REVIEW ARTICLE

Some Points to Consider in a Task-Based fMRI Study: A Guideline for Beginners

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Abstract

Functional Magnetic Resonance Imaging (fMRI) is a technique widely used to probe brain function, and has shown many research and clinical applications. Despite its popularity and strength, performing an fMRI study needs careful consideration of the design of the experiment, as well as the techniques and methodologies implemented in it, due to the high potential of these factors to alter the outputs of the study. The influences of the demographics of the participants, stimuli design, image acquisition, and data analysis methods on the fMRI results are illustrated previously. Therefore, it is of utmost significance to have an understanding of the critical considerations when designing an fMRI study. In this manuscript, by reviewing the methodology of over one hundred task-based fMRI studies, around 300 substantial tips regarding the different stages of an fMRI experiment are gathered. These could only be found scattered through the literature, and such a collection would act as a guideline for the beginners in the field of fMRI.

Keywords: Functional Magnetic Resonance Imaging; Task-Based; Experiment Design.

1. Introduction

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive method capable of identifying the brain areas active in a cognitive function, along with their pattern and extent of activations. The popularity of fMRI is mostly due to its widespread availability, being non-invasive, low cost, and appropriate spatial resolution [1]. It has shown many research applications, such as in studies relevant to imaging genetics [2], addiction [3], language [4], memory [5, 6], emotion regulation [7], motor [8], sensory [9], and vision [10]. Besides, numerous reports are available on the clinical applications of fMRI, and examples include depression [11], bipolar disorder [12], Alzheimer's disease [13], aging [14], autism [15], epilepsy [16], and coma [17]. It is also used as a biomarker for diseases [18], to monitor a therapy [19], or for studying pharmacological efficacy [20].

In recent years functional MRI has rapidly matured, from an experimental imaging method to a very widely available and widely used tool in cognitive and clinical neuroscience. Despite its strengths and extensive applications, selecting appropriate settings and designs for such a study is very vital. In two recent studies, we illustrated how the fMRI findings would be altered based on the experimental settings [8, 21]. Other reports are also available on the influence of task stimulus [22], task performance [23], fMRI data analysis method [24], and task types [25] on its findings. These show that the methodology of an fMRI study should be precisely selected.

In addition, performing an fMRI study is very complex, and becoming an expert in fMRI needs time and effort; therefore, integrating the literature to provide an outline for the process of fMRI is important [26]. This manuscript aims to provide a guideline which collects the major points relevant to performing a task-based fMRI experiment. The aspects covered here include selecting participants, task design, imaging, preprocessing, GLM analysis, covariates, signal change, and ROI analysis.

We identified a number of previous studies with similar aims; however, they may need an update [1, 27–32] or are required to provide more practical instructions for a broader range of researchers [33–35]. A few further prestigious studies are also available; however, they are different from the current study in a few aspects: Nichols *et al.* [36] mostly defined best practices for fMRI data analysis, results reporting, and algorithm and data sharing; Poldrack *et al.* [37] outlined a set of guidelines for the reporting of methods and results in fMRI studies; Caballero-Gaudes *et al.* [38] focused on cleaning the BOLD fMRI signal; Price *et al.* [39] presented the underlying physical, technical and mathematical principals of BOLD fMRI; Skup *et al.* [40] and Telzer *et al.* [41] provided a brief summary of fMRI longitudinal analysis approaches; Lee *et al.* [42] and Smitha et al [43] reviewed the methods of resting-state fMRI data analysis; Li *et al.* [44] reviewed the methods for functional brain connectivity detection using fMRI; and Bowring *et al.* [45] explored the impact of analysis software on task fMRI results. In addition, the reports by Dimoka [26] and Soares *et al.* [46] are excellent studies with similar aims, and we have tried here to cover the aspects provided by them along with some additional information and updates.

For this aim, more than one-hundred studies on healthy participants and patients were selected, and their methodologies are summarized here. Most of the included studies used task-based fMRI to study human cognition; however, a few studies from other modalities were also included due to their important information such as in subject inclusion. The studies were identified through the Pubmed database; their title and abstract were studied, and the papers which met the following criteria were selected: I) published in a peer-reviewed journal to ensure the quality of the report (and in English language); II) studying normal subjects or patients; and III) to have clearly explained the methodology of the study. We did review the literature in search of a quantitative or qualitative instruction for quality check of the studies, but no instruction was found. Our current criteria for including studies are in agreement with many previous reviews [7, 36–39, 47].

The suggestions provided here are peer-reviewed and are among the mostly-used ones; however, not all studies consider these criteria in their methods, either because they are not applicable to every study, or otherwise they would be regarded as a limitation of those studies. It is not feasible to prescribe an exact methodology for an experiment [36], and studying the

original works elucidates the reasons of selecting an approach. The paper has tried to provide information for both the intrinsic and extrinsic aspects of the fMRI, so that the researchers pay attention to the both sides.

2. Participants

2.1. Age

The age range of the included subjects largely depends on the aims of the study. One study may have a hypothesis which should exclusively be tested on a particular age range, e.g., children, adolescents, young adults, or elderly. Besides, studying diseases is better performed on a particular age group, for example studying Autism in children, or Alzheimer's disease in older adults. Furthermore, some tasks need participants in a particular age range, such as the autobiographical memory which looks for the middle-aged subjects to obtain a sufficient number of remote autobiographical memories and to avoid their memories to have become semanticized [48]. However, there is no definitive range reported for the age groups [49], and therefore the groupings may need to be based on a previous report [50]. Finally, when comparing two groups of participants in a study, they are better to be from similar age ranges [51], unless studying ageing effects. Ageing is well understood to significantly affect the structure [47, 52] and function [13, 14] of the brain, and as a result, selecting the participants from a proper age range is necessary.

