# The need for research on non-human primates in cognitive neuroscience

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This article is restricted to the use of non-human primates in research in cognitive neuroscience. The aim of these experiments is to help us to understand the mechanisms of cognition in the human brain, and the crucial question is whether recent methodological developments will enable us to answer these questions directly by studies of humans.

Here I will consider what can be discovered from behavioural studies of neurological and neurosurgical patients, from studies of normal subjects using functional brain imaging, from studies using transcranial magnetic brain stimulation, and from anatomical and electrophysiological studies of the human brain. I will then indicate whether work on non-human primates can get over the limitations of these methods as applied to the human brain. Finally, I will discuss whether connectionist modelling and neural network modelling can replace work on non-human primates.

## Human studies

The classical technique in behavioural neurology has been to study the symptoms caused by lesions, whether strokes, tumours or neurosurgical excisions. Much information about the localization of the major functions has been derived in this way, and the method continues to be valuable given the ability to localize lesions accurately using magnetic resonance imaging (MRI). There are two approaches, studies of single cases and group studies. The advantage of the first is that one can occasionally find patients with small but critical lesions and these can be very informative about the localization of function or the dissociation between different abilities. The advantage of the second approach is that one can study the area of overlap between the various lesions, and thus reach conclusions about localization based on a larger sample. Whichever method is used, one needs sophisticated psychological testing to evaluate the exact nature of the impairments.

### *Limitations*

1. The lesions are never restricted to one area as defined by cytoarchitecture (cellular structure), and the functions of the different cytoarchitectonic areas differ.
2. The lesions always include the white matter underlying the grey matter. Thus, these lesions also disconnect paths running between other areas and passing under the cortex. This means that the impairment might be due to an interruption in the function of these other areas.
3. One usually studies the patients some time after the insult, and that allows for other areas to re-organise functionally. Thus, one may be misled about the function of the area in the normal brain.

## Imaging (PET and fMRI)

Brain imaging solves all three problems. The peaks of activation are confined to cytoarchitectonic areas, the peaks lie in grey and not white matter, and the normal brain is studied so that there is no re-organization. This is true whether positron emission tomography (PET) or functional magnetic brain imaging (fMRI) are used. The exact functions of an area are demonstrated by contrasting tasks that differ in only one respect. The control tasks eliminate all but the critical factor. Recent developments in fMRI also allow one to measure the covariance in activity between different activated areas, and thus to study the functional interactions between areas. New methods such as structural equation modelling and dynamic causal modelling have been developed so as to interpret these interactions[1].

### *Limitations*

1. It is one thing to show that an area is activated during a task, and another to show that that activity is essential for accurate performance of the task. For example, many studies have reported activity in the

anterior cingulate cortex when subjects engage in tasks that require subjects to make judgements about the thoughts of others (theory of mind)[2]. However, a patient with a large bilateral lesion of this area has no problems in succeeding on tasks of theory of mind[3]. This shows that the activation in this area is not essential for performance on these tasks. Price et al.[4] specifically propose a methodology in which imaging studies are carried out both in normal subjects and patients with lesions in the activated areas so as to work out whether the activations are necessary and sufficient for good performance.

2. The methods for studying interactions in imaging data still depend on tables of covariance between activity in different areas. But as is widely accepted, correlations may not reflect causal relations. To demonstrate that A causes B, one needs to prevent A and show that B no longer occurs. This can only be done by interfering in the system or studying the effect of a natural interference such as a lesion.
3. The signal measured in fMRI is the BOLD signal (Blood Oxygenation Level Dependent). This is an indirect measure of blood flow. PET differs in that it measures blood flow directly. In either case, there is one measure for the whole population of cells in an area. This is a suitable level of measurement for studies of function, but cannot give information about the mechanisms by which the area functions in that way. That depends on the activity of many cells with different functional specificity, and imaging is not able to record at that level. This means that it is unable to work out the mechanism, that is the method of coding.
4. PET has a temporal resolution of 60 seconds and fMRI of roughly 1-3 seconds. The cellular machinery works at a resolution of milliseconds. Again these techniques are unable to give us information about mechanisms.
5. Because of the poor temporal resolution of fMRI, it is only able to give us very limited information about the order of events in the brain. The interpretation of the data is always confounded by the fact that the vascular bed, and thus the shape of the BOLD signal, differs in different areas, and thus differences in shape may mislead one into thinking there is a difference in temporal order.

