NEUROPSYCHOLOGY OPTION **Supplementary handout, Oct 17th, 2006**

Phantom Limbs — Introduction

[below are several short sections adapted from —
Ramachandran, VS and Hirstein, W (1998) The perception of phantom limbs. The D.O. Hebb lecture. *Brain, 121*, no 9., pp. 1603- 1630.

- A characteristic feature of the adult primate brain is the existence of a multiplicity of specialized areas, including distinct topographically organized 'maps' concerned with different sense modalities).
- In the visual domain alone, for example, over 30 distinct areas have been described which contain either partial or complete maps of the visual field.
- A hundred years of neurology, as well as three decades or single-unit recordings using microelectrodes, have established these basic ideas beyond any reasonable doubt
- One or the most important early findings was that much of this intricate circuitry, especially in the primary visual cortex, is specified by the genome and remains largely stable throughout life, under ordinary circumstances (Wiesel and Hubel, 1963).
- This finding provided a vindication of what neurology has always believed: that no new neural connections can be formed in the adult mammalian brain.
- Once connections have been laid down in foetal life, or during certain critical periods in early infancy, it was assumed that they remain fixed throughout life.
- Indeed, it is this stability of connections in the adult brain that is often used to explain why there is usually very little functional recovery after damage to the nervous system and why neurological diseases are so notoriously difficult to treat.
- In the last two decades, however, several experiments on the effects of deafferentation (or amputation) on somatosensory maps in adult primates and other mammals suggest that we may need to revise this conception of the nervous system.
- These animal experiments have shown that sensory maps can indeed change in the adult brain, and they have been largely responsible for the current resurgence of interest in the clinical phenomenon of phantom limbs (Ramachandran, 1993b).
- Taken collectively, the work on animals and human patients provides a valuable experimental opportunity to investigate not only how new connections emerge in the adult human brain, but also how information from different sensory modules, e.g. touch, proprioception and vision, interact.

Phantom Limbs — Incidence

Almost immediately after the loss of a limb, between 90 and 98% of all patients experience a vivid phantom. There are hints that the incidence may be higher following a traumatic loss, or if there has been a pre-existing painful condition in the limb, than after a planned surgical amputation of a nonpainful limb.

Phantoms are seen far less often in early childhood.

Onset

Phantoms appear immediately in *75%* of cases, as soon as the anaesthetic wears off and the patient is conscious, but their appearance may be delayed by a few days or weeks in the remaining *25%* of patients (Moser, 1948).

Duration

In many cases the phantom is present initially for a few days or weeks, then gradually fades from consciousness. In others, it may persist for years, even decades (30% of patients, according to

Sunderland, 1978). There are case reports of phantoms which persisted (or 44 years (Livingston, 1945) and 57 years (Abbatucci, 1894).

Some patients are able to recall a phantom limb at will after its disappearance with intense concentration or sometimes merely by rubbing its stump. Mitchell (1872) was able to resurrect a long-lost phantom by faradic stimulation applied to the stump of an above- knee amputee, it is perhaps findings such as this that have led to the widespread clinical opinion that neuromas are the primary cause of phantom limbs.

Congenital phantoms

- It was originally claimed by Simmel (1962) that children with congenitally missing limbs do not experience phantoms,
- but it soon became apparent that this was not always true (Weinstein *et al.,* 1964; Poeck, 1969; La Croix *et al.,* 1992). Weinstein *et al.* (1964) studied 13 congenital aplasics with phantom limbs, seven of whom were able to move the phantom voluntarily, and four of whom experienced 'telescoped' phantoms.
- The presence of phantom arms in a patient (D.B.), a 20-year-old woman whose arms had both been missing from birth was reported by Ramachandran (1993b). All she had on each side were the upper ends of the humerus—there were no hand bones, and no radius or ulna.
- However, she claimed to experience very vivid phantom limbs that often gesticulated during conversation (Ramachandran, 1993b).
- It is unlikely that these experiences are due to confabulation or wishful thinking, for two reasons.
- First, she claimed that her arms were 'shorter' than they should be by about a foot. (She knew this because her phantom hand did not fit into the prosthesis like a hand in a glove 'the way it was supposed to.')
- Secondly, her phantom arms did not feel as though they were swinging normally as she walked; they felt rigid.
- These observations suggest that her phantom limbs did not originate simply from her desire to be normal. We suggest that these vivid sensations arise from the monitoring of reafference signals derived from the motor commands sent to the phantom during gesticulation.
- What is remarkable, however, is that the neural circuitry generating these gesticulatory movements is **'hardwired'** and has actually survived intact for 20 years in the absence of any direct visual or kinaesthetic reinforcement from her own limbs (although watching other people's limbs might have played a role).

