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1. Introduction

Emergent experimental and clinical evidence supports the notion that the cortico-basal ganglia–thalamo-cortical loops progress along parallel circuits connecting cortical and subcortical regions subserving the processing of sensorimotor information, associative and affective knowledge [1]. In particular the role of the basal ganglia has long been known to be involved in motor control because of the marked deficits associated with their damage. However, the exact aspects of motor control that they have under normal conditions have not been clear at all. The traditional view is that the basal ganglia are involved in the selection and inhibition of action commands [2], but an increasing number of brain-imaging studies show that the basal ganglia, besides being involved in motor tasks are also involved in more integrative and cognitive processes such as mental imagery [3,4], sensory processing [5,6], planning [7], attention [8,9], and language [6,10,11]. This evidence supports the view that the basal ganglia output not only targets the primary sensory-motor cortices, but also specific areas of premotor and prefrontal cortex, which include the oculomotor area of the cortex, the dorsolateral prefrontal cortex, lateral orbitofrontal cortex, and anterior cingulate/medial orbitofrontal cortices [12]. Thus, having the ability to influence not only sensory-motor control, but also several different types of cognitive and limbic affective functions [12] which underlie complex and integrative processes such as self-awareness, introspective perspective of one’s own self and consciousness [13]. This integrative role between lower afferent input and higher integrative and executive stages of information processing require an intact and closed loop of information flow to generate the primary experience of self and thus self-agency. Self-agency has tentatively been defined as the feeling of being the author of one’s own actions [14]. Thus, when we move our arm, we know (a) that it is our arm and (b) that it is us, who moves the arm. One approach to understand the complex integration of afferent and efferent information processing and the integration in the self is the internal model theory of motor control [15]. According to this theory there are two functionally different components in the motor system, inverse and
forward circuits. It is assumed that inverse models provide the motor commands necessary to achieve a desired consequence of an action, specified by higher-level goals (e.g., intentions). One is fully aware of the desired consequences of an action, but unaware of the motor programs per se. Forward models predict the sensory consequences of each motor program to be executed, an idea known as the efference copy, a model first put forward in von Holst and Mittelstaedt [16] and which has been extended in recent years with the “null” hypothesis of Ramachandran [17]. Accordingly, it is claimed that, whenever a motor program is issued, an efference copy is produced in parallel, this is, a prediction of the sensory consequences expected after the execution of the program based on exactly this efference copy. The internal model theory of motor control has been successfully applied to explain a whole variety of disorders related to the awareness of actions [for a review see 17] but the role played by the basal ganglia in this model has not been very clear. Here we follow this model extending it to the performance of a complex cognitive task, such as mental imaginary movement of a limb and the coexistent conscious awareness of just imagining it and actually refraining from moving it which involves exactly this subtle combination between the forward model requiring intact peripheral efferent/afferent information pathways and the inverse model requiring intact higher-level cortical areas which include the basal ganglia-thalamus-cortex pathway [19]. Moreover, we contrast the normal integrity of this forward/inverse model loop in healthy subjects with an abnormal open loop in amputees where an essential part of the loop has been disrupted. We thus argue that because of this abnormal and open loop involving the basal ganglia and the thalamocortical system the conscious awareness of the phantom phenomenon is created.

