Faculty of Sciences

Design Optimization in fMRI studies

Sanne Roels

Master dissertation submitted
to obtain the degree of
MASTER OF STATISTICAL DATA ANALYSIS

Promoters:
dr. Tom Loeys
Prof. dr. Beatrijs Moerkerke

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This master in statistical data analysis program was, it must be said, pretty demanding. Having spent numerous evenings in the spare light of my desk spot making reports for the continuing stream of homeworks, working on this thesis, studying, ... I nevertheless have to admit I have appreciated the experience. Throughout this foreword I want to show my appreciation to several people whom I’m very grateful to, especially with regard to this master dissertation.

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# Contents

**Foreword**  

**Abstract**  

## 1 Introduction

1.1 In the Magnetic Resonance Imaging (MRI) scanner  
   1.1.1 The origin of the functional MRI data: from magnet to image  
   1.1.2 The experimental setting  

1.2 Analysis of fMRI data  
   1.2.1 The data structure  
   1.2.2 Pre-processing  
   1.2.3 Inference  

1.3 Design optimization  

1.4 An introduction to the datasets:  
   1.4.1 Blocked design: Van Opstal, Verguts, Orban, & Fias [2008]  
   1.4.2 Event-related design: Santens, Roggeman, Fias, & Verguts [2010]  

1.5 Research Goals  

## 2 Method

2.1 General formulation of the optimality-criteria  
   2.1.1 Detailed Statistical model of fMRI data  
   2.1.2 c-Optimality: minimal variance of the contrasts of interest  
   2.1.3 Factors excluded from the optimization  

2.2 Design matrix and statistical model of Van Opstal et al. [2008] and Santens et al. [2010]  

2.3 Implementation of design optimization in Van Opstal et al. [2008] and Santens et al. [2010]  
   2.3.1 Design optimization of Van Opstal et al. [2008]  
   2.3.2 Design optimization of event-related designs  
   2.3.3 Design optimization of Santens et al. [2010]  

## 3 Results

3.1 The design of Van Opstal et al. [2008]  
   3.1.1 Efficiency original design  
   3.1.2 5 Suboptimal Designs for 3 situations in the learning phase  
   3.1.3 Application of the High-Pass filter in the suboptimal designs  


Abstract

Functional magnetic resonance imaging is a widely-used non-invasive technique for measuring brain activity in cognitive neurosciences. Brain activation gets detected by changes in the blood oxygen level because oxygenated and desoxygenated blood have different magnetic properties. By relating the activated brain regions to specific task components of cognitive experiments, brain regions are attributed functions. The aim of this master dissertation is to improve the designs of 2 studies conducted at the department of experimental psychology of Ghent university. By improving the design unwanted design related variability can be kept out the analyses.

In the Introduction the mechanisms of the scanner are sketched. The experimental setting is further also described in order to clearly define what happens while scanning. Additionally, the steps in the analysis of fMRI data are outlined: the data structure, the pre-processing steps and the inferential framework. The data are both temporally and spatially complex, that is why the preprocessing steps have to be conducted. These steps allow the data to be validly analysed. Additionally the importance of design optimization is argumented, as more optimal designs result in less unwanted variance. Next the two datasets used for the optimization of the designs are highlighted (i.e.: Van Opstal, Verguts, Orban, & Fias, 2008; Santens, Roggeman, Fias, & Verguts, 2010). Throughout the Method the exact implementation of the search for optimal design is worked out.

The two considered studies are of the two most common design types in the neuro-imaging literature: a blocked design and an event-related design. As such we aimed to cover the optimization for the most frequently used design types. Design efficiency was determined based on the contrasts of interest, since these are typically of major importance in the studies. By means of the c-optimality criterion and by a clearly defined protocol we investigated whether is was possible to find more efficient designs. Furthermore as the search for optimal event-related design is complex, we opted for a Genetic Algorithm search algorithm (Kao, Mandal, Lazar, & Stufken, 2009).

We found that for both design more efficient designs could be determined. By changing some of the design parameters we found large increases in the efficiency. These are presented in the Results Section. The more optimal designs and the search for the optimal designs are discussed.
1 Introduction

For most cognitive neuro-scientific studies the goal is to map cognitive activities (from perception over motor control to thinking processes) onto particular brain areas. A very widespread method to perform this brain localization is called functional Magnetic Resonance Imaging (fMRI), for which a study has to be set up and a choice between available design types has to be made.