2.2. Gender

Most studies include both male and female participants, but very rarely they have an equal number of them [53]. Including an equal number of both genders would increase the statistical power of the study if gender association is of interest [54]. Some studies include only one gender [55]; if there is no particular hypothesis to be tested, the generalizability of such findings would be difficult. There are numerous reports on the association of gender with brain activations [56]. Sex hormones act throughout the entire brain via both genomic and nongenomic receptors, and therefore the structure and function of neural systems, as well as the behaviors such as mood, cognitive function, motor coordination, pain, opioid

sensitivity, and learning and memory ares different between males and females [57, 58], which show the importance of considering the gender distribution of the participants.

2.3. Health Assessments

For including healthy participants, it is required that none of the following conditions be met: neurological impairments, psychiatric illness and disorder, history of learning disability and developmental delay, history of prematurity, birth injury, school problems, major depressive episode, current psychotropic medication use, neurological illness and injury, mental retardation, medical disorders with effects on the central nervous system, or a history of a disease in immediate family [51, 53, 59].

Also, the subjects are required to have a normal, or corrected-to-normal vision when there is visual stimuli [60]; the same applies to the hearing ability [61]. Sometimes these abilities are more rigorously tested. A study reported that all its participants had pure tone thresholds below 30 dB HL for the octave frequencies in the range of 250 to 8000 Hz [62]. Further clinical checks for specific aims are also possible, for example using physical examination, chromosomal analysis, or metabolic testing.

There are some factors which are considered as exclusion criteria. Head trauma and acquired brain injury is a risk factor for a healthy brain [53]. Lifetime/current substance use disorder, other than nicotine dependence, is mostly an exclusion criterion unless studying addicted subjects [59]. The list of medications a participant takes will have information relevant to his/her health status [62]. Taking allergy, asthma, or antibiotic medication is usually allowed. Regarding alcohol drinking and cigarette smoking, three approaches are selected: I) the subjects are excluded for any level of drinking or smoking; II) As long as this is not an addictive behavior, based on strict criteria and standard questionnaires [63–65], the subjects will be included; III) the level of consumption or smoking is only regarded as covariates in the study. A telephone screening before the face-to-face interview could easily exclude those participants who do not meet the criteria.

2.4. Handedness

Handedness is sometimes assessed by self-report [66], but mostly the Edinburgh Handedness Inventory [67], or the Lateral Dominance Examination from the Halstead-Reitan Neuropsychological Test Battery [68] are used. Most studies only include right-handed participants; however, left-handed individuals are also part of the population, and a more general finding could be obtained when including both groups [61]. Many studies have illustrated the association of handedness with brain function alteration, such as in auditory verbal memory task [69], semantic task [70], and in language [71], and this shows the importance of the handedness of the participants. As a result, the suggestion is to simply perform a handedness test for each participant, which takes only a few minutes.

2.5. Comparability

It may be necessary for the subjects to be native in the language of test [60]. The years of education is vital in some studies, and this should be either considered as an inclusion criterion, or the results should be corrected for this measure [53]. In addition to age, gender, and education level, the Intelligence Quotient (IQ) and race of the participants are also important and need to be matched between the case and control groups [72]. Despite all the endeavors to match the two groups, it happens that one group is different in one measure with the other; an example could be a higher anxiety score in one group. In such occasions, the analyses should be corrected for the different measure [73]. The subject should not have any risk factors for MR scanning, such as a pacemaker, metal object, or other non-MR compatible parts in the body. Intolerability to MR scan, or claustrophobia, are other exclusion criteria [47].

2.6. Ethical Issues

The subjects could be recruited by advertisement or orally from the community. In some studies, the participants are paid for their participation, e.g., 25$ per hour [74]. Their participation could also be indirectly appreciated, for example by university course credit [75].

Informed assent/consent should be obtained from each individual before participating in the study [53]. For the participants below the age of 18, this should be signed by their parents [51]. The participants should be informed about the study, but they could be naive to the specific aims and experimental questions of it [75]. The Institutional Review Board (IRB) of each institution should have approved the study, and the study should be conducted in compliance with the safety guidelines for MR research on humans [76].

There may be occasions when the researcher observes abnormalities in the brain of the participant. The local IRBs usually have standard procedures for these instances, such as consulting a trained radiologist or notifying the participant; however, as fMRI is not a diagnostic tool, making medical diagnoses based on fMRI should be very limited [26].

2.7. Patient Treatment

In studies on patients, diagnosis of the disease is very critical. It should be done by an expert, such as a licensed psychologist or psychiatrist, according to standard diagnostic criteria such as DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) [73]; standard tests could also be used, such as the MMSE [77] for dementia diagnosis [78]. Psychiatric and medical history of the patients [59], confirmed by expert clinical opinion [72], are also advantageous to be collected. Patients should be allowed to take their medications on the scan/test day [72], and a thorough history of the disease, including the age of onset, the severity of the disease, and the prescribed medication, should be collected for each patient [79].

2.8. Excluded Data

Several factors could exclude a datum. The MRI data with excessive head motion are usually excluded, and the criteria for this are reported as higher than two voxels [80], or above 2 [51] or 3.5 mm [72]. Only the slices with excessive motion could be removed, or the whole dataset if (for example) more than 17 volumes had a high motion [51]. In general, incomplete data are subject to exclusion [51], such as when the behavioral responses are missed. The data with chance performance [80], or when the subject falls asleep in

the scanner and fails to follow the instructions properly [81] are subject to exclusion. A novel approach to identify inattention during the stimulus is to observe an abnormal activation time course in the occipital areas of the brain [72]. Technical problems in data acquisition [82], an MRI data with a weak signal or low quality [80], and observing an abnormality in the MRI scans such as a vascular malformation [53], could lead to exclusion. A study excluded the data with a low Signal-to-Noise Ratio (SNR), with the criteria of the Standard Deviation (SD) of the functional time series exceeding 1.5% of the mean [80].