Melzack, R, Israel, R, Lacroix, R, Schultz, G (1997) Phantom limbs in people with congenital limb deficiency or amputation in early childhood. Brain, Vol.120, No.Pt9, Pp.1603-1620.

- It is widely believed that people who are congenitally limb-deficient or suffer a limb amputation at an early age do not experience phantom limbs.
- The present study reports on a sample of 125 people with missing limbs and documents phantom experiences in
- 41 individuals who were either born limb-deficient (n = 15) or underwent amputation before the age of 6 years (n = 26).
- These cases provide evidence that phantom limbs are experienced by at least 20% of congenitally limb- deficient subjects and by 50% of subjects who underwent amputations before the age of 6 years.
- The phantoms are detailed and can be described in terms of size, shape, position, movement and temporal properties.
- The perceptual qualities of the phantoms can also be described by sensory descriptors and are reported as painful by 20% of subjects with phantoms in the congenital limb deficient group and 42% of young amputees.
- It is argued that these phantom experiences provide evidence of a distributed neural representation of the body that is in part genetically determined.

Phantom Limbs — Patient VQ.

Patient V.Q. was an intelligent, alert 17-year-old who was involved in a car accident.

- Immediately following the accident, his left arm was amputated 6 cm above the elbow — 4 weeks prior to testing. He also had minor head injuries (including a concussion) but at the time of testing he was mentally lucid, intelligent and fluent in conversation.
- He experienced a vivid phantom hand that was 'telescoped', so that it felt as if it were attached just a few centimeters below his stump.
- The investigators studied localization of touch (and light pressure) in this patient using a cotton swab that was brushed twice in rapid succession at various randomly selected points on his skin surface. His eyes were shut during the entire procedure and he was simply asked to describe any sensations that he felt and to report their perceived location.
- The investigators found that even stimuli applied to points remote from the amputation line were often systematically mislocalized to the phantom arm.
- Furthermore, the distribution of these points was not random. They appeared to be clustered on the lower left side of the face (i.e. ipsilateral to amputation) and there was a systematic one-to-one mapping between specific regions on the face and individual digits (e.g. from the cheek to the thumb, from the upper lip to the index finger and from the chin to the little finger).
- Typically, the patient reported that he simultaneously felt the cotton swab touching his face and a tingling sensation in an individual digit. By repeatedly brushing the swab on his face it was possible to plot 'receptive fields' (or 'reference fields') for individual digits of the (phantom) left hand on his face surface. The margins of these fields were remarkably sharp and stable over successive trials. Stimuli applied to other parts of the body such as the tongue, neck, shoulders, trunk, axilla and contralateral arm were never mislocalized to the phantom hand.
- A second cluster of points that evoked referred sensations was found about 7 cm above the amputation line. Again there was a systematic one-to-one mapping with the thumb being represented medially on the anterior surface of the arm, and the little finger laterally, as if to mimic the pronated position of the phantom hand. Stimulating points halfway between these two areas elicited referred sensations in the index or ring fingers.
- The whole procedure was repeated after 1 week resulting in an identical distribution of points. It was concluded, therefore, that these one-to-one correspondences are stable over time, at least over the 1-week period that separated our two testing sessions (Ramachandran et al., 1992a).

Phantom Limbs — The ‘Phantom nose’ illusion.

Although we ordinarily regard phantoms as pathological, it is relatively easy to generate such illusions, even in otherwise normal individuals. Consider the **'phantom nose'** illusion (Ramachandran and Hirstein, 1997).

- The subject sits in a chair blindfolded, with an accomplice sitting in front of him, facing the same direction.
- The experimenter then stands near the subject, and with his left hand takes hold of the subject's left index finger and uses it to repeatedly and randomly to tap and stroke the nose of the accomplice,
- while at the same time, using his right hand, he taps and strokes the subject's nose in precisely the same manner, and in perfect synchrony.
- After a few seconds of this procedure, the subject develops the uncanny illusion that his nose has either been dislocated, or has been stretched out several feet forwards, demonstrating the striking plasticity or malleability of our body image.
- The more random and unpredictable the tapping sequence the more striking the illusion.
- It is suggested that the subject's brain regards it as highly improbable that the tapping sequence on his finger and the one on his nose are identical simply by chance and therefore 'assumes' that the nose has been displaced—applying a universal Bayesian logic that is common to all

sensory systems (Ramachandran and Hirstein, 1997). The illusion is a very striking one, and we were able to replicate it on 12 out of 18 naive subjects.

