An Illusory Hand Changes Amputees' Brain Activity

Robert Beetel [1] and William Craelius [1]

1. Department of Biomedical Engineering
   Rutgers the State University of New Jersey
   Piscataway, NJ 08854

   Corresponding Author

   William Craelius
   Department of Biomedical Engineering
   Rutgers the State University of New Jersey
   599 Taylor Road
   Piscataway, NJ 08854
   848-445-6558
   craelius@soe.rutgers.edu

Keywords: fMRI, brain, amputee, insula, hand, prosthesis, illusion

Authors declare no conflict of interest

Abstract

Persons with upper-limb amputations can experience pain and other bothersome sensations that seem to emanate from their missing limb, a phenomenon known as, the 'phantom limb' (PL). To better understand the origin and possible regulation of the PL, we compared brain activities of amputees and controls during tasks involving moving their hands, both with and without the presentation of illusory limbs. We recorded functional Magnetic Resonance Images (fMRI) of the brains of four persons with traumatic right trans-radial amputation, during tasks in which they experienced an illusory hand and compared these with images from eleven controls. Trials with amputees involved moving their sound (left) hand, while watching a mirrored image of it superimposed on their residuum; control subjects experienced analogous illusions by observing their left hand and its mirror image simultaneously moving, while keeping their right hand stationary. Both amputee and control subjects thereby visualized an illusory hand opposing their left hand during hand motions. Results with BOLD (Blood Oxygen Level Dependency) signals revealed the following primary results: (1) during natural motions of their real hands, controls and amputees exhibited similar brain activities primarily within the primary motor cortices, (2) amputee subjects exhibited prominent activity bilaterally in the insula regions of the brain during volitions for moving their missing right hand, and, (3) the insula activity was not present when the amputee subjects perceived a restored hand moving from their right limb, as represented by their own reflected left hand. Thus, incongruence between single-limb volition and perception activated the insula bilaterally, and this activation was quieted by illusory restoration of the hand. These results suggest possible strategies for improving prosthetic control and relieving phantom limb pain via real-time feedback of brain signals .

Keywords: fMRI, brain, amputee, insula, hand, prosthesis, BOLD, illusion.

1. Introduction

Requirements for restoring lost mobility to upper-limb (UL) amputees are: (1) a device to register user commands for manual actions and (2) a machine to faithfully execute these commands (Craelius 2002). The first requirement is known as the human-machine interface (HMI), since the user's commands, expressed somewhere in his/her residual anatomy, must be translated into language the machine understands. While most amputees have some ability to express their motor volitions through nervous and/or muscular activity at either their residual limbs or at alternate sites on their body, these signals do not contain sufficient resolution for true dexterity (Phillips and Craelius 2005; Yang, Gu et al. 2014) . Thus the main challenge for limb restoration is the HMI, since the second requirement can be met by many available dexterous robotic arms and hands (Cipriani, Controzzi et al. 2011; Castellini, Artemiadis et al. 2014).

While the HMI is generally a limiting factor for humans' interaction with machines, it is particularly troublesome for amputees, whose sensorimotor control system does not readily adapt to limb absence. Specifically, amputees often experience cognitive and sensory dissonance when perceiving an absent limb; these phenomena are actively expressed in the brain, and are likely associated with phantom limb (PL) pain (Kooijman, Dijkstra et al. 2000; Willoch, Rosen et al. 2000). The nature and possible neural origins of PL pain have been intensively researched (Ramachandran, Rogersramachandran et al. 1995) and are associated with brain regions that respond to incongruence between volition and perceived action (Fink, Marshall et al. 1999) (Bengson, Kelley et al. 2015). The anterior insula in particular is a brain region that activates during motor-sensory conflicts, which are associated with error agency, i.e. a loss of body ownership or "selfness" (Koban, Corradi-Dell'Acqua et al. 2013); (Ronchi, Bello-Ruiz et al. 2015); (Allen, Fardo et al. 2016). Insula activity has also been associated with pain (Segerdahl, Mezue et al. 2015). While error agency is reflected in the insula, a positive sense of agency correlates with activity in the parietal and prefrontal cortical areas illustrated by a rise in oxyhemoglobin levels, in response to a real-time virtual tool experiment (Wakata and Morioka 2014). Further evidence of parietal cortex involvement with agency was provided by a study on amputees in which the size of their posterior parietal cortex correlated inversely with their amount of prosthetic usage and also with the intensity of PL pain they experienced (Preissler, Dietrich et al. 2013). These results underscore the role of agency in PL sensations and its localization to particular brain regions.

Strategies to mitigate PL pain by exploiting the brain's response to agency have included mirror imagery (Casale, Damiani et al. 2009); (Ramachandran and Altschuler 2009); (Diers and Flor 2013); (Wosnitzka, Papenhoff et al. 2014), and sensory feedback from surrogate and virtual limbs (Alphonso, Monson et al. 2012); (D'Alonzo, Clemente et al. 2015); (Hellman, Chang et al. 2015);(Dietrich, Walter-Walsh et al. 2012);(Ortiz-Catalan, Sander et al. 2014). A contrasting result was reported in a recent study wherein PL pain intensified when amputee subjects used their brain-signals to control an advanced prosthetic hand; surprisingly, pain was reduced when subjects used a brain-machine interface to dissociate their use of a prosthetic hand from their PL (Yanagisawa, Fukuma et al. 2016). Thus, manipulating perception can profoundly influence clients' neural activity, which may or may not be desirable.

