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Inferring causality in brain images: a perturbation approach

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When engaged by a stimulus, different nodes of a neural circuit respond in a coordinated fashion. We often ask whether there is a cause and effect in such interregional interactions. This paper proposes that we can infer causality in functional connectivity by employing a 'perturb and measure' approach. In the human brain, this has been achieved by combining transcranial magnetic stimulation (TMS) with positron emission tomography (PET), functional magnetic resonance imaging or electroencephalography. Here, I will illustrate this approach by reviewing some of our TMS/PET work, and will conclude by discussing a few methodological and theoretical challenges facing those studying neural connectivity using a perturbation.

Keywords: transcranial magnetic stimulation; positron emission tomography; neural connectivity; cerebral cortex

1. INTRODUCTION

Over the past decade, functional neuroimaging moved from mapping various cognitive, perceptual and motor processes onto discrete brain regions towards exploring functional interactions between specialized modules. The primary tool in this endeavour has been a statistical analysis of changes in neural activity, indexed by regional cerebral blood flow or blood oxygenation-level dependent (BOLD) signal, measured during the subject's performance of various tasks. Such analyses provide a wealth of information about a coordinated neural response to a given stimulus throughout the brain. It has become obvious, however, that the current neuroimaging methods do not allow us to discern the nature of such interregional interactions *vis-à-vis* their possible causality. For example, if a given stimulus 'activates' regions A, B and C in a coordinated fashion, we do not know whether region A influences region B, or region C drives both regions A and B with no direct interactions taking place between A and B. Several contributions in this issue address this problem at a mathematical level (Eichler 2005; Penny *et al.* 2005; Harrison *et al.* 2005). Many evoke so-called Granger causality, which is based on the notion that an effect cannot precede its cause in time (Granger 1969). Given the poor temporal resolution of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), our ability to infer Granger causality in brain images is limited. Here, an alternative approach is reviewed; namely, the use of physical perturbation of neural activity to evaluate possible cause and effect in the context of neural connectivity.

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One contribution of 21 to a Theme Issue 'Multimodal neuroimaging of brain connectivity'.

2. PERTURBATION

Perturbation as a tool for studying brain–behaviour relationships has a long history. Irreversible perturbations (i.e. brain lesions) told us, for example, that the inferior frontal cortex is essential for language production (Broca 1861) and the hippocampal system for declarative memory (Scoville & Milner 1957). Reversible perturbation of neural activity with direct electrical stimulation revealed the somatotopic organization of the motor cortex (Fritsch & Hitzig 1870; Leyton & Sherington 1917; Penfield & Rasmussen 1950). More recently, reversible inactivation of specific brain regions could be achieved in experimental animals with local cooling or by microinjections of local anaesthetics and agonists/antagonists of neurotransmitters (reviewed in Payne *et al.* 1996; Martin & Ghez 1999). In these (and other similar) studies, changes in neural activity have been recorded at the site of perturbation. Intracortical microstimulation has also been used, for example, to 'activate' briefly distinct populations of neurons in motion-sensitive cortical areas biasing, in turn, the monkey's perception of visual motion (reviewed in Cohen & Newsome 2004).

Beyond the local effects, several investigators explored consequences of perturbing one region on neural activity measured in adjacent or distal regions. Using a neural network with connectivity derived from experimental data, Kotter & Sommer (2000) demonstrated that the pattern of anatomic connectivity predicts cortical propagation of activity significantly better than networks with different types of neighbourhood-based connectivity or random connections. Experimentally, the role of feedback connections within the visual cortex has been studied by perturbing (with local cooling or GABA microinjections) activity in one area (e.g. MT or V2) on receptive-field neuronal properties in another area (e.g. V1; Angelucci & Bullier 2003). It is of note that such feedback effects are very

fast (less than 10 ms) and are therefore unlikely to provide sufficient temporal separation for statistical approaches based on the Granger causality in most human studies. Another example of the unique insights gained by combining local perturbations with the assessment of their consequences on neural activity is the work by Vanduffel *et al.* (1997), who inactivated the middle suprasylvian (visual) cortex of the cat by cooling and measured neural activity indirectly with 2-deoxyglucose throughout the brain. Compared with the strengths of the *anatomic* connections, cooling-induced decreases in metabolic activity were found to be stronger upstream than downstream of the inactivated region. For example, cooling effects in the cingulate cortex and the primary visual cortex were greater and smaller, respectively, than predicted from the density of anatomic connections (Vanduffel *et al.* 1997). It was also observed that feed-forward effects extended beyond one synapse and also affected regions not directly connected with the cooled cortex. These two examples illustrate the power of the perturb and record approach—one in the real-time assessments of neural connectivity between two sites and the other of the connectivity between one site and the rest of the brain. The latter approach is now described in the context of studies of neural connectivity in the human brain.