- This 'phantom nose' effect is quite similar to one reported by Lackner (1988) except that the underlying principle is different. In Lackner's experiment, the subject sits blindfolded at a table, with his arm flexed at the elbow, holding the tip of his own nose.
- If the experimenter now applies a vibrator to the tendon of the biceps, the subject not only feels that his arm is extended, because of spurious signals from muscle stretch receptors, but also that his nose has actually lengthened.
- Lackner invokes Helmholtzian 'unconscious inference' as an explanation for this effect (I am holding my nose and my arm is extended, therefore my nose must be long). The illusion described above , on the other hand, does not require a vibrator and seems to depend entirely on a Bayesian principle: the sheer statistical improbability of two tactile sequences being identical. (Indeed, the illusion cannot be produced if the subject simply holds the accomplice's nose.)

-- A few more recent papers –

de Vignemont, F., Ehrsson, H. H., & Haggard, P. (2005). Bodily illusions modulate tactile perception. *Current Biology, 15*(14), 1286-1290.

Farne, A., Roy, A. C., Giraux, P., Dubernard, J. M., & Sirigu, A. (2002). Face or hand, not both: Perceptual correlates of reafferentation in a former Amputee. *Current Biology, 12*(15), 1342-1346.

Funk, M., Shiffrar, M., & Brugger, P. (2005). Hand movement observation by individuals born without hands: phantom limb experience constrains visual limb perception. *Experimental Brain Research, 164*(3), 341-346.

Haigh, R. C., McCabe, C. S., Halligan, P. W., & Blake, D. R. (2003). Joint stiffness in a phantom limb: evidence of central nervous system involvement in rheumatoid arthritis. *Rheumatology (Oxford), 42*(7), 888-92 . (3 cases where joint stiffness was perceived in both a normal and a phantom limb − and is therefore due to “secondary plastic changes in the CNS”)

Ramachandran, V. S. (2005). Plasticity and functional recovery in neurology. *Clinical Medicine, 5*(4), 368-373.

Roux, F. E., Lotterie, J. A., Cassol, E., Lazorthes, Y., Sol, J. C., & Berry, I. (2003). Cortical areas involved in virtual movement of phantom limbs: Comparison with normal subjects. *Neurosurgery, 53*(6), 1342-1352.

Schicke, T., & Roder, B. (2006). Spatial remapping of touch: Confusion of perceived stimulus order across hand and foot. *Proceedings of the National Academy of Sciences of the United States of America, 103*(31), 11808-11813.

Topper, R., Foltys, H., Meister, I. G., Sparing, R., & Boroojerdi, B. (2003). Repetitive transcranial magnetic stimulation of the parietal cortex transiently ameliorates phantom limb pain-like syndrome. *Clinical Neurophysiology, 114*(8), 1521-30. (The results “support the concept that phantom pain is due to a dysfunctional activity in the parietal cortex.”

Phantom limbs and 'unmasking'

Since face-to-hand referral of sensations had been seen 4 weeks after amputation in one patient, it was originally suggested that reactivation of previously silent pathways might be involved (Ramachandran *et al.,* l992a, *b*)

A recent discovery made by Borsook *et al*. (1997)[1] at the Massachusetts General Hospital strongly supports this concept of 'unmasking'. They examined two patients (one after amputation and one after brachial plexus avulsion) just **24 h** after the deafferentation and found that touch sensations from the lower face were referred to the hand and that the referral was topographically organized. Even more remarkably, if the tactile stimuli were delivered with a paintbrush, finger or a pin, the particular sensation (e.g. 'brushing', 'rubbing' or 'pin') was also carried over into the phantom with exquisite precision. lf these results are confirmed, they would provide compelling evidence that activation of dormant connections can indeed occur at least in some patients. Such rapid activation of latent horizontal connections has recently also been observed in area 17 (striate cortex; Gilbert and Wiesel, 1992) and other extrastriate visual areas (De Weerd *et al*., 1995) following restriction of visual input, and it may form the basis of perceptual 'filling in' of scotomas (Ramachandran, 1992, 1993a, *c;* Ramachandran and Gregory, 1991).

The recent MEG results of Flor *et al*. (1995)[2] are also broadly consistent with this. Flor *et al*. (1995) obtained MEG recordings from 20 arm amputees and found that in all of them the input from the face and upper arm could now activate the hand territory. Also, many (but not all) of these patients reported that the tactile stimuli on the face were also felt in the phantom, which is essentially identical to previous reports. Interestingly, Flor *et al.* (1995) also found that there was a high correlation between the extent of remapping (observed with MEG) and the extent to which the patient reported phantom pain.

