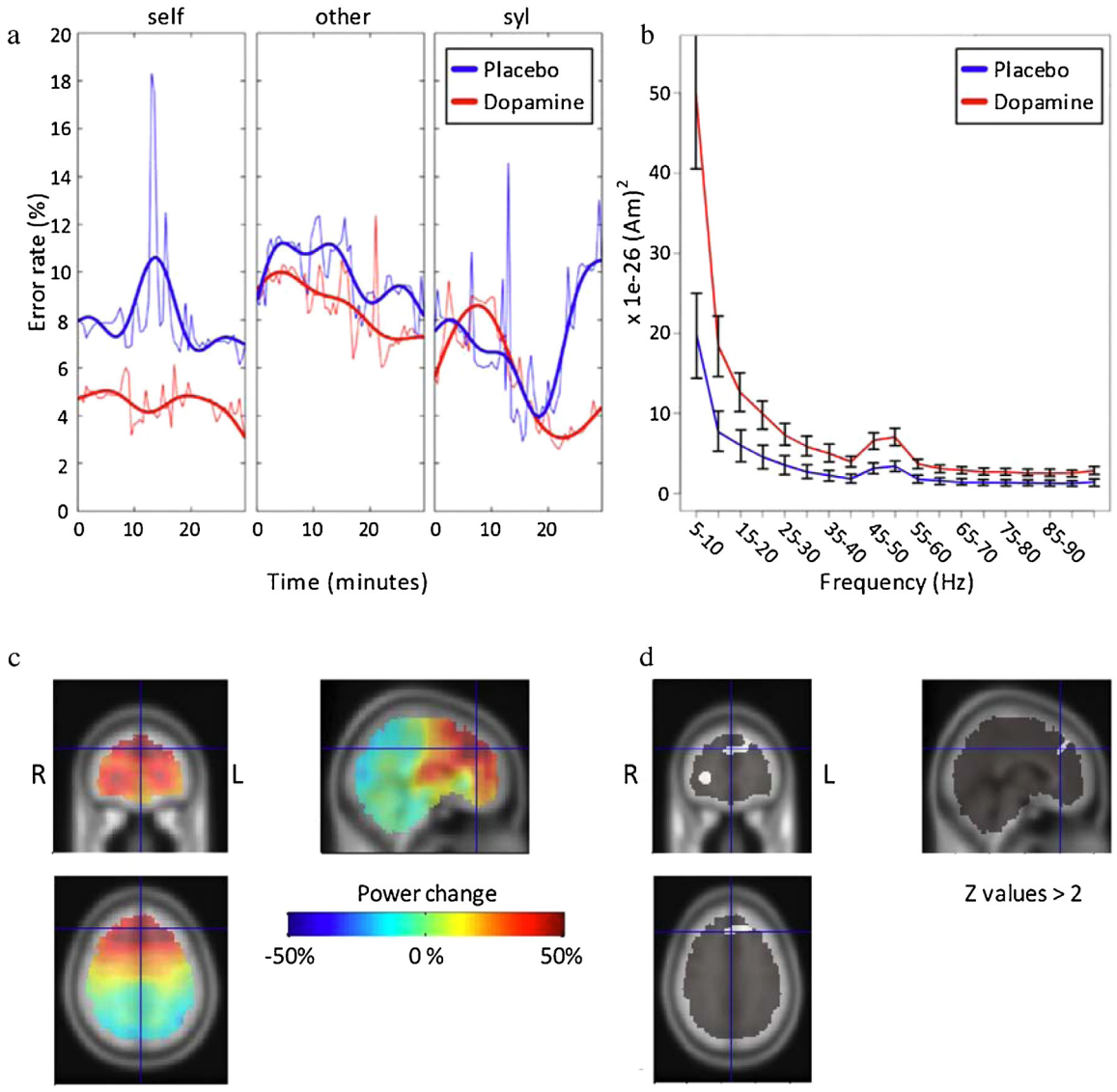

Fig. 4. Dopamine improves self-awareness and increases gamma power through medial prefrontal/anterior cingulate cortex. With dopamine (sinemet 100 mg p.o.) compared to placebo, a decreased error rate is seen in retrieval of previous judgment on whether adjectives fitted one-self or not compared to placebo (a). In contrast, retrieval of judgment of a control person (best friend) is not changed significantly (b). Whole brain MEG showed preferential power increase in anterior medial prefrontal/anterior cingulate region and right insula (gamma range (30–100 Hz) (c, d) (see Joensson et al., 2015 for details) (with permission).

