Tamar Makin (centre right) with David Henderson Slater and study participants Kirsty and Clay.

Limb loss and the brain

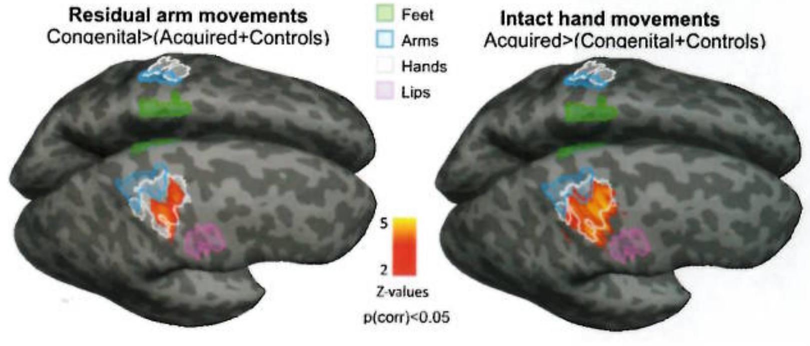
Functional imaging studies are suggesting that much of what we think happens to the brain after amputation may be wrong...

Loss of a limb can be devastating. Many everyday tasks, from getting dressed to preparing food, are infinitely harder for those with one hand. In addition, most amputees continue to experience sensations, usually painful, that seem to originate from their lost limb – phantom pain. Influential theories have been developed to explain the origins of phantom pain – but, says **Tamar Makin** in Oxford, they are probably wrong.

"I feel like I'm tearing out a few leaves from the textbook," she says. "Almost everything that has been established by previous work, I find opposite evidence for."

Phantom pain is part of a wider range of research interests: "My primary interest is in brain plasticity, this notion that a brain area could be reassigned to carry a new functional role later in life," says Dr Makin. "I call it plasticity, but it's actually more like reorganisation, an extreme form of plasticity." As well as shedding light on fundamental aspects of brain function, she hopes that a better understanding of such reorganisation could ultimately help those whose brains are affected by injury, ageing, neurodegeneration or disease.

Her studies focus primarily on arm amputation which, she suggests, has two important consequences for the brain. Firstly, it provides a natural trigger for reorganisation, as brain areas are deprived of inputs they previously received from a hand. But although deprivation has dominated research, loss of an arm causes people to change their behaviour markedly: "There are a million little things in your routine that are disrupted and you have to figure out how to solve. So there's very strong behavioural pressure to learn to use your body in a different way, to adapt to your disability."



Brain activations for intact hand and residual arm movements, superimposed on the sensorimotor homunculus.

These behavioural adaptations could potentially also be major drivers of changes in the brain.

Remapping the brain

Much of what is known about the brain's response to amputation has come from studies in monkeys. Deprived of inputs from the missing limb, the area of somatosensory cortex previously devoted to the hand is 'taken over' by neighbouring regions of cortex. According to the 'maladaptive plasticity theory', the mismatch between the existing neural architecture and these new inputs creates the experience of phantom pain. "It's a hugely influential theory," says Dr Makin.

Oddly, though, the hand area is typically taken over by the lower part of the face and lips. "This is a bit curious, because the lower part of the face is not a cortical neighbour of the hand. The representation has to jump over the upper part of the face."

An alternative explanation is that the lips take over hand territory because the animals start using them to compensate for the loss of a limb. Although difficult to test directly in monkeys, Dr Makin realised this idea could be addressed in amputees.

Having lost a limb, amputees are forced to make multiple adaptions in everyday life. "They come up with unique strategies to solve simple problems like how to open a bottle of water with one hand," says Dr Makin. However, amputees vary significantly in the extent to which they use their residual arm. In particular, individuals who are born without a limb due to a congenital abnormality typically make extensive use of their residual limb.

To gain an objective measure of laterality, or asymmetry in limb usage, Dr Makin fitted accelerometers to participants' upper arms. "We just asked them to go back home and go through their regular routine for a few days." Participants also completed surveys on their use of their residual arm in bimanual tasks.