Brain scanning with fMRI has provided insight on the role of agency in persons both with and without intact upper limbs. One study examined brain activities of subjects with intact limbs while they performed repetitive grasping by their right hand in three conditions: (1) eyes closed, (2) watching their moving hand, and (3) watching a virtual prosthetic hand which they controlled from myoelectrical signals from their arm (Maruishi, Tanaka et al. 2004). Results showed that activity in the right posterior parietal cortex was seen in both conditions 1 and 2, but condition 3 shifted the activity laterally from that of condition 1 and also produced unique activity in the right ventral premotor cortex. These patterns may represent a perceptual assimilation of the virtual hand into the body schema. Another study of amputees who simply viewed a moving virtual limb, demonstrated activations in their contralateral (appropriate) motor cortex (Collins, Guterstam et al. 2017). In a study of amputees with and without PL pain, it was found that subjects with PL pain broadly activated their contralateral M1 cortex when controlling a prosthetic hand via myoelectric signals, in contrast to those without PL pain, who showed no such contralateral activation (Maruishi, Nishikawa et al. 2000).

The above studies from individuals during real and simulated hand movements have highlighted the rapid adaptability of the brain to perceptual changes, which have motivated the present study. Here we tested the hypothesis that illusory restoration of a moving limb would normalize the brain's responses to volitions. Results show that abnormal brain activity arising from the absence of a hand can be abolished by presenting an illusory natural hand onto the residuum.

2. Material and Methods

2.1 Human Subjects

Four persons with traumatic trans-radial amputation of their right arm, occurring at least 3 years previously, and eleven persons with sound limbs were recruited. Ages of subjects ranged from 21-31, and all were of approximately average body build and weight. Subjects reported feeling sensations from the phantom limb, but no quantitative measures of these were made. All subjects read and signed an informed consent approved by the Rutgers University Internal Review Board, and all subjects completed the entire protocol. Brain imaging was acquired during experiments that manipulated their visual feedback from their limbs.

2.2 Subject Testing Protocol

To set up the trials, subjects situated themselves comfortably supine in the coil and positioned both arms on their torso, so that both their hands (or in the case of amputee subjects, their left hand and residuum) were facing each other and were visible to them in the overhead coil mirror. Each subject was asked to raise his/her hand(s) a few times by extending their wrists such that their hand (or residuum) movements were visible in the head coil mirror. Next, a small mirror was placed on the lap at waist level of the subject, adjusted at an angle, approximately 45° to the body axis, such that for control subjects, the lap mirror obscured the subject's view of his right hand and reflected the mirror image of his left hand, at the position where the obscured right hand would be. The visual effect was an illusion of the left hand connected to the right wrist. A similar procedure was done for the amputees. Movement of the left hand could thus represent the illusion of a right hand moving, simulating bilateral motion, in the absence of right hand motion.

After the preliminaries described above, formal trials began according to the sequence depicted in Figure 1. Each subject performed trials of simple hand movements both with and without a mirror present. Subjects were asked to repetitively open and close their hand(s) at a rate of 1 to 2 per second. Control subjects moved their right hand first then their left hand and then both hands. The amputee subjects were first asked to imagine moving their phantom hand and then their left hand, while watching in the mirror. Controls performed 9 trials each, and amputees performed 10 trials. Each trial was divided into five-30 second epochs of alternating rest (hands stationary) and activity beginning with a 30 second rest.

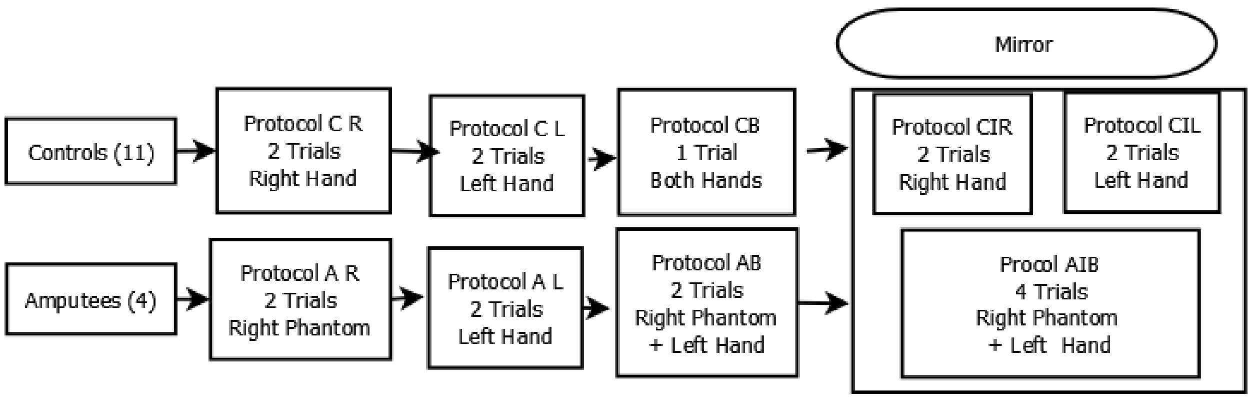

Figure 1. Experimental Protocol. Control subjects performed 2 trials moving their right hand (Control-Right, CR), then 2 trials moving their left hand (Control-Left, CL), then 1 trial moving both hands (Control-Both, CB). Next the mirror was placed nearby and they did 2 trials moving first their right hand while projecting its mirror image (Control-Illusion-Right) , CIR), and then 2 trials moving their left hand (Control-Illusion-Left, CIL) while projecting its mirror image onto their right hand. The amputee subjects (all right-hand missing) performed analogous trials (AIB).