of the functional architecture from mainly sensori-motor hubs to the medial paralimbic hubs (Cho et al., 2015; Fransson et al., 2011).

The functional anatomy of the two core hubs of self-awareness, the medial prefrontal/anterior cingulate and medial parietal/posterior cingulate cortices, has been analyzed in detail by Amodio and Frith (2006); Fleming et al. (2010); Cavanna and Trimble (2006); Peer et al. (2015). The core regions are usually accompanied with activity in the insula, angular gyri, and sub-cortical regions, depending on the special characteristics of each particular form of self-awareness. An example is awareness of the own body, which is linked to gamma-butyric acid (GABA) composition in the insula as determined by magnetic resonance spectroscopy (Wiebking et al., 2014). This finding is consistent with earlier results showing that damage to both right insula and adjacent parts of the parietal cortex, and their connections with the medial prefrontal cortex may impair sensation of own body (Damasio, 2000; Orfei et al., 2008). They are also consistent with the out of body experience with a temporary disruption in multi-sensory integration processes (Heydrich and Blanke, 2013). Likewise, in self-generated movements activity in supplementary motor regions is linked to the paralimbic circuitry of self-awareness (Nguyen et al., 2014). Finally, the so- called the "default mode network" of idleness is characterized by a high degree of self-referential thinking, but not without exceptions (Gusnard et al., 2001; Salomon et al., 2014; Davey et al., 2016). Its major hubs are medial prefrontal/anterior cingulate and medial parietal/posterior cingulate cortices like pure examples of self- awareness. These hubs are exceedingly metabolically active in idleness, while their activity is decreased with the diminished self-awareness during goal-directed action in the outside world (Gusnard et al., 2001; Luber et al., 2012; Salomon et al. (2014). This change reflects the brainís capacity to shift allocation of resources according to changing needs (Lou et al., 2011a,b,c).

3. From association to causality

The ascription of the medial paralimbic network to self-awareness in Section 2 is mainly based on imaging data, and can, as

such, only be correlative. It could therefore be an epiphenomenon. Accordingly, the significance of the network for self-awareness has been disputed (Legrand and Ruby, 2009; Smith, 2012). In order to establish an eventual causal relationship between objective measurements and the subjective perception of self-awareness, a series of intervention studies has been carried out. These include investigating the behavioral consequences of electromagnetic as well as neurotransmitter manipulation of the paralimbic network. Transcranial magnetic stimulation (TMS) has been used for this purpose. With TMS, the neural function of a given region is transiently disturbed by applying a strong, short-lasting magnetic field to the scalp targeting the region. Specifically targeting the medial parietal/posterior cingulate (Lou et al., 2004) and prefrontal/anterior cingulate (Luber et al., 2012) regions has unequivocally shown that the former region is instrumental in retrieval of self-related episodic memory (narrative self-awareness), while the latter region is instrumental in self-evaluation (introspection). At the two sites there was a simultaneous maximal depressing effect at 160 ms on self-awareness measured by contrasting accuracy and reaction times to respond to stimuli with different degrees of self-information (Fig. 3). The interaction between the two sites is bi-directional and recurrent mainly in the lower gamma range providing a "bootstrapping" effect as evidenced by Granger causality analysis of magneto-encephalographic signals (MEG) (Lou et al., 2011a,b,c). This conceivably increases signal duration and strength at medial parietal and medial prefrontal sites facilitating access to consciousness (Libet, 1991). The simultaneously emerging self-awareness components at widely separated regions is consistent with the global neuronal network theory for access to consciousness and the simultaneous "ignition" of separate brain regions in the course of conscious processing (Dehaene and Changeux, 2011). Causality of lower gamma oscillations in the frontal regions for self-awareness has recently been confirmed by induction of self-reflective awareness in dreams using synchronous oscillations around 25 and 40 Hz over the frontal cortical regions (Voss et al., 2014).

