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## *Unconscious Neural Specificity for ‘Self’ and the Brainstem*

**Abstract:** *The self/non-self distinction is essential for survival, but its neural bases are poorly understood. Studies have sought neural specificity for ‘self’ in cortical regions. However, behavioural evidence showing that humans are able to single out self-relevant information in the absence of awareness (e.g. during sleep) suggests that the cognitive self/non-self distinction might be rooted in subcortical structures involved in automatic, unconscious functions. Here we employ subliminal presentation of self and non-self faces and repetition suppression to show neural specificity for ‘self’ in the brainstem reticular formation, providing the first evidence for self/non-self distinction in subcortical structures. Our finding suggests that the brainstem may act as a neural substrate for the sense of ‘self’.*

Distinguishing ‘self’ from ‘non-self’ is an essential ability for survival (Simpson and Hines, 2002). While the immunological self/non-self distinction has been well characterized, at a cognitive level the neural

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bases of self-specificity are poorly understood. Specificity for ‘self’ has been investigated through visual (Brédart, Delchambre and Laureys, 2006), auditory (Moray, 1959), and lexical (Nuttin, 1985) modalities, with behavioural evidence indicating that self-related stimuli (such as one’s own face, or one’s own name) are especially salient (Brédart, Delchambre and Laureys, 2006; Moray, 1959; Nuttin, 1985; Tong and Nakayama, 1999). However, the neural basis for this self-specific salience has been more difficult to pin down.

The neural specificity for ‘self’ has been predominantly investigated through imaging techniques, where the most commonly cited evidence for brain specificity is both anatomical (i.e. where information is processed) and functional (i.e. how it is processed). For example, face recognition is considered anatomically and functionally unique because it engages a distinct brain region (the fusiform face area) and it involves a more holistic representation than other types of object. Language, likewise, is considered ‘specific’ because it relies on distinct brain networks that are not needed for non-linguistic sound recognition or vocalization. Neither unique brain regions (i.e. not involved in other cognitive functions) nor a specific type of response (e.g. specific large-scale, distributed pattern of neural activity, or neural synchronization on certain frequency bands) have so far been consistently identified in relation to the ‘self’, leading some investigators to question — and ultimately reject — the notion of brain specificity for self (Gillihan and Farah, 2005).

So far, imaging studies have sought brain responsiveness to self-related stimuli in cortical (particularly frontoparietal) regions (Uddin *et al.*, 2005; Devue *et al.*, 2007; Sui and Han, 2007; Sugiura *et al.*, 2000; Kircher *et al.*, 2001; Kelley *et al.*, 2002; Platek, Thomson and Gallup, 2004; Platek *et al.*, 2006). However, a common point emerging from the behavioural literature is that humans’ ability to single out self-relevant information does not require consciousness, as it has been observed during sleep (Oswald, Taylor and Treisman, 1960), inattention (Brédart, Delchambre and Laureys, 2006; Moray, 1959), and under subliminal perceptual conditions (Howarth and Ellis, 1961). The fact that the self/non-self distinction is operated automatically and unconsciously prompts consideration of an alternative possibility, namely that specificity for ‘self’ is not fully captured in terms of cortical activity, but rather is also characterized by neural responsiveness in evolutionarily ancient subcortical structures involved in automatic, unconscious functions. However, evidence for neural specificity for ‘self’ at a subcortical level has been sparse, and limited to conscious processing (Schneider *et al.*, 2008). Here we employ

functional magnetic resonance imaging during exposure to subliminal presentation of self and non-self faces.

The brainstem includes nuclei that not only regulate vital functions (e.g. breathing, heartbeat, sleep), but also integrate converging information originating from external (e.g. sensory) and internal (e.g. viscera, muscles) domains in order to generate survival-appropriate behaviour (Churchland, 2002; Angeles Fernández-Gil *et al.*, 2010). Specifically, a region within the rostral brainstem, corresponding with the midbrain portion of the reticular formation, has recently been shown to respond to highly salient external stimuli with phasic (i.e. temporary) elevation of vigilance (Kinomura *et al.*, 1996). Importantly, the phasic excitation found in cholinergic neurons ascending from the brainstem and originating from the midbrain reticular formation (Mesulem *et al.*, 1983) has been shown to reduce or disappear upon repetition of stimulation (Kayama and Ogawa, 1987). This neurophysiological phenomenon, known as 'repetition suppression' and consisting in a decreased neuronal response to a given stimulus following prior processing of an identical stimulus (or stimulus attribute), has been observed both in terms of reduced firing rate (Desimone, 1996) and of decreased BOLD (blood oxygen level dependent) responses (Grill-Spector and Malach, 2001; Jenkins, Macrae and Mitchell, 2008). Since, in a given neuron, repetition suppression only occurs if that neuron is sensitive to the repeated stimulus feature (such that the two stimuli are considered to be 'same', even though they may differ in other dimensions to which that neuron is not sensitive), observing self-specific repetition suppression within the midbrain reticular formation would provide evidence for self-specificity in that region.