2.3 Imaging

Blood Oxygen Level Dependent (BOLD) analysis of fMRI scans was used to identify regions of activity in the brain during experimental conditions. Images were taken using the GE *Signa* 2000, 1.5 Tesla at the Laurie Imaging Center in NJ. High resolution images were taken using the minimum echo time (TE) and repetition time (TR) both of 400 ms. High resolution field of view (FOV) was 40 mm with slice thicknesses of 10 mm and inter-slice spacing of 1 mm. Acquisition frequency was 512 Hz, the number of phase encoding steps was 256 and the phase FOV was 1 mm. Functional images were acquired using single shot echo planar image (EPI) with TE of 60 milliseconds and a flip angle of 90 degrees. The maximum frequency and phase steps during acquisition for functional BOLD images was 128 . The number of excitations was one and the phase FOV was 1 mm. Scan time was 158 seconds, during which time 52 volumes of 9 slices each were recorded. Prior to analysis, the first 2 volumes were discarded from each run to allow the MR signal to reach a steady state, following which the remaining 50 volumes were analyzed.

Statistical parametric maps were done off-line and based on the Z test using SPM97 software.

3. Results

3.1 Protocols CR and AR

Patterns of neural activation in the brain during the protocols of Figure 1, were recorded with fMRI. The first trials involved right hand motions by controls (CR) and right hand volitions by amputees (AR). As seen in Figure 2, controls showed activity in the left post-central gyri , i.e., primary motor cortex ($p < 1e^{-8}$), in the superior frontal gyri ($p< 1e^{-4}$) and small bilateral activity in the insula regions ($p< .001$). When amputees imagined moving their phantom (right) limb, there was activity in the left primary motor cortex ($P < 1\ e^{-8}$) , and prominent activity in the left and right insula areas ($p< 1e^{-4}$).

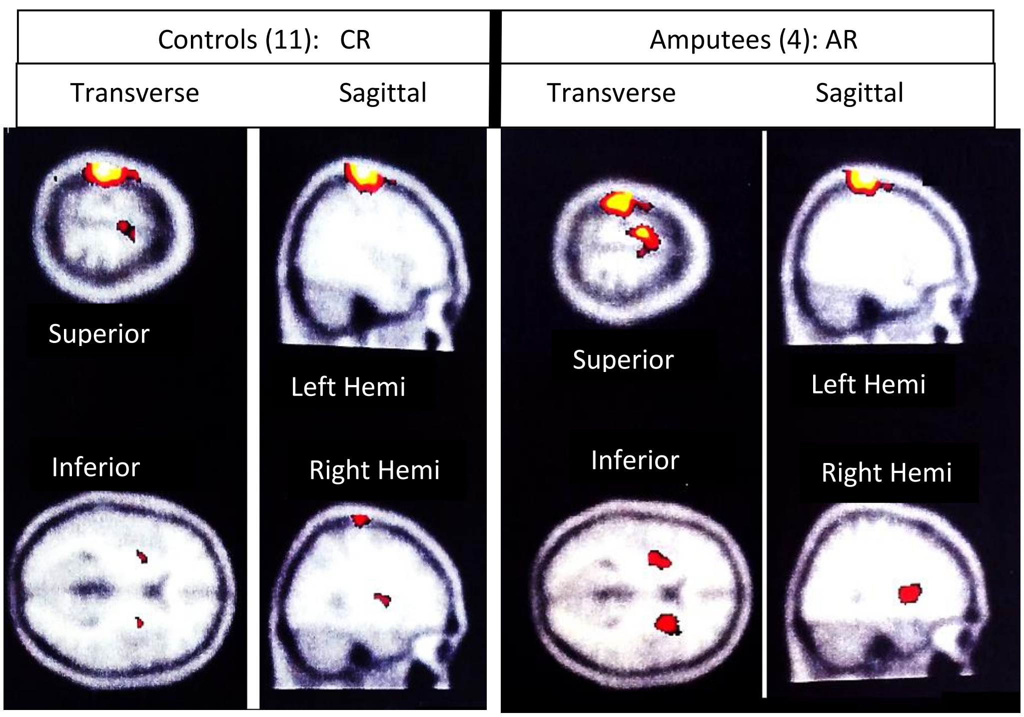

Figure 2. Averaged neural activity in subjects moving right hands only. Controls (N=11) show activity in the left primary motor cortex ($p < 1e^{-8}$), and a small amount of activity in the bilateral insula areas ($p < 1e^{-4}$). Amputees (N=4), who imagined moving their right hands, show activity in the left primary cortex ($p < 1e^{-8}$) and also in the medial superior frontal gyri ($p < 1e^{-6}$) and a small amount of activity in the right frontal lobe superior to the lateral sulcus ($p < 1e^{-4}$).

3.2 Protocols CL and AL

3.1 Protocols CL and AL

Protocol CL shown in Figure 3, revealed activity in the right primary motor cortex of controls, as expected, but also slightly in the left insula region ($p< 1e^{-4}$). In protocol AL, amputees similarly showed prominent activity in the right primary motor cortex and also in the medial superior frontal gyri ($p, 1e^{-6}$). There was weak activity in the right frontal lobe superior to the lateral sulcus ($p< 1e^{-4}$). No activity from amputees was registered in the insula area, in contrast to that seen in protocol AR (Figure 2).