Generation of gamma frequency oscillations depends on fast-spiking, parvalbumin −ergic interneurons. Thus, transgenic mice deficient in these interneurons have deficient gamma oscillations and behavioral abnormalities, which may be restored optogenetically (Kim et al., 2015). In humans, Hall et al. (2010) showed that GABA-ergic stimulation induced gamma power increase in the prefrontal cortex. The development of GABA-ergic inhibition of pyramidal cells, essential for generation of gamma synchrony, begins already in utero and is not completed until adulthood. Direct recording of $GABA_A$ receptor-mediated inhibitory post-synaptic currents showed their amplitude to increase during childhood (Gonzalez-Burgos et al., 2015), with concomitant changes in GABA synapse-related gene products (Datta et al., 2015). In mice, this development has been shown to be directly concomitant with development of multisensory integration through the insula (Gogolla et al., 2014). Common to all GABA-ergic neurons is the synthesis of GABA, catalyzed by two isoforms of glutamic acid decarboxylases (GAD), GAD67 as the rate-limiting enzyme, which may be deficient in many neuropsychiatric disorders. By removing one allele of this enzyme in the mouse prefrontal cortex the level of GAD67 was artificially decreased, with deficits in transmission from interneurons to pyramidal neurons and synaptic inhibition necessary for gamma oscillations as a consequence (Lazarus et al., 2015).

More specifically, we have shown that self-awareness is regulated by dopamine through the medial prefrontal/anterior cingulate cortex (Lou et al., 2011a,b,c) (Joensson et al., 2015) (Fig. 4), and that this occurs via the GABA system: dopamine activation in humans elicits GABA activity directly in the medial prefrontal/anterior cingulate cortex of the paralimbic network and

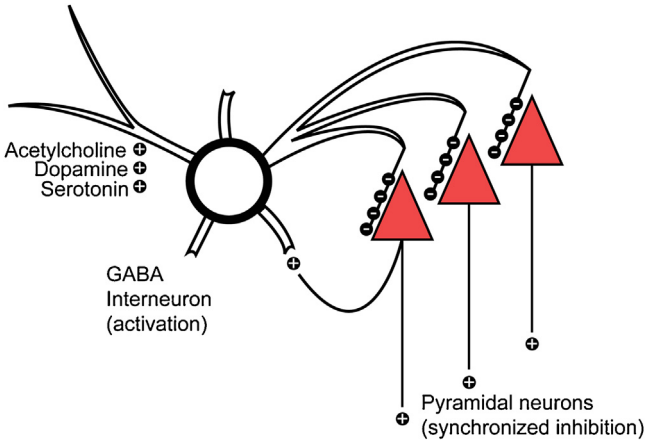

Fig. 5. Schematic illustration of neurotransmitter regulation of pyramidal cell synchrony via GABA-ergic interneurons. Fast-spiking GABA-ergic interneurons are responsible for the synchrony by inhibitory influence on pyramidal cell excitation. In their turn, interneuron activity is enhanced by D1 and D2 receptors located at or near the soma. By this common path dopamine enhances paralimbic synchrony for self-reference, a crucial constituent of any conscious experience. (Modified from Changeux and Lou, 2011; Gonzalez-Burgos and Lewis, 2008).

the associated right insula (Lou et al., 2016, (Fig. 5), thus accounting for the effect of dopamine in its regulation and also for the preferential role of right hemisphere in self-recognition (Keenan et al., 2001). Causal effects may also be inferred by the influence of acetylcholine (Changeux and Lou, 2011), serotonin (Juckel, 2015), and of oxytocin (Liu et al., 2013; Muthukumaraswamy et al., 2013), making interneurons a natural "mini brain", balancing a wide spectrum of neurotransmitters in the regulation of pyramidal cell activity.