2.9. Sample Size

A considerable portion of published fMRI studies are statistically under-powered, due to their limited sample size and large number of comparisons [83]. This shows the importance of using power analyses to choose the appropriate number of subjects for obtaining statistically significant activations, albeit this is challenging [84]. There are many guidelines for calculating the number of subjects [83, 85, 86]. Software tools are also developed for the calculation of the statistical power of a study [87], and they need the mean activation, the variance, the type-I error rate, and the sample size [46, 87]. The power calculation uses either the pilot statistical images [88], the estimated parameters in the regions of interest [86], or the prevalence of active peaks [46]. The study by Mumford [87] is a good guideline for power estimation.

In addition, estimating the effect size is advantageous in fMRI studies, as this is a simple way to show the actual difference between the activation of the groups or brain regions, and is independent of the sample size [89]. The significance of the findings obtained from a large sample can be illustrated with the magnitude of the effect size [26].

3. Task Design

3.1. Image Quality

The images presented in a task should have good quality and enough resolution. Colorful or black-and-white images have different influences [75]. A study

very precisely reported the quality of the color of their images in the RGB measure [76]. Another study converted all images into black-and-white, and adjusted the contrast and brightness of the images, to maintain the consistency [80]. The visual angle of the presented images is also essential; examples include five by six degrees [61], 1° in width and 0.3° in height for each presented digit [80], and 1.2°×1.2° for each symbol [90]. The distance between the location of the object in the image and the edges of the screen is also important [91].

3.2. Image Content

When presenting faces, the sex [61], race, color, emotion, and identity [80] of the faces are important. Sometimes faces of different sexes are intermixed, and it is better to have an equal number of faces for each sex [80]. In some studies each block contained faces of only one sex [61]. Face images are usually downloaded from a standard database, as they have standard quality [92]. One study used four different databases of faces to design their experiment, including the Karolinska Directed Emotional Faces (KDEF), the Ekman set, the Ishai-NIMH set, and the Nimstim Face Stimulus Set [80].

In a few studies, images were simply downloaded from Google Images, but with limitations on the size, number of voxels, and resolution of the images [92]. In such cases, the faces should be rated by a group of normal subjects, for example regarding their emotional load [93]. It is vital that the participant be familiar with the contents of the task; for example, presenting the pictures of unknown or unfamiliar animals may have no/less influence [75]. Symbols or unknown characters could also be presented in particular aims [93].

3.3. Audio Stimuli

If a sentence or word is going to be read for the participant, using a male [61] or female [81] speaker is different. Using a text-to-speech software is another option [81]. Also, the sound stimuli could be accessed from databases, such as the Psychology Experiment Building Language (PEBL) Sound Archive [82]. The onsets and offsets of the sounds could be shaped by a Kaiser window so that they all have the same duration

[62]. To produce neutral stimulations for the audio stimuli, the presented audio files could be time-reversed [4].

3.4. Verbal Stimuli

If sentences are to be presented in a task, the length of the sentence (number of syllables) and their grammatical complexity should be the same. The length of words (number of letters), number of syllables, and the frequency of words in that language are also important [74]. Words could be selected from a standard database [74]. When presenting alphabets, the vowels could be excluded to minimize chunking of letter sequences into words [81]. The style and size of fonts of the alphabets are also important [94]. It is noticeable that the same fonts should be selected for all blocks of the experiment [94].

3.5. Type of Design

There is no optimal design for an fMRI study, but optimizing the parameters improves the study efficiency. The concepts relevant to designing an fMRI experiment are reviewed previously [29, 46, 95]. When multiple types of stimulus are included in a task, different approaches are possible to present them, including a counterbalanced approach [92], in which blocks, or the contents of the blocks, are counterbalanced [51]. This is the suggested approach across subjects of the same study [46]. Pseudo-randomly intermixed is another approach [61], but it is better that no two similar trials be presented consecutively [96]. Randomizing the sequence of trials for each subject is also possible [75]. Previous studies have provided further details on study design [29].

The two major types of fMRI experiment design are blocked and event-related. In blocked, the stimuli are continuously presented for an extended time interval (block) to keep the participant engaged in the experiment, and different conditions are alternatively presented. This design is robust [97] and has a good BOLD signal change and power [98]. Limitations of this design are the participant's habituation to task, and the inability of defining the accurate response-time courses [29, 46].

Event-related designs aim to identify brain activations in discrete events, separated by an interval. It has a good flexibility, and the participant cannot predict it; however, its power is low due to a decreased Signal-to-Noise Ratio (SNR) and a complex analysis process [99, 100]. This design detects transient variations in hemodynamic response, enables analysis of responses to each trial, and has low sensitivity to head motion [97]. The interval between trials is usually random (jittered), which minimizes confounds from a subject's habituation and expectation [101].

There are three models for experiment design: I) subtraction is the most basic model which compares two or more conditions, including a control (rest) condition; II) factorial design, which expands the subtraction principle to two or more factors; and III) parametric design, which is used when estimating the association of the BOLD signal to a varying parameter [46].

For a better comparison, it is better that the type of stimuli, test item history, and trial duration be matched between different blocks [92]. For the tasks that are modified/electronic versions of the available cognitive tests, such as the Corsi Block-Tapping test [102], less alteration of the details is required. A task should be demanding enough to be able to stimulate the relevant areas of the brain, and at the same time, it should be simple to guarantee good performance of the subject [93]. The image should be presented so short to minimize eye movements, and still long enough for scene categorization [103]. If multiple images are presented, they should all be at the same location, to minimize the brain activations relevant to eye movements [53].

Rest blocks are located between one or a couple of act blocks, in order to have the baseline fMRI signal needed for data analysis, and also to give the subject a rest. There is no standard for the rest block; however, in visual experiments, a black cross on a white background is very popular [51]. A fixation cross in the center of the screen, when there is no stimulation, is also beneficial to reduce ocular artifact [91]. The interval between different trials is better not to be fixed and is preferred to be in a range [74]. A random timing of the trials is sometimes an approach to lower the predictability of the experiment and to increase its power. This randomness could be both for the timing

of trials, and for the Inter Trial Intervals (ITI) [96]. A proper baseline should have maximum sensitivity in the detection of brain activity related to the target function, and control as many unrelated confounds as possible [104]. "Rest" is not always an appropriate control condition, because in some occasions it interferes with the "act" block activations, such as the "inner speech" [105]. "Rest" has also been shown to result in a greater medial temporal activation than a number of alternative baseline conditions [106].