2. Problem statement

Waking up from anesthesia, an amputee faces the conflict in the experience of self, between the conscious vividness of his phantom limb (PL) and the lack of correlation with reality [20–23]. In the urge to discover whether he was actually amputated, the patient looks under the sheet for visual self-recognition and is, in a flash, confronted with this new reality of an absent limb. The resulting cognitive conflict between the seen embodiment and the felt one, in most cases carries on resulting in the perception of a ghost of their amputated limb as a phantom [24]. Giummarra et al. [20] report phantom limb experiences that include phenomena of (a) perception of bodily aspects of phantom limbs such as size (in relation to the intact limb), shape, posture, and telescoping (or shortening) of the phantom; (b) exteroceptive and proprioceptive sensations and (c) prosthesis embodiment. Early studies of phantom limb movement were carried out using combined techniques of EEG, MEG, and fMRI in order to locate its representation in the sensory-motor cortex [25–28] and in the cerebellum [29,30]. Later studies described the distinct functional anatomy of the mental representation of imaginary movements [31], during planning, visualizing, and motor intention [32], both in healthy subjects as well as in patients with different neural diseases. Other studies have centered on the difference between imaginary movement and executed movement [3,33]. A recent study by Diers et al. [34] showed activation in the supplementary motor area (SMA) cortex after PL imagined movement. And in a more recent study Pasaye et al. [35] have described neurocorrelates of the PL perception using fMRI. Since the first
conceptualization of the phenomenon of phantom limb in amputees in 1915, as the manifestation of the persistence of the body schema of the missing limb [36], many theories have arisen. Most of these theories suggest a central role of reorganization of the somatosensory cortex, others advocate for a perceptual completion [37], or the product of conflicting cues from central reorganizational changes [38]. Although some degree of sensory or motor impairment is constant, recent models of motor awareness suggest that the reduction in afferent information may be less critical than higher-level reorganization related to the subjective correlates of action planning and motor intention [15,39]. In contras, a number of studies of patients with amputated limbs encourage that a conscious perception of a body part by tactile stimulation does not necessarily require the integrity or even existence of the tactile receptors on the skin, or the body parts themselves. That is, the neural representation of the body in the brain is sufficient to elicit an awareness of the body part or tactile stimuli in the absence of its physical counterpart (e.g., the limbs themselves) [40]. We believe that the reduction or absence in afferent information is a key factor that in combination with higher-level reorganization generates the conscious awareness of the phantom phenomenon. Here we hypothesize that for the performance of a complex cognitive task, such as imaginary movement of a limb, and the concomitant conscious awareness of just imagining it and actually refraining from moving it, an involvement of a subtle combination between intact peripheric (efferent/afferent) information pathways and intact higher-level cortical areas (basal-ganglia-thalamus-cortex pathway) are needed [19].

In amputees, this normal combination of lower- and higher-level processes is disrupted and could be the underlying cause of conscious awareness of the phantom limb. This arrangement of processes was reported by Staub et al. [41], who found an increased blood oxygen level dependent (BOLD) signal in the Basal Ganglia-Thalamic-Motor-Cortex loop pathway during imaginary movement of a patient with chronic supernumerary phantom limb, which developed only in association with motor intent directed at a hemiplegic-anesthetic upper limb. Staub’s finding is analogous to what Ramachandran proposes as the “null” signal hypothesis in the mirror neuron system (MNS), which prevents activity in the basal-ganglia-thalamus-cortex loop and intact higher-level cortical areas (basal-ganglia-thalamus-cortex pathway) are needed [19].

Hence the inhibition of activity in the basal ganglia-thalamus-cortex pathway is disrupted, thereby generating an abnormal open loop functioning of the thalamocortical system and its consequent activation. This abnormal activation of the thalamocortical system, we suggest, could be the underlying cause of the conscious awareness of the phantom phenomenon. This hypothesis is also in accordance with an emergent change of view in the functionality of the basal ganglia, from the classic view of being just part of the common motor pathway, to a more integrative, dynamic and resource-selection mechanism that participates in the sensory-motor, affective, and cognitive process related to the executive planning and selection of an action mechanism [43]. Furthermore, the conscious awareness and the subsequent sense of
agency [44] which patients report to have had as they perform imagined tasks with their amputated limbs has never been between contrasted with healthy subjects.

In the current study, we tested the hypothesis that the basal ganglia-thalamus-cortex pathway is disrupted in amputees, as compared to control subjects, and that this disruption is the key to the cascade of conscious awareness of the phantom limb. We contrasted between lower limb amputees and control subjects as they performed a simulated neurocognitive motor-imagery task with their phantom toes or intact toes respectively.

3. Method used

3.1. Subjects

Six unilateral lower limb amputees, 3 with left lower limb (LLL) and 3 with right lower limb (RLL) amputation (mean age 35.3, range 15-60 years, for details see Table 1), and 6 healthy controls (HC, mean age 29.16, range 20-59 years) participated in the study. All participants gave written informed consent prior to taking part in the study and the local institutional review board approved the protocol, which adhered to the Declaration of Helsinki. None of the subjects had neurological or psychiatric disorders.

