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Study design in fMRI: Basic principles

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Abstract

There is a wide range of functional magnetic resonance imaging (fMRI) study designs available for the neuroscientist who wants to investigate cognition. In this manuscript we review some aspects of fMRI study design, including cognitive comparison strategies (factorial, parametric designs), and stimulus presentation possibilities (block, event-related, rapid event-related, mixed, and self-driven experiment designs) along with technical aspects, such as limitations of signal to noise ratio, spatial, and temporal resolution. We also discuss methods to deal with cases where scanning parameters become the limiting factor (parallel acquisitions, variable jittered designs, scanner acoustic noise strategies).

Keywords: fMRI; Study design; Neuroimaging; Cognition; Methodology

1. Introduction

Functional magnetic resonance imaging (fMRI) is a widely used technique to probe brain function, although the mechanisms underlying the information produced are not fully understood (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). An fMRI experiment depends upon techniques and methodologies derived from different fields of expertise, making it intrinsically multidisciplinary. From image acquisition to final data analysis, fMRI represents a challenge to the neuroscientist wishing to make the best use of the technique. It is therefore of the utmost importance to achieve some level of common understanding of the concepts involved in an fMRI project, to allow for efficient information exchange.

This manuscript is aimed at those not familiar with designing fMRI experiments, providing a framework for understanding the techniques available in the field and bringing together concepts otherwise only found scattered through the literature. Our focus will be on experiment design techniques, and we encourage the reader to refer to other excellent reviews for a broader view of fMRI in general (Matthews & Jezzard, 2004; Ramsey, Hoogduin, & Jansma, 2002). There is a wide range of fMRI study designs available for the neuroscientist who wants to investigate cognition. In fact, the search for new methods is endless, and neuroscientists are often found in a state of helpless disappointment at the lack of 'simple push button solutions' in fMRI. In this article, we hope to clarify some aspects of the technique, describing the major factors influencing the measured signal, introducing a practical view of cognitive comparison strategies, describing conventional acquisition schemes (i.e., block designs, event-related) and new 'self driven' approaches, and introducing common issues in fMRI studies. We briefly mention special cases, such as problems related to the effects of acoustic noise from the scanner, and other technicalities, such as limitations in the signal to noise ratio (SNR) and the spatial and temporal resolution of the method, providing an introduction to the major concepts inherent in the field. Next, we highlight the main issues that emerge when trying to integrate 'smart' cognitive comparison strategies (factorial, parametric designs) with 'limited' scanning parameters like brain coverage and temporal resolution (variable jittered designs, parallel acquisitions). Finally, as selecting the

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correct combination of strategies in each aspect of the technique is crucial to interpretation of the results, we encourage the use of study designs with the minimum degree of complexity possible.

2. Magnetism and brain function

Imagine yourself lying down inside a 60 cm wide, 120 cm long tube, exposed to 120 dB acoustic noise (with mechanical vibration), trying not to move (or possibly restrained) while trying to perform a cognitive task. This scenario is what thousands of people have experienced as volunteers for fMRI studies. To briefly introduce the concepts of magnetic resonance imaging in general, and fMRI studies in particular, to the widest possible audience, we have used some 'didactic license' in the following paragraphs. We believe that the explanations below, while simplified, remain factually correct, but suggest that the more advanced reader may also wish to refer to the many excellent text books available for a more rigorous and detailed approach (Huettel, Song, & McCarthy, 2004; Jezzard, Matthews, & Smith, 2003; Moonen & Bandettini, 2000).

Magnetic resonance imaging (MRI) systems include a 5–10 ton superconductive magnet, carefully designed to provide a strong magnetic field with high homogeneity inside the *bore* where the object to be imaged is positioned. Certain nuclei, including the hydrogen nuclei in the water and lipids which compose a large proportion of most biological samples, display magnetic properties—they have a *magnetic moment* (due to their *spin*) which acts similarly to a bar magnet or compass needle exposed to the earth's magnetic field. The MRI system's magnetic field creates a situation in which the magnetic moment of a small percentage of these hydrogen nuclei (or *protons*) align with the main magnetic field vector (Lange, 1996). For instance, if a person is lying inside the magnet, each point within their body [which will be represented in the final image as a particular 'pixel' (*picture element*) or 'voxel' (*volume element*)] will have a certain number of protons (proportional to the water content of the tissue) aligned with the main magnetic field. The effect of these aligned spins is to produce a bulk magnetization that precesses (the circular motion that the axis of a gyroscope—or a child's spinning top—displays as it spins under the influence of gravity) around the direction of the magnetic field with a specific frequency (known as *the Larmor frequency*), directly dependent on the magnitude of the magnetic field. By applying a radiofrequency (RF) pulse with a frequency exactly matching the precession frequency, the orientation of the spins can be changed until their magnetic moments are perpendicular to the main magnetic field. In this orientation, the precessing spins will induce a voltage in a surrounding electrical circuit (in exactly the same way that spinning magnets within a generator produce electricity). After the RF pulse ceases, the spins slowly return to their original orientation, but not before this radiofrequency voltage can be detected by a suitable antenna (or *coil*), placed around the area of the object to be imaged. The source of this radiofrequency signal can be assigned to a specific position by using magnetic field gradients to vary the strength of the magnetic field, and therefore the corresponding resonance frequency, from point to point. The signal's other characteristics depend on the magnetic properties of the spins' micro-environment; the strength of the signal depends on the number of spins involved, allowing the amount of water (or lipid, or other hydrogen containing tissue component) to be determined at any point within the body, while the rate at which the signal decays depends on a number of factors (known as *relaxation times*) describing the interaction of the spins with their surroundings. Acquisition methods (*pulse sequences*) have been developed to sensitize the MR signal to one or more of these properties, producing images with strong (and tunable) tissue contrast. As a mnemonic rule, the complete process is reflected in the technique's name: *magnetic* (nuclear magnetic spins) *resonance* (the matching of frequency between the RF pulse and the precession of the spins) *imaging* (the process by which the signal measured by the MR scanner is spatially encoded and the computer algorithm that produces the images).