"We immediately saw a very clear dissociation between the acquired amputees and the congenitals [people born with a missing hand]," recalls Dr Makin. The latter were much better at using their residual arm on daily tasks, while the 'acquireds' tended to rely heavily on their remaining 'good' arm.

These differences were associated with major differences in brain activity. When acquireds wiggled the fingers of their good hand or congenitals moved their residual arm, activity was markedly higher than normal in a single area – the territory of the missing hand.

"I FEEL LIKE I'M TEARING OUT A FEW LEAVES FROM THE TEXTBOOK..."

"That was a really nice proof of concept that whatever body part you are taking advantage of to compensate for your disability is also the body part that benefits from overrepresentation specifically in that hand area," points out Dr Makin. Rather than neighbouring territories encroaching on the 'redundant' areas, it is actually those associated with body parts that are used more – even if they normally activate regions in the opposite hemisphere.

More recently, Dr Makin has begun to use resting state fMRI to look across the whole brain and at networks rather than individual areas. Normally, hand areas form part of extensive networks showing a high degree of symmetry between left and right hemispheres. This symmetry was greatly reduced in congenitals. But the more people used their residual arm, the more normal patterns of connectivity were – to the extent that the congenitals who used their residual arms extensively showed almost symmetrical activity patterns. "That's a very powerful demonstration of how adapted usage can really shape brain activity and connectivity."

Resting state fMRI has also provided a way to examine linkage to other brain networks – an issue that, with the strong focus on the missing hand territory, has been largely overlooked. These studies showed that the missing hand territory typically loses contact with the sensorimotor network, but begins to couple with the default mode network (DMN). "Normally the hand area has nothing to do with the DMN, it's completely uncoupled, but in amputees they are positively connected. The more you break free from the sensorimotor network the more you get affiliated with the DMN. It's a really beautiful example of inter-network plasticity."

Phantom pain

These results may be highly relevant to phantom pain. The maladaptive plasticity theory has dominated thinking about phantom pain, yet Dr Makin's work has called its very basis into question.

As well as showing that behavioural adaptations may be strong drivers of cortical reorganisation (and that the lips have little or no impact on the missing hand territory), her work also suggests that deprivation of inputs from the limb may not be as complete as once thought. When amputees were asked to try to move their phantom fingers, it proved possible to measure responses in the missing hand territory (and even see motor activity in the residual arm). Furthermore, phantom pain showed a strong positive relationship with the degree to which the hand representation was maintained – "the exact opposite of what you would predict based on the maladaptive plasticity theory."

Study participant Clay in the MRI scanner.

Dr Makin suggests that residual input is maintaining the hand representation to some degree. But the integrity of the territory cannot be wholly preserved, as evidenced by the shift in connectivity from the sensorimotor network to the DMN. Phantom pain, she suggests, may be linked to this loss of connectivity.

Her findings have not gone down well with adherents to the old model. Yet the implications could be huge for patients. Dr Makin has been running a trial of transcranial direct current stimulation in order to enhance network connectivity in amputees with phantom pain. She is cautiously optimistic, but reluctant to make any bolder statements until data analysis is complete for fear of raising expectations too high.

Although a basic scientist, she is committed to using new knowledge to aid patients. She praises the collaborators who have provided access to patients – David Henderson Slater and colleagues at the Oxford Centre for Enablement and the Opcare prosthesis company. But most of all she is in awe of the participants: "They are the most enthusiastic group of people you could imagine to work with. They come from all over the country and give us their brains for as long as we need them. They are an amazing bunch – a really inspiring group of people to work with."

Makin TR *et al.* Phantom pain is associated with preserved structure and function in the former hand area. *Nat Commun*. 2013;4:1570.

Makin TR *et al.* Deprivation-related and use-dependent plasticity go hand in hand. *Elife*. 2013;2:e01273.

Hahamy A *et al.* Normalisation of brain connectivity through compensatory behaviour, despite congenital hand absence. *Elife*. 2015;4.

Makin TR *et al.* Network-level reorganisation of functional connectivity following arm amputation. *Neuroimage*. 2015. [Epub ahead of print]