<table>
<thead>
<tr>
<th></th>
<th>Age¹ Ctrl</th>
<th>Age² Pat</th>
<th>Amp³ side</th>
<th>Amp⁴ site</th>
<th>Cause of⁵ Amputation</th>
<th>SP⁶</th>
<th>PLP⁷</th>
<th>PLS⁸</th>
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<td>34⁺</td>
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<td>21</td>
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<td>RLL</td>
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<td>5</td>
<td>29</td>
<td>33</td>
<td>LLL</td>
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<td>Traumatic</td>
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</tbody>
</table>

Table 1. Clinical data description of controls and patients. All subjects are right handed males. ¹Column for control subjects’ age. ²Column for patients’ age. ³Three patients had right lower limb amputation and three had left lower limb amputation. ⁴Site of surgery. ⁵Car or train accident was main cause of amputation. ⁶All the patients reported stump pain (SP), but none ever had Phantom Limb Pain (PLP). ⁷All patients were able to move at will their phantom toes (extension/flexion).

3.2. Experimental procedure

The experiment consisted of two parts. In the ‘executed movement’ condition the participants were instructed to make a flexion/extension movement with the intact (amputees) or non-dominant (HC) toes. In the condition ‘imagined movements’ the amputees imagined making a flexion/extension movement with the phantom toes and the HC imagined the same movement with their dominant toes. For all conditions the subjects had their eyes open. All movements or
imagined movements were observed under close scrutiny by the researcher. All conditions were separate blocks of fMRI measurements with durations of 30 seconds each, separated by resting periods of 30 seconds. Each condition was repeated three times. There was no training session for either the control subjects or the amputees.

3.3. fMRI measurement

The fMRI scans were conducted with a GE 1.5 T GE LX Magnetic Resonance instrument (Milwaukee, WI, USA) using the standard quadrature headcoil. Subject’s head was securely fastened in the head holder to minimize movement. Functional images were acquired with GE EPI-BOLD pulse sequence with 90° flip angle TE=60 ms, TR=3000 ms, over seven contiguous coronal sections, 8.0 mm thick with zero gap. Imaging was centered near the central gyrus. Structural images localized exactly over the same seven sections of the functional studies were obtained using a high resolution T1 weighted protocol. The activation was done in boxcar block paradigm of 30 seconds of stimulated state and 30 seconds of un-stimulated state, over a total of three blocks each.

3.4. Image analysis

All MR data was transferred to an offline workstation all images were translated into time-ordered stacks using the software MRIcro (Chris Rorden, http://www.cabiatl.com/mricro/). The experiments were analyzed subject by subject following a standard motion correction with image registration, to do a more precise alignment, since the study was acquired in coronal slices, the high resolution T1-weighted images were aligned to the T1-weighted SPM mask in MNI space, the transformations were saved and applied to the functional EPI time ordered stacks, and then the functional images were normalized to a ROI of the EPI standard provided by SPM, spatial smoothing using a Gaussian kernel of FWHM 6mm and high pass temporal filtering. Functional signal was obtained with a block model convolved with an hemodynamic response function (HRF) without time derivative correction these single subject analysis resulted in contrast maps used in the second level analysis. The second level analysis was executed to estimate group average activation using a Student–t maps limited and adjusted with p = 0.05 with no Volterra interactions.

4. Results

Analysis of the data was carried out for each subject individually, to see if there were statistically significant activation clusters, and then by group after combining all subjects. The average functional maps obtained revealed ipsilateral or contralateral brain activation sites, which were colored according to the tasks performed on each lower limb of all subjects: green-colored brain activation sites correspond to the right leg, while red-colored brain activation sites correspond to the left leg. Yellow-colored sites correspond to areas of overlapping activation during the performance of the tasks on each limb. The results of the three groups’ brain activation sites are summarized in Table 2.
<table>
<thead>
<tr>
<th>BRAIN REGION</th>
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<th>z</th>
<th>BRAIN REGION</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
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<td>Middle Temporal Gyrus</td>
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<td>-20</td>
<td>64</td>
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<td>-8</td>
<td>4</td>
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<td>Left amputee, executing right imaginary motion</td>
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<tr>
<td>Medial Frontal Gyrus</td>
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<td>-8</td>
<td>-11</td>
<td>50</td>
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<td>2</td>
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<td>6</td>
<td>6</td>
<td>-9</td>
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<tr>
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<td>-25</td>
<td>1</td>
<td></td>
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<tr>
<td>Precentral Gyrus</td>
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<td>-42</td>
<td>-11</td>
<td>47</td>
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</table>