Throughout this introduction, in the first part we will focus on what happens in the scanner. Two issues are covered: the scanning procedure and the experimental settings for the cognitive experimental tasks.

In the second part we will focus shortly on what happens after the scanning. The data structure, data pre-processing and the inferential framework will be outlined.

Next, we will focus on the importance of the optimization of design. In the fourth part of this introduction, we focus on the two datasets that will further be used for optimization. Finally, in the last part, the research question will be phrased explicitly.

1.1 In the Magnetic Resonance Imaging (MRI) scanner

For the purpose of design optimization, in the MRI scanner two simultaneous events are of major importance. There is the registration of the data and the occurrence of cognitive activity. Firstly, the accurate registration of fMRI data is both complex and time-intensive. The first part of this section is meant to give some basic insights in the process of data-sampling. Some restrictions due to the apparatus show up here and impact the feasibility of the study design. Secondly, the nature of the experimental procedure is explained. It will become clear that a balance has to be found while scanning.

1.1.1 The origin of the functional MRI data: from magnet to image

Basic principles underlying MRI Magnetic Resonance Imaging (MRI) is a widely-used non-invasive medical imaging technique. It allows physicians to visualise several anatomical structures and properties of human tissue (e.g. fat tissue, fluid, ...) that are invisible for the naked eye by employing magnetic properties. Patients are put in a large scanner like Figure 1. This scanner consists of a massive magnet with a strength many times stronger than the natural magnetic field of the earth. In this way the magnetic properties of different types of tissue can be extracted. From these magnetic properties images can be constructed.

A clear differentiation between MRI and fMRI should be made from the beginning of this section. Typically in MRI, especially in medical contexts, the objective is to have accurate anatomical scans in order to determine whether there is an indication for a kind of abnormal-
ity. The transformation from MRI into functional MRI implies that the main objective shifts. In the latter case the main objective is to map brain activation related to cognitive activity. This brain localization process consists of an analysis based on functional images. A whole analysis process precedes the conclusions. It is however crucial to start with the principles underlying MRI.

![Figure 1: 3T MRI scanner -Siemens Trio (Tim)- of the Ghent University Hospital.](image)

**From the magnet and collecting the signal ...** MRI relies on physical properties of atoms, more exactly their spin. These atoms (more precisely protons) show a natural random spin. This is called *precessing* and can be seen as the spinning of a *gyroscope*. More interestingly is, however, the behaviour of these atoms when brought in the MRI-scanner. A comparison that is often made is that these behave, when the scanner magnet is activated, like a *compass needle*: i.e. they will align in the external magnetic field induced by the scanner. During this external magnetisation the spinning occurs around the induced magnetic field vector. The presence (and the amount) of protons is then detected by the use of *resonance frequency*. During a short period, by an electromagnetic wave with the resonance frequency (i.e. an RF pulse) the protons are tilted. If protons are tilted they emit, while going back to their (external aligned) initial position, a signal that can be detected. This phenomenon can be compared with an FM radio, tuned to a specific frequency. During a short period, by an electromagnetic wave with the resonance frequency (i.e. an RF pulse) the protons are tilted. If protons are tilted they emit, while going back to their (external aligned) initial position, a signal that can be detected. This phenomenon can be compared with an FM radio, tuned to a specific frequency. However, by the sole detection of the atoms no image can be constructed since spatial information is needed in 3 dimensions. The positioning is done by a frequency analysis (Fourier transformation) of the signal spectrum after the initial pulse in several gradients. By combining a read gradient (for the x-direction: left/right), a phase encoding gradient (for the y-direction: anterior/posterior) and a slice
selective gradient (for the z-direction: superior/inferior) a 3D image is constructed after the signal analysis. Of course these signals have to be detected by a receiver which is also part of the scanner, the RF coils. More details about this procedure can be found in Deichmann et al. (e.g. 2010, p.40-43). The intensities at a pixel (a 2D graphical element) are furthermore proportional to the number of protons in the voxel (a 3D graphical element) (Lazar, 2008a).

In medical contexts, because the $^1\text{H}$ isotope of hydrogen is abundantly present in human tissue, images are very often based on these isotopes (Lazar, 2008a). A last remark concerns the fact that any other proton can be used for the purpose of imaging. The feasibility will, however, depend on the properties of these protons.

