Out-of-Place Bodies, Out-of-Body Selves

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In this issue of *Neuron*, Ionta et al. (2011) combine behavioral and fMRI approaches with anatomical lesion data to show that illusory perception of one's own body from an external point of view or at a different physical location is linked to modulation of neural activity in the temporo-parietal-junction, a cortical region fundamental to body-consciousness.

Although central to psychology, the study of corporeal self-awareness has been left out of scientific research for quite a long time. However, clinical and experimental investigations on the cerebral representations of body and self date back to the beginning of the 20th century and have steadily grown since then (review in Berlucchi and Aglioti, 2010).

Bodily self-consciousness is a complex mental construct linked to the strong sense that, at least under normal circumstances, we recognize that our body belongs to us, our conscious self is housed within our physical body in a first-person perspective, and that our body inhabits a specific physical location in external space. Thus, the core feeling of bodily self-consciousness is based on three major components: (1) self-identification, indexed by the degree to which we feel that our body or body parts belong to us; (2) first-person perspective, expressed by the extent to which our primary viewpoint of the outside world is from within our body; and (3) self-location, defined by the ability to place and experience ourselves in physical space.

Bodily self-consciousness can be conspicuously modified by pathological and physiological factors. An example of a body-part-specific self-identity disorder is the feeling that one's own limb does not belong to oneself. These complex misperceptions and misconceptions are comparatively common after cerebral lesions in the right temporo-parietal lobe and typically affect the left limb (Berlucchi and Aglioti, 2010). Patients with disruptions in full-body self-awareness, generally referred to as autoscopic phenomena (AP), report bizarre feelings and exhibit strange behaviors that mimic psychiatric more than neurological disease symptomologies. AP are characterized by the illusory sensation of a second body seen in extracorporeal space. At least three different forms of AP have been described, namely autoscopic hallucination (the person sees a second own body with self-location normally anchored to the physical body), heautoscopy (self-location is perceived at both the physical and the illusory body), and out-of-body experience (OBE) characterized by a sense of disembodiment, with the illusory body, to which self-location is attributed, perceived in a position elevated with respect to the physical body (Blanke and Metzinger, 2009). Studies of patients with OBEs suggest that the feeling of being outside the real body and looking at the world from another perspective might be linked to temporo-parietal and vestibulo-insular brain dysfunction (Blanke and Metzinger, 2009). Tellingly, OBEs, as well as the somatosensory feeling that someone else is close to us even if nobody is around, have been induced by electrical stimulation of the temporo-parietal regions (Blanke and Metzinger, 2009; Arzy et al., 2006).

Our clear and stable sense of bodily self-consciousness can also be challenged by simple psychophysical manipulations. For example, touch stimuli delivered to one's visually obscured or "unseen" hand while observing the synchronous stroking of a seen rubber hand induces the subjective perception that the rubber hand belongs to oneself (rubber hand illusion, Botvinick and Cohen, 1998; Ehrsson et al., 2004). Inclusion of an inanimate rubber hand into one's own body representation is not observed when a time lag between visually perceived and physically sensed tactile stimulation is introduced (asynchronous stimulation condition, Botvinick and Cohen, 1998). Using a similar visuotactile stimulation paradigm and virtual reality techniques, Lenggenhager et al. (2007) have been able to induce the subjective feeling of whole-body self-identification with an avatar. These studies have provided a very fruitful experimental paradigm for exploring basic phenomenological aspects of first-person perspective and self-location.

The study published in this issue of *Neuron* provides new insights into the behavioral and neural correlates of fundamental components of bodily self-awareness. Using robotically-controlled synchronous presentation of visually perceived and physically sensed tactile body stimulation, Ionta et al. (2011) disrupt two features of self-awareness in healthy subjects: first-person perspective and self-location. These phenomena were assessed and documented via subjects' self-reports, questionnaires, and estimation of the perceived distance between their body and the ground (Mental Ball Dropping task, MBD; Lenggenhager et al., 2009) under various tactile and visual stimulus conditions. Only during synchronous stimulation subjects reported feeling as though the observed virtual body was their own. Moreover, the MBD task showed that subjects perceived their physical body drifting toward the illusory one. Thus, in keeping with their previous studies, the authors were able to easily change subjects' self-location and first-person self-perspective, both features of self-awareness that are usually stable, in a gradual and measurable manner.