The MR imaging method most often used to produce information related to brain function is called BOLD (blood oxygenation level dependent) contrast imaging. This method is based on MR images made sensitive to changes in the state of oxygenation of the hemoglobin (Ogawa, Lee, Nayak, & Glynn, 1990). This molecule has different magnetic properties depending on the concentration of O_2; when it is fully saturated with oxygen (oxyhemoglobin) it behaves as a diamagnetic substance, while when some oxygen atoms have been removed (deoxyhemoglobin) it becomes paramagnetic. Within any particular imaging voxel (representing a small part of the brain) the proportion of deoxyhemoglobin relative to oxyhemoglobin dictates how the MR signal will behave in a BOLD image: areas with high concentration of oxyhemoglobin give a higher signal (a brighter image) than areas with low concentration.

To understand how tissue oxygenation is related to neuronal activity we must return to experiments performed in the 19th century, when it was noted that there is "…an automatic mechanism by which the blood supply of any part of the cerebral tissue is varied in accordance with the activity of the chemical changes which underlie the functional action of that part. Bearing in mind that strong evidence exists of localization of function in the brain, we are of the opinion that an automatic mechanism, of the kind just referred to, is well fitted to provide for a local variation of the blood supply in accordance with local variations of the functional activity." (Roy & Sherrington, 1890, p. 105). The details of this mechanism (the *neurovascular coupling*) are still largely unknown, although the underlying principle is used successfully in most neuroimaging modalities, including fMRI, that are based on hemodynamic responses to neuronal activity (Logothetis et al., 2001).

The increase in blood flow related to neuronal function is also accompanied by an increase in oxyhemoglobin

concentration in a particular 'activated' area of the brain. This is an apparent contradiction, as one would initially expect that an increase in oxygen extraction fraction (Fiat, Dolinsek, Hankiewicz, Dujovny, & Ausman, 1993), associated with high metabolic demand due to neuronal activity, would reduce the tissue concentration of oxyhemoglobin. In fact, oxygen is passively transported from the interior of the red blood cells to the plasma, then to extra vascular space (interstitial space), to the intra-cellular space, and finally reaches the interior of the mitochondria via a pressure gradient (Buxton, Wong, & Frank, 1998). To increase this pressure gradient it is necessary to increase the local concentration of oxyhemoglobin in the blood. As a result, although there is an increase in oxygen consumption, this is more than offset by an increase in oxygen supply (Fox & Raichle, 1986), causing the ratio between oxy/deoxy-hemoglobin tissue concentration to increase and leading to a high signal in BOLD images (Hyder, Shulman, & Rothman, 1998; Kwong et al., 1992; Le Bihan et al., 1993). These events related to the neurovascular coupling phenomena are partially intermixed in time, producing a complex MR signal function related to the neuronal stimulus: the hemodynamic response function (HRF).

The temporal evolution of the BOLD effect from a brief stimulus presentation is not static. Rather it is a dynamic process that can be modeled using mathematical functions, providing different parameters regarding the neurovascular coupling (Glover, 1999). The BOLD effect is also influenced by cerebral blood flow and volume, and as such is not a simple measurement parameter. The researcher have to be aware of the implications when associating the results from an fMRI experiment with the underlining neuronal physiology.

The first moments of stimulus processing in a certain brain region is accompanied by a transient increase in deoxy-hemoglobin concentration: the initial dip (Yacoub et al., 2001). This effect is regarded as a potential mean to increase spatial specificity to the BOLD effect, although the initial dip is not consistently detected and its experimental demonstration is controversial (Vanzetta & Grinvald, 2001). Nevertheless, after this initial component, the MR signal evolves as described in the previous paragraph: there is an increase in the oxy/deoxy-hemoglobin ratio leading to high MR signal. This signal increase (the positive BOLD effect) is proportional to the underlining neural activity (Logothetis & Pfeuffer, 2004) and eventually reaches a plateau if the stimulus is maintained for a sufficient time (Buxton, Uludag, Dubowitz, & Liu, 2004). After the cessation of the stimulus, the MR signal returns to the baseline, and eventually underpasses it: the undershoot effect (Buxton et al., 1998). This effect is believed to derive from the venous bed capacity, which tends to cause the regional blood volume normalize at a slower rate than the changes in blood flow, thus leading to relative high deoxy-hemoglobin concentration (Jones, Schirmer, Lipinski, Elbel, & Auer, 1998). These events are depicted in Fig. 1.

The practical implication is that, by using BOLD images, one can indirectly detect the increase in neuronal activity at the moment that a subject performs a particular

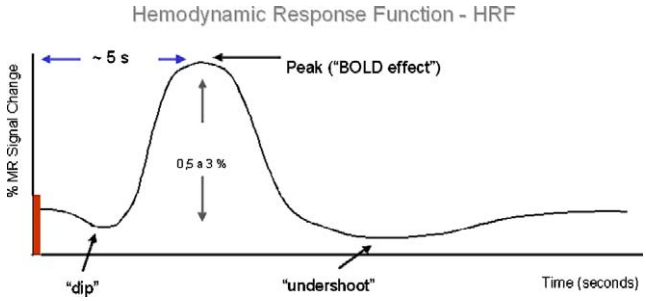

Fig. 1. Hemodynamic response function from a hypothetical short duration stimulus (*gray bar—red bar in the web version*); the BOLD effect peaks after circa 3 s from the start of stimulus presentation (*black bar*).

task, compared to another moment when that task is not executed. The basic concept of fMRI is to have the person inside the scanner performing a series of cognitive tasks (the paradigm, which contains epochs or events of interest along with control epochs or events) whilst BOLD images representing the brain are collected (Le Bihan et al., 1995). A set of images covering the whole brain (a brain volume) is typically acquired every 2–3 s, and (to increase sensitivity) hundreds of brain volumes are typically accumulated during the execution of a complete fMRI scan, lasting around 2 ~ 10 min. The signal intensity of each pixel within the image is compared to a model of the expected BOLD response to the paradigm, and any signal changes detected are statistically tested for significance, allowing detection of small increases in the signal of the brain areas correlated with the behavior. The need for statistical processing, and signal averaging, is due to the difficulty in detecting signal changes, of the order of 1–5% when measured in a scanner with a magnetic field of 1.5 T, against a background of physiological noise of similar magnitude (Purdon & Weisskoff, 1998). BOLD sensitivity is directly proportional to the magnetic field strength, however, so that in a 3.0 T magnet the BOLD effect typically gives a 2–10% signal change (Kruger, Kastrup, & Glover, 2001). This is one of the reasons for the current demand for higher magnetic field MR systems (although it must be recognized that this increased sensitivity may come at the expense of an increase in artifacts and other drawbacks).