The total duration of the fMRI experiment is very different among studies; the critical point is to keep the subject in the scanner before he/she mentally or physically get tired, lose concentration, or fall asleep [51]. The number of blocks, time-points, and conditions should be designed to collect enough number of data per condition [51]. In a block-design task, at least four blocks per condition are suggested [74]. The duration of the presentation of each image should be efficiently selected; not too long to allow the subject to lose concentration, and not too short to avoid the subject of correctly doing the task. If the task is taking long, a break could be provided in between; it is better that the participant does not move during the break so that all the images be obtained from the same orientation [91], although in a few studies the subject left the scanner between sessions [93].

3.6. Instructions

The participant should be informed about the instructions of the fMRI experiment, and this could happen in three stages. I) Before the MRI day: A training session day before the scanning session is helpful, which for example could include a description of the task to the participant, and then two runs for practice, each containing a few trials [51]. In some experiments, the participant has some duties in advance, such as memorizing or practicing a list of words [60], which should be done days before the scanning. This helps ensure that the experimental protocol is clear to the subjects during the fMRI study [26]. II) Before the experiment: A practice session minutes before the scanning, or reminding the participant of the instructions, is helpful [76]. III) During the experiment: It is essential to remind the participant at the beginning of the task about the instructions; also, some tasks may have more than one

type of stimuli, and in these situations, we have to inform the participant on how to follow the task [61]. One study even provided a practice trial at the beginning of each block [81]. In some occasions, it may be required that the participant not be informed of some aspects of the experiment when for example the question of the study is relevant to the unconscious processing of information [93].

Sometimes the instruction could remain on the screen until the participant presses a button which means he/she has understood the instructions and is ready to begin the task [61]. The practice session could be repeated as many times as the subject feels necessary to be familiarized with the experiment, or until the participant shows an acceptable performance [107], such as 80% accuracy [108]. Providing the instruction is not always through a sentence; a cue which has been explained to the participant could also work [109]. In the visual tasks, the participant should be told that he/she should keep his eyes open during the task. Providing a fixation dot on the screen helps the participant to be always focused on the experiment [107]. During some tasks, such as the ones with verbal/auditory stimuli, the subject may be asked to have his eyes closed [62].

3.7. Response

Asking the participant for a response is required in some tests, as sometimes only the correctly performed trials will be analyzed; for example the trials relevant to the successfully encoded or retrieved items in a memory experiment [93]. When a response is needed from the participant, on average, make 50% of the answers correct and 50% false. For example, in a memory test, the probe stimulus was either from the initial set or was a novel image [61]. A probability of 0.5 for response switches (yes, no) is suggested [75]. Responses are not needed to be only "yes" and "no"; other options are also possible. For example, a recognition test to remember new items could have any of these four responses: 1- definitely new; 2: probably new; 3: probably old; 4: definitely old. Besides, the participant can give his answer by pressing any of the five keys on his response box, and for example, express his level of fear or anger by selecting one of the keys from 1 to 5. Responses are not always answers to a series of questions; sometimes

the participant can be asked to rate himself on his performance in the experiment [109]; only trials with a good performance could later be included in analysis [109]. In rare situations, the experiment was terminated after the error rate of the participant did fall below a predefined criterion; albeit this should be set somehow that enough number of trials be collected for data analysis [75]. A surprise test after the imaging session is also possible. This, mostly in memory tests, happens without prior knowledge of the subject, and tests the performance of the participant (for example) about 15 minutes after the fMRI session [93].

An MR-compatible response pad or joystick is needed to record the responses [62]. When the participant is giving response by pressing buttons, a neutral button press condition should also be provided to cancel the effects of motor activation [92]. Responses could be collected using five fingers of one hand, using index finger and middle finger of one hand, or using both the right and left hands [53]. The order of keys to respond to a question could change in each trial, to avoid motor anticipation related effects [73]. In a rare study, overt responses in the fMRI scanner were also recorded, using a noise canceling fiber optic microphone system [81].

Usually, there is a fixed amount of time for the participant to respond, and also, a failure to respond should not inhibit the start of the subsequent trials [53]. One study changed the duration of responses based on the type of the stimulus. For easy and difficult questions it was 6000 and 12000 ms, respectively [76]. The time required for the participant to respond was selected based on prior behavioral assessments [76]. If a participant responded earlier than the end of the interval, the next trial could begin, or the extra time could be used as a rest period [76]. When collecting responses, estimating reaction time, defined as the interval between the time of stimulus onset and the button press, would be helpful [109]. Subjects should respond fast to the questions, as the Response Time (RT) is also important, in addition to the accuracy of responses [53].

3.8. Feedback

The performance of the participant during the experiment could be provided to him/her as a feedback [61]. One study showed "correct" in green and "wrong" in red to give feedback to the participant [75], in addition to presenting his/her overall performance at the end of each block. The reasons for providing feedbacks are to help the participants increase their performance, more precisely follow the experiment, decrease their error rate, and to activate the error-monitoring system [110].

3.9. BOLD Effect

There are many fMRI techniques available, as comprehensively reviewed previously [46], but detection of the BOLD signal is the most commonly used technique due to its ease of implementation and good contrast [46]. Information transfer between neurons is metabolically demanding and this increases the oxygenated arterial blood, which leads to an increase in the MRI signal. This Hemodynamic Response (HRF) can be determined using T2* weighted MRI acquisitions, which is the basis of the BOLD signal [46]. Typically, the fMRI software packages model the HRF with a set of gamma functions, which has a gradual rise, peaks around 5-6 seconds after the stimulus, returns to baseline at 12 s, and has a small undershoot before stabilizing again, 25–30 s after [111]. Nevertheless, the variability of HRF across brain regions [112], scanning sessions [113], tasks [114], physiological modulations [115], subjects [112], and populations [116] should be considered during analysis [111].