Importantly, half of the experimental subjects had the impression of looking upward at the virtual body, congruent with their actual supine physical position and perspective (Up-group). By contrast, the other half had the impression of looking downward at the virtual body from an elevated perspective, in contrast with their actual supine physical position and perspective (Down-group). This divergence in perception of the illusory double was independent from the visuo-tactile synchronicity, implying that interindividual differences in vestibular signals influence the way in which the virtual double is perceived.

Using fMRI, the authors investigated the neural correlates of full-body self-mislocalization and out-of-body self-illusions and observed changes in BOLD activity in the left and right temporo-parietal junction (TPJ) during these AP experiences. This result is in line with the notion that the TPJ is involved in perspective-taking and mentalyzing tasks where ''cognitive'' self-relocation is required. Moreover, the results further substantiate the role of the TPJ in transcending body-related sensorimotor contingencies, which commonly occur during states of focused concentration and meditation (Urgesi et al., 2010).

Interestingly, an opposing pattern of modulation of TPJ activity during synchronous/asynchronous visuo-tactile stimulation was observed in the Up- and Down-groups. When the virtual body was perceived as facing up and seen from below, TPJ activity was comparatively enhanced when no illusion was perceived (i.e., no change in self-location; asynchronous stimulation condition) with respect to when a change in self-location occurred (synchronous stimulation condition). Conversely, when the virtual body was perceived as facing down and seen from above, TPJ activity was enhanced during the synchronous stimulation (i.e., when the illusory self-relocation occurred). Therefore, the link between TPJ activity and self-relocation may be rather complex. One possible way of reconciling this seemingly contradictory pattern of results is to consider the impact of vestibular-visuo-tactile conflicts and the relative neural effort required to relocate the self from the physical body into the virtual body between groups. In the Up-group, the observed virtual body coherently matches the subjects' real physical orientation. Therefore, the virtual body may be more easily embodied because vestibular and visuo-tactile signals are less incongruent. This may explain why neural activity in TPJ is higher in asynchronous than synchronous stimulation conditions where embodiment and relocation typically occur. In the Down-group, the illusory relocation into the virtual body can only take place after resolving the vestibular conflict between the actual physical position of the subject and that of the illusory body. Since the embodiment process requires more neural effort in the Down-group, TPJ activity in this group was higher during the synchronous visuo-tactile condition. Such an interpretation, which is slightly different from the one provided by the authors, may explain why bilateral TPJ activity is differentially modulated by the visuo-tactile stimulation in the Up- versus Down-group.

It is also important to mention that the authors analyzed the structural scans of nine brain-damaged patients with reported OBEs to investigate the possible association of OBEs with specific lesional loci. Although a correlational analysis between the lesioned voxels and the degree of individual self-representation deficits could not be performed, the overlap of lesion location across subjects indicated a significant group-level association between OBEs and right TPJ. This result supports the claim that TPJ is involved in modulating self-location in space and first-person perspective.

As an interesting aside, the authors report a modulation of BOLD signal in the right extrastriate body area (EBA), a cortical region closely related to visual processing of bodies (Downing et al., 2001; Urgesi et al., 2007; Moro et al., 2008). This change in activity was contingent upon synchronous versus asynchronous stimulation, suggesting that this region might also be involved in self-identification.

In sum, by combining behavioral results with fMRI, Ionta et al. (2011) have been able to empirically and convincingly relate the phenomenological aspects of the induced OBEs and changes of first-person perspective to neural activity in specific cortical regions, namely the left and the right TPJ.

The Ionta et al. (2011) study is important because it may open new avenues for the study of full-body self-consciousness and inspire new theoretical and translational research. Self-relocation is a step toward a basic sense of embodiment, which, however, needs to be integrated with the sense of having control of the action the virtual projection of the body is performing. Only the full integration of the virtual and physical self would induce the illusion of being and acting elsewhere outside one's physical self and location. The Ionta et al. (2011) study paves the way for future research that further defines the different variables that influence modulation of full-body self-representations and induce changes in self-awareness in physiological and pathological conditions. For example, the relationship between synchronicity of visuo-tactile stimulation, visuo-proprioceptive, visuo-motor, and vestibular signals that mediate the interaction between the position of the physical and of the virtual body still has to be elucidated. Systematic and controlled manipulations of these different variables will provide valuable insight that may be of interest for a number of different research fields (e.g., clinical neuroscience, rehabilitation, and computer science) and may have important societal implications (e.g., improvement of recreational virtual reality applications).