In summary: the subject performs a task in the scanner while BOLD images of the whole brain are collected every 1–3 s. The images show small changes in the brightness levels of certain brain areas (related to blood oxygen concentration changes, which reflect brain activity), and the areas in which the brightness changes relative to the task can then be determined using statistical analyses.

2.1. Study design

The strategy in an fMRI (and indeed any) experiment is based on an intervention in a system (brain) and observation of the modulation of the system response (BOLD effect) resulting from this 'provocation' (cognitive task, or in this context, *paradigm*—see below). We have divided the

following sections of this manuscript so as to provide a didactic view of the study design process in fMRI, not easily and sequentially separated, in Sections 2.2, 2.5, and 2.6.

2.2. Paradigm design

Paradigm is defined here as the construction, temporal organization structure, and behavioral predictions of cognitive tasks executed by the subject during an fMRI experiment. As a general principle the experimenter has to decide in as much detail as possible what he/she wants from the experiment. The scientific question may not be suitable for neuroimaging, and this very basic point must be addressed at the beginning of every research project. The next step involves the formulation of a hypothesis, ideally with neuroanatomical basis, and this necessarily will influence the scheme adopted for the cognitive task conditions, and image acquisition parameters. In the following paragraphs, we will present a series of concepts based on an overview of the literature.

2.3. Comparison strategies

2.3.1. Subtraction

Since the initial studies from PET (positron emission tomography) the idea of 'subtracting' images acquired when the subject was performing a 'control' condition from images acquired when the subject was performing the 'active' condition has been used in neuroimaging (Friston et al., 1996). The technique assumes that the two (or more) conditions can be cognitively added, a principle known as "pure insertion," implying no interactions among the cognitive components of a task. In most cases, if not all, this assumption is invalid. Nonetheless, it produces information that can be very useful, especially when used in association with blocked designs (see below) allowing for simple modeling of the BOLD response, resulting in robust and reproducible results (Friston, Zarahn, Josephs, Henson, & Dale, 1999). Perhaps for this reason a number of studies based on subtraction are still performed and published today, most of them designed to assess activity in primary (or phylogenetically old) areas of the brain. Basically, an fMRI study employing the subtraction principle would depend on acquisition of at least two conditions, and the images would be analyzed assuming that any BOLD signal difference, above the statistical level chosen, would represent all brain regions involved in the performance of that task (Fig. 2).

2.3.2. Factorial

As an alternative to cognitive subtraction, the experiment can be designed in a way such that cognitive conditions are processed in a factorial manner, thus allowing tests for interactions between each component (Friston et al., 1996). This technique relies upon neuropsychological evidence for precise definition of the task components, and if possible, complementary behavioral data (Hall et al., 2000). The principle is to have the subject perform a task

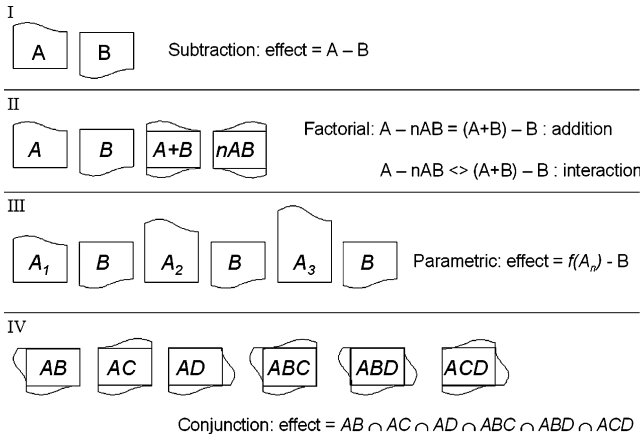

Fig. 2. Cognitive comparison strategies: (I) subtraction, based on 'pure insertion' principle; (II) Factorial, which provides a framework for testing 'pure insertion' theory; (III) Parametric, in which the 'nature' of the cognitive process is maintained, but its intensity is modulated; (IV) Conjunction, in which the conditions sharing the same cognitive component can the further analysed using an 'intersection' approach. Symbols: *A*, *B*, *C*, and *D* represent cognitive components in a given experimental condition in the experiment; *nAB* represents a condition where the cognitive components 'A' and 'B' are absent; A_1, A_2, A_3 represent the 'A' cognitive component of a condition with three different cognitive 'loads.'

where the cognitive components (or dimensions) are intermingled in one moment, and separated in another instance of the paradigm (Fig. 2). The technique relies on an assumption of linearity between the BOLD responses resulting from the conditions (although it is possible to apply a non-linear approach), otherwise some of the findings may be contaminated by non-predicted interactions (Stark & Squire, 2001). Nevertheless, this technique is very useful when it comes to investigating cognitive interactions (Gurd et al., 2002).

2.3.3. Parametric

Certain cognitive tasks can be performed at different levels of difficulty. The idea of increasing the cognitive demand associated with a particular cognitive task, without modifying its intrinsic nature is the basis of parametric design. The increase in the BOLD effect associated with an increase in cognitive demand (Buchel, Holmes, Rees, & Friston, 1998) would imply a heavy association of a particular area to the intrinsic nature of the parameter being manipulated. The technique would allow for an analysis separating these areas from other brain regions involved in the 'maintenance' or 'basis' for the main cognitive process, since the change in BOLD signal in those areas would not depend on the manipulation of the parameter (Benson et al., 2001; Jansma, Ramsey, Coppola, & Kahn, 2000; Maguire, Henson, Mummery, & Frith, 2001; Seidman et al., 1998). However, although the principles are quite simple, the increased demand to perform a cognitive process and maintain it poses a challenge. Often increasing one parameter over a certain limit can involve recruiting other cognitive processes not necessarily present at a low level of performance of the neural system.