3. TMS AND PET

During the 1990s, we (Paus *et al.* 1997) and others (Fox *et al.* 1997; Siebner *et al.* 1998) applied the above perturb and record approach in order to map neural connections in the living human brain. This method combines two well-established tools of brain research: transcranial magnetic stimulation (TMS) and PET. TMS is used to stimulate directly a selected cortical area while simultaneously measuring changes in brain activity with PET. At about the same time, other investigators combined—for the same purpose—TMS with electroencephalography (EEG; Ilmoniemi *et al.* 1997) and fMRI (Bohning *et al.* 1998). Since the initial reports, this approach has been applied in a number of studies of neural excitability and connectivity of various regions of the human frontal cortex (reviewed in Paus 2002). Rather than reviewing this growing body of literature, the focus here will be on some basic principles of the combined TMS/PET method and its limitations.

TMS uses a time-varying magnetic field to induce, through the skull, electrical current in a spatially restricted region of the cerebral cortex. TMS can be used in three different modes: (i) single-pulse TMS ($> \sim 4$ s interval between two pulses), (ii) short trains of high-frequency TMS (e.g. 1 s train of 10 Hz stimulation); and (iii) long trains of low-frequency TMS (e.g. 15 min train of 1 Hz stimulation). The nature of the perturbations induced by TMS depends on the stimulation mode.

At a behavioural level, single pulses can elicit an overt response, a muscle twitch when stimulating the motor cortex or a phosphene when applied over the visual cortex, or modulate excitability of the stimulated region. Modulatory effects are relatively brief (tens of milliseconds), and could either increase or decrease responsiveness of the stimulated tissue to the subsequent stimulus. In the motor cortex, for example, 'intracortical' inhibition and excitation are assessed using the paired-pulse paradigm, whereby two TMS pulses are applied in rapid succession (1–30 ms between-pulse interval). Paired-pulse TMS with short (1–5 ms) and long (8–30 ms) between-pulse intervals elicits suppression and facilitation, respectively, of the muscle response (Kujirai *et al.* 1993; Ziemann *et al.* 1996*a*; Nakamura *et al.* 1997). Early suppression and later facilitation suggest somewhat different dynamics of inhibitory and excitatory processes activated by TMS in the motor cortex under these conditions. Pharmacological (Ziemann *et al.* 1996*b*; Werhahn *et al.* 1999) and *in vitro* (Avoli *et al.* 1997) studies suggest that the short (paired-pulse) and long (silent period) lasting cortical inhibition is mediated by GABA-A and GABA-B receptors, respectively. It appears, however, that local and distal blood-flow response to the paired-pulse stimulation correlates positively with the amount of modulation regardless of its direction (Strafella & Paus 2001). This observation suggests that the conditioning stimulus might have induced the release of glutamate that activated both excitatory and inhibitory interneurons; glutamate release is known to be associated with the production of nitric oxide and, in turn, with local increases in blood flow (reviewed in Paus 2002).

Effects of single-pulse TMS in non-motor regions are less well understood. Although single-pulse TMS is typically used to interfere with ongoing neuronal activity in the stimulated region ('virtual lesions'; reviewed in Pascual-Leone *et al.* 2000), we have seen facilitation of visual attention (Grosbras & Paus 2002) and visual awareness (Grosbras & Paus 2003) shortly (50 ms) after single-pulse stimulation of the frontal eye field (FEF). These latter findings were explained as mediated by either local (i.e. FEF) increases in cortical excitability or feedback modulation of extrastriate visual areas. Other examples of distal effects of single-pulse TMS include transcallosal modulation of cortico-spinal excitability (Chen *et al.* 2003) and interactions between primary and secondary visual cortex (Pascual-Leone & Walsh 2001).