4. Imaging

4.1. Pilot Imaging

Before the study with all subjects, it is suggested to conduct a pilot study with approximately three to five subjects. This helps to fine tune the experiment and identify the problems in the procedures, and the analysis of the pilot study data reveals some further problems of the fMRI protocol [26]. The pilot study could also be used to test whether the subtler brain effects could be uncovered, as well as in power analysis [117]. Another application would be in generalizability, which uses pilot data in test-retest reliability on the same scanner, same subject within 30 min, or different scanners on the same subject within one week [36].

Another beneficial step in pilot imaging is to run the fMRI protocol on a phantom [39]. For this, several thousand EPI images are acquired over a 10–20 mins. Period, and the mean signal within an ROI is compared among all images; the acceptable coefficient of variation for the ROI signal is 0.3% for a properly functioning MR system [39].

4.2. Preparation

The participants are usually asked to abstain from consuming drinks that act as stimulants or depressants, for several hours before the scan [91]. Using an MRI simulator scanner to acclimate the participant with the scanner environment is helpful [72]. Earplugs could be used to reduce the scanner noise, and also sufficient foam pads and tape for head motion [74]. The acoustic pads could suppress the scanner noise by 25 dB [62]. Participants usually lay in a supine position in the MR scanner [118], and a training during the pre-scan to reduce head motion is advantageous.

Since the participant may need to move his hands, e.g., to use the joystick for responding, using restraining devices should be limited. In addition, in subjects who are anxious and claustrophobic, using rigorous head restraints could be self-defeating [39]; good communication with these participants is more important than rigorous head restraint. Also, it is reported that even if the head movement is limited, the MRI shim may change when the subject moves his leg or arm, but a whole-body restraining device is not participant-friendly [39].

4.3. Presentation

The visual stimuli could be presented using an MR compatible LCD projector [53] or 3D goggles [51], standard CRT monitor [75], back projection screen near the tube aperture observed by a dual-mirror mounted on the head coil [118], or an LCD projector outside the scanner room which projects the images onto a screen located at the end of the scanner bore [90]. The refresh rate, resolution, and size of the display, as well as the distance of the display to the participant are important [107, 119].

The level of volume for auditory stimuli should be adjusted before the experiment, separately for each individual, so that the participant feel comfortable and can hear and understand the audio files against the scanner noise [61]. A few studies did set the audio levels on a fixed loudness, such as 88 dB [62], or 75 dB [82]. MR-compatible headphones [62] or form-fitting foam insert earphones [81] could be used for stimuli delivery. For nonvisual tasks, it is advised to turn off the room and magnet-bore lights, and ask the participant to close his/her eyes in order to eliminate the confounding activation of the visual cortex [39].

Psychophysics toolbox driven by MATLAB [53], MacStim psychological experimentation software [51], or the Presentation software [81] could be used to design and present the stimuli. A comprehensive list of these software tools is collected previously [46]. Sync pulses (trigger pulse) is received from the scanner [51] and helps to synchronize the onset of the stimulus presentation with the beginning of the image acquisition [90]. Wires and tubes used during stimulus presentation must pass into and out of the MRI exam room through RF filters or waveguides [39].

4.4. Imaging

Different types of MR machines, as well as different head coils, are being used. A higher Tesla of the scanner and a higher number of channels for the head coil are preferred. Since the BOLD effect increases in higher B0 fields, there is interest to perform fMRI studies in 3–4 T magnets [39]. The MR sequences also vary between studies; their details will not be discussed here, but mostly a fast spin echo sequence [53], single-shot T2*-weighted gradient echo spiral pulse sequence [120], multi-slice Echo-Planar Imaging (EPI) with a gradient echo EPI sequence [51], or half Fourier acquisition single-shot TSE (mHASTE) sequence [121] are used.

Gradient Echo-Echo Planar Imaging (GE-EPI) is the most commonly used technique for BOLD fMRI, due to its high data acquisition efficiency, high sensitivity to T2* effects, and low specific absorption rate [121]. However, GE-EPI signal is sensitive to the T2* changes in and around veins as well [122], which lead to a mismatch between the observed BOLD signal and the actual neuronal activities, and this reduces the specificity of function localization [122].

To concur this problem, EPI based on spin echoes (SE) is suggested [121]. The benefits of SE-EPI for

function localization is enhanced at high fields ($\geq$ 3T) [123], and this protocol is insensitive to through-plane susceptibility gradients which results in signal voids [121]. The SE-EPI suffers from in-plane distortions, and as a result, Turbo Spin Echo (TSE) methods are suggested for fMRI [121].

It is better that the sequence be insensitive to cardiac pulsatility motion [124], the whole brain be covered [53], have sufficient temporal and spatial resolution, be sensitive to T2* changes, detect the smallest BOLD effect [125], and the images be collected in the anterior commissure-posterior commissure plane [51]. A few important parameters of a pulse sequence include Repetition Time (TR: shorter than the hemodynamic response function is preferred, typically 1-4 sec), Echo Time (TE: the best value is near the T2* of the tissue, typically 30-35 ms), Slice Thickness (low signal-to-noise ratio when this is too thin, and partial volume artifact when this is so thick, typically 2-4 mm), Slice Order (typically interleaved), and Matrix Size (a higher matrix size has a better spatial resolution, but it increases the imaging time and reduces signal-to-noise). More details about sequences are provided in previous reports [126–128].

Prior to the functional scans, structural T1-weighted anatomical images are usually obtained, for co-registration of the functional images, and also to check any abnormalities in the brain [62]. It is advantageous to acquire a three-dimensional dataset with isotropic voxels [39].

4.5. Physiologic Measures

Physiological respiratory waveform recorded using the bellows [62], the cardiac pulsation recorded using the photoplethysmograph device [62], and the skin conductance response [80] are recorded in order to remove their nuisance effects from the fMRI time-series data [129].