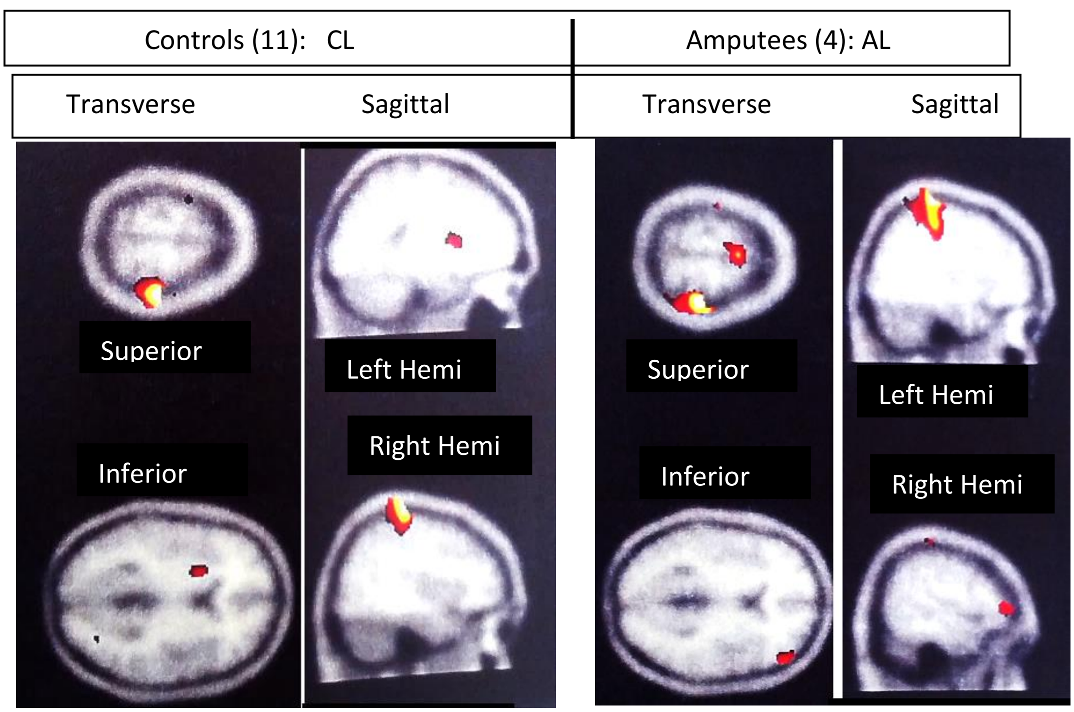

Figure 3. Averaged neural activity in subjects moving left hands only. Controls (N=11) show activity in the right primary motor cortex ($p < 1e^{-8}$), and a small amount of activity in the left insula area ($p < 1e^{-4}$). Amputees (N=4) show activity in the right primary cortex ($p < 1e^{-8}$) and in the medial superior frontal gyri ($p < 1e^{-6}$) and a small amount of activity in the right frontal lobe superior to the lateral sulcus ($p < 1e^{-4}$).

3.3 Protocols CB and AB

Protocol CB showed activity in both primary motor cortices of controls ($p < 1\ e^{-6}$), as shown in Figure 4. A small amount of activity in controls was noted in both frontal lobes (p<.01), as seen in the inferior slice. In protocol AB, when amputees moved their left hand while imagining moving their the phantom hand, bilateral activity in the primary motor cortex was seen (p< .001) , and prominent bilateral activity was present in the in the insula area, as seen in the inferior slice (p< .001).

Controls (11): CB Amputees (4): AB

Transverse Sagittal Transverse Sagittal

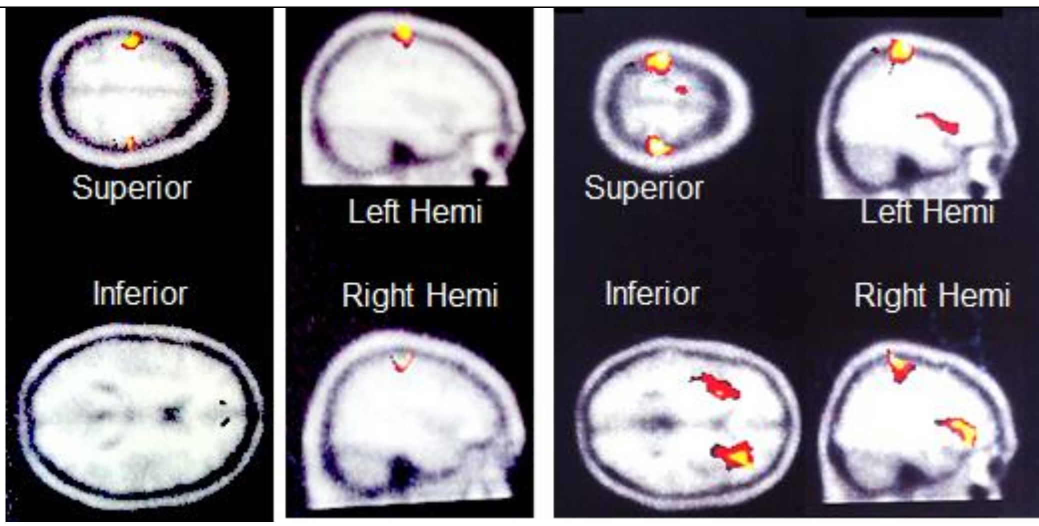

Figure 4. Both hands moving; protocols CB and AB. Note controls (N=11) show bilateral activity in motor cortex, and slight activity in Inferior frontal lobes (p<.001; N=11). Amputees (N=4) show bilateral activity in the motor cortex, and prominent activity bilaterally in the insula areas, seen in the inferior and hemispheric slices (p< .001).

3.4 *Comparing Protocols AB and AIB*

When an illusory hand was superimposed on the residua of the amputees (Protocol AIB) as shown in figure 5 , activity was seen in the primary motor region (p < .0001), but in contrast to the AB protocol (same data as in Figure 4), the inferior slice exhibited no activity. These results show that the insula response to phantom limb volitions can be quieted by incorporating an illusory hand into the visual field.