2.3.4. Conjunction analysis

In essence, this design is just a subtle deviation from the factorial design, in that at least two or more conditions of the fMRI paradigm share the cognitive component of interest (Bremmer et al., 2001). Whereas other designs are based on detecting differences between conditions, this approach is based on 'commonalities' between them and allows for another angle of analysis: what is the common pattern of BOLD response present in the conditions analyzed, or subjects present in a group study (Friston, Holmes, Price, Buchel, & Worsley, 1999). The 'intersection' of the BOLD response derived from different conditions present in a paradigm could help to distinguish basic processes involved in the performance of the entire run, directing this technique to studies where 'multimodal input' or 'functions supporting a determined cognitive performance' are the main object of interest (Calvert, 2001; Carpentier et al., 2001; Friston et al., 1999; Hyder, Renken, Kennan, & Rothman, 2000; Just et al., 2001).

Finally, it is possible to combine the above-mentioned designs, and in fact it is very common nowadays to have parametric and factorial designs, obtaining the benefits from both sides. Moreover, such datasets can be used for conjunction analysis, provided that the requisites and the hypothesis are congruent, as well as orthogonality (no interaction between cognitive conditions in the paradigm) is maintained (Friston et al., 1999).

2.4. Stimulus presentation strategies

Initially, fMRI studies relied on sequentially presented stimuli within blocked conditions, mainly due to an historical influence: PET studies had investigated changes in blood flow measured over time periods of up to 1 min, while the subjects had to maintain their cognitive engagement. Over the last decade, fMRI has matured to employ a variety of presentation schemes, summarized in Fig. 3, and briefly described in the next paragraphs.

2.4.1. Blocked

This particular category of paradigm is based on maintaining cognitive engagement in a task by presenting stimuli sequentially within a condition, alternating this with other moments (epochs) when a different condition is presented. The alternation of two conditions is known as an 'AB block' design, in which a 'cycle' corresponds to two epochs of each condition. This design dominated the first years of fMRI experimentation, adopting a subtraction comparison strategy, leading to much criticism related to the neuropsychological drawbacks, and numerous assumptions involved. In spite of the negative points, the robustness of results (Brockway, 2000; Loubinoux et al., 2001; Machielsen, Rombouts, Barkhof, Scheltens, & Witter, 2000; Rombouts, Barkhof, Hoogenraad, Sprenger, & Scheltens, 1998, 1997), increased statistical power (Friston et al., 1999) and relatively large BOLD signal change related to baseline (Buxton et al., 1998; Glover, 1999) still make it a valuable technique.

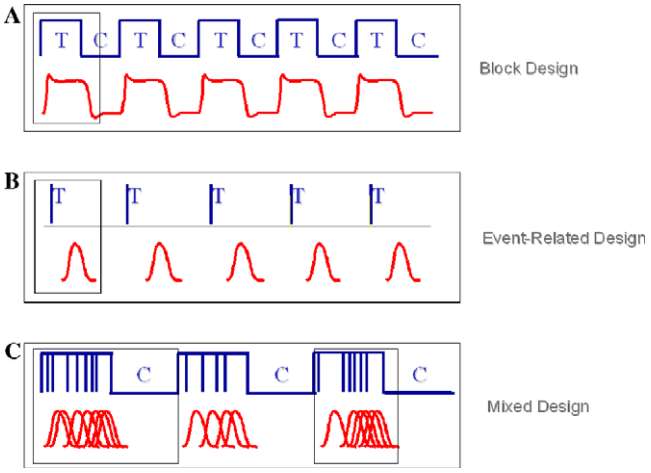

Fig. 3. Stimulus presentation strategies. (A) Block design: stimulus of the same condition are presented subsequently, the BOLD response is actually composed from individual HRFs from each stimulus, and is generally of higher magnitude; (B) event-related design, each stimulus' HRFs is detected, and can be analysed in detail; (C) mixed design, a combination of events closely presented, intermingled with control condition provides the technical needs for analysis event-related analysis as well as 'cognitive state' information.

2.4.2. Event-related

fMRI has superior temporal resolution compared to PET. Although this fact has been known since the first publication of MRI images relating to brain function (Belliveau et al., 1991; Ogawa et al., 1990), it was only after a series of studies published from the mid '90s that new experimental designs making use of the faster image acquisition emerged: event-related fMRI (erfMRI) designs (Amaro et al., 1999; D'Esposito, Zarahn, & Aguirre, 1999; Friston et al., 1998; Josephs, Turner, & Friston, 1997; Rosen, Buckner, & Dale, 1998; Wiener et al., 1996; Zarahn, Aguirre, & D'Esposito, 1997). The main advantage is the ability to detect transient variations in hemodynamic responses, allowing the temporal characterization of BOLD signal changes: the HRF introduced above (Buxton et al., 2004; Rosen et al., 1998). Brain regions correlated to the task can have different HRF, although both are detected as active (Kruggel & von Cramon, 1999). Event-related designs also allows for analyses related to individual responses to trials, providing the means to analyze neural correlates of behavioral responses, such as errors in a challenging paradigm (Braver, Barch, Gray, Molfese, & Snyder, 2001; Kiehl, Liddle, & Hopfinger, 2000; Schacter, Buckner, Koutstaal, Dale, & Rosen, 1997), or a subjective judgment of emotional content of each stimulus presented (Buchanan et al., 2000; Williams et al., 2001). The rapid technique has less sensitivity to head motion artifacts (Birn, Bandettini, Cox, & Shaker, 1999; Huang, Carr, & Cao, 2002), can be used to assess practice effects (Celsis et al., 1999; Liu, Frank, Wong, & Buxton, 2001; Lohmann et al., 1998; Loubinoux et al., 2001), allows for randomization of the order of conditions presented (Rosen et al., 1998) and one can also vary the time between stimulus presentation (interstimulus interval—ISI) reducing the subject's ability to predict when and

what will happen, thus maintaining the attention level across the experiment (D'Esposito et al., 1999). Another interesting application is the use of post hoc methods to detect 'internal processes,' or a subjective perception of a state not driven by the experimenter, e.g., auditory hallucinations (Shergill, Brammer, Williams, Murray, & McGuire, 2000) or visual rivalry (Kleinschmidt, Buchel, Zeki, & Frackowiak, 1998). The initial implementations of erfMRI were time consuming, since the ISIs were regulated by the temporal evolution of the HRF (Bandettini & Cox, 2000), and experiments were longer than blocked designs. In the next section, a method to overcome this problem is presented, although at the expense of dealing with spatial variations in the linearity of the neurovascular coupling in parametric designs (Birn, Saad, & Bandettini, 2001; Pfeuffer, McCullough, Van de Moortele, Ugurbil, & Hu, 2003).