5. Preprocessing

Pre-processing steps are performed on the fMRI data before the analysis, due to multiple reasons: the fMRI signal is very noisy; the BOLD signal represents a relatively small percentage of the variance of the signal [38]; non-neuronal confounds contribute to the BOLD signal, including thermal noise, instrumental drifts, artefactual signals, as well as a multitude of physiological fluctuations such as head motion, cardiac and respiratory noise, changes in arterial CO2 concentration, vasomotion effects, and changes in blood pressure and cerebral autoregulation mechanisms [38].

1) Quality Check: The functional images should be screened for artifacts or large motion [130]. The first quality control point is during the acquisition phase. It is important to visually check the images on the display of the MRI console, to repeat the acquisition if the data has some obvious artifacts, or in search of any brain abnormality [131]; using two different contrast settings, including standard anatomical and background noise contrast is an appropriate strategy here [46]. Several studies have proposed methods to check the quality of fMRI scans [132, 133], such as creating the plot of scans [134].

2) Data convert: The original scanner data format (dicom) should be converted to the format used by fMRI processing tools (e.g., nifty) [46]. In NIfTI most of the DICOM header information is discarded and only basic information is kept. Several packages perform this conversion: dcm2nii, MRIConvert, and NiBabel, as introduced previously [46].

3) Delete volumes: Sometimes the first few volumes of the fMRI data are discarded, such as the first 2[107], 3[118], 4[80], or 10 volumes [62], or the first 12 seconds [94] of the fMRI volumes, to avoid transient signal changes due to unstable brain magnetization at the beginning of the scan.

4) Slice timing correction: Between-slice timing differences are corrected in the "slice timing correction" step, to correct each voxel's time series. Usually several slices are acquired from the whole brain in either of the ascending, descending, or interleaved slice acquisition, and therefore the adjacent slices may be acquired at different times. Slice-timing compensates for these effects and increases the robustness of the data analysis [135]. This step needs a reference slice which is usually the slice acquired in the middle of the sequence, but any slice can be used.

5) Intensity normalization: it involves setting the mean values of all voxels by the same factor, and to a predefined level such as 100 [80].

6) Non-brain removal: it is applied to the structural scans [136] so that both the structural and functional images involve the same types of brain tissue.

7) Motion correction: Head movements influence the quality of the fMRI signal, particularly when the head motion is correlated with experimental tasks [38]. It challenges the interpretation of functional connectivity studies, as for instance it is reported that motion adds more spurious variance to the nearby voxels than between distant voxels, causing distance-dependent modulation of signal correlations [38].

For correcting the fMRI data for the possible motion artifacts, the data are realigned to the first [61], fifth [137], or the middle volume of the fMRI series [51]. This realignment, for example, could be performed using a 6-parameter rigid body motion correction procedure [61]. Head motion is a rigid process and thus, an affine transformation, including 6 directional parameters, is sufficient [38]. Slice-wise motion correction approaches are also introduced for compensating within-volume motion [138].

It is noticeable that this process cannot correct the data as if there was no motion [38]; therefore, the remaining motion-related signal changes should also be corrected. The most common approach for this is to include the time-series of the 6 estimated realignment parameters as nuisance regressors in the GLM model [38]. Several studies have provided precise guidelines for fMRI data motion correction [38, 139, 140].

8) Smoothing: As functional anatomy differs between subjects, smoothing helps to overcome the spatial variance. A spatial Gaussian filter is usually applied to the fMRI data to spatially smooth it, using an 8-mm [141] or 5-mm [53] isotropic Gaussian kernel, depending on the voxel size of the images. This step is helpful to optimize the signal to noise ratio of the scans, by removing high spatial frequencies.

9) Filtering: High pass temporal filtering is also applied to remove the noise associated with low frequency confounds (e.g., respiratory artifact) [94], and to compensate for the slow fMRI signal drift [107]. A cut-off period of 50s for this is an example [51]. A notch filter (at the Nyquist frequency) is similarly helpful to remove the noise associated with the alternations of the applied radio frequency field [94].

10) Registration: Finally, the coregistration step is applied. First; anatomical and functional images are co-registered together. It could be the structural scan to be registered onto to the mean motion-corrected functional image [53], or more usually, the EPI data to be registered to the structural scans [51]. Second; both the anatomical and functional images are spatially normalized to a standard stereotactic space. The space could be the Montreal Neurological Institute (MNI) template or a study-specific group template [81]. For this, the structural image is first co-registered to the standard space, and then the transformation parameters obtained from this step are applied to the functional slices [60].

11) Denoising: Despite correcting data for head movements, the effects of blood pulsatility and respiration exist in the fMRI signal. Cardiac pulsatility generates small movements in the brain, and its associated noise is localized close to large arteries and draining veins, as well as in the edges of the brain and sulci [142]. In addition, the thoracic movements associated with breathing changes the magnetic field of the head, which changes the phase of the MR images [143]. Furthermore, both cardiac pulsations and respiratory cycles cause bulk motion of brain regions, such as the diencephalon or the brainstem [144]. Multiple methods and approaches are introduced for such denoising [38]. Another source of noise is a near linear drift in the MR signal during the course of a study, which could originate from the heating of RF and gradient coils during an extended pulse sequence. Linear baseline drifts can be incorporated in the GLM model and be effectively diminished [39].

6. Statistical Analysis

6.1. Packages

The statistical analysis of fMRI time-series is carried out using different packages, mainly including SPM (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm), FSL [FMRIB Software Library;

https://fsl.fmrib.ox.ac.uk/fsldownloads_registration], and AFNI [Analysis of Functional NeuroImages; https://afni.nimh.nih.gov/]. In previous studies, several fMRI software tools have been introduced, and they have been evaluated in terms of the functionality and features [46, 145].