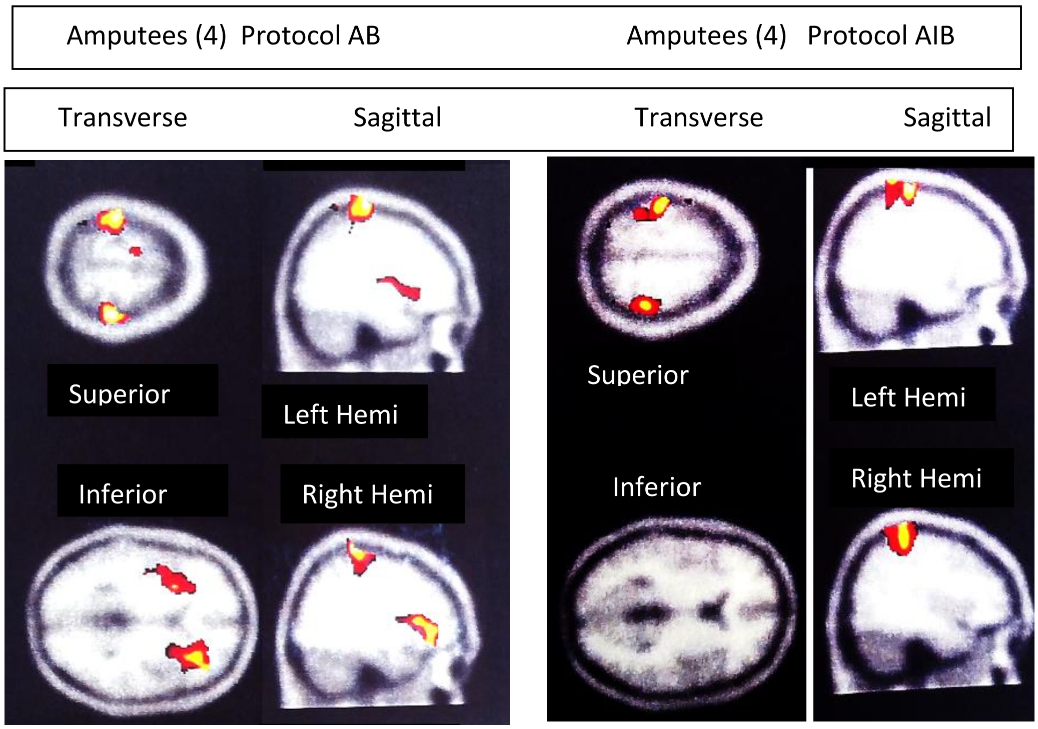

Figure 5. Conditions AB and AIB: Comparing response of amputees (N=4) moving both sound and missing hand (AB, same as Figure 5) with just moving sound and illusory hand. Note the absence of insula activity in the AIB condition.

4. Discussion

4.1 Validity of Study

Average BOLD signals from four persons with right arm amputations were compared with those from 11 matched controls, doing similar protocols. Imaging was done with a 1.5 T MRI, similarly to other studies of sensorally-active regions in the brain (Hu, Olulade et al. 2010), and the SPM statistical parametric mapping software package was used for signal analysis, similarly to other studies of the insula and its real-time regulation (Caria, Veit et al. 2007) .

Protocols were designed to test the hypothesis that perceptual dissonance, occurring when volition for moving the hand is incongruent with action, can be modulated by an illusory limb. Our overall results have proven this hypothesis by demonstrating the strong positive relationship between insula activity and dissonance in amputees. The first observation from Figure 2 is normal activation in left M1 region by both controls and amputees, with the latter only imagining moving their right hand. Secondly, controls exhibited a small amount of insula activity bilaterally, relative to the amputees, whose average insula activity was quite prominent. The small signal noted in the controls could be due to a certain incongruent feeling among any subject within the MRI while moving his hand. Since there is no expectation that all subjects within each group responded identically, it is possible that a few control subjects exhibited a large signal that skewed the average signal; such skewing is less likely a factor in the large amputee average signal from 4 subjects. While no firm conclusions can be drawn from the results of Figure 2, our further results illustrate the distinct brain responses produced by amputees. Figure 3 shows a small insula response in controls moving their left hand, but no measurable response by amputees. In Figure 4, a large bilateral insula response is seen with amputee moving both the left hand and the right phantom, is contrasted by the controls moving both hands, and exhibiting no insula activity. Finally Figure 5 shows that the large bilateral activity seen when amputees move their left hand and imagine moving their phantom hand, is absent when an illusory moving hand is present.

The hand restoration illusion consisted of reflecting the amputee's left hand onto the end of his residuum, by arranging a small mirror on the subject's lap, to reflect the left hand. The illusion was not anatomically perfect, since it was a double reflection of the left hand. An analogous illusion for controls was made by obscuring his right hand with the lap mirror which reflected his left hand near to his right arm. In this way, all subjects could experience the illusion of right hand moving when only the left hand was moving.

The mirror hand illusion evokes responses similar to the well-known "rubber hand" illusion, which has shown that humans in general and amputees in particular, can experience bodily agency with the rubber hand illusion, and incorporate it into their own body scheme (Schaefer, Noennig et al. 2006; Ehrsson, Rosen et al. 2008);(Slater, Perez-Marcos et al. 2008); (Ramakonar, Franz et al. 2011); (Filippetti and Tsakiris 2017). Mirror therapy, using mirror box or similar apparatus, has been extensively used to treat PL pain (Ramachandran and Altschuler 2009) (Maruishi, Nishikawa et al. 2000); (Hernandez, Yokoi et al. 2006); (Fukui, Kimura et al. 2009); (Ortiz-Catalan, Sander et al. 2014); Wosnitzka, Papenhoff et al. 2014; Allen, Fardo et al. 2016). The simple mirror box has been upgraded with a computerized display that enhances the visual experience using a virtual display of the limb (Shibuya, Unenaka et al. 2017).