2.4.3. Rapid erfMRI

This is a variation in which the ISI is shorter than the duration of the HRF generated from previous stimuli. As such, it allows for ISIs closer to those used in classical neuropsychological experiments (Buckner et al., 1998; Dale, 1999; Rosen et al., 1998), making it easier to understand the neural correlates of many psychophysical (Klingberg & Roland, 1997; Volz et al., 2001) experiments. The increased number of stimuli presented per time unit is also a desirable effect, since it enhances the statistical power (Buckner et al., 1998; Friston et al., 1999). However, the reduced ability to estimate the HRF properties of a single stimulus, and the problems related to the linearity versus non-linearity of the BOLD interaction in overlapping HRFs (Friston, Josephs, Rees, & Turner, 1998; Glover, 1999; Hinrichs et al., 2000) are limitations to this technique. A practical rule of thumb is that ISIs should be varied (Burock, Buckner, Woldorff, Rosen, & Dale, 1998; Dale, 1999; Friston et al., 1999; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000), with a minimum of 4 s between consecutive stimuli, so that deconvolving the overlapping HRFs is possible according to reasonable assumptions concerning linearity (Glover, 1999). We do encourage the reader to carefully check ISIs variations.

2.4.4. Mixed designs

A combination of block and event-related designs can provide information relating to 'maintained' versus 'transient' neural activity during paradigm performance (Donaldson, Petersen, Ollinger, & Buckner, 2001; Otten, Henson, & Rugg, 2002). This technique is an interesting mixture of the characteristic block design measurement of repetitive sets of stimuli and the transient responses detected by event-related designs. It allows for extracting brain regions exhibiting an item-related pattern of information processing (transient), or a task-related information processing (sustained). In doing so, mixed designs have added a new perspective to psychologists to explore fMRI in understanding 'what' is the role of certain node of a network subsiding a task. Although it has been applied successfully in memory studies (Donaldson et al., 2001), it involves more assumptions than other designs, and the researcher will have to tackle issues associated with poorer HRF shape estimation, and post hoc analysis of behavior correlated activation (Donaldson, 2004).

2.4.5. Behaviorally driven fMRI

All of the above stimulus presentation strategies request that the individual in the MR scanner follows a previously explained task; one that may require participation of control processes engaged throughout the experiment (one of the nightmares of the neuroimager: brain areas detected may be modulated by the paradigm instructions per se, instead of emerging only from the contrast between the conditions). An alternative to the paradigms used in conventional designs is to let the subject lay inside the MR scanner doing nothing, and observe variations of the BOLD response related to spontaneous activity, or 'resting state'—often measured by other methods such as galvanic skin response (Buchel, Dolan, Armony, & Friston, 1999; Critchley, Elliott, Mathias, & Dolan, 2000), electroencephalography (Nagai et al., 2004, Nagai, Critchley, Featherstone, Trimble, & Dolan, 2004) or in combination with conventional paradigms (Babiloni et al., 2002; Foucher, Otzenberger, & Gounot, 2003; Gotman, Benar, & Dubeau, 2004; Krakow, Allen, Lemieux, Symms, & Fish, 2000; Laufs et al., 2003; Lemieux et al., 2001; Menon, Ford, Lim, Glover, & Pfefferbaum, 1997; Nagai et al., 2004, 2004; Salek-Haddadi, Merschhemke, Lemieux, & Fish, 2002; Stancak et al., 2005; Williams et al., 2000; Williams et al., 2001). It has similar properties to event-related designs, intrinsically have a variable ISIs, and may have limitations related to linearity properties of overlapping HRFs, that can vary according to different brain regions (Birn et al., 2001). One caveat: this design is intrinsically dependent on each subject performance, and the intersubject variability, number of events per condition and consequently the statistical power of the study is largely unknown beforehand, even if a pilot study is performed.

2.5. Image acquisition techniques

The process of data acquisition is very flexible in fMRI and is paramount to an effective study design. Parameters influencing temporal and spatial resolution, as well as image acquisition plane and considerations regarding scanner acoustic noise can be used in different settings, providing a wealth of options. In this section we will limit the discussion to techniques sensitive to BOLD effect, bearing in mind that this is the most used technique, mainly because of its practical and easy implementation. On the other hand it has limitations, since the nature of the signal measured is not quantifiable or related to a specific physiological parameter, rather it is a complex interplay between cerebral blood flow, volume, and cerebral metabolic rate of oxygen ($CMRO_2$) (Buxton et al., 1998; Logothetis et al., 2001; Silva, Lee, Yang, Iadecola, & Kim, 1999). Other methods allow for direct cerebral blood flow measurements

(Alsop & Detre, 1996), $CMRO_2$ (Aguirre, Detre, Zarahn, & Alsop, 2002; Hoge et al., 1999; Silva et al., 1999; Silva, Zhang, Williams, & Koretsky, 1997) and oxygen extraction fraction (An & Lin, 2002) providing quantitative assessment of brain physiology (Buxton et al., 2004) but tend to be difficult to implement and generally are not as flexible as BOLD-based techniques.

Ideally, one should acquire more than just the image information during an fMRI experiment. Behavioral data are crucial to correct interpretation of the data and are sometimes used to model the expected HRF. The magnetic environment of the scanner room is a challenge to the use of electronic equipment conventionally used to collect subject responses, or measure physiological parameters (Baumgart et al., 1998; Bilecen, Radu, & Scheffler, 1998; Fishbein, McConville, & Spencer, 2001; Hinterberger et al., 2004). Nevertheless, recent data from different laboratories are increasingly contemplating the use of systems providing multiple sources of information acquired jointly with brain images (Bestmann, Baudewig, & Frahm, 2003; Fishbein et al., 2001; Guimaraes et al., 1998; Hamandi, Salek-Haddadi, Fish, & Lemieux, 2004; Williams et al., 2000). This approach is desirable, and should be encouraged in most experiments, providing that it does not work against the paradigm, i.e., it might increase the discomfort level for subjects, interfere with the image quality, and ultimately compromise the results.