The nature and nurture of phantom limbs

- Do phantom limbs arise mainly from epigenetic factors such as remapping and painful stump neuromas or do they represent the ghostly persistence of a genetically specified body image?
- The answer seems to be that the phantom emerges from a complex interaction between the two.

For example —

There are a few instances in which the stump of a below-elbow amputee has been refashioned surgically into a lobster claw-like forked appendage. Subjects with this type of surgery often learn to use the pincers to grasp objects, pronate, supinate, etc. Intriguingly the phantom hand also feels split into two with one or more fingers occupying each pincer and it is felt to mimic the movements of the appendage vividly. Remarkably, subsequent amputation of this forked appendage results in a phantom that is also equivalently fork-shaped (Kallio, 1949)!

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[1] Borsook, D., Becerra, L., Fishman, S., Edwards, A., Jennings, C. L., Stojanovic, M., Papinicolas, L., Ramachandran, V. S., Gonzalez, R. G., & Breiter, H. (1998). Acute plasticity in the human somatosensory cortex following amputation. *Neuroreport, 9*(6), 1013-1017.

[2] Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, & Taub, E. (1995) Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature*. Jun 8;375(6531):482-4.

Savoy, R. L. (2001). History and future directions of human brain mapping and functional neuroimaging. *Acta Psychologica, 107*(1-3), 9-42. (Another "wide-ranging reference".)

> It has long been known that there is some degree of localisation of function in the human brain, as indicated by the effects of traumatic head injury. Work in the middle of the 20th century, notably the direct cortical stimulation of patients during neurosurgery, suggested that the degree and specificity of such localisation of function were far greater than had earlier been imagined. One problem with the data based on lesions and direct stimulation was that the work depended on the study of what were, by definition, damaged brains. During the second half of the 20th century, a collection of relatively non-invasive tools for assessing and localising human brain function in healthy volunteers has led to an explosion of research in what is often termed "Brain Mapping". The present article reviews some of the history associated with these tools, but emphasises the current state of development with speculation about the future. (C) 2001 Elsevier Science B.V. All rights reserved.

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There is **no shortage of things to be worried about in the domain of functional brain mapping**. The theme of this section will be a collection of related concerns that all stem from the limitations of reporting data as a collection of activated voxels. The variations on this theme concern "thresholds", the consequences of increasing statistical power of the tools, and the interpretation of the "most active" voxels across a small set of stimulus classes.

Consider, first, the question of thresholds. In a typical block design fMRI or PET experiment the data collected during one type of block are compared to the data collected during another type of block. A statistical test is applied at each voxel in space to decide when the difference between the distributions collected during the two types of blocks are statistically significant. A "map" is presented, typically showing anatomy in the background, with a coloured overlay indicating those voxels for which the statistic exceeds some threshold. How is that threshold determined?

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This problem is likened to the classic question raised by Paul Meehl in the context of general experimental questions in psychology. Meehl's observation was simply that if psychological questions take the form "Will Group A differ from Group B by scoring statistically differently (either higher or lower) on some behavioural measure X"?, then as we increase the power of our statistical tests, the answer will almost certainly be Yes, *for any A*, *B*, *and X*! That is, while correlation between two presumptively equivalent groups on an unrelated task (e.g., Group A – persons with red hair; Group B – persons with brown hair; and the task X is IQ score) is likely to be insignificant when the number of subjects is modest (say, *N*=20 in each group), the story changes when *N*=55,000. The reason is simply that even hair colour has some association with ethnicity, which might be associated with religious orientation, which might be associated with emphasis on education, etc. The associations are weak enough that they do not yield a significant relationship between the groups and the task when *N* is small, but they do when *N* is large. As a dramatic demonstration of this point, Meehl cites a study of 55,000 Minnesota high school seniors, for whom statistically significant correlations were found in 91% of pairwise comparisons among miscellaneous measures such as sex, college choice, club membership, mother's education, dancing, interest in woodworking, birth order, religious preference, number of siblings, etc. These were not "spurious" correlations, but real associations that were detected because of the form of the question and the power of the test made possible by a very large *N*.

Savoy 2001, bottom of page 30

- It is believed that there is a highly analogous problem lurking in the context of functional neuroimaging.
- The analogous concern applies to questions of the form, "Will area A in the cortex show a change in activity (an increase or decrease) in response to task X, compared to its response to task Y?";
- If our imaging system is powerful enough;
- if we design more effective receiver coils for the MR scanner;
- if we use more subjects;
- if we collect data for a longer period of time),
- then the answer will almost always be Yes, for any A, X, and Y.
- Once we get past the peripheral sensory systems (i.e., once we have reached the thalamus), there are only about 5 synapses between any two neurones in the brain.