## Studies using EEG and MEG

The last of these limitations can be overcome by electroencephalography (EEG) and magneto-encephalography (MEG), both of which have a millisecond temporal resolution. Thus, they can give good information about temporal order, as in the MEG study by Nishitani and Hari[5]. Thus these methods can be used to study temporal dynamics.

### *Limitations*

1. EEG has a very poor spatial resolution compared with fMRI because it difficult to localize the dipole sources. MEG has a better spatial resolution though less good than fMRI. Combined studies of fMRI and MEG achieve a good spatial and temporal resolution for functional studies.
2. Like PET and fMRI these are correlational methods: one observes activity during a task.

## Transcranial magnetic brain stimulation

This can overcome some of the limitations of the methods discussed so far. One of the limitations cited earlier for studies of patients with lesions is that there is functional re-organization after the lesion. This problem can be avoided by using transcranial magnetic brain stimulation. Either single pulses (TMS) or repetitive pulses (rTMS) are imposed on the brain through the skull and these cause a brief and temporary interference with normal activity in the area affected. Thus, one can study the behavioural impairments that are caused by the stimulation.

TMS and rTMS are experimental rather than correlational methods, in that they show whether whether interfering with activity in an area disrupts performance. They can also be used to check whether interactions between areas are causal. This can be done by applying TMS to one area and recording activity in the connected area, for example using fMRI or EEG.

### *Limitations*

1. It is only possible to use TMS and rTMS over dorsal and lateral areas of the neocortex. The most anterior frontal, orbital frontal and temporal neocortex are not accessible.
2. These methods cannot reach tissue deep in the sulci (fissures).
3. They cannot reach deep brain structures such as the thalamus and basal ganglia.
4. TMS and rTMS usually produce minor changes in reaction time. They rarely cause the subjects to make errors in the way that permanent lesions do.

## Anatomical studies

To study function one needs to be able to differentiate between areas anatomically. This can be done directly

in the human brain by using an observer independent method to draw borders between different cytoarchitectonic areas[6]. It is also possible now to chart the difference in the density of the various receptors in different areas[7]. Methods are also available for matching activation peaks in fMRI to areas as defined by architecture.

## Diffusion Weighted Imaging

It is a finding of anatomical work carried out on non-human primates that anatomical connections respect cytoarchitectonic boundaries[8]. In other words it is these areas that send and receive connections, whether cortico-cortically or cortico-subcortically. Until recently there were only two methods for charting these connections. The first was to find rare cases of patients with small infarcts and to chart the areas in which there are degenerating terminals[9]. The second was to study the diffusion of materials along axons in the post-mortem brain[10], but noone has succeeded in getting the material to diffuse far. It may be that future developments may improve this method.

More recently Diffusion Weighted Imaging has been developed which allows an MRI scanner to detect the orientation of long fibre tracts. One can seed one area and then use probabilistic methods to chart where the fibres terminate. This has proved useful, for example, both in charting the interconnections between different nuclei of the thalamus and cortical subareas[11] and in differentiating between two neighbouring cortical areas on the basis of their pattern of connections[12].

### *Limitations*

1. It is not yet possible to follow the connections into the grey matter, though this may later become possible.
2. Though one may be able to chart some long range cortico-cortical connections, there is no possibility of using this method to chart these connections in the detail that is possible using tracers methods in non-human primates[8].
3. It will not be possible to identify in which of the six neocortical layers the cells terminate or originate.

## Electrophysiological studies of patients

There are some studies in the literature in which electrophysiological recording have been taken from cells or groups of cells in patients. This has been done, for example, in the temporal lobe[13] and the anterior cingulate gyrus[14] using single electrodes. There are also studies with implanted electrodes to record the intra-cortical EEG, for example in the prefrontal cortex[15]. There are plans in the future to implanting multiple electrodes in the human brain and use the signal to operate a cursor or prosthetic arm[16].

### *Limitations*

1. Recording taken during surgery[13,14] have the disadvantage that it is only possible to gather data on a limited number of cells and to carry out a crude characterization of their specificity. By comparison one can record from 100 to 200 cells in non-human primates, and test each cell on a variety of tasks and controls. This may take one hour per cell, depending on the task. It is not possible to do this during a single surgical operation on a patient where there is a very limited time window.
2. When multi-electrode arrays have been implanted in the brains of patients, one will be able to record from a large sample of cells. However, these arrays cannot be implanted anywhere: the site will be determined by the clinical needs of the patient.
3. Although recording electrode implantation in human patients has been undertaken at a number of centres in preparation for surgical ablation of epileptic foci[17], there appears to be a growing consensus against this procedure, particularly where multiple electrode tracks might be used.