Thus the midbrain reticular formation is involved in 1) temporary shifts of arousal in response to highly salient sensory stimuli, and 2) habituation upon repeated exposure to them. Given the behaviourally documented high salience of the self-face, we hypothesized that a selective response to the self-face would be observed within the midbrain reticular formation as well, and that this selective response might be the neural underpinning of specificity for 'self'. We tested the hypotheses that 1) exposure to one's own (and not to someone else's) face is associated with activation within the midbrain reticular formation, and 2) that this response decreases upon subliminal repeated stimulus exposure.

We employed fMRI to identify responses to single and repeated exposure to the self-face. Our experimental approach is based on a masked priming design involving self and non-self faces, and has

been described in previous reports (Pannese and Hirsch, 2010; 2011). Briefly, twelve subjects indicated whether self and non-self faces (targets) were 'male' or 'female'. Unbeknownst to them, in some trials (primed trials) other self or non-self faces (primes) were very briefly flashed immediately prior to the targets, and were not perceptible. In each primed trial, relative to the visible target face, the prime face belonged either to the same gender (congruent) or to a different gender (incongruent). Furthermore, within the congruent trials, the prime face belonged either to the same individual (repeated) or to a different individual (non-repeated). The analysis reported here focuses on the latter two trial types, in which the difference between repeated and non-repeated primes had no relevance for the purpose of task performance, and involved intrinsic, pre-existing associations based on whether or not target face and prime face belonged to the same individual. (Other analyses and results from this study have been reported in Pannese and Hirsch, 2010, 2011.)

The midbrain reticular formation was selectively activated upon exposure to the self-face, as determined by a whole-brain analysis during unprimed self and non-self trials. This analysis revealed self-specific activation within a cluster in the midbrain (Figure 1a) whose coordinates ( $x = -2$ ;  $y = -26$ ;  $z = -12$ ) are consistent with those of the reticular formation. In addition to self-specific activation, this cluster exhibited habituation (repetition suppression) to prior exposure to a different photograph of the same individual (Figure 1b). Activity during subliminally primed repeated (i.e. preceded by a subliminal prime of same identity) and non-repeated (i.e. preceded by a subliminal prime of different identity), was compared for self and non-self trials. Since the prediction about the direction of change was made *a priori* (we had specifically hypothesized that stimulus repetition would induce response *suppression*), a one-tailed test was used. This analysis revealed midbrain selective sensitivity to the repetition of the self-face ( $t(11) = 1.98$ ,  $p = 0.036$  one-tailed).

The self-specificity we found in the midbrain is characterized both by selective activation upon single exposure to the self-face (Figure 1a) and selective habituation to repeated exposure to it (repetition suppression, Figure 1b). Selective activation with subsequent habituation has been shown for the reticular formation, as distinguished from other brainstem sensory responses (French, 1960). Consequently, the self-responsive cluster we report here behaves as one would expect from known patterns of neuronal responses in the reticular formation, suggesting a possible implication of the arousal system in self-specificity.

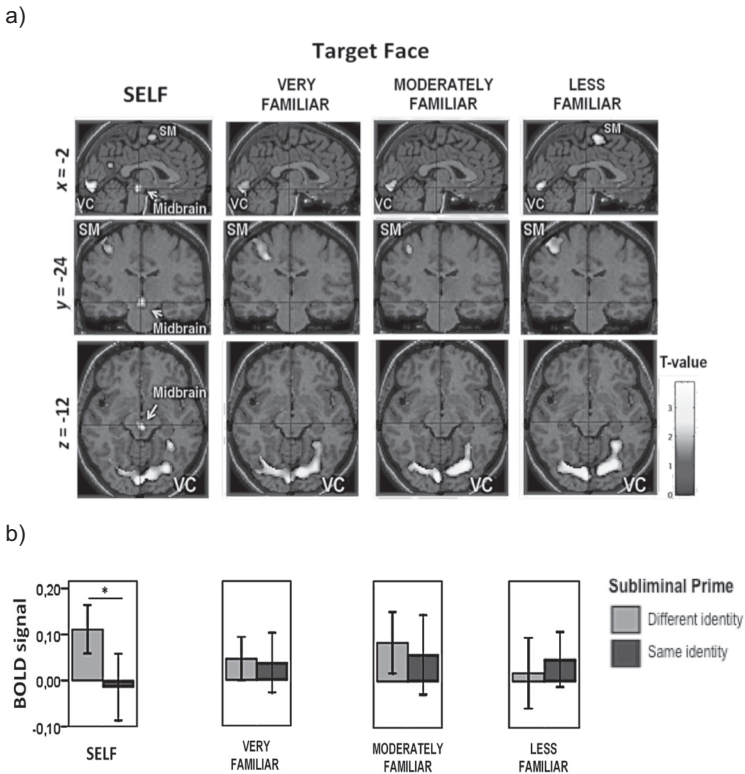


Figure 1. Self-specific response in the midbrain.