- It is likely that the **activity in any one neurone (or collection of neurones, given the spatial resolution of our non-invasive imaging techniques) is going to influence almost any other neurone,** albeit weakly.
- Data collected across multiple subjects on the same task give a hint of such a conclusion, in that the apparent area of activation increases as the number of subjects increases, as long as the threshold for statistical significance is held constant.

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It is important to note that the enterprise of brain mapping did not begin with fMRI or any other non-invasive imaging tool. The understanding that localisation of function is pervasive in the human brain has been well established for more than 50 years. Consider, for example, the summary of this knowledge represented by Fig 1, reproduced from a book published in 1957 (Polyak, 1957). There are at least two kinds of questions that should be asked about this figure. The first questions are methodological: What is the basis for this figure? Where did the data come from? What were the technologies that gave rise to this data? The answer to these first questions is that the figure is based upon two techniques: study of people with lesions (caused, for example, by stroke, disease or traumatic wounds) and the direct electrical stimulation of the cortex of patients undergoing brain surgery. More about these techniques will be written below.

Fig. 1. This figure schematically summarises the state of knowledge of localisation of human functional brain in 1957. It is based on data from lesions and studies using direct cortical stimulation during neurosurgery. (Reproduced with permission from the publisher from Fig. #275, p. 456 of "*The Vertebrate Visual System*", by Stephen Polyak).

Thus, Fig. 1 teaches us that we were far from ignorant or misguided about localisation of brain function in 1957. So, what is all the current excitement about? The primary answer is that today there are a host of technologies that can be used to give us information non-invasively that address the same issue. The study of patients with lesions, or those who are undergoing direct cortical stimulation during surgery, has substantial limitations. For ethical reasons, neither lesions (obviously) nor direct electrical stimulation of the brain via surgery (for reasons of general risk associated with exposing the brain) may be used in the study of healthy human subjects

Meehl, P.E., 1967. Theory-testing in psychology and physics: a methodological paradox. *Philosophy of Science* **34** 2, pp. 103–115.

Polyak, S., 1957. *The vertebrate visual system*, The University of Chicago Press, Chicago.

Conclusion

"To what extent can psychological functions be localized in the brain?"

- The general answer is likely to be a compromise (not necessarily boring), between extreme forms of localization (in which, as in sea slugs, every neuron in every individual has innately specified functions) and extreme forms of anti-localization (mass-action and equipotentiality).
- The phantom-limb theory of Ramachandran and Hirstein (1998) suggests an interaction between experience and aspects of a genetically specified body-image, both in terms of gradual changes with experience, and instantaneous 'unmasking' of previously hidden inter-relationships.
- Results with the special cases of deafness and blindness again suggest an interaction between innately prepared specializations and experience.
- On the whole the interactions take the form of changes in the details of localization, and effects of reciprocal influences of different brain levels or brain parts rather than in the reduction of the **amount** of localization per se.

A **subsidiary question** is "Will cognitive psychology be replaced by cortical physiology?"

There are many reasons for saying "No", including the necessity for behavioural methodologies (Savoy, 2001) and the likely existence of fairly general purpose, less localized, psychological mechanisms (Fodor, 1983; Savoy, 2001). However, the last paragraph of Albright, Kandel and Posner (2000) is as follows (with added bullet points) —

- In the decade of the 1990s, cognitive neuroscience thrived by bringing together psychology and neurobiology.
- We now have every reason to expect that the next decade will yield a similarly mature molecular biology of cognition, in which powerful molecular and genetic tools find their calling in the service of cognitive neuroscience, and that the field will continue to advance through
- **a global circuit-based approach to cognitive representation by the brain**.
- Although, as noted by Hebb 50 years ago, there still is "a long way to go before we can speak of understanding the principles of behavior to the degree that we understand the principles of chemical reaction", the time for that understanding is now — at least — in full view.

A few additional references (mostly to go with the main handout)

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Gallese, V., Keysers, C., & Rizzolatti, G. (2004). A unifying view of the basis of social cognition. *Trends in Cognitive Sciences, 8*(9), 396-403.

Buccino, G., Lui, F., Canessa, N., Patteri, I., Lagravinese, G., Benuzzi, F., Porro, C. A., & Rizzolatti, G. (2004). Neural circuits involved in the recognition of actions performed by nonconspecifics: An fMRI study. *Journal of Cognitive Neuroscience, 16*(1), 114-126.