## Non human Primates

The aim of research in cognitive neuroscience is first to establish the functional of the brain and then to go on to understand the mechanisms by which it performs the functions that it does. The basic reason for carrying out studies on animals is that to understand mechanism; and to establish causal relations one need to intervene, whether the intervention takes the form of recording or interference. As mentioned above there are severe limitations to the electrophysiological recordings that can be taken from the human brain, to the areas accessible to TMS and rTMS, and to the conclusions that can be drawn by studying patients with lesions. Imaging whether PET, fMRI, EEG or MEG is a correlational method in which one observes a relation between

activity in an area and performance of a task.

## Anatomy

To understand the mechanism one needs to first have a full description of the anatomical circuitry. These have been establish by injecting tracers into localized areas and studying the transport of the material along the axons. Very detailed maps of this are now available for the macaque brain[18,19,20]. The information is available in a web data base www.cocomac.org which at the moment collates information from 391 papers. It includes data on 7007 sites, and has 36918 connection details. Where available it also includes information on which of the six cortical layers receives or sends the connection. It is this level of detail that could never be approached in studies of the human brain. The poverty of our information on the lack of information on anatomical connections of the human brain has been commented by Frances Crick[21]. The macaque brain therefore forms that model for interpreting the results of brain imaging experiments on humans.

It might be said that there may be important differences between the connections of the macaque and human brain. There are already underway studies comparing connections as established by diffusion weighted imaging in the macaque and human brain, and so far no major differences have been observed. However, as stressed above we will never achieve the level of detail for the human brain that we have for the macaque brain.

It might also be thought that one could use tracer methods on the human brain, given that it has now been demonstrated that one can localize the area to which tracers are transported using a non-invasive method, that is MRI[22]. The problem is not with the measurement but with the fact that tracers need to be injected. It is not ethical to do this in human subjects.

Finally, it might be supposed that, given the detail that we already have on the connections of the macaque brain, no further research is now needed in this area. This is not true. There are important issues still to be resolved. The first is that tracers give information about projections to the first synapses, but the brain operates via chains of connections. To study these one needs to use techniques involving viruses which transmit across synapses[23,24], and studies using this method are in their infancy. Second, we need quantitative information about the relative size of projections to different areas, and this information is only beginning to be gathered[25]. Next, we need more information about the specific layers in which connections terminate and originate[26]. Finally, we need detailed information about the differences in microstructure between different areas, that is in the intrinsic connections within an area[27,28] Diffusion weighted imaging will not be able to provide any of this information, yet that information is essential for understanding the basic circuitry.

## Interference

There are advantages of placing lesions in the brains of non-human primates compared with studying patients with neurological or neurosurgical lesions.

1. It is possible to place the lesion in a single cytoarchitectonic area. This is made possible by the fact that most, though not all, cytoarchitectonic boundaries occur at sulcal borders.
2. It is possible to use neurosurgical techniques to remove the grey matter while leaving the underlying white matter undisturbed. This gets over the problem of interpretation in studies of patients where the lesions invariably include the underlying fibres of passage.
3. It is possible to place exactly the same lesion in several animals so as to ensure that the results are reliable. One does not have to depend on the overlap between lesions, as in patient studies, so as to achieve accurate localization.

One problem of placing permanent lesions is that with time re-organization can occur. This can be overcome by interfering with the activity of an area temporarily by applying muscimol, a GABA agonist. This allows one to study the acute effects of the interference. This method is being increasingly used in studies in which one first records activity from cells in a particular area, and then infuses muscimol to see if the activity is essential for performance[29,30].

However, there is a more important reason for wishing to interfere in the brains of non-human primates. This is that the brain works as a distributed system, and to understand how the whole system works we need to study interactions between activity in different areas. Structural equation modelling and dynamic causal modelling provide data on the covariance between activity in different areas of the human brain, but to check that these genuinely reflect causal relations one needs to intervene. This can be done by directly cutting fibre bundles or

placing a lesion in area A in the right hemisphere and a lesion in area B in the left hemisphere (cross-lesion method). This achieves a disconnection because the remaining area B no longer has an input from area A.