In particular, a better understanding of relocalization and body-ownership phenomena may be important for patients suffering from a variety of neurological and psychiatric disturbances. For example, patients with bodily awareness disorders may benefit from coherent (visual, haptic, proprioceptive, auditory) sensory stimulation of a virtual body that is experienced as being their own. Moreover, identification of the cortical loci mediating in- and out-of-body experiences may inform future studies exploring the use of brain-modulation techniques, that may up- or downregulate neural activity in specific regions, for the therapeutic treatment of patients affected by disorders of corporeal awareness. The Ionta et al. (2011) study may also be important for understanding the processes underlying immersive virtual embodiment through which powerful links between the physical body and the surrogate body can be created (Slater et al., 2009). Moreover, mapping the cortical circuitry involved in self-localization and virtual-body-immersion could ultimately guide the development of applications where surrogate bodies can be used for navigating the world and interacting with others.

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Cracking the Combinatorial Semaphorin Code

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In this issue of *Neuron*, Wu et al. describe a combinatorial code of repulsive Sema-2a and attractive Sema-2b signaling that mediates mechanosensory axonal guidance, fasciculation, and synaptic target selection within the CNS of *Drosophila*. Their work exemplifies how a detailed, multilevel molecular-genetic analysis (from molecules to behavior) provides fundamental insights into neural circuit development.

One of the challenges facing developmental neurobiology is to understand how axons find their way through the developing embryonic landscape to establish functional neural circuits. Progress in understanding the mechanisms governing guidance and connectivity came with the discovery of chemotropic ligands and their receptors, molecules that include the Netrins, Cadherins, Semaphorins, Ephrins, and a host of Ig superfamily proteins. These chemotropic agents are either attractive or repulsive, in some cases acting over long distances via diffusible topographic gradients, and in other cases acting through direct contact (Kolodkin and Tessier-Lavigne, 2011). Not surprisingly, chemotropism is complex: the same ligand can be either attractive or repulsive depending on the receptor complexes expressed by the growth cone. Axons, in turn, usually express several guidance receptors. The combination of multiple guidance cues and receptors effectively constitutes a combinatorial "guidance code" that defines how an axon (or dendrite) will find its way. An intriguing hypothesis is that synaptic partners might share similar guidance codes, ensuring that their processes meet at specific locations within the developing nervous system, as a first step in forming a neural circuit.

In this issue of *Neuron*, Wu et al. (2011) provide compelling evidence to support this hypothesis. They show that a combinatorial code involving Semaphorins and their Plexin receptors guides the construction of a central neural circuit in the *Drosophila* embryo, involving sensory neurons and their interneuronal partners. The developing *Drosophila* CNS expresses three Semaphorins, a transmembrane Sema-1a protein that signals through the Plexin A (PlexA) receptor, and the secreted Sema-2a and -2b proteins. While Sema-2a was known to act as a chemorepellant, signaling through the Plexin B receptor (PlexB; Ayoob et al., 2006), much less was known about either Sema-2b or its receptor.

Sensory innervation of the embryonic CNS is perhaps less well known than other model systems in *Drosophila*, such as the eye, CNS midline, olfactory neuropil, or neuromuscular junction. Nevertheless, this paper shows it to be enormously powerful. The authors examined a group of mechanosensory neurons called chordotonal (ch) cells, that are born in the periphery and whose axons grow along peripheral nerves to innervate the CNS. Once there, the axons are faced with the daunting challenge of identifying the correct tracts to lead them to their synaptic partners. In the CNS, they find that the roadways are still under construction, with axon tracts and fascicles actively being established. Wu et al. (2011) show that the ch neurons and their interneuron partners use the same molecular guidance system to rendezvous at a specific site within the developing ventral nerve