Left amputee, executing left virtual motion

Right amputee, executing left imaginary motion

<table>
<thead>
<tr>
<th>BRAIN REGION</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>BRAIN REGION</th>
<th>BA</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Superior Temporal Gyrus</td>
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<td>-65</td>
<td>-42</td>
<td>15</td>
<td>Superior Temporal Gyrus</td>
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<td>Postcentral Gyrus</td>
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<tr>
<td>Cingulate Gyrus</td>
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<td>Cingulate Gyrus</td>
<td>24</td>
<td>-8</td>
<td>-12</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thalamus</td>
<td>*</td>
<td>18</td>
<td>-9</td>
<td>13</td>
</tr>
</tbody>
</table>

Right amputee, executing right virtual motion

Precentral Gyrus        | 4  | -12    | -32    | 62 | Precentral Gyrus       | 4  | -12    | -32    | 62 |
| Medial Frontal Gyrus   | 6  | -10    | -26    | 58 | Medial Frontal Gyrus   | 6  | -10    | -26    | 58 |
Table 2. Anatomical location of activation clusters during imaginary and virtual motion.

The average functional maps obtained from LLL amputee during the imaginary movement of the toes of both feet also present distinct cortical and subcortical activity. Performance of imaginary movement of the toes of the right intact toes showed activation sites bilaterally at the STG (BA 21,22), contralateral interhemispheric M1 (BA 4), contralateral SMA (BA 6), and contralateral Putamen. During the performance of imaginary movement with the left amputated toes, distinct cortical and subcortical activities were observed at the following sites: bilateral interhemispheric SMA (BA 6), bilateral STG (BA 21,22), ipsilateral M1 (BA 4), ipsilateral Subgyral (BA 37), ipsilateral Thalamus, and contralateral Substantia Nigra (figure 1,A).
Figure 1. Average functional activation maps during imaginary movement of the right leg (in green) and left leg (in red) for A) left lower limb amputees, B) right lower limb amputees and C) control subjects. All images are presented in radiological convention.
Average functional activation maps acquired from RLL amputees during the imaginary
movement of the toes of both feet depict both cortical and subcortical activities. During the
performance of imaginary movement of the toes of the left intact toes, there is bilateral
Temporal activity (BA 22), and bilateral Anterior Cingulate Cortex (ACC, BA 24), ipsilateral
Primary Somatosensory Cortex (SI, BA 3), contralateral SMA (BA 6), and contralateral
Thalamic activity, while during the performance of imaginary movement with the right
amputated toes, there is a distinct activation, namely of the bilateral STG (BA 42, 22),
contralateral Primary Motor Cortex (M1, BA 4), contralateral SMA (BA 6), contralateral
Basal Ganglia at the Medial Globus Pallidus and at the Substantia Nigra (figure 1, B).

The average functional maps obtained from the six control subjects as they performed
imaginary movement with (a) the toes of their right leg show activated contralateral sites
corresponding to interhemispheric Supplementary Motor Area (SMA, BA 6), Superior
Temporal Gyrus (STG, BA 22), and Ipsilateral Postcentral Gyrus (IPG, BA 43); while the
performance of the same tasks with (b) the toes of their left leg, activated similar
contralateral interhemispheric SMA (BA 6) and ipsilateral prefrontal (PF, BA 45) brain areas
(figure 1,C).