6.2. GLM Model

General linear model (GLM) is the most used approach to analyze fMRI data [146], which models the effects of interest and other confounding effects (e.g., head movement and magnetic field drift) in the time-series. It is performed on the preprocessed data, and all data in a study are better to be similarly analyzed. GLM convolves a canonical hemodynamic response function (HRF; a gamma variate function) to the paradigm of onsets of the conditions in a stimulus; the paradigm is a set of square wave functions of width equal to the duration of the block [62]. This step provides the regressors needed for data analysis, and the GLM fits them to the data.

In GLM, the aim is to estimate to what extent a predictor contributes in each voxel's time-series [147]; however, there are many critiques on the application of GLM for fMRI data [147]. The main reason is the GLM method being relied on a number of assumptions, which may not be valid: I) errors are independently distributed; II) the regressors in the X matrix are independent of error and are non-stochastic; and III) no regressor is a linear transformation of one (or more) other regressors [147]. Multivariate techniques are introduced to identify the specific information each brain region includes [148].

6.3. Regressors

Separate regressors are usually defined for the conditions of interest [51], and a different activation map is produced for each condition/regressor versus baseline [62]. The baseline is the periods of the data that are not explicitly modelled [93]. The contrasts between different conditions are also tested. The boxcars should be prepared based on the stimulus design; however, some studies consider a 3-second delay period at the beginning of each condition to avoid an overlap with the previous condition's BOLD activity [149]. In few occasions, all conditions were

combined into a single GLM analysis to increase the statistical power [93] and the efficiency of the model [118].

Sometimes several regressors are added to the analysis to account for variances due to baseline shifts between time series, linear drifts within the time series, and head motion [90]. One of the most important ones is the motion, as head motion-related artifacts may contaminate results even after volume realignment [73]. The effect of head motion is usually regressed out by including the realignment parameters estimated at the preprocessing stage in the GLM model, and one study considered all the 24 motion regressors in the analysis [73].

The values of the resulting maps of the GLM analysis are expressed as statistical t-values for each voxel [74], representing the correlation of the fMRI signal to the regressors. These parametric maps are better to be overlaid on the structural images of the individuals to visualize the areas of brain activation [79]. The active brain areas could be identified using standard atlases and labels [150].

6.4. Thresholding

Different criteria are selected to threshold the activation clusters, including Z-score>1.7 [51], Z-scores >2.3 [93], t-value >5 [108], or an uncorrected statistical threshold of 0.005 [80]. The size of the activation cluster is another criterion. In order to improve the selectivity of fMRI, and to minimize the contribution of the voxels contaminated by artifacts, a cluster criterion can be applied to the fMRI results [39]. In studies, the minimum cluster sizes were considered as 20 voxels [137], 10 voxels [118], 5 voxels [80], or even 3 voxels for smaller brain structures such as amygdale [80]. One study did set the minimum cluster size as 1, to include all activations [79].

6.5. Multiple Comparison

Correcting the statistical images for multiple comparisons is a necessary step in the fMRI analysis. Since there are thousands of voxels in the whole brain, type-I error is very probable to occur. To control the false positives, the analyses should be corrected for family-wise error, using the methods such as

Bonferroni correction or False Discovery Rate (FDR). They are used to account for the multiple comparisons across voxels. Family Wise Error (FWE) correction method with P<0.05 [79], or the False Discovery Rate (FDR) method [151] with P<0.05 [81], on a voxel wise basis, are used to correct the maps. The multiple comparisons could be limited to the grey matter voxels to reduce the number of comparisons [152, 153]. An alpha threshold of p<0.05 is stringent, especially when coupled with cluster-size thresholding. There are also other ways to apply the correction, such as using experiment-wise error rate or non-parametric procedures [154].

6.6. Longitudinal Analysis

The major feature of a longitudinal data is that each subject's responses are repeatedly measured, enabling study of changes over time. The longitudinal approach has a good power, each subject serves as his/her own control, and it separates the aging effects from cohort effects. The fundamental objective of a longitudinal analysis is therefore to assess within-individual changes. A previous study has reviewed all the necessary information about a longitudinal fMRI experiment [40].

6.7. Covariates

Sometimes the question is about the association of a factor (e.g., memory performance) with brain activations. One method of doing this is to define separate contrasts for each type of condition versus baseline and then compare those contrasts [102]. By this, the factor of interest is considered as a covariate in the analysis. In another method, the beta values (which represent BOLD signal changes for the particular conditions of interest) from different contrasts and for the brain areas of interest are extracted separately for each individual, and then, along with the covariates, are inserted in a repeated measures ANOVA test [102]. ANOVA is mostly used for this type of analysis, in particular for a pairwise comparison of conditions [107]. The significant t-values estimated for an association could be either positive or negative, signifying the increment or decrement of the brain activations with increasing the considered factor, respectively [53]. Both linear and nonlinear relationships are tested [155], and the

unsuccessful trials could be included as covariates of no interest [155].

6.8. Signal Change

Signal change is a measure for the extent of activation in a brain area [109] and is the average percentage of changes of fMRI signal relative to baseline. It is usually performed in brain regions where a significant activation has been observed [62], separately for each component event and each condition [130], and in the peak voxel, or in an ROI [62].

To estimate the signal change, the time-series of each voxel is divided by its mean intensity [107], or by the intensity of the activity measured at the first time point of that trial [90], to convert the data units to fractional signal change. This step is also to prevent differences in mean signal across voxels and conditions to influence the results [61], and also helps in averaging the time-series among the participants [90]. The peak percent signal change is defined as the peak activity in the averaged time course across all conditions and participants [156].

The relationship between the signal change and the target factors could also be tested, for example using the Pearson r correlation [62]. The Marsbar software is usually used for signal change estimations [103], and a few previous studies have provided clear instructions on how to calculate the percent signal change [157].

6.9. ROI Analysis

In some studies, identifying activation in the whole brain level is not an aim, and there is a clear idea on investigating activations in particular brain regions [93]. The idea may come from a priori hypotheses or reports [118], or the area of interest may have shown activations in the whole brain analysis [107]. As a result, the ROIs of brain areas are used either to study brain activation only in the areas of interest [93] or to do further tests on the activation of the ROIs, such as studying its association with a covariate [130].