2.5.1. Temporal resolution and experiment duration

Most researchers would start from the premise that an fMRI experiment should provide maximum amount of information per time unit, and try to use the maximum time in the scanner per subject unit. In fact, this approach is not optimal. Although echo planar images (a technique in which all information necessary to produce brain slice image is collected after a single RF excitation) have a very high temporal sampling rate, in the order of few milliseconds (Wiener et al., 1996), this speed is achieved with a compromise of spatial resolution, with the exception of high field MR systems (Pfeuffer et al., 2002). The parameter that regulates temporal resolution, for practical purposes, is called 'time to repetition,' or TR, and corresponds to the time between two excitation pulses, or put simply, the time it takes to collect one brain volume (composed of many slices). It determines the temporal resolution (sampling rate) of the experiment. But the speed comes with the expense of space: the shorter the TR, the lesser the number of slices collected by TR—thus brain coverage is limited. Conversely, one can reduce spatial resolution in order to achieve high temporal resolution. On the other hand, the temporal characteristics of the HRF limits the usefulness of very rapid image acquisition techniques, with apparently no need to collect images at a TR lower than 1 s (Constable & Spencer, 2001), providing that no connectivity analysis is planned (see further). So, what is the best TR? In general, a TR lower than 1.5 s provides ~12% more statistical power, but other acquisition parameters (i.e., flip angle) have to be changed in order to avoid contribution from blood inflow in the signal (Lu, Golay, & van Zijl, 2002). On the other hand, keeping the subject inside the scanner for hours, until sufficient sampling for a large statistical power between conditions has occurred, can test the rapport, not to mention lead to uncooperative and fidgety volunteers. In practice, one should get the maximum amount of useful information per time unit, and the minimum time in the scanner per subject unit. Practical numbers (in this context, to be used as guidelines) are around 2 min expended per condition, not more than 12 min per run, and total section time less than 40 min from our experience with clinical fMRI studies. In a modern 1.5 T MR system (gradients > 30 mT/m), using $3 \times 3\,mm^2$ voxels one can collect ~20 slices in 2 s, and using parallel acquisition techniques, this number can be even higher (Preibisch et al., 2003).

2.5.2. Spatial resolution and brain coverage

Ideally, one would want data with the smallest voxel size possible, and acquisition of the whole encephalic tissue available in a subject. Similarly to the issues discussed above, the resolution can be increased at the expense of signal to noise and time, and should be approached according to the aims of the study. The spatial resolution unit is the voxel (volume element) that represents the minimum unit of brain tissue sampled in each image. The images are two dimensional, and each picture element represents one voxel. Increasing voxel size (lowering the spatial resolution) actually produces an increase in the amount of tissue detected as active using conventional analysis (Howseman et al., 1999), and may be interesting when sensitivity to BOLD effect is desired over spatial resolution. Reducing voxel size has a negative impact in the signal to noise ratio of the images, reducing the sensitivity to BOLD effect, but produces more spatially specific information, has less susceptibility artifact partial voluming (for instance, a larger voxel in the cortical boundary would also include CSF, resulting in less signal originating from gray matter). The anatomical characteristics of brain tissue, specifically the cortical thickness, are good guides to set the optimal voxel size, and since this value averages 3–4 mm, it seems that larger voxels would be more prone to partial volume effects. On the other hand, there is a compromise between spatial resolution, amount of brain tissue sampled by the images, and temporal resolution. This triangular relation is constantly challenged by advances in MR physics (see parallel imaging below) but basically if the spatial resolution is increased, keeping the temporal resolution fixed, then the amount of brain tissue sampled (i.e., number of image slices) has to be reduced; or if the spatial resolution is increased, and the brain coverage is maintained, then temporal resolution has to be less. Generally, in the last case, it will increase the experiment time. This is not a fundamental problem with animal studies lasting for hours, but is not feasible with humans. Keeping this in mind, there is also the post-processing step in neuroimaging, which has an impact in spatial resolution: it is a frequent practice to spatially smooth the data. This process, fundamental to image analysis algorithms based on Gaussian principles, reduces the

effective spatial resolution, but tends to facilitate conventional group mapping techniques, and parametric signal modeling. Finally, it is fair to remember scanner limitations and it is wise to use the right voxel size according to your scanner specifications and obtain the brain areas related to your neuroanatomical hypothesis.

2.5.3. Spatial and temporal resolution

From the points discussed above, it is clear that an ideal scenario would need technical advances in order to accommodate the needs for both higher spatial and temporal resolution. There are two main approaches to deal with that: jittering and parallel imaging. While the first is less dependent on hardware upgrades, and can be performed in any MR scanner, the second relies heavily upon state of the art instrumentation. On the other hand, jittering relies upon signal composition, ideally not desirable in real-time applications, whereas parallel imaging provides real improvement in spatial/temporal resolution (although to the cost of lower SNR).

Jittering refers to the use of different delays between the start of the sampling of brain volume images relative to the start of stimulus presentation to the subject. If all images are collected with the same delay from stimulus presentation (the 'time-lock' strategy) all brain regions would be sampled at the same time points at every ISI, with periodicity rate exactly equal to the TR. On the other hand, if one jitters (offsets) the stimulus presentation time to image acquisition, then different time points would be sampled at each stimulus presentation. This can be achieved by using an ISI that is not a multiple of TR (the so called fixed jittering scheme) or varying the ISI (variable jittering). In this manner, the acquisition of one brain volume with high spatial resolution can take up to 6 s, and will still be able to sample time points closely spaced in time. As one can see, this strategy will result in increased total acquisition time. Moreover, if an analysis of HRF characteristics is planned based on subject behavior, since jittering is not enough to sample the HRF characteristics from a single event, the subject has to behave similarly in a few events in order to provide sufficient information (when analyzing multiple subjects, the frequency of the behavior should be similar, a rare situation). However, it also requires more trials, and would only be recommended if behavioral performance is reasonably predictable, and/or the MR scanner limits your sampling rate and/or if connectivity analysis is planned. In summary, jittering is advisable if full brain coverage is needed, as well as temporal resolution—but behavior analysis and long scanning sections are not critical.