4.2 Agency and the role of the insula

The real-time plastic change in the insula region of amputees responding to an illusory limb is a manifestation of agency: the feeling that a person is in control of his or her own body parts (Chambon, Sidarus et al. 2014); (de Vries, Byrne et al. 2015); Koban, Corradi-Dell'Acqua et al. 2013). A positive sense of agency contributes positively to the control of limbs, whether they be original or artificial; error agency contributes negatively to limb control, and is associated with regional brain activations, notably the anterior insula (van Veen, Krug et al. 2009). The insula's role in integrating bodily information with sensory inputs with high-level efferent signals coming from the prefrontal and cingulate cortex is well known (Sethi, Suzuki et al. 2012); Allen, Fardo et al. 2016). The insula, in particular its dorsal posterior portion, plays a critical role in pain perception, as shown by brain imaging of subjects reporting their own pain, (Budell, Kunz et al. 2015); (Segerdahl, Mezue et al. 2015), and also in those who merely observed the pain of others (Koban, Corradi-Dell'Acqua et al. 2013) . Right insular damage decreases heartbeat awareness and alters cardio-visual effects on bodily self-consciousness (Ronchi, Bello-Ruiz et al. 2015). The insula has been specifically associated with error agency of the hand, since it becomes active when subjects (non-disabled) view images of their hand motions which are discordant with their volition (Farrer, Franck et al. 2003) . This study, using brain positron emission tomography, found that the activation level of the inferior part of the parietal lobe related to the degree of agency, as measured by the error between the movement executed by the non-disabled subjects versus its representation on a prompter. As noted in the Introduction, the volume of the posterior parietal cortex in amputees depends on the degree of prosthetic usage, shrinking with more usage (Preissler, Dietrich et al. 2013). Further evidence of parietal involvement in agency is provided by a study of non-disabled subjects whose right inferior parietal lobule became activated when they merely observed subjects with missing upper-limbs move their residual limb (Liew, Sheng et al. 2013).

4.3 Implications for Amputees

Agency is a well- recognized factor in users' overall satisfaction and performance with their prostheses (Pirowska, Wloch et al. 2014); (Crawford 2015)Crawford 2015). The present results show that restoring agency by itself profoundly reduces or abolishes the activity associated with error agency in the insula of amputees. Agency, as indicated by absence of insula activity, was immediately restored to the amputee subjects by presentation of an illusory restoration of their hand. Since insula activity is associated with phantom limb pain (Willoch, Rosen et al. 2000), and may interfere with motor control circuits in the brain (Chand and Dhamala 2017), its removal can be a useful target for reducing pain and improving the human-machine interface. (Maruishi, Tanaka et al. 2004; (Powell, Kaliki et al. 2014).

In combination with mirror and illusion therapy, neuroimaging could become a valuable adjunct for prosthetic training. It is known that subjects can self-regulate their brain activities in various regions, including their insula, using real-time biofeedback of their

BOLD signals (Weiskopf, Scharnowski et al. 2004) (Caria, Veit et al. 2007). Such neurofeedback training could possibly be done with simpler modalities, such as EEG, since it correlates with BOLD signals from the anterior insula (Yin, Liu et al. 2016; Sitaram, Ros et al. 2017). Before real-time neurofeedback can become useful tool for prosthetic training, however, a better understanding of the brain's responses to restored artificial limbs is needed. Specifically, we need to know how the perception of and sensations from particular limb restorations influence the brain, and which features of the prosthesis, both structural and functional, are most important to agency. Such information is needed to explain the peculiar finding that some prosthetic restorations may augment rather than relieve phantom pain, thereby adversely affecting the human machine interface (Yanagisawa, Fukuma et al. 2016).

5. Conclusions

BOLD responses in fMRI were measured in four persons with right trans-radial amputations and in eleven control persons while performing motions of their hands. Prominent activity was seen in the insula regions of amputees brains while they imagined moving their missing there missing right hand; this activity was absent when an illusory hand was superimposed on their residuum.

6. Acknowledgements

This study was a collaboration with our cherished colleague Dr. Evangelia Micheli-Tzanakou, may she rest in peace. Dr. Ilker Hacihaliloglu advised and processed the images. We thank Dr. James K. DiMarco for neuroanatomical interpretations, and Michael Schlenk and Talita Soares for assistance with MRI data acquisition. This research did not receive a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

7. Declaration of interest

The authors have no financial, personal, or other relationship that could influence this work.

8. References

Allen, M., F. Fardo, M. J. Dietz, H. Hillebrandt, K. J. Friston, G. Rees and A. Roepstorff (2016). "Anterior insula coordinates hierarchical processing of tactile mismatch responses." Neuroimage **127**: 34-43.