There is therefore now ample functional anatomical and molecular evidence for that the paralimbic network is not only active in self-awareness; it is also instrumental in self-awareness and its regulation.

4. Pathophysiology - the importance of oxygen homeostasis

Due to its fundamental significance for human development and nature described in Section 1, disturbance of self-awareness and its paralimbic network is a basis for much pathology. Thus gamma synchrony is dysfunctional in behavioral addiction without drug abuse (Rømer Thomsen et al., 2013), a mono-symptomatic condition with deficient conscious self-monitoring. Addiction is conceptualized as deficiency of self-regulation, impulse control, decision making, and emotion processing. The addicted subject loses conscious self-regulation of behavior, *i.e.*, will power (Rømer Thomsen et al., 2013) (Fig. 6). Drug addiction can be viewed as the end point of a series of transitions from initial voluntary substance use to the complete loss of conscious "voluntary" control over this behavior, such that it becomes habitual and, ultimately, compulsive, confounded by toxic effects. One prominent example is the influence of nicotine on nicotinic acetylcholine receptors on prefrontal cortical neurons (Changeux, 2010; Heath et al., 2010; Lambe et al., 2003; Lena et al., 1993), thereby further disturbing normal functioning of the paralimbic network in a vicious circle (Changeux and Lou, 2011; Tang et al., 2015). Disturbance of paralimbic function also prevails in more complex disorders of self-monitoring such as adhd (Castellanos et al., 2008; Lou, 1996), borderline personality disorder (Salvador et al., 2016), autism spectrum disorder (Oblak et al., 2009), schizophrenia (Gallinat et al., 2004), the dementias (Liu et al., 2014a,b), and following traumatic brain injury (Ham et al., 2014). Even in a pervasive dysfunctional state such as the vegetative state, recovery of the paralimbic network is tightly linked to clinical recovery (Laureys et al., 2006).