A technique based on the spatial coding of signals from coil sensitivity profiles—parallel acquisition schemes—has emerged as an interesting tool to reduce the compromise between temporal and spatial resolution, with other interesting properties, from which only a few are discussed here for scope and space limitations (Golay et al., 2000; Klarhofer, Dilharreguy, van Gelderen, & Moonen, 2003; Preibisch et al., 2003; Schmidt, Degonda, Luechinger, Henke, & Boesiger, 2005; Tsao, Boesiger, & Pruessmann, 2003). Parallel acquisition was rapidly adopted by the scientific community (Golay, de Zwart, Ho, & Sitoh, 2004), and reduces the acquisition time by a factor set by the experimenter (usually between 2 and 3). The physics involved also reduce the amount of susceptibility artifacts, improving the detection of signal from basal frontal and mesial temporal regions, thus having a positive impact on studies involving memory, emotion, and executive function tasks. The reason for this improvement is based on a simple fact: instead of spending a considerable fraction of the time in the acquisition coding the signal using electric currents to produce magnetic gradients (which take precious milliseconds), this technique uses the differences in the MR signal measured by the coils—which depends on the proximity of the part of the body. In our case, coils placed around the head have different sensitivity profiles, and this information is used to code the MR signal spatially (Golay et al., 2004). As a drawback, the SNR ratio is reduced, but this seems not to impact negatively with the same magnitude on the BOLD effect sensitivity (Preibisch et al., 2003). In summary, parallel imaging will likely have a deep impact upon fMRI, helping to overcome the related limitations of spatial resolution, temporal resolution, and brain coverage.

2.5.4. Acquisition plan

Brain images are acquired in a pre-determined plan across the area of interest. Most studies target 'total brain coverage' in order to fully sample any possible area responding to the paradigm. Some other studies aim for specific regions, and in this case the acquisition plan is of more concern. While in the first approach acquisitions parallel to the bi-commissural plan (a line connecting the upper part of the anterior commissure to the lower part of the posterior commissure) are usually employed, in the second case, the coronal acquisition is generally preferred. More specifically, the rule of thumb is to *acquire the data perpendicular to the longest axis of the structure of interest*. For instance, for studies interested in the hippocampal formation, it is wise to angle the acquisition plan perpendicular to the hippocampal axis. Moreover, the size of the voxel is very important (Merboldt, Fransson, Bruhn, & Frahm, 2001) and should not only be regulated by the size of the area of interest, but also aim to reduce image artifacts. One particular type of image distortion is the susceptibility artifact: areas close to air filled bone structures (where the magnetic characteristics is very different from those of the adjacent brain parenchyma), such as the basal frontal lobes, as well as basal and mesial temporal structures are particularly affected. Reducing the voxel size is one of the ways to reduce susceptibility artifacts. Depending on where the study focus is, and if it is only related to practical acquisition in most installed MR scanners, these suggestions can be useful: $2 \times 2 \times 2$ mm coronal acquisitions for amygdala and hippocampus; $3 \times 3 \times 3$ mm or lower for 'flat brain' post-processing; $3 \times 3 \times 5$ mm for practical time/space compromise; isotropic voxels are generally encouraged, since later re-slicing are less prone to sub sample one

axis. These guidelines are prone to aging as new MR systems are rapidly marching to submillimeter voxel sizes and full brain coverage.

2.5.5. Scanner acoustic noise

The process of image acquisition for fMRI generates a very loud acoustic noise, up to 120 dB (Mansfield, Glover, & Beaumont, 1998) which can interfere with paradigms that involve auditory processing (Anderson et al., 2001; Bandettini, Jesmanowicz, Van Kylen, Birn, & Hyde, 1998; Barch et al., 1999). This effect can be minimized by directly reducing the source of the noise (Mansfield et al., 1995), or using the hemodynamic delay of the BOLD response, and inserting 'silent periods' in the acquisition process (Amaro et al., 2002; Hall et al., 1999). Because of hardware modifications requirements, the first approach usually involve dedicated solutions, or even purchase of new equipment. Therefore, most attempts to reduce scanner noise in fMRI studies are based on modifications to the acquisition sequence and the stimulus presentation strategy. In fact, one can present the stimulus and collect data insensitive to scanner acoustic noise, but to the cost of an increase in acquisition time. Basically the subject is presented with acoustic stimuli in a silent background (no images are collected), after which the BOLD response elicited is produced and only then the images are acquired (Fig. 4). This is possible because the HRF peaks after 3–5 s from the start of the stimulus presentation (Hall et al., 1999), thus one can dissociate image acquisition (scanner noise produced) from the subject's perception of the stimuli. The same strategy can be used to record overt responses from the subject in language paradigms. This later use is very practical, since it also helps dealing with movement artifacts (Birn et al., 1999) and provides evidence of subject verbal output, which allows for further application of voice analysis. Finally, parallel acquisitions can also be used to reduce the source of scanner noise (de Zwart, van Gelderen, Kellman, & Duyn, 2002).

2.6. Image analysis strategies

The choice of the image analysis method for fMRI is fundamentally defined by the hypothesis of the experimenter. There is a multitude of software packages available from different laboratories. The advantages of one approach are often very specific for a group of scientific questions (i.e., exploratory vs. hypothesis driven, population specific vs. highly generalizable), and frequently the analysis approach for one experiment is not the best choice for another type of study. Many software packages are now available on the internet (e.g., FSL at http://www.fmrib.ox.ac.uk/fsl; XBAM at http://www.brainmap.co.uk; Brain Voyager at http://www.brainvoyager.de; SPM at http://www.fil.ion.usl.ac.uk/spm; AFNI at http://afni.nimh.nih.gov/afni).

Needless to mention, there is no consensus in the literature about 'the best method for fMRI image analysis,' mainly due to the flexibility of the method allowing for different approaches. Although this fact is the source of the difficulty found by researchers when trying to compare results, it is also possible to use original data and then submit different studies to the same streamline of analysis using particular software (Casey et al., 1998; Gordon, 1999).