... over $T_1$, $T_2$ and $T^\star_2$ ... Recall from the previous section that RF pulses take place. These pulses are non-constant: after a pulse, there is time at which no additional energy is induced. During this period protons start to relax. Protons then stop precessing and get aligned again in the magnetic field induced by the scanner. There are three times related to this relaxation period (Lazar, 2008a): $T_1$, $T_2$ and $T^\star_2$. $T_1$ is the relaxation time related to the z-axis. This is the time it takes to get the longitudinal part of the magnetization vector relaxed. After $T_1$ there is no longer movement of the protons previously made active by the gradient pulse of the z-axis. $T_2$ is the relaxation time related to the transverse (x-y plane) component of the magnetization vector. After $T_2$ there is no longer movement of the protons previously made active by the gradient pulse in the transverse plane. In order to explain $T^\star_2$ a short sidestep needs to be made to focus on gradient echoes. If after an initial decay of the precessing after the RF-pulse an inverse RF-pulse is given, in e.g. the x-axis, the precessing signal will build up again. The exact mechanism behind this can be found in (Deichmann et al., 2010, p. 44-45). The time after which the proton’s activation decays again (after this gradient echo pulsation) is called the effective $T^\star_2$ relaxation time. Furthermore, $T^\star_2$ will be considerably shorter than $T_2$. The time difference between the start of the RF pulse and the center of the gradient echo is denoted as TE (echo time). A logical consequence of a short TE that there is only little time for despinning so there will be little information gained. Too long TE’s are on not good either since the signal to noise ratio will be poor.

in most cases using Echo Planar Imaging (EPI) ... EPI is a method of RF-pulse planning in the transverse plane. This is nicely described in Lazar (2008b) (p. 23) as the boustrophedonic pattern (literally translated as "the oxen turns while plowing") of filling in the image space. As a consequence the image is filled up going from left to right, to left, to right. Since every transverse plane has to be taken fast to jump to the next slice (on the z-axis), images are usually of lower spatial quality. Typically 64x64 or 128x128 voxels are
registered per slice. A single image (i.e. a slice), using this procedure can be obtained in 30-50 ms. A whole brain volume can be scanned in 2-4 s. Here the slice thickness will determine the time to complete a volume. This duration is closely related to the time to repetition (TR), an indication of the time it takes to start the pulsation for a new volume. This is thus the time it takes between the data gathering of two brain volumes. As the TR increases there is more time for relaxation but it limits clearly the opportunities for rapid tasks. This is clearly a limitation with which designs have to cope properly.

through the Blood-oxygen-level dependence (BOLD) signal ... The above procedure has been quite general. For the purpose of fMRI, i.e. the detection of task-related brain activity, a method of brain activation had to be developed such that a measure of cognitive activation could be related to brain activation. In the 1990s it was discovered that oxygenated blood and deoxygenated blood consist of different magnetic properties, detectable in the MRI scanner \cite{Ogawa90}. The technique to do this is based on changes in the blood-oxygen level, hence its name: Blood Oxygen Level Dependent (BOLD) signal changes. The exact relation of this phenomenon with neural activation is not entirely known \cite{Logothetis01}. It should thus be stressed that this is no direct measure of neural or brain activity \cite{Lazar08}. While conducting fMRI studies, one has to bear in mind that the mapping is based on an indirect measure. Nevertheless, it is one of the most popular methods used in cognitive neurosciences \cite{Maus10}.

and the Hemodynamic Response Function (HRF)... The HRF is a pattern that describes the expected changes in cerebral blood flow (CBF) and hence in BOLD changes since oxygenated blood is delivered by an increased blood flow. Stimulus-induces brain activation has no linear relation with BOLD signal changes. Because of the modelling of this relation, we are able to describe the relation between cognitive activity (induced by a cognitive task) and something that can be detected in the scanner. The shape of the HRF is described as: 1) a small initial dip, 2) a peak around 5-6s; 3) an undershoot around 15 s and 4) at last after 30s the baseline level is again achieved. The course is presented in Figure 2. This figure is denoted as the canonical HRF. The exact shape of the HRF (within regions, subjects, . . . ) is of debate. Some studies aim to determine first the exact HRF course and use this information for the determination of the activation (see e.g. \cite{Henson07} for some techniques to model the HRF). Although it allows for more precision, it is common practice to use the canonical HRF.
... to the final image. Typically two types of images are taken. One anatomical image (high spatial resolution) that rely on the properties of the $^1$H atoms. Besides this, several functional images are taken. These are taken using the EPI. These rely on the above mentioned magnetic characteristics of (de)oxygenated blood. These images are typically of lower spatial resolution. Although this is a drawback of fMRI, techniques are developed to circumvent the low resolution and gain back some spatial information. They nevertheless allow for a faster image acquisition.