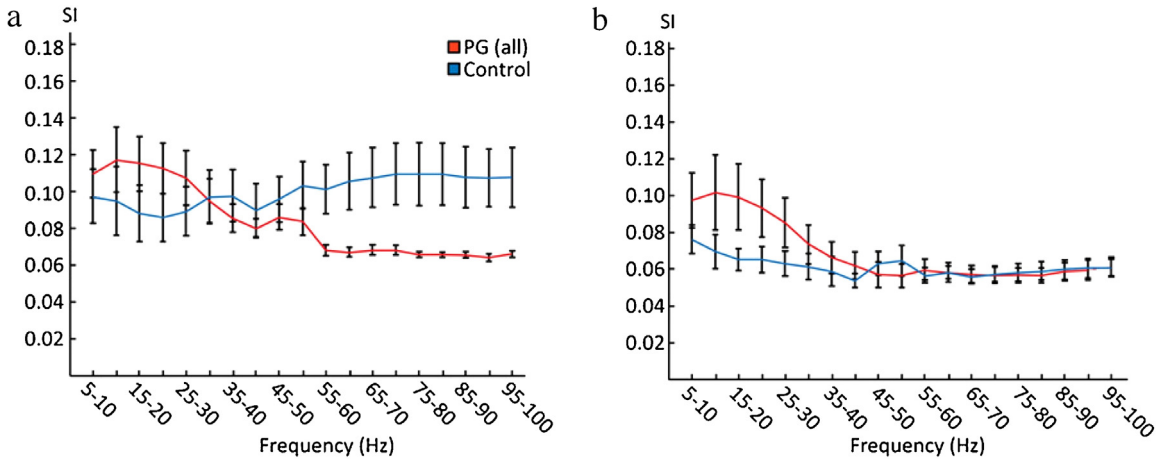

Fig. 6. Abnormal gamma synchronization (SI) in pathological gamblers. (a) During rest, pathological gamblers had lower synchronization than controls in gamma band (30–100 Hz). Subgroup analysis showed that this difference was found for both gamblers with and without a history of comorbid stimulant addiction (both $P < 0.05$). (b) During a stop-signal task there is no difference between gamblers and control. This finding illustrates abnormal function in the paralimbic network of self-reference, and, by inference, abnormal conscious self-control and metacognition, in individuals susceptible to gambling (Rømer Thomsen et al., 2013) (with permission).

The widespread dysfunction of self-awareness in pathology is likely to be a consequence of the exceedingly high oxygen demand of the paralimbic network (*e.g.* Raichle et al., 2001). The high metabolic requirement is mainly due to dense concentrations of parvalbumin GABA-ergic interneurons in the richly connected hubs of the paralimbic network (Tomasi et al., 2013) with their GABA-ergic synapses responsible for pyramidal cell synchronization (Kann, 2015). Especially the fast gamma oscillations are highly energy-demanding and therefore susceptible to metabolic disruptions (Kann et al., 2011). This makes self-awareness and meta-cognition particularly vulnerable in deficient oxygen and glucose supply. Accordingly, conditions with cerebral hypoxia-ischemia often lead to a dysfunctional paralimbic network with associated failing conscious self-awareness. Such consequences are seen following neonatal hypoxia-ischemia with deficient autoregulation in the newborn infant, particularly in prematurity (Lou, 1996), following heart failure (Kumar et al., 2011), in the long-term cognitive outcome in teenage survivors of arrhythmic cardiac arrest (Maryniak et al., 2008), and in severe obstructive sleep apnea (Peng et al., 2014). In agreement with the theory of impaired oxygen homeostasis in pathogenesis of self-awareness, also *hyper*oxygenation may be culpable, for instance in schizophrenia (Powell et al., 2012). In the future, more detailed information may be expected from the newly developed mini-brain technique of stem cell grafting (Willyard, 2015).

5. Consequences for treatment and prevention

The new understanding of the physiology and pathophysiology of self-awareness outlined in Section 4 may lead to the application of unconventional therapeutical strategies to increase dopaminergic activity and to improve paralimbic interaction. These strategies include relaxation meditation like yoga nidra or mindfulness meditation, which in independent studies have been shown to increase dopaminergic tone and induce growth in paralimbic structures (Kjaer et al., 2002a,b; Tang et al., 2015), and targeted training aiming at increasing the availability of dopaminergic receptors (McNab et al., 2009). Also improvement of sensory input may be an important venue to increase dopaminergic tone (Dommett et al., 2005; Overton et al., 2014) and induce growth in relevant structures. A prominent example of the latter is the induction of growth in the V2 region following cataract surgery (Rosenstand Lou et al., 2013). In addition, frontal electromagnetic stimulation of paralimbic oscillations could have a role (Voss et al., 2014). Finally, further improvement in characterization of the paralimbic network and associated disorders may be obtained for instance with the mini-brain grafting technique (Willyard, 2015), and advances are to be foreseen for stem cell grafting therapy of interneuron function (Tang et al., 2014).

More generally, the new discoveries provide impetus to efforts to maintain oxygen homeostasis in neural tissue ranging from decreasing oxygen demand by cooling, for instance in distressed neonates (Papile et al., 2014) and assuring optimal capillary flow distribution (Ostergaard et al., 2015) to controlling cerebral perfusion pressure and autoregulation of cerebral blood flow. The latter is particularly vulnerable in premature infants, which are prone to many developmental disorders related to deficient oxygen delivery to the brain, like cerebral palsy, adhd and autism spectrum disorder (Lou et al., 1979; Tsuji et al., 2000; Howlett et al., 2013). Newly developed oximetry techniques may be helpful in this regard (Hyttel-Sorensen et al., 2015).

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