ROI analysis focuses on certain brain areas and is more precise as it is not affected by spurious activations in unrelated brain areas [158]. This

analysis is also used to limit corrections for multiple comparisons to a smaller set of voxels, as opposed to the whole brain. There are different approaches for creating masks. In the first approach, the ROIs are made based on anatomical information, mostly in the native space [61]. These include making masks by hand-drawing of the ROIs using published guidelines [109]; extracting the ROIs from standard templates, such as the Automated Anatomical Labelling (AAL) atlas [150], or the Harvard–Oxford atlas [81]; or creating masks in the native space using cortical reconstruction, volumetric segmentation and parcellation methods, for example using the Freesurfer image analysis suite (https://surfer.nmr.mgh.harvard.edu/) [119].

The second approach for creating masks is based on the functional results. Different methods are suggested for this, such as selecting the cluster of 40 contiguous voxels exhibiting the highest t-values from the contrast of interest [61]; selecting the ROIs of activation in the group analysis, reverse normalize (using each subject's inverse MNI to native EPI space transformation) it to the native space, and finding the top-10 statistically significant contiguous voxels within the resulting search space masks for each subject [81]; and using the local-maximum voxel (at the group level) of the contrast as the center of a 5-mm radius sphere, and averaging the time series of the significantly activated voxels ($p < 0.05$) within the sphere [80]. The radius of the sphere is also suggested to be 10 mm [81], 8 mm [103], or 4 mm [93].

The third approach is based on the localizer task, which is beneficial for identifying the brain regions involved in the function of interest [61]. The localizer task is usually performed before the main experiment [61], or rarely after it [103].

It is suggested that the brain areas (ROIs) that have a different pattern of functional and structural connectivity be separated and not be involved in a single ROI; an example includes the anterior and posterior IFG [81]. Finally, the results obtained here also need a multiple comparisons correction. The approaches to define ROIs, as well as the strengths and assumptions of each method, are described in a previous report [158].

## 7. Interpreting and Reporting the Results

according to other related studies in the literature. There is a wealth of knowledge on brain functionality in the literature, which enables identifying the differences and similarities of the results with previous findings [26]. However, a few points should be in mind when making inferences of the fMRI results. First, the voxel-wise analysis of the fMRI data is statistical in nature, and therefore a definite statement about the name of the brain region being active should be avoided [26]. Second, the fMRI results should not be interpreted with a strong causal language. Third, given the nature of the BOLD effect, the alternative possible explanations of the findings could not be neglected.

Reporting the methodology and results of fMRI studies does have standard rules. There are many details in such studies which should be precisely reported if the study aims to be replicable. The demand for reproducibility is increasing in scientific research [159]. The lack of methodological details may also have negative effects on the assessment of a report [39]. The results should also be sufficient, so that the reader has a good understanding of the study. A study which evaluated the reporting of methodological choices across 241 fMRI articles illustrated that many fMRI studies do not report critical methodological details with regard to experimental design, data acquisition, and analysis [160]. There are comprehensive studies on how to report the fMRI methods and results [26, 161]. There may also be particular rules in a journal for reporting the methods and results of a study [162].

8. Conclusion

There are suggestions on the future directions of fMRI [163–165], which show that this method will still help us in the future for better understanding the mechanisms of the brain functionality, and in diagnosing diseases. As a result, in this manuscript some of the significant points for performing an ideal fMRI experiment were collected. There is no claim that all the necessary information are provided here; many of the details are missing, which could be found

in other reports. In addition, resting-state fMRI, functional and effective connectivity analyses, as well as the more sophisticated statistical approaches for data analysis are not covered here. Furthermore, only around one-hundred papers were summarized here, including a larger number of papers would enrich more the manuscript. Despite all, this study has provided over 300 tips on designing and running an fMRI experiment and performing the data analysis, and could be a help for the researchers who want to start using fMRI in their research. Preparing similar guidelines for other imaging methods and other modalities would also be helpful.
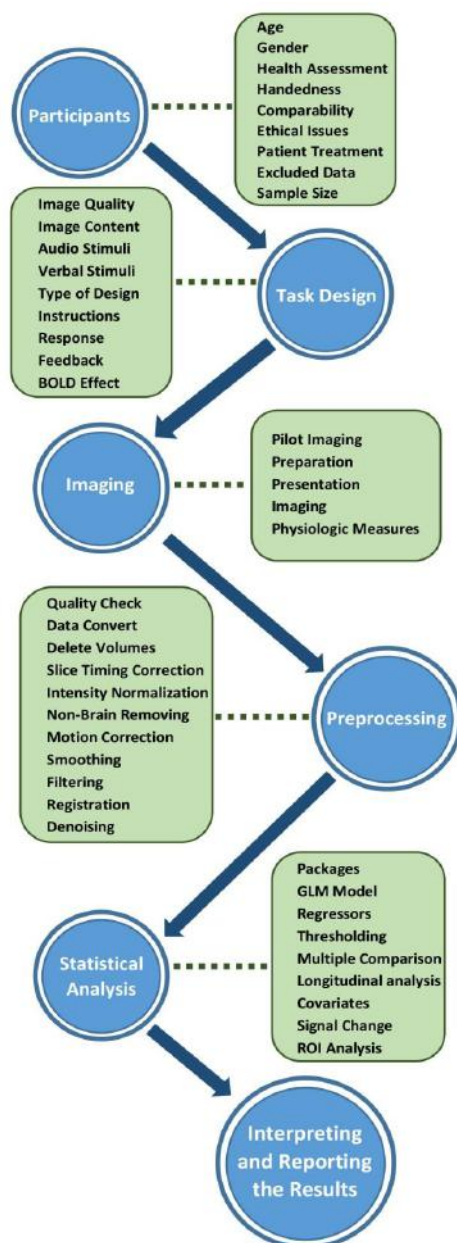
Figure 1. The outline of the procedures for an fMRI study experiment design and data analysis

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