Summary of the imaging procedure In short, we have subjects lying in a scanner waiting to perform a task that aims to gain more insight in the relation between the cognitive functioning and the localisation in the brain. Because of the magnet and the RF pulsations we are able to measure and locate the brain activation by exploiting magnetic characteristics of oxygenated blood. This enables us to make graphical representations of brain activation. Of course there are parameters/ settings inherent to the apparatus that put restrictions: amongst other factors the slice thickness and resolution of the functional images. At this cost there is however a temporal gain. Because of the temporal gain, brain activation measurements can be related to the execution of relatively fast psychological tasks. In the next section the experimental procedure of such tasks is outlined in more detail.

1.1.2 The experimental setting

Using a metaphor, the previous section described the camera. Of course, a movie without action (in a broad sense) would be, from a functional point of view, a rather boring movie. Through the experimental setting, the movies (and thus the brains) get animated. The camera
of the previous part registers the action.

While creating a difference between MRI and fMRI, the trade-off between spatial resolution and speed was mentioned. Although it can be considered as a great loss that lots of scans are preferred above anatomical precision, in cognitive experiments, timing is crucial. The importance of time in these experiments arises from both well-known behavioural computer tasks and processes inherent to the human being (such as boredom, fatigue, ...). This is the point where an equilibrium has to be found between two extremes: on the one hand no time restrictions and slow (but anatomically perfect) scans and on the other hand being able to set whatever time restriction and fast (but anatomically poor) scans. Fortunately, the EPI-scanning procedure allows for balance. Relatively fast scanning at a reasonable price (defined by the sampling rate of the TR). Cognitive experiments can thus be built around this basic architecture. Of course, as the TR decreases, fewer restrictions occur. As the TR increases, some constraints have to be kept in mind. So, a first criterion for an optimal in-scanner experiment is a good combination between the machinery and the experimental procedure, which will be the topic of this section.

The experimental procedure coincides in most cases with the design. It can however be distinct in one aspect. Not every aspect in the experimental procedure is planned, contrary to a design. For the sake of clarity, we first define the notion of experimental procedure. We denote it as the moment at which the task starts till its end. It thus also consists of the response registration. This is important since it can make a difference if subjects have to respond to the task or not. It can e.g. induce additional individual variability, difference in time in the scanner while being in a certain condition. As the response might be the indication of the end of a cognitive process, the process terminates at the response and not at the foreseen time. Furthermore, sometimes only correct response to tasks are further analysed.

Most behavioural cognitive psychological experimental settings have conditions so that contrasting the conditions results in sensible theoretical conclusions. E.g. subjects might have to determine on a computer screen whether a square is green or red in the presence/absence of a pain inducing stimulus. From the analysis of some kind of behavioural measure (e.g. reaction time, pain intensity, ...) sensible conclusions about pain perception in relation to a simple cognitive task (i.e. colour determination) can be drawn. This task can be executed while only behavioural measures are taken, but this can also be executed in the above-mentioned scanner. By using the BOLD-signal changes an additional response can be measured: brain activity.

Since the main focus of fMRI research is the detection of task-related brain activation, one needs to relate these differences between the conditions to differential –if there is any– brain activation. This is often done by using the pure insertion assumption (Henson 2007, p. ...
193). According to this assumption conditions can be created in such a way that they only differ in one (crucial) property. Consequently, by contrasting the activation elicited by these two conditions, this will result in active region(s) that are related solely to the differentiating property. As such, unique regions can be determined. This can simply be seen as a subtraction of conditions (e.g. AB – A = B). This reasoning is not without criticism because two regions that are in theory \textit{contrastable} are in practice not always contrastable or separable or vice versa (see e.g. Henson, 2005).