5. Discussion

Here we compared the brain activations of imagined and executed movements of the intact
toes and phantom toes in lower limb amputees, with the imagined and executed movement
of the toes of healthy controls, using fMRI. Both, patients and control subject expressed that
they initially had to exert greater effort in this self-generating dual process of 1) trying to
resolve an apparent conflict between the simultaneous intent to move their toes and
refraining from moving them or closing the sensory-motor feedback loop; and 2) locating,
by means of imagery monitoring, a distant portion of the body-image, which is an
attention/memory task. This sensation can be do to the increased contribution of the
prefrontal cortex, in particular the dorsolateral prefrontal cortex (DLPFC), which is known
to participate in motor imagery, not just in the sensory-motor integration and the
attention/memory neurocognitive task with the anterior cingulate cortex, but also in a joint
route with the posterior parietal cortex (PPC) during motor imagery [30,45–47]. The PPC, as
a multisensory integrative cortex, plays an important role in the cognitive dynamics for
spatial representation (limb-position) and movement intent, attention, working memory,
and guidance of action [48,49]. As Jeannerod proposed “If motor imagery occurred with
execution deliberately blocked or delayed, the representation would be protected from
cancellation and would become accessible to conscious processing” [50]. Additionally,
controls and amputees reported that they were consciously aware of their intact toes or, in
the case of amputees, that they had the conscious perception of their phantom toes during
the imaginary task. The brain activations show similarities but also differences between
amputee groups during the imaginary movement tasks of their intact and amputated toes.
The differences were: First, both amputee groups activate Basal Ganglia areas during the
performance of the imaginary movement of the amputated toes. Second, the RLL amputee
group shows more lateralized brain activation than the LLL amputee group. Third, during
the imaginary movement task, the RLL amputee group seems to require a greater attention control (ACC) as they performed the imaginary movement with their left intact toes than the LLL amputee group with their right intact toes. Additionally, the brain activations observed in the amputee group during the imagery movement task of the amputated toes involved the Basal Ganglia loop (RLL amputee group = Lentiform Nucleus, Medial Globus Pallidus, and Substantia Nigra; LLL amputee group = Thalamus and Substantia nigra). Thus, the imagined movement task in amputees demands different circuitry subsets for its accomplishment, namely: 1) the attention/memory/guidance loop, 2) the kinesthetic imagery loop, and 3) the conflict intention loop. The computational logistics for such activity can only be carried out by means of the intracortical and cortical-subcortical loops between Thalamus and Basal Ganglia nuclei. The kinesthetic representation of an action or a planned motor intent is the combined result of a widely distributed neuronal ensemble between DLPFC, inferior frontal cortex, and the SMA [31], together with the posterior parietal cortex (PPC) and the ACC for spatial awareness, attention and multisensory integration [49,51]. It is of major importance to notice here that the activation of the Basal Ganglia loop was not seen during imagery movement task of the intact toes in amputees or the healthy control group. As far as the motor intent is concerned (Fig 1, B): a) in the control group, the performance of the task with the left (non-dominant) toes activated contralateral SMA (BA 6) and ipsilateral inferior frontal cortex (BA 45), while the same task with the right (dominant) toes activated contralateral SMA (BA 6), STG (BA 22), and contralateral postcentral gyrus (BA 43). The minimal brain activity found in the controls’ kinesthetic representation correlates with the ensemble proposed [52,53], b). In the RLL amputee group, in the coronal volumes (Fig 1, A), the performance of the imaginary motor intent with the left intact toes activated the bilateral ACC (BA 24), STG (BA 22), ipsilateral S1 (BA 3), and broad contralateral interhemispheric activity from SMA (BA 6) and contralateral thalamus. However, during the right imagined movement task of the amputated toes, there is bilateral activation at STG (BA 22/42), contralateral SMA (BA 6), M1 (BA 4), contralateral Lentiform Nucleus (medial globus pallidus), and Substantia Nigra. The RLL amputees’ brain activity for the kinesthetic representation differed between the performance of the intact imaginary movement and the amputated imaginary movement, since Lentiform Basal Ganglia activity is only present during the amputated toes imaginary movement. c) In the coronal-volumes of the LLL amputee group (Fig 1, C) during the performance of the imaginary movement task with the right intact toes, besides a bilateral MTG (BA 21/22) activation, there is clear contralateral Lentiform Nucleus-Putamen activation, together with SMA (BA 6) and M1 (BA 4). However, during the imagery movement task with the amputated toes of the left leg, there is an ipsilateral thalamic and a Subgyral (BA 37) activation and a contralateral Substantia Nigra activation besides the large bilateral SMA (BA 6) and a bilateral MTG (BA 21/22) activations observed during the intact toes imaginary movement. The LLL amputee brain activity for the kinesthetic representation differed slightly between the performance of the imaginary movement of intact versus amputated toes, since there is Basal Ganglia activity (Putamen) during imaginary movement of the intact toes, while during amputated toes imagined movement there is Thalamic and Substantia Nigra activity. This Basal Ganglia-Thalamo-Motor-Cortex loop subserves several cortex functions, such as memory tasks, orientation in space, and the ability to change behavioral set [43,54]. In the motor
imagery task, in particular in LL amputee research literature, the role of this ganglia-thalamo-motor-cortex loop has never been mentioned. In this study we set out to establish its presence using the already mentioned task in the amputee and control groups. Thus, by comparing control and amputee groups, we found that there is minimal cortical activation difference between them, however, the difference occurs in the subcortical activation of the Basal Ganglia loop, since in both, the control group and during intact toes imaginary movement of amputated subjects there is no Basal Ganglia activation, while the activation of distinct Lenticular-Substantia-Nigra-Basal-Ganglia-Thalamic loop is clear in the amputee group performing imaginary movement of the amputated toes. We thus propose that the recruitment of these Basal Ganglia plays an important role in the process of conscious awareness of a missing limb reported by amputees.