a) Conscious response. Statistical parametric maps of brain activity during unprimed trials. Sagittal (top row), coronal (middle row), and axial (bottom row) views of brain activity associated with viewing one's own (self, left column) and other (very, moderately, and less familiar, 3 right columns) faces compared to baseline. While activity in sensorimotor (SM; encompassing Brodman areas 3,4,6) and visual cortices (VC; encompassing Brodman areas 17,18,19) is present in all conditions, activity in the midbrain (MNI coords:  $x = -2$ ;  $y = -26$ ;  $z = -12$ ) is only detected during self-face trials. Images are displayed in neurological convention (the right side of the image is the right side of the brain), at a statistical threshold of  $p = 0.05$ , uncorrected.

b) Repetition suppression to unconscious stimulation. Blood oxygen level dependent (BOLD) % signal change extracted during subliminally primed repeated (dark bars), and non-repeated (light bars) trials from the previously identified midbrain cluster. Repetition suppression (i.e. decreased activity for repeated compared to non-repeated trials) was only detected upon subliminally repeated (unconscious) exposure to the self-face ( $t(11) = 1.98$ ,  $p = 0.036$  one-tailed). No repetition suppression was detected for subliminally repeated exposure to non-self (very, moderately, less familiar) faces. BOLD signal is expressed in arbitrary units. Error bars represent the standard error of the mean.

The brainstem's ascending influence on arousal is currently known to involve both direct cortical projections and indirect pathways reaching the cortex via relay points in the central thalamus (dorsal pathway, also known as *ascending reticular activating system*, or ARAS) and in the basal forebrain (ventral pathway) (Paus, 2000). Importantly, some of these indirect pathways connecting the brainstem to the central thalamus generate shifts of arousal associated with exposure to highly salient sensory stimuli. Given the documented high salience of the self-face, it is likely that our finding of self-specific responsiveness within the midbrain may reflect engagement of these subcortical pathways, regulating arousal via centrothalamic relays.

Centrothalamic nuclei are reciprocally connected with regions known to be engaged in multisensory integration, and action planning and execution (e.g. posterior parietal cortex — Goldberg *et al.*, 2006 — frontal eye fields, supplementary motor area). Given their ability to integrate invariance in goal-representation and adaptation to changing contingencies, centrothalamic nuclei are suitably placed to support large-scale cerebral activity associated with goal-directed behaviour (Schiff, 2008). This makes centrothalamic pathways ideal candidates to provide a neural substrate for the sense of 'self', which also requires maintaining a coherent and continuous representation in the face of constantly evolving biological needs, emotional states, and environmental circumstances (Scheibel, 1997).

Given the documented high saliency of self-related stimuli, and in consideration of the role of the reticular formation in general arousal, these results are also consistent with the recruitment of a general function brain region in self-recognition. According to this interpretation, viewing one's own face elicits activity in the midbrain reticular formation as a result of a modulatory effect exerted by self-related *content* of visual perception on the global *level* of awareness. In other words, what makes the 'self' special is its ability to modulate arousal. Modelling self-specificity from the perspective of arousal regulation provides a unifying framework for the interpretation of our results: on the one hand, the activity increase observed in the midbrain upon single exposure to one's own face reflects a sudden and transient increase in arousal due to the stimulus's high saliency; on the other hand, the activity decrease found when exposure to one's own face is repeated reflects habituation, a typical phenomenon associated with repetition, and observed in other orienting reflexes. Moreover, by shifting the focus of self-specificity away from cortical differences, and on arousal-related subcortical structures, our results suggest that the

cortical discrepancies found in the literature do not necessarily imply absence of neural specificity for 'self'.