Although single-pulse TMS has the advantage of having high temporal resolution and could thus provide information not only about where but also when a perturbation affects neural activity, the poor temporal resolution of PET and fMRI does not allow us to measure neural consequences of a single TMS pulse. At present, even TMS-compatible EEG appears to be inadequate for capturing short-latency (<20 ms) neural responses; several laboratories are working on overcoming this limitation.

(a) *Short-trains of high-frequency TMS*

Repetitive TMS provide a more robust way of perturbing neural activity, which are detectable with PET and fMRI. Typically, high-frequency TMS applied over the motor cortex increases cortico-spinal excitability (Chen 2000). In our first TMS/PET study (Paus *et al.* 1997), we used a parametric design and, during each scan, applied a different number of trains of 10 Hz stimulation over the FEF; the distal response

was observed in a subset of cortical regions known to be connected to the FEF in the cerebral cortex of non-human primates. In subsequent studies, we used a somewhat different approach and applied a series of 10 Hz trains between scans to modulate neural activity of the mid-dorsolateral frontal cortex (MDL-FC; Paus *et al.* 2001; Barrett *et al.* 2004). In these experiments, we observed a robust blood-flow response in brain regions presumably connected with the stimulation site, such as the anterior cingulate cortex and the caudate nucleus. Using direct electrical stimulation of the frontal cortex, we have also confirmed the presence of similar changes in the fronto-cingulate connectivity in an anaesthetized rat (Paus *et al.* 2001).

Moving beyond the indirect assessment of neural activity with ^{15}O-H_2O, we used ^{11}C-raclopride to assess TMS-induced changes in dopamine release in the human striatum. When stimulating the left MDL-FC, a decrease in the ^{11}C-raclopride binding potential was observed, indicating an increase in local release of endogenous dopamine, in the left caudate nucleus (Strafella *et al.* 2001). On the other hand, TMS applied over the left primary motor cortex resulted in a decrease in binding potential (increase in dopamine release) in the left putamen (Strafella *et al.* 2003). As illustrated in figure 1, these results are consistent with the known cortico-striatal connectivity in the monkey; namely, the existence of efferent connections from the prefrontal and motor cortices to the caudate nucleus and the putamen, respectively. We believe that cortical stimulation led to an 'activation' of specific cortico-striatal *glutamatergic* pathways, which, in turn, induced local release of dopamine at their terminations in the striatum.

(b) *Long-trains of low-frequency TMS*

Low frequency TMS is often used to decrease excitability of the stimulated neural system (Chen 2000; Hilgetag *et al.* 2001; MacDonald & Paus 2003). Such stimulation has not only local effects (Chen *et al.* 2003; Maeda *et al.* 2000; Muellbacher *et al.* 2000) but can also affect distal sites. This has been demonstrated behaviourally by measuring motor evoked potentials (MEPs) elicited by single-pulse TMS applied over the primary motor cortex; MEPs are reduced after low-frequency (1 Hz) stimulation of the premotor cortex, presumably through direct cortico-cortical connections (Gerschlager *et al.* 2001). Using PET, several investigators applied low-frequency TMS over the primary motor and premotor cortices to examine their connectivity (Siebner *et al.* 1998, 2000, 2001; Chouinard *et al.* 2003). It has been shown that low-frequency (1 Hz, 2×15 min) TMS applied over the primary motor cortex induced changes in MEPs that correlated with those in blood flow in a limited set of brain regions presumably connected with the stimulation site, including the contralateral primary motor cortex, the putamen and the cerebellum (Chouinard *et al.* 2003). When the same stimulation was applied over the dorsal premotor cortex, again, changes in MEPs were observed but this time, they correlated with blood-flow response in a different and more extended set of regions, including the ventral premotor cortex, supplementary motor area, mid-dorsolateral and mid-ventrolateral frontal cortex, and the superior parietal lobule (Chouinard *et al.* 2003). These findings are again consistent with the known anatomic connectivity of the primary motor and dorsal premotor cortices in the monkey (Parent & Hazrati 1995; Matelli & Luppino 1997, 2000). In these and other TMS/PET studies, however, significant blood-flow response is observed only in a subset of regions known to possess anatomic connections in the monkey homologue of the stimulated cortical site. A few possible reasons for this discrepancy will be discussed in the following section.