Besides the strategy to detect brain activation by relative changes between tasks, task activation can also be detected by comparing gradual or non-linear changes across a series of trials or tasks (see e.g. Buckner & Logan, 2006). The implication of both strategies (the pure insertion approach and the gradual changes approach) is however that there is no absolute measure of brain activity. This urges thus for an optimal design in order to compare (and discriminate) two tasks/conditions/. . . as optimal as possible.

**Design types** Roughly speaking, there are two main design types, making a classification straightforward and worth mentioning: the blocked design and the event-related design. Besides these main types some less-used design types occur in the literature (for an overview see: Amaro & Barker, 2006). The two broad classes will be discussed in the next two paragraphs. It should be noted that in most cases it is assumed that the pure insertion assumption strategy can be applied validly. Sensible contrasts can thus be extrapolated to theoretical conclusions.

**Blocked design** A predecessor (in temporal terms) of fMRI studies is PET (Positron Emission Topography), an invasive method to determine brain activation. Because of temporal limitations of this method, blocked designs were mostly preferred. Blocked fMRI designs are characterized by conditions that endure rather long periods. These blocks could be an enduring state or the repeated presentation trials of a condition. Blocks of several conditions are interchanged. In its most simple form (i.e. the situation with only two conditions), a blocked design can be seen as a binary situation, i.e. either the condition is on or the condition is off. This is why this design is sometimes described by a box-car function. This design type can of course be extended to situations where more than two blocks are desired or necessary. Its simplest form is graphically presented in the left panel of Figure 3. In the upper left panel one can see that the condition is on during the interval between 2 and 3 and from 4 on. The same base structure is shown in the upper middle panel. There it is however the continuous presentation of a trial of a certain condition. Because of the earlier described non-linear relation between cognitive activity and the BOLD signal, the stimulus function is convoluted with the HRF (see Figure 2) in order to show the pattern of the expected BOLD
Although this design type might seem suboptimal because of the slow transitions between conditions, for certain psychological experiments this method is appropriate. This is illustrated in one of the studies used in this master dissertation, the study of Van Opstal et al. (2008). In that study different stages in a learning process were compared. The study is explained further in more detail (see 1.4.1).

![Trial course for 2 blocked and event-related designs.](image)

**Event-related design** The basic principle underlying event-related fMRI designs is very simple: one looks for stimulus-induced activity. Here the stimulus can be seen as e.g. the onset of a condition or the beginning of task. The distinctive feature of this design is that it permits to relate changes in the BOLD signal to specific stimuli/trials/events contrary to the blocked designs where the activation is related to a longer time period. Since the relation between the stimulus and the BOLD-signal is known or can be estimated, one can declare regions or voxels active if there is an increased activity on moments predicted to be active. This is what is described in the right panel of [Figure 3](image). In the lower right panel the convoluted consequence of the trials is shown.

As mentioned before, fMRI offers more temporal flexibility (albeit not unlimited) than PET. Additionally, with fMRI a more precise estimation of the HRF can be obtained. Although this is considered as a major advantage (Amaro & Barker 2006), this is not used in the major part of the cognitive neuroscience studies (Lindquist, Loh, Atlas, & Wager 2009). From a pure psychological perspective the gain in temporal flexibility is probably
more interesting as it allows for the execution of an abundance of task types, some of them with well-known behavioural effects. By employing this kind of tasks, that are less state dependent, event-related designs offer the ability to acquire useful brain activation information related to more complex tasks (in terms of operationalisation).

Event-related designs further have the advantage to be less restricted concerning the trial order, because of the sole dependence on the event itself. Additionally the inter stimulus interval (ISI) can be prolonged or shortened. These two advantages can keep the subjects more alert than in blocked designs. Some authors make an additional distinction between designs with a ISI shorter than the HRF (smaller than 16-20s) and those with an ISI equal to the HRF (e.g. Amaro & Barker [2006]). The implication of ISIs shorter than the HRF is an increased statistical power due to the fact that more trials can be presented in an equal amount of time. This comes however at a reduced ability to estimate the HRF properties and problems in defining overlapping HRF’s (see also Lindquist et al., [2009] for additional topics concerning the estimation of properties of the HRF).

