fMRI Paradigm Design

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Data generated during fMRI experiments form 4-dimensional datasets, i.e. series of volumes acquired in time. From these sets specific patterns are to be extracted, in time and in space, which signify functional topographical information about the brain. To identify the location of brainregions that are involved in a particular aspect of behaviour or a function, a pattern has to be brought into the system. This is typically accomplished by presenting a subject with a task. In contrast to tasks that are used in neuropsychology, fMRI tasks are accurately organized in time. This is necessary because a clearly defined pattern of events (i.e. the sequence in time) is required in order to search the fMRI datasets for that particular pattern. In this chapter issues are described that are relevant for designing an fMRI paradigm. These issues pertain to choice of adequate comparison task(s) to isolate the brain function of interest, the optimal scheme of stimulus presentation for detection and discrimination of brain activity, and the use of performance as an index of a subjects' engagement in the task

Tasks and input functions

For an fMRI experiment one has to devise a task which contains at least two different conditions in order to create a pattern, or a so-called input function. The sequence of these conditions can be organized according to various schemes, with the restriction that for an optimal dataset each condition should constitute an equal length of time. Quite often a more complicated scheme is required to address the questions of the investigator. Simple designs are appealing because they appear to be straightforward and thus easy to interpret. Unfortunately this is rarely the case, and this essentially due to the fact that there is more than one dependent variable. Suppose that one finds a difference in brain activity between two tasks. This can be due to one brain function being invoked by one task and not by the other, in which case the regions involved in that function are identified. However, with equal plausibility the difference may be associated with other functions that are not associated with the function one is interested in, such as those that are involved in perceptual, attentional or response generation processes. On another note, regions involved in the function of interest may remain undetected because they are, unintentionally, invoked by both tasks. Studies involving neurological or psychiatric patients are even more complicated, because they may use a strategy that is different from the one applied by healthy subjects, for instance because they interpret instructions differently, or they cannot devote their attention to the task. When comparing patients to controls it is necessary to avoid such confounds, and to show that both groups engage the same brain functions. Failing to do so can result in misinterpretation: one may conclude that region 'x' fails to activate, and may associate such hypoactivation with a cognitive impairment, whereas failure to activate 'x' may well be due to non-compliance resulting from an inability to perform any demanding task.

These problems can be overcome by constructing an fMRI paradigm in such a way that confounds can be controlled for. Essentially one needs to obtain a clearly defined input function, i.e. one that matches the hypothesized neuronal events in the brain, and to ensure that subjects can adopt only one particular strategy in performing the task(s). In investigating potential pathology in particular brain systems one has to be sure that that particular system is invoked by the task, and this can only be accomplished with a tightly controlled paradigm. Performance is a valuable measure in fMRI, because it can indicate not only whether a function is invoked (very poor performance can reflect disengagement from the task), but also the demand imposed by the task on the underlying brain system(s). It is not unusual for cognitive tasks to be processed differently depending on whether it is easy to perform or difficult, and different brainsystems may be utilized.

In the design of a paradigm the statistical algorithms play a significant role. One can predict the statistical power for detection of brain activation by analyzing the input function, and this allows for adjustment of the design before applying it in an experiment. In many cognitive tasks the design will affect performance, and therefore a novel design is best tested in healthy subjects in a "table and chair" setting to assess whether the paradigm produces the expected results (i.e. invokes the targeted function). Many of the currently available fMRI data analysis programs make use of multiple regression algorithms (based on the General Linear Model)[1]. This type of analysis essentially determines whether the fMRI signal timeseries in each voxel correlates with the task, but it does so in a sophisticated manner. Importantly, it requires the investigator to describe, in a coded format, the events that take place when the task is performed, as well as factors that contribute to noise in the dataset.

Interpretation of results of fMRI experiments is rarely straightforward. Issues that complicate interpretation result in uncertainty about the meaning of the results. Once an fMRI protocol, which includes data acquisition method (pulse sequence), task design (paradigm) and image analysis (preprocessing and statistical algorithms) has been composed, it can be tested in an fMRI experiment. For testing one can assess the qualities of the protocol much like cognitive psychological test instruments are tested, i.e. on the basis of validity, sensitivity and reliability. Validity (am I measuring what I think I am measuring?) can be assessed by comparing results to other techniques, or by testing whether experimental manipulations have the expected effect. Sensitivity (can I measure what I want to measure?) can be assessed by testing whether brain activity can be detected in a priori defined regions with a simple version of the task. Reliability (are my results reproducible?) can be assessed by repeating the experiment in the same or another group of subjects. There are many factors that affect the quality measures, ranging from pulse sequence and tuning of the scanner to choice of the paradigm and data processing procedures to subject sample selection. Based on an assessment of these qualities one may decide to alter one or more of the elements of the protocol. Choice of the paradigm is perhaps one of the most difficult issues, given that very little is known about how brain functions are organized, and deserves careful consideration.

Stimulus properties

The choice of a paradigm depends on the objective of a study. In general, formulation of a specific hypothesis benefits the interpretation of the results, particularly if the design is optimized to address that hypothesis. For novel concepts, it may be most effective to start out with a straightforward on-off design in order to maximize power of detection of brain activity, i.e. to first assess sensitivity of the constructed protocol. Having obtained a description of involved brain regions, subsequent studies will typically require more sophisticated designs in order to exclude confounds (e.g. functions one is not interested in) and to assess the neuroscientific or behavioural significance of activity patterns .