Alphonso, A. L., B. T. Monson, M. J. Zeher, R. S. Armiger, S. R. Weeks, J. M. Burck, C. Moran, R. Davoodie, G. Loeb, P. F. Pasquina and J. W. Tsao (2012). Use of a Virtual Integrated Environment in Prosthetic Limb Development and Phantom Limb Pain. Annual Review of Cybertherapy and Telemedicine

2012: Advanced Technologies in the Behavioral, Social and Neurosciences. B. K. Wiederhold and G. Riva. **181:** 305-309.
Bengson, J. J., T. A. Kelley and G. R. Mangun (2015). "The neural correlates of volitional attention: A combined fMRI and ERP study." Human Brain Mapping **36**(7): 2443-2454.
Budell, L., M. Kunz, P. L. Jackson and P. Rainville (2015). "Mirroring Pain in the Brain: Emotional Expression versus Motor Imitation." Plos One **10**(2).
Caria, A., R. Veit, R. Sitaram, M. Lotze, N. Weiskopf, W. Grodd and N. Birbaumer (2007). "Regulation of anterior insular cortex activity using real-time fMRI." Neuroimage **35**(3): 1238-1246.
Casale, R., C. Damiani and V. Rosati (2009). "Mirror Therapy in the Rehabilitation of Lower-Limb Amputation Are There Any Contraindications?" American Journal of Physical Medicine & Rehabilitation **88**(10): 837-842.
Chambon, V., N. Sidarus and P. Haggard (2014). "From action intentions to action effects: how does the sense of agency come about?" Frontiers in Human Neuroscience **8**.
Chand, G. B. and M. Dhamala (2017). "Interactions between the anterior cingulate-insula network and the fronto-parietal network during perceptual decision-making." Neuroimage **152**: 381-389.
Collins, K. L., A. Guterstam, J. Cronin, J. D. Olson, H. H. Ehrsson and J. G. Ojemann (2017). "Ownership of an artificial limb induced by electrical brain stimulation." Proceedings of the National Academy of Sciences of the United States of America **114**(1): 166-171.
Craelius, W. (2002). "The bionic man: restoring mobility." Science **295**(5557): 1018-1021.
Crawford, C. S. (2015). "Body Image, Prostheses, Phantom Limbs." Body & Society **21**(2): 221-244.
D'Alonzo, M., F. Clemente and C. Cipriani (2015). "Vibrotactile Stimulation Promotes Embodiment of an Alien Hand in Amputees With Phantom Sensations." Ieee Transactions on Neural Systems and Rehabilitation Engineering **23**(3): 450-457.
de Vries, J., M. Byrne and E. Kehoe (2015). "Cognitive dissonance induction in everyday life: An fMRI study." Social Neuroscience **10**(3): 268-281.
Diers, M. and H. Flor (2013). "Phantom limb pain. Psychological treatment strategies." Schmerz **27**(2): 205-211.
Dietrich, C., K. Walter-Walsh, S. Preissler, G. O. Hofmann, O. W. Witte, W. H. R. Miltner and T. Weiss (2012). "Sensory feedback prosthesis reduces phantom limb pain: Proof of a principle." Neuroscience Letters **507**(2): 97-100.
Ehrsson, H. H., B. Rosen, A. Stockselius, C. Ragno, P. Kohler and G. Lundborg (2008). "Upper limb amputees can be induced to experience a rubber hand as their own." Brain **131**: 3443-3452.
Farrer, C., N. Franck, N. Georgieff, C. D. Frith, J. Decety and A. Jeannerod (2003). "Modulating the experience of agency: a positron emission tomography study." Neuroimage **18**(2): 324-333.
Fink, G. R., J. C. Marshall, P. W. Halligan, C. D. Frith, J. Driver, R. S. J. Frackowiak and R. J. Dolan (1999). "The neural consequences of conflict between intention and the senses." Brain **122**: 497-512.
Fukui, T., T. Kimura, K. Kadota, S. Shimojo and H. Gomi (2009). "Odd Sensation Induced by Moving-Phantom which Triggers Subconscious Motor Program." Plos One **4**(6).
Hellman, R. B., E. Chang, J. Tanner, S. I. H. Tillery and V. J. Santos (2015). "A robot hand testbed designed for enhancing embodiment and functional neurorehabilitation of body schema in subjects with upper limb impairment or loss." Frontiers in Human Neuroscience **9**.
Hernandez, A., H. Yokoi, T. Ohnishi and T. Arai (2006). An f-MRI study of an EMG Prosthetic Hand Biofeedback System.
Hu, S. W., O. Olulade, J. G. Castillo, J. Santos, S. Kim, G. G. Tamer, W. M. Luh and T. M. Talavage (2010). "Modeling hemodynamic responses in auditory cortex at 1.5 T using variable duration imaging acoustic noise." Neuroimage **49**(4): 3027-3038.
Koban, L., C. Corradi-Dell'Acqua and P. Vuilleumier (2013). "Integration of Error Agency and Representation of Others' Pain in the Anterior Insula." Journal of Cognitive Neuroscience **25**(2):