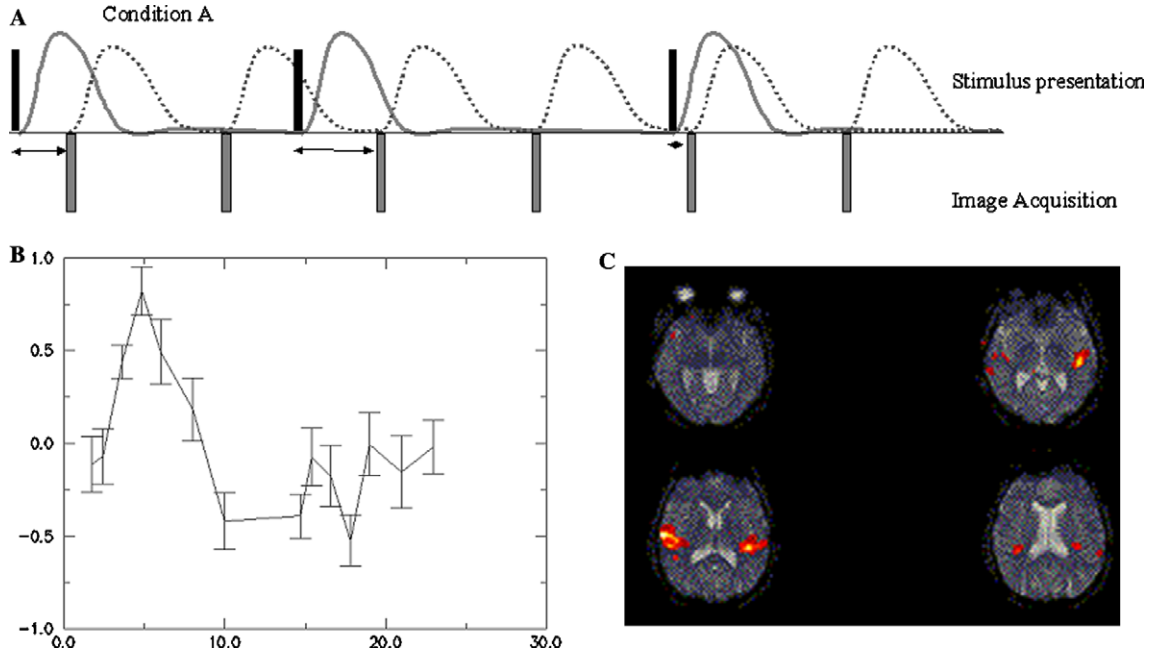

Fig. 4. Strategy to minimize the effects of the scanner acoustic noise. (A) Stimulus presentation scheme: *dashed lines* represents the HRF from the scanner acoustic noise, that are not detected by the next image acquisition, *solid lines* represents the HRF from stimulus presentation, which is sampled twice, and in different time-points thus providing a variable jittered scheme; (B) HRF generated from the scanner acoustic noise in the primary auditory cortex; (C) image results from an experiment probing the scanner acoustic noise: a clear activation of the auditory regions is seen ($p < .003$).

There are actually some common steps in fMRI image analysis, adopted by the majority of software 'packages' used currently. The data are first pre-processed, and that includes movement correction (and realignment), spin history correction (when a subject moves the head inside the magnetic field, not only the images are now representing different regions, but the signal intensity is modulated—i.e., some regions become brighter), and optional steps such as spatial/temporal filtering, re-sampling and even re-ordering of data. After this initial step, the HRF has to be modeled to represent the fMRI signal evolution in time in a hypothetically activated region. Although there are various approaches, including some devoid of HRF modeling, the general rule is to use mathematical functions representing the empirical 'shape' of the BOLD response, more often represented by gamma or Poisson functions. Finally, the statistical inference is performed via parametric or non-parametric approaches. Implementation of this step includes techniques such as Gaussian random field theory (Friston, Holmes, Poline, Price, & Frith, 1996), permutation testing (Brammer et al., 1997), analysis at cluster level, correction for multiple comparisons (since the number of voxels are typically in the order of ten to twenty thousands) and methods to deal with signal noise (Bullmore et al., 2003).

The processing steps described above will result in an 'activation map' of a single subject: the areas surviving a statistical threshold are presented in a color scale. This is also known as 'first level analysis' by some authors. The majority of the studies proceed to a 'second level analysis' to interrogate questions based on group statistics. In this phase, generally voxel-based transformations are used in algorithms that 'normalize' and 'register' each subject's brain volume, thus all data are analysed in a common space. An excellent revision of the issues related to brain image transformations, and concepts in automated group analysis is given by Brett, Johnsrude, and Owen (2002).

A critical issue related to any study design in neuroimaging is the level of statistical power to make inferences about the parameters measured (Friston et al., 1999). In fMRI the variables under the experimenter control are vastly interdependent, and any attempt to improve the SNR in the data, number of events sampled, number of images acquired, and even the choice of model for the MR signal should be a balance between the SNR of the signal changes measured and subject's tolerance. We recommend the reader to consult the literature related to the research in question, and carefully look at pilot data.

It should be also emphasized that techniques used for detecting interactions between brain regions using connectivity analysis are maturing. Thus, it is possible to advance beyond 'phrenology' in neuroimaging (Goncalves, Hall, Johnsrude, & Haggard, 2001). There is great hope that intrinsic problems related to physiological noise, multiple equation solutions, and temporal limits are gradually and successfully being addressed (Arfanakis et al., 2000; Cordes et al., 2001; Goncalves et al., 2001).

2.7. Desire and practicality: Final considerations

fMRI offers a very powerful method to probe brain responses to cognitive tasks. The increased use of the technique is due to its flexibility, availability, high spatial resolution, relatively high temporal resolution, and lack of ionizing radiation or need for external contrast agents. It also offers a dilemma to the researcher, who has to spend considerable time resolving questions related to spatial and temporal resolution, limits to brain coverage, and image artifacts in sophisticated experimental designs, *or* instead choose simple designs, moderate expectations, and ask simple questions. This involves understanding the limitations and making the best use of the equipment available. We prefer the last option.

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