What stimuli are presented depends firstly on what functions one wants to measure, and secondly on how closely comparison stimuli can be matched. To separate a particular function, the comparison stimuli should invoke all the functions that are invoked by the experimental stimuli, except for the function of interest. This is not easy to achieve because the cognitive processes involved in processing stimuli are generally complex, and can differ considerably when comparison stimuli are processed by a subject [2]. For instance, suppose one wants to investigate which regions are involved in working memory. One often used task for this purpose is the "2-back task", where stimuli have to be maintained in short-term memory while additional stimuli are processed. The control task typically involves making simple decisions for each stimulus as it is presented, which controls for visual input and motor output processes. However, the working memory element involves not only maintaining information in memory, but also coordination of processing the additional stimuli, i.e. switching between making decisions for each stimulus and holding information on line. To isolate the latter component, a more complicated design is required, for instance one where the interval between stimuli is varied within the task. Activity that correlates with the inter stimulus interval might then be regarded as specific for maintenance of information.

There are various cognitive functions that require more than one type of control stimulus due to complicated interactions between brain systems [3]. One way of dealing with this is to devise multiple tasks, each of which contains the function of interest plus several functions that need to be filtered out. This is referred to as "conjunction design" [4] and is used for instance in language studies. In order to isolate "language comprehension", comparing a visual language task with a visual control task may not yield an activity pattern that is selective for comprehension. The patterns obtained after subtraction analysis are likely to include orthographical processes as well. One solution is to add a second set of tasks where experimental and comparison stimuli are presented aurally instead of visually. By selecting brain activity that emerges from both subtractions, modality-selective elements are in principle eliminated.

Organization of stimuli in time

The organization of stimuli in time has received considerable attention in recent years. A popular approach is referred to as the "event-related" or "single-event" design [5;6]. The name suggests a distinct approach in fMRI, but there is some confusion regarding the underlying concepts. The terms simply indicate that events are regarded as separate instances, and as such virtually all cognitive experiments are event-related. The term is however generally used to indicate the type of data analysis that is applied, in that the BOLD response is an important factor in building the factors for regression analysis. For instance, a task may involve presentation of series of experimental stimuli with an interval of 2 or 3 seconds, alternated with series of comparison stimuli. The data can be analyzed with a boxcar ("on-off") function, but alternatively each stimulus can be modeled as a brief event (i.e. as an impulse function), that can transformed to a series of BOLD response curves. The second is often called an event-related fMRI experiment, in spite of the fact that the event itself cannot be characterized in any detail. Extraction of the BOLD response from the data requires a special scheme of varying stimulus onset times and/or inter stimulus intervals, and can sometimes be achieved without any comparison stimuli.

In choosing a particular scheme, several issues are important. Firstly, the characteristics of the brain processes that are invoked by a stimulus determine whether a block design or an event-related design should be used. For instance, perception of simple visual stimuli (eg moving dots) involves predictable rapid and brief instances of neuronal activity, and can be modeled adequately. Moral judgment however can not be modeled very well (in time), making it difficult to construct an adequate impulse function. In this case a block design is better suited.

For each task, an optimal scheme can be estimated based both on the temporal characteristics of the invoked processes, and on the mathematical characteristics of the scheme in terms of factor variance and degrees of freedom in the statistical analysis. An important constraint in the design is the effect of the sequence of stimuli on the mental process one is interested in. For instance, making the inter stimulus interval variable enhances the ability to extract BOLD curves, but it also can make the task more difficult, thereby increasing numbers of errors, and it potentially affects the strategy that is adopted by the subject, thereby altering the brain systems that are used. This is of particular concern when studying neurological or psychiatric patients, who tend to disengage from the task when it becomes difficult.

Considering performance

Performance is not a trivial issue, particularly when comparing patients to controls. In neuropsychology, performance is generally the readout variable, and is used to characterize a persons cognitive abilities. In fMRI performance can give rise to problems in interpretation. Consider a group of patients who perform poorly on tasks that require working memory. Comparing them to controls during scanning while performing such a task typically reveals reduced activity in prefrontal brain regions. It is then tempting to conclude that these brain regions are impaired, causing poor performance, but that is not quite what the data support [7]. Poor performance may be associated with different strategies: some subjects will keep on trying to perform the task as intended, but others may switch to a strategy of processing only some of the stimuli (and ignoring the other stimuli) in order to achieve at least some success. Other may even revert to guessing. Obviously, the strategy determines how much the working memory system is taxed, and this affects the levels of brain activity as measured with fMRI. This changes the interpretation of hypoactivation considerably: it may simply reflect reduced engagement in the task. The reason for the poor performance may be quite different from frontal dysfunction. It may be associated with a general slowing of information processing or response generation, leading to conflicts between processing of one stimulus and of the next, simply because there is not enough time for that particular subject.

The fact that one does not know for certain whether patients (partially) disengage when the task is difficult, argues in favour of adjusting the task such that performance is approximately equal for both patients and controls [8]. The level of difficulty may also adjusted for each individual subject, based on a practice session before scanning. An alternative solution is to adjust the statistical analysis to performance by separating scans acquired during correct responses from scans acquired during incorrect responses. This can be achieved by modeling the two types of responses in separate input functions. There is, however, still the possibility that subjects are guessing. Group-wise difference in statistical power is another problem inherent in this approach, but this may be solved to some extent by discarding scans in such a way that equal numbers of scans remain for both types of responses.

To summarize, careful design of fMRI paradigms benefits interpretation of brain imaging results. Many of the important design issues can be dealt with before any fMRI scans are acquired, based on prior knowledge about the neuronal mechanisms underlying the function of interest, and on mathematical properties of the input function(s).

Suggested Reading:

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