In this study we did not find activity in cortical midline structures, which are often thought to be involved with self-related processing (Northoff *et al.*, 2006). This could be due to the physiological properties of the cortical midline regions with respect to task performance and resting state. The cortical midline structures have been shown to exhibit a high degree of activation during resting conditions, which has led to their characterization as the brain's 'default mode' (Gusnard and Raichle, 2001). Performing a cognitive task based on external information (such as the visual stimuli used in our study) disrupts the resting state by orienting the subject's attention towards the external environment. It is therefore possible that in our study we could not detect activity in the cortical midline structures because of an interaction between two equal — and opposite — responses: activation in response to the self-referential stimuli; deactivation in response to task performance (and relative disruption of the resting state). Therefore, our results do not exclude that cortical midline regions may have been engaged, and prompt further efforts aimed at elucidating the dynamics and mutual interaction between self-referential and exteroceptive processing. Moreover, given the extensive reciprocal connections between the cortical midline structures typically associated with self-referential processing, and medial aspects of the brainstem (Holstege, Bandler and Saper, 1996; Panksepp, 1998) — in close proximity to the midbrain cluster we detected — our findings are consistent with recent models purporting that the sense of 'self' is subserved by an integrated cortico-subcortical midline system, linking sensory perception to high-order self-referential processing (Schiff, 2008).

Our results provide the first evidence for neural specificity for 'self' in subcortical structures typically associated with regulation of arousal, suggesting a new model for specificity for 'self' characterized by modulation of arousal elicited by self-relevant information. The converging evidence we found for self-selective responsiveness in the midbrain (self-specific increased activation upon single exposure, and self-specific suppression upon repeated exposure) satisfies both anatomical and functional criteria for self-specificity, and suggests that the brainstem may act as a neural substrate for the sense of

'self', consistent with its ability to coordinate and integrate internal bodily signals originating from different sources in a coherent whole.<sup>3</sup>

### Materials and Methods

Twelve healthy and normally-sighted subjects (7 males) were recruited according to IRB approved procedures. Each subject brought three individuals: one close friend (or domestic partner), one friend of medium familiarity, and one acquaintance.

Prior to the experiment, 208 photographs were taken of each participant and their three friends. These photographs, cropped into 500 x 500 pixels and converted into black and white (Adobe Photoshop), served as stimuli for the 'self' and three 'non-self' (very, moderately, and less familiar) conditions. Additional photographs portraying non-familiar (celebrities and anonymous) individuals were obtained from publicly available databases. Self-face photographs were mirror-reversed.

Self and non-self targets were presented either in isolation (unprimed), or preceded by either 33 ms or 17 ms primes. Based on a subsequent discriminability test, only 17 ms primes were shown to be subliminal: we therefore excluded from our analysis 33 ms trials. Subjects categorized targets as 'male' or 'female' through a button press. The existence of primes was not revealed to the subjects until after the study was completed. Each trial lasted 200 ms (200 ms for the unprimed; 17 ms + 183 ms, or 33 ms + 167 ms for the primed), followed by a blank screen with a central crosshair, at jittered intervals ranging from 2.2 to 6.6 seconds. Photographs were presented in pseudo-randomized order, counterbalanced for gender and identity. Relative to the target face, primes could portray either an individual of different gender, or of different identity and same gender, or of same identity. The present report focuses on the latter two trial types, and on the corresponding fMRI correlates, since behavioural facilitation in repeated trials was non-specific, being present both in self ( $t(11) = 3.13, p = 0.005$ , one-tailed) and non-self (moderately familiar) trials ( $t(11) = 4.32, p = 0.0005$ , one-tailed). The experimental paradigm was developed using Matlab (Mathworks). Stimuli were administered through fMRI-compatible LCD goggles. fMRI images were acquired on a GE 1.5 T scanner (TE = 40 ms, TR = 2 s, flip angle

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[3] The sense of 'self' discussed in this article refers to the identification and salience of one's own body parts (e.g. face), in contrast to the identification and salience of the body parts of other people. It does not refer to the sense of 'self' used by some authors to refer to the 'subjective' or 'pure' Ego.



= 60 degrees, resolution =  $64 \times 64$ , voxel size =  $3 \times 3 \times 4.5$  mm, FOV = 190 mm).

Functional data were analysed using SPM5 (Wellcome Department of Cognitive Neurology, London), and were pre-processed, co-registered, and normalized into the T1 Montreal Neurological Institute template. Subject-level analysis was performed using general linear model and a canonical hemodynamic response function (HRF). Brain activity related to unprimed trials was obtained from subject-level contrasts (trial versus baseline), and subsequent group-level one-sample t-test. Voxels surviving a threshold of 0.05 were retained (Figure 1a). Blood oxygen level dependent % signal change was extracted from the previously identified self-face-responsive cluster within the midbrain using MarsBar (Figure 1b). Statistical analyses on the mean % signal change were performed with SPSS software.

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Author contributions: AP and JH designed the study and wrote the paper. AP created the stimuli, performed the experiments, and analysed the data.

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