It is important to point out that we set out to find the involvement of the Basal Ganglia-Thalamic-Motor-Cortex loop by means of this motor imagery task, as part of our hypothesis that the amputee can and does move the phantom limbs at will, this, do to his framework of body awareness as part of a self-related neurocognitive experience that can be as diverse as the perceiving of size, shape, posture, itch, touch, pressure, vibration, temperature, ‘electric’ sensations and prosthesis embodiment and has been well documented [20]. Similar to Ramachandran’s “null” hypothesis [17] we think that the interruption of the thalamic afferences/afferences may explain the persistence of an open loop functioning of the thalamocortical system and its consequent activation, which is a key factor to the cascade of conscious awareness and stability of the phantom phenomenon. This open loop functioning of the thalamocortical system is revealed in the present study by the increased blood oxygen level-dependent (BOLD) signal in the Basal Ganglia-Thalamic-Motor-Cortex loop pathway during imaginary movement of the amputated toes. Thus, supporting our hypothesis of the abnormal closed-loop functioning of the thalamocortical system as underlying the phantom phenomenon.

6. Conclusion

To conclude, we have put forward evidence of amputee patients’ indirect responses to PL experiences for an objective evaluation that suggests that the conscious awareness of a phantom limb emerges from both the reduction in afferent information and the higher-level brain reorganization of the cognitive representations of the amputee’s own body. We based our assumptions on the hypothesis that the thalamocortical loop is closed in healthy subjects, which enable them to distinguish an imaginary movement as actually being just imagined. This, do to the feedback received from intact peripheric (afferent/efferent) information pathways. The evidence shown here thus suggests that this abnormal open loop of the basal-ganglia-thalamocortical system underlies the conscious awareness of the phantom limb. The current approach further suggests that the basal ganglia within this basal-ganglia-thalamocortical system loop play a crucial and complex integration of afferent and efferent information processing. Furthermore, this integration creates the conscious awareness of the self and is in line with the internal model theory of motor control [15] where inverse and forward models of information processing interact continuously and
reciprocally. The inverse model component in the motor system providing the motor commands necessary to achieve a desired consequence of an action, specified by higher-level goals and the forward model predicting the sensory consequences of each of these motor programs to be executed. Accordingly, whenever a motor program is issued, an efference copy is produced in parallel and an accurate prediction of the sensory consequences expected after the execution of the program, which in turn informs the inverse program of the actual state of the self and closing the loop for the next command. With this normally closed loop, the integration of the self is achieved and a normal body ownership and awareness is created which is necessary to create the autobiographical experience of self.

Glossary of terms

**Bottom-up**: direction of information flow from the periphery (i.e. sensory cells or mechanoreceptors) to the central nervous system.

**Top-down**: information flow from central nervous system toward peripheral effector cells (i.e. muscles).

**Efferent**: Conveying away from the central nervous system

**Afferent**: Conveying towards a central nervous system

**Phantom limb**: is the sensation that an amputated or missing limb is still attached to the body

**Somatosensory system**: sensory system composed of the receptors and processing centers to produce the sensory modalities such as touch, temperature, proprioception (body position), and nociception (pain).

**Proprioception**: sensory modality that processes the body position

**Ipsilateral**: same side of the body

**Contralateral**: other side of the body

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7. References