In either case one studies the effect of the lesions on behavioural performance. However, there is another way of studying interactions and that is to interfere with activity in area A and to simultaneously record activity in area B[31]. This method is becoming increasingly important because comparisons of activity in related areas suggest that many cells have similar properties[32,33]. The question then arises whether particular cells in area B derive their specificity from cells in area A.

## Electrophysiology

The advantage of recording in monkeys, whether from cells one at once or from subpopulations of cells, is that one can record in any area, and in a brain that is not abnormal. Recordings taken during surgery in the human brain are necessarily taken in brains that are not normal. Most of the information that we have so far is taken from studies in which a single electrode is used. This allows one to characterize the properties of cells one at once, and in a typical study this will be done for 100 to 200 cells. As mentioned above, the advantage of studies on non-human primates is that one has time to test each cell in a variety of conditions. For example, one can study the memory for spatial locations by recording the activity of each cell for a variety of spatial locations; recordings in the prefrontal cortex have shown that many cells fire for specific locations[34]. By comparing the activity of cells on a variety of different tasks one can work out exactly what each cell codes for[35].

To understand how an area works, however, one needs to know how the information from the different cells is combined. This can be done either by combining data from all the cells that are recorded singly[36] or by recording with many electrodes simultaneously and using computer models to integrate the information from the different cells[37]. Either method provides information about the way in which the area codes information.

It is not possible to obtain information about the code by measuring the population activity using imaging. The experiments give one measure of the activity, that is its amplitude. It is not possible to work out from this what is coded for by the different subpopulations of cells within the whole population. However, this can be done in experiments on non-human primates[38].

It might be thought that this could also be done by electrophysiological experiments on the human brain, and indeed several groups are going on from multi-electrode experiments on non-human primates [37,16] to plan similar experiments on patients. However, the basic work of finding out how to interpret the code is necessarily first carried out in non-human primates.

It might also be thought that there is a problem in interpreting human imaging data on the whole population of cells with data on the activity of particular cells as derived from experiments on non-human primates. How does one know that the area that is activated in the human brain is the same as the area from which recording have been taken in the monkey brain? The gap can now be bridged by carrying out studies of monkeys using fMRI. Thus, one can first identify an area that is activated in the human brain, then find the same area in the monkey brain because it is activated during performance of the identical task, and then interpret the activations in terms of what is known about the properties of cells in that area as derived from electrophysiological studies. The same method provides a link to the detailed information we have on the anatomical connections of an area. Having carried out the imaging study on humans, one tests monkeys on the same task in fMRI, and then make use of what is known of the anatomical connections to the areas that are activated. Many groups round the world are now developing fMRI for use with monkeys. When we have more information from these studies we will be able to make a detailed comparison between functional areas in the macaque and human brain[39]. Thus, we will know in much greater detail than at present in what respects we are, or are not, justified in generalizing from a macaque model to the human brain.

A further advantage of fMRI studies in monkeys is that it can give us information about the basis of the BOLD signal that is measured in fMRI. One can compare this signal as measured in monkeys with spiking activity as measured with microelectrodes or local field potentials[40]. Only experiments of this sort will clarify to what extent an increase or decrease in activity as measured by the vascular response reflects an increase or decrease of activity in the cellular response[41].

## Why primates?

Even if all the arguments above are accepted, it is still reasonable to ask why the animal experiments need to

be carried out on macaques rather than marmosets, or rats and mice rather than primates.

Most of the experiments in behavioural neuroscience are indeed conducted on rats and mice. These animals have many advantages. Their brains are not nearly as variable as those of macaque monkeys, and thus it is much easier to place subcortical lesions reliably in rodents than macaque monkeys. The different neurotransmitter systems were first demonstrated and are best documented in the brains of rats. Most experiments in behavioural pharmacology are performed on rats. Finally, the development of transgenic mice has provided a powerful new tool for understanding the relation between different receptor systems and aspects of cognition such as memory[42].

The limitations of experiments on rodents come when one wants to study the relations between activity in different neocortical areas and higher cognitive abilities. The neocortex forms 28% of the brain in rats, 72% in macaques and 80% in humans. The neocortex in rats is also smooth, and does not have the sulcal boundaries by which one can make rough estimates of the different cytoarchitectonic areas. Furthermore, there are cytoarchitectonic areas in the macaque brain that do not exist in either the brains of rats[43] or prosimian primates[44], including crucial subdivisions of the prefrontal cortex. Also rats have poor vision, and lack many of the 30 or so specialized visual areas that one can demonstrate in a monkey[18].