258-272.
Kooijman, C. M., P. U. Dijkstra, J. H. B. Geertzen, A. Elzinga and C. P. van der Schans (2000). "Phantom pain and phantom sensations in upper limb amputees: an epidemiological study." Pain **87**(1): 33-41.
Liew, S. L., T. Sheng and L. Aziz-Zadeh (2013). "Experience with an amputee modulates one's own sensorimotor response during action observation." Neuroimage **69**: 138-145.
Maruishi, M., D. Nishikawa, Y. Mano, W. Yu, H. Yokoi, Y. Kakazu and T. Nakagawa (2000). Functional MRI of amputees during use of myoelectric prosthetic hand.
Maruishi, M., Y. Tanaka, H. Muranaka, T. Tsuji, Y. Ozawa, S. Imaizumi, M. Miyatani and J. Kawahara (2004). "Brain activation during manipulation of the myoelectric prosthetic hand: a functional magnetic resonance imaging study." Neuroimage **21**(4): 1604-1611.
Ortiz-Catalan, M., N. Sander, M. B. Kristoffersen, B. Hakansson and R. Branemark (2014). "Treatment of phantom limb pain (PLP) based on augmented reality and gaming controlled by myoelectric pattern recognition: a case study of a chronic PLP patient." Frontiers in Neuroscience **8**.
Phillips, S. L. and W. Craelius (2005). "Residual kinetic imaging: a versatile interface for prosthetic control." Robotica **23**: 277-282.
Pirowska, A., T. Wloch, R. Nowobilski, M. Plaszewski, A. Hocini and D. Menager (2014). "Phantom phenomena and body scheme after limb amputation: A literature review." Neurologia I Neurochirurgia Polska **48**(1): 52-59.
Powell, M. A., R. R. Kaliki and N. V. Thakor (2014). "User Training for Pattern Recognition-Based Myoelectric Prostheses: Improving Phantom Limb Movement Consistency and Distinguishability." Ieee Transactions on Neural Systems and Rehabilitation Engineering **22**(3): 522-532.
Preissler, S., C. Dietrich, K. R. Blume, G. O. Hofmann, W. H. R. Miltner and T. Weiss (2013). "Plasticity in the visual system is associated with prosthesis use in phantom limb pain." Frontiers in Human Neuroscience **7**.
Ramachandran, V. S. and E. L. Altschuler (2009). "The use of visual feedback, in particular mirror visual feedback, in restoring brain function." Brain **132**: 1693-1710.
Ramachandran, V. S., D. Rogersramachandran and S. Cobb (1995). "TOUCHING THE PHANTOM LIMB." Nature **377**(6549): 489-490.
Ramakonar, H., E. A. Franz and C. R. P. Lind (2011). "The rubber hand illusion and its application to clinical neuroscience." Journal of Clinical Neuroscience **18**(12): 1596-1601.
Ronchi, R., J. Bello-Ruiz, M. Lukowska, B. Herbelin, I. Cabrilo, K. Schaller and O. Blanke (2015). "Right insular damage decreases heartbeat awareness and alters cardio-visual effects on bodily self-consciousness." Neuropsychologia **70**: 11-20.
Schaefer, M., N. Noennig, H. J. Heinze and M. Rotte (2006). "Fooling your feelings: Artificially induced referred sensations are linked to a modulation of the primary somatosensory cortex." Neuroimage **29**(1): 67-73.
Segerdahl, A. R., M. Mezue, T. W. Okell, J. T. Farrar and I. Tracey (2015). "The dorsal posterior insula subserves a fundamental role in human pain." Nature Neuroscience **18**(4): 499-+.
Sethi, A. K., K. Suzuki and H. D. Critchley (2012). "An interoceptive predictive coding model of conscious presence." Frontiers in Psychology **3**.
Shibuya, S., S. Unenaka and Y. Ohki (2017). "Body ownership and agency: task-dependent effects of the virtual hand illusion on proprioceptive drift." Experimental Brain Research **235**(1): 121-134.
Sitaram, R., T. Ros, L. Stoeckel, S. Haller, F. Scharnowski, J. Lewis-Peacock, N. Weiskopf, M. L. Blefari, M. Rana, E. Oblak, N. Birbaumer and J. Sulzer (2017). "Closed-loop brain training: the science of neurofeedback." Nature Reviews Neuroscience **18**(2): 86-100.
Slater, M., D. Perez-Marcos, H. H. Ehrsson and M. V. Sanchez-Vives (2008). "Towards a digital body: the virtual arm illusion." Frontiers in Human Neuroscience **2**.
van Veen, V., M. K. Krug, J. W. Schooler and C. S. Carter (2009). "Neural activity predicts attitude change

in cognitive dissonance." Nature Neuroscience **12**(11): 1469-1474.
Wakata, S. and S. Morioka (2014). "Brain activity and the perception of self-agency while viewing a video of tool manipulation: a functional near-infrared spectroscopy study." Neuroreport **25**(6): 422-426.
Weiskopf, N., F. Scharnowski, R. Veit, R. Goebel, N. Birbaumer and K. Mathiak (2004). "Self-regulation of local brain activity using real-time functional magnetic resonance imaging (fMRI)." Journal of Physiology-Paris **98**(4-6): 357-373.
Willoch, F., G. Rosen, T. R. Tolle, I. Oye, H. J. Wester, N. Berner, M. Schwaiger and P. Bartenstein (2000). "Phantom limb pain in the human brain: Unraveling neural circuitries of phantom limb sensations using positron emission tomography." Annals of Neurology **48**(6): 842-849.
Wosnitzka, M., M. Papenhoff, A. Reinersmann and C. Maier (2014). "Mirror therapy for the treatment of phantom limb pain after bilateral thigh amputation. A case report." Schmerz **28**(6): 622-627.
Yanagisawa, T., R. Fukuma, B. Seymour, K. Hosomi, H. Kishima, T. Shimizu, H. Yokoi, M. Hirata, T. Yoshimine, Y. Kamitani and Y. Saitoh (2016). "Induced sensorimotor brain plasticity controls pain in phantom limb patients." Nature Communications **7**.
Yang, D. P., Y. K. Gu, R. Q. Liu and H. Liu (2014). "Dexterous motion recognition for myoelectric control of multifunctional transradial prostheses." Advanced Robotics **28**(22): 1533-1543.
Yin, S. Y., Y. L. Liu and M. Z. Ding (2016). "Amplitude of Sensorimotor Mu Rhythm Is Correlated with BOLD from Multiple Brain Regions: A Simultaneous EEG-fMRI Study." Frontiers in Human Neuroscience **10**.