4. CHALLENGES

The most obvious reason for revealing only a subset of regions with known anatomic connections with the stimulation site is statistical power; given the complexity of the experimental set up, TMS/PET studies typically include only six to eight subjects. Another possible factor, common to all neuroimaging studies, is interindividual variability in the exact location of a given cortical area and its connectivity (e.g. MacNeil *et al.* 1997; Hilgetag & Grant 2000). For some regions, this may not be an issue. For example, the physical location of the primary motor cortex is fairly invariable across individuals and, furthermore, correct coil location can be simply verified by the presence of a behavioural response to TMS, i.e. a muscle twitch. But other regions, such as the MDL-FC, may be more variable in their location and, at the same time, are less easy to verify functionally. A standard 'functional probe' known to engage the MDL-FC, such as a working memory task, may give different locations in different subjects for two reasons: (i) the same functional area is located in a different part of the prefrontal cortex; and (ii) different (albeit related) cortical area was engaged, perhaps owing to different ways the same task was performed by the subjects. In a group of subjects, do we position the coil over the same anatomic location, or do we vary the coil location based on the outcome of a functional scout? In the past, both strategies have been used in different studies (anatomic locations: e.g. Paus *et al.* 1997, 2001; Strafella *et al.* 2001; Chouinard *et al.* 2003; functional scout: e.g. Rushworth *et al.* 2002; Köhler *et al.* 2004) but whether or not they may result in different outcomes has never been evaluated. If we take the pattern of cortico-cortical connectivity as one of the main defining features of a given region, then the TMS/PET approach may be ideal for answering this question. The prediction is simple: stimulation of the 'true' MDL-FC would yield a more robust, or a more plausible pattern of neural connectivity.

The final and theoretically most interesting issue is that of possible biological reasons for differences between anatomic and 'perturb and record' connectivity estimates. Recall the findings of Vanduffel *et al.* (1997), in which distal effects of cooling a particular cortical region did not match the density of anatomic connections in their magnitude and extended beyond one synapse. Clearly, the perturbation modulates neural activity differently in the different nodes of the

