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Shape alterations of basal ganglia and thalamus in xenomelia

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ABSTRACT

Xenomelia is a rare condition characterized by the persistent desire for the amputation of physically healthy limbs. Associations with morphological alterations such as reduced cortical thickness and surface area. Nothing is known, however, about the potential involvement of subcortical structures. The thalamus and basal ganglia process, relay, and integrate sensorimotor information and are involved in the preparation and execution of movements. Moreover, both of these structures house somatotopic representations of all body parts.

We therefore investigated subcortical correlates of xenomelia by assessing basal ganglia and thalamus by means of vertex-wise shape analyses. For that purpose, we compared the shape of the thalamus, putamen, caudate nucleus, and the pallidum in 13 men suffering from xenomelia, all desiring a leg amputation, compared to 13 healthy control men. We hypothesised that the target leg is misrepresented in subcortical structures of individuals with xenomelia, especially in locations with a somatotopic representation.

Shape analyses showed thinning of bilateral dorsomedial putamina, left ventromedial caudate nucleus and left medial pallidum associated with xenomelia. This was accompanied by thickening of bilateral lateral pallida and the left frontolateral thalamus. These shape differences were mainly located in sensorimotor areas of somatotopic leg representations.

The present study provides strong evidence for shape differences in striatal, pallidal, and thalamic subregions housing subcortical body part representations. It adds to previously described neural correlates of a condition one can barely empathize with and invites future connectivity analyses in cortico-subcortical networks.

1. Introduction

A good decade ago, the American psychiatrist Michael First described a peculiar disorder he dubbed “body integrity identity disorder” (BIID) (First, 2005). Persons with BIID are dissatisfied with their body and its functionality. Since childhood or early adolescence they feel that they are “in the wrong body” and are increasingly longing for a live as a disabled person, striving for limb amputation, paraplegia or functional impairments such as deafness or blindness (First and Fisher, 2012). Xenomelia (McGeoch et al., 2011) is one variant of BIID. As its Greek-derived label suggests (xeno stands for “foreign” and melos for “limb”), it consists in the feeling that one or more limbs do not belong to the bodily self. Individuals with xenomelia typically report that they would feel “more complete” if their unwanted limb had been removed (Blanke et al., 2009). While it is hard to empathize with such feelings and desires, extensive psychiatric examination of participants suffering from xenomelia showed a normal mental status and, in particular, the absence of any psychotic disorder (First, 2005; Hilti et al., 2013; van Dijk et al., 2013). In fact, persons affected with the condition feel themselves embarrassed about the bizarreness of their desire for amputation and usually keep it secret. Internet communities have helped them with their “coming out”, which has let some researchers claim that BIID is a clinical entity largely manufactured by the Internet (Charland, 2004). However, scattered reports about early cases of BIID e.g. (Money et al., 1977; Wakefield et al., 1977) clearly show that, even if social media may significantly influence incidence and manifestation of the disorder (Brugger et al., 2013; Davis, 2012), the biological basis of BIID cannot be denied.

Aetiology and pathophysiology of BIID in general and xenomelia in particular are currently unknown. Most medical practitioners are unfamiliar with the affliction and, when confronted with a patient desiring the amputation of a healthy and fully functional limb, will find themselves to be at their wits' end. Manuals of mental disorders will not provide assistance in a diagnosis, as the proposal to include the disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was

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turned down in a late decisional phase (Zucker, 2013). This nosological and diagnostic palsy helped mushroom attempts to "neurologize" the disorder on insufficient empirical grounds. For instance, the superficial phenomenological similarity between somatoparaphrenia (Vallar and Ronchi, 2006) and xenomelia as acquired vs. innate forms of an absent ownership over a body part has led to the assumption of a conceptual relatedness (Brang et al., 2008). The denial of ownership over paralyzed limbs is seen after right parieto-insular lesions and can be transiently alleviated by neuro-otological procedures (Rode et al., 1992). However, recent empirical work has shown that these procedures do not influence the strength of the desire for amputation (Lenggenhager et al., 2014), questioning the value of hastily comparisons between somatoparaphrenia and xenomelia, specifically with respect to the claimed suitability of common intervention methods (Ramachandran and McGeoch, 2007). Nevertheless, a neurological origin of xenomelia was suggested by recent empirical research. Among the first to seek empirical evidence for its neurological roots were Brang and colleagues (Brang et al., 2008). In that study, pinpricks to two individuals suffering from the condition have been applied and the authors reported an abnormally strong galvanic skin response evoked by the stimulation of the undesired compared to the accepted parts of their bodies. This has been interpreted as resulting from a pathologically exaggerated sympathetic outflow from areas of the limbic system such as the insula to the parietal cortex. This sympathetic hyper-responsibility might have interfered with the formation of a proper representation of the unwanted limb during early brain development. Therefore, the desire for amputation might be the direct consequence of a misrepresentation of a particular body part, despite the fact that their participants' limbs showed intact primary sensory and motor functions (Brang et al., 2008).