Given the difference in size between the macaque and human brain it could be argued that there may be problems in generalizing from the macaques to humans. Fortunately, one can use warping methods to directly compare the size and organization of different cytoarchitectonic areas in the macaque and human brain[45,39]. The macaque brain is non-linearly transformed into the format of the human brain. Thus, we can make judgements about where we can or cannot generalize.

Finally, there are many tasks that it is possible to train a monkey to perform but not a rodent. For example, many electrophysiological studies of monkeys depend on the ability to train these animals to fixate a central point for some time[46], to report their perceptions[47] or decisions[48], or to manipulate joysticks so as to move a cursor to a target[49]. In fMRI experiments on monkeys it is crucial that they can be taught to fixate a central point as in the comparable human experiments, or to perform difficult attentional tasks at the same time[50].

The limitations of rats or mice are partly to do with their peripheral equipment, for example their eyes or paw. But there are also strong cognitive limitations. Rats cannot be trained to perform many of the perceptual and cognitive tasks that are used in behavioural and electrophysiological studies of macaque monkeys. It is because the rat and mouse neocortex is so underdeveloped that studies of the higher aspects of perception and cognition can only be carried out in non-human primates. It is true that there have been great successes in studying emotional learning[51] and spatial memory[52] in rats, but this is not true for higher cognitive functions.

But why study macaques rather than marmosets? The answer is partly that these animals are very difficult to train reliably, and their performance on learning tasks is much inferior to that of macaque monkeys[53]. Even macaques can take 3-6 months to train on the most difficult cognitive tasks. However, the most important limitation of studies on marmosets or squirrel monkeys is that we do not have the very detailed knowledge that we now possess for macaques on the anatomical connections of the brain. Furthermore, their brains are in general smooth, and this greatly restricts the ability to localize specific cytoarchitectonic areas so as to study anatomical connections or record. It is for this reason that imaging experiments are necessarily interpreted in the light of the macaque model.

## Why not network modelling?

If the basic reason for studying animals and non-human primates in particular is to establish mechanisms, one might finally ask why we cannot use connectionist and neural network modelling to suggest mechanisms. The advantage of connectionist models is that they can be used to model abilities that are unique to humans, such as language[54], and these models can be used to account for the errors that children or patients make[55]. The disadvantage of these models is that they are often not biologically plausible. In particular the learning rules rarely correspond to the way in which studies on animals suggest that learning occurs. It would, of course, be possible to produce more plausible models.

Neural network models differ in that they attempt to model how the nervous system actually works. Once one has detailed information on the inputs and outputs of an area and of the intrinsic connections within an area, and once one has detailed information on the firing properties of cells within that area, one can start to model how that area might perform its functions. The same approach can be used for interactions between areas.

Indeed it is essential that such models be set up, because we need testable theories about the mechanisms of the brain. Once one has a model one can make predictions and then test them in the real brain.

It is now more common for those engaging in electrophysiology on macaque monkeys to go on to develop models of how areas might work[56,57,58]. It will, however, be obvious that these models do not replace the experiments on non-human primates on which they are based. Instead they serve to interpret the results and to make further empirical predictions. Models can also be used to interpret data from multielectrode recordings so as to drive a robot or prosthetic arm[37]. These models will be important when multielectrode assemblies are implanted in the human brain. However, again it is important to note that the models depend on the data, and the human experiments will depend on experiments first carried out in non-human primates so as to establish the technique.

## Conclusions

One of the most important aims of scientific research is to understand the human brain, and in particular the mechanisms that allow higher cognitive functions such as recognition, attention, memory, decision making and the ability to understand the thoughts of others. It is inconceivable that humans should understand their place in the universe and their world, but not the way in which their own brains achieve this understanding.

What makes us human is the extraordinary size of our brain, and in particular the development of the neocortex. Humans do not differ greatly in their internal organs from other animals, and thus most physiology can reasonably be carried out on rats and mice. It is certainly true, as has been emphasized above, that it is now possible to find out more directly about the human brain than was possible 10 or 15 years ago. The limit concerns the mechanisms by which the brain operates so as to generate higher cognitive functions. It is not sufficient to understand the functional organization of the brain as revealed by imaging studies. We need to understand how the cellular mechanisms acts so as to make these functions possible. We deny ourselves this understanding if we forbid experiments on non-human primates. It would be odd to have such an understanding for the heart but not for the brain.

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## Tags

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