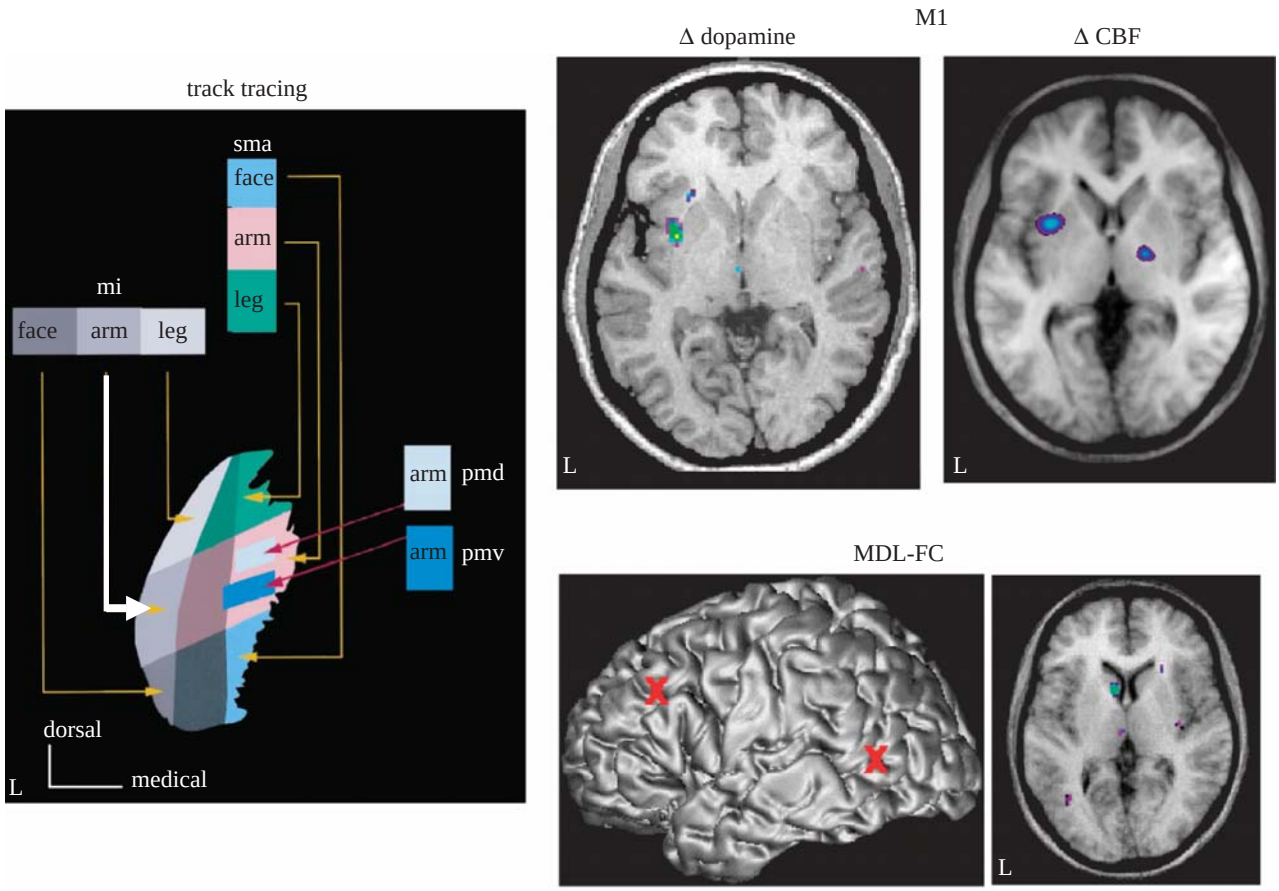

Figure 1. Dopamine release induced by repetitive TMS of the frontal cortex. Left: organization of cortico-striatal projections to the monkey putamen (from Takada *et al.* 1998). Top right: changes in dopamine release (from Strafella *et al.* 2003) and blood flow (from Chouinard *et al.* 2003) in the human putamen following rTMS applied over the left primary motor cortex (M1). Bottom right: changes in dopamine release (from Strafella *et al.* 2001) in the human caudate nucleus following rTMS applied over the left mid-dorsolateral frontal cortex (MDLFC). Location (red markers) of the two stimulation sites, the left MDLFC and the left occipital (OCC) cortex, on the MRI of one subject in stereotaxic space. Reprinted with permission from Paus & Barrett (2004).

same circuit. We can only speculate about the possible reasons. In the rat visual system, for example, ultrastructural studies show that the number of inputs on GABAergic interneurons is significantly lower for feedback, as compared with feed-forward, connections (Johnson & Burkhalter 1996). This observation would suggest a relative absence of inhibition in feedback, relative to feed-forward, pathways. Indeed, this prediction was confirmed by neurophysiological studies carried out in slices of rat visual cortex (Shao & Burkhalter 1996, 1999) and is consistent with the Vanduffel *et al.* findings. Another important variable to consider is the rate of spontaneous neural activity in different nodes of the stimulated circuit during the recordings. As single-unit recordings make abundantly clear, cortical neurons continue to fire even in the absence of a specific input/output or task requirement; the rate of spontaneous firing varies from region to region but, on average, often exceeds 10 spikes s^{-1} (Schall, personal communication). In the case of a 60 s scan, this amounts to a total of 600 spikes per neuron. With an estimated 50 million neurons cm^{-3} of cortex (Pakkenberg & Gundersen 1997), even if only 0.01% of all neurons discharged at any given time, a total of 3 million spikes could be generated within a single resolution element of the PET image and affect post-synaptic neurotransmission in another resolution element. It is probable that the local and distal effects of high- or low-frequency TMS applied over a given cortical region would be a product of an interaction between the rate of spontaneous activity in the different nodes of the stimulated circuit and the type of local circuitry. In turn, these may vary as a function of the subject's state during the experiment, and also as a function of long-term changes in local-circuit structural or functional properties, such as those induced by learning or a disease. While the former factor represents a potential confounder and should be controlled as much as possible, the latter examples illustrate the potential of the 'perturb and record' approach in studying modifications of neural connectivity in healthy and disordered human brain.

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