In a subsequent study with four persons suffering from xenomelia, magnetoencephalographic signals to tactile stimulation below and above the line of desired amputation have been recorded. In contrast to touch on accepted body parts, touch on the undesired limb failed to elicit a cortical response in one particular brain area, i.e. the right superior parietal lobule (SPL; (McGeoch et al., 2011). It has been suggested that this part of the parietal lobe is the core region for establishing and maintaining a coherent sense of having a body, i.e. the body image (Berlucchi and Aglioti, 2010; Giummarra et al., 2008; Moseley et al., 2012).

Intriguingly, a structural imaging study in participants suffering from xenomelia using surface-based morphometric procedures (Hilti et al., 2013) identified neuroarchitectural anomalies in exactly those cortical areas, i.e. in the right anterior insula (Brang et al., 2008) and the right SPL (McGeoch et al., 2011). Decreased cortical surface area in the right primary somatosensory (SI) cortex representation of the left leg and in the right secondary somatosensory (SII) cortex has been reported in addition (Hilti et al., 2013).

While our previous work had been confined to cortical structures (Hilti et al., 2013), we here set out to investigate subcortical correlates of xenomelia by assessing the basal ganglia and thalamus by voxel-based volumetric analysis as well as by means of vertex-wise shape analyses (Patenaude, 2007; Patenaude et al., 2011). For that purpose, the shapes (and volumes too) of the putamen, pallidum, caudate nucleus, and the thalamus derived from 13 participants with xenomelia (the same as in (Hilti et al., 2013), all of whom desiring an amputation of one or two legs, have been compared with those of 13 healthy control men.

We hypothesised that the faulty cortical representation of the unwanted limb would also manifest itself on a subcortical level, notably by local volume and/or shape differences, i.e. either by a negative local tissue displacement (local "thinning") and/or a positive local tissue displacement (local "thickening") of thalamic and basal ganglia structures known to house somatotopic representations of feet and legs (Bingel et al., 2004; Gerardin et al., 2003; Lehericy et al., 1998).

2. Material and methods

2.1. Subjects and study design

Thirteen men suffering from xenomelia were recruited via an Internet site. Their medical history was free of any neurological and psychiatric disease, and thorough neurological and psychiatric examinations proved normal (Hilti et al., 2013). We also recruited control subjects who did not differ from the xenomelia group with respect to sex, handedness, footedness, age, and education. The participants with xenomelia all desired an above-knee amputation; eight of the left leg, two of the right leg, and three participants desired the amputation of both legs. All subjects suffering from xenomelia completed the Zurich Xenomelia Scale (Aoyama et al., 2011), a 12-item questionnaire that assessed the degree of xenomelia and that of associated symptoms such as the erotic attraction by amputees and the urge to pretend to be an amputee (Brugger et al., 2013).

The study protocol complied with the Declaration of Helsinki and was approved by the local ethics review board of the University Hospital Zurich. All study subjects provided written informed consent prior to participation.

2.2. Magnetic resonance imaging data acquisition

Scans were acquired on a 3.0 Tesla Philips Achieva whole-body scanner (Philips Medical Systems, Best, The Netherlands) equipped with a transmit-receive body coil and a commercial eight-element sensitivity encoding (SENSE) head coil array. For each participant, a volumetric 3D T1-weighted fast field echo sequence was applied twice to obtain two scans each with a duration of 468 s and a spatial resolution of $0.94 \times 0.94 \times 1.0$ mm^3 (acquisition matrix: 256×256 pixels, 160 slices). Further imaging parameters were field of view $= 240 \times 240$ mm^2, echo time $= 3.7$ ms, repetition time $= 8.06$ ms, flip angle $= 8°$ and sensitivity encoding factor $= 2.1$. The two scans were then coregistered and averaged to increase both the signal-to-noise as well as the contrast-to-noise ratio.

2.3. FMRIB's integrated registration and segmentation tool (FIRST)

FMRIB's Integrated Registration and Segmentation Tool (abbreviated as FIRST, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST) (Patenaude, 2007; Patenaude et al., 2011) is a computerized and in the FMRIB's software library (FSL) implemented (Smith et al., 2004) subcortical segmentation tool based on T1-weighted MRI scans using shape and appearance models. On the one hand, FIRST performs volumetric analyses indicating changes in the overall volume of each subcortical structure between different groups or across time. On the other hand, FIRST conducts vertex-wise analyses showing the location of differences in the shape of subcortical structures between different groups (Brian et al., 2007, 2008; Fernandez-Espejo et al., 2010; Morey et al., 2010; Patenaude, 2007; Patenaude et al., 2011; Seror et al., 2010).

2.4. Structural and landmark information for shape analysis

The structural and landmark information of the shape models in FIRST were constructed from manually segmented and labelled T1-weighted images of the brain from 336 subjects, comprising the whole spectrum from children to adults (age range: 4–87 years) as well as pathological populations including schizophrenia and Alzheimer's disease participants. All these brain images have been provided by the Center for Morphometric Analysis, Massachusetts General Hospital in Boston, USA (http://www.cma.mgh.harvard.edu). The manually generated volumetric labels were parameterized by a 3D deformation of a surface mesh model based on multivariate Gaussian assumptions and then modelled as a point distribution model in which the geometry and variation of the shape of the structures were submitted as prior