By playing with the TR and the onset of an “event” one can gain information about what happens in the brain during this event by showing one “event” per TR. Furthermore, for designs that would have a trial every e.g. every 4s with a TR of 2s, it is a common practice to add an amount of jitter to the event/trial duration. Consequently, the next event is not presented on a pair amount of seconds. This allows for a better estimation of the HRF (Miezin, Macotta, Ollinger, Peterson, & Buckner [2000]). Furthermore, more variability will be related to the cognitive activities per se as the BOLD signal will be captured on different points in the HRF. If this is not applied on the onset times, then the imminent risk is that every event is related with the same expected signal (Miezin et al. [2000]).

This design type is applied in the first experiment of Santens et al. (2010). The study will be discussed further in the Introduction section.

Other design types Although both classes can be distinguished clearly, mixture designs exist as well. These designs have the advantage to separate transient states from more sustained activity (see e.g. Visscher, Miezin, Kelly, Buckner, Donaldson, McAvoy, Bhalodia, & Petersen [2003]).

When appropriate also parametric designs can be applied. In these designs the level of a predictor variable is varied. Finally, factorial designs in which interactions of conditions occur are mentioned. It should however be noted that this is not always feasible between all possible conditions.
1.2 Analysis of fMRI data

Here the analysis protocol for fMRI data will be outlined briefly. This protocol is the base for further calculation for the optimization of the design. All design types are mostly dealt with in a similar way, i.e. the data are analysed by means of the General Linear Model (GLM) after a pre-processing stage. Throughout this section 3 parts will be considered. First the the data structure will be discussed, next the pre-processing steps will be focused on. In the end the inferential framework will be discussed briefly. We deliberately tried to keep this section as intuitive as possible. For a more technical approach we refer to the Method section where the implementation of the analysis is outlined in greater detail.

We furthermore remind that the analysis aims to determine voxels that show significant activation related to conditions of interest. The information of the conditions of interest is stored in the design matrix. Graphically the purpose of the analysis is to map significant activation on a brain-slice of interest. The mapped activity is based on the test statistic for a parameter of a condition of interest in a certain voxel. Hence it’s name: Statistical Parametric Mapping.

1.2.1 The data structure

Spatial relationships Since the brain is not supposed to be a random interplay of non-communicating regions or neurons, but rather a complex interplay of neighbouring and distal regions and neurons, spatial relationships exist and have to be acknowledged. However, although regions of interest (ROI) can be defined, the extent to which neurons (represented by voxels on the images) are related is not fully known. For example, if a memory task is presented to participants in order to detect memory-related regions, it might be that the hippocampal region (i.e. a region functionally related to memory) is active. Other -not commonly related- regions might nevertheless also show increased activity due to the content of the memories. This spatial co-occurrence is problematic for further statistical modelling as voxels measuring the activation are not independent from each other. Some strategies are developed to tackle these spatial relations (see further in 1.2.2).

Temporal relationships As with all observations that are registered closely in time, the observations in fMRI studies, i.e. the scans, are not independent from each other. They have a temporal course that connects them which results in autocorrelation between the observations. This implies adequate modelling in order to obtain valid interference.

Convolution of the design matrix To detect the condition-related activation of voxels, the design matrix needs to be adapted to the properties of the BOLD signal. The pattern of
the BOLD signal can be described by the HRF. This implies that from the start of an expected event or block, it takes some time before an increase in the BOLD signal can be observed. In order to fully capture all activation, the design matrix $\mathbf{X}$ has to be post-multiplied with the HRF. As such the information in the design matrix is straightforwardly related to the expected changes in BOLD signal if a voxel is involved in the cognitive activity.

1.2.2 Pre-processing

By definition pre-processing takes place before the actual processing. In fMRI data analysis, the pre-processing stage is conducted before the actual model fitting. In order to approach several assumptions underlying the models of analysis for fMRI data, a preprocessing stage is of major importance for a valid analysis. Furthermore, by conducting these pre-processing steps, several acquisition artefacts can be reduced or even removed from the data. We distinguish 5 steps in the preprocessing stage of the data analysis. We remind that the dependent variable is the voxel-wise BOLD signal. While analyzing voxels it should thus be verified that voxel $i$ is identical over the experimental procedure. This might seem trivial, but due to head motion this might be problematic. This should hold both on the within-subject and between-subject level.

Slice Timing Correction It was already mentioned that the acquisition of the images is consecutively proceeded along the longitudinal axis by transverse planes. Consequently, because of machinery restrictions, the first acquired plane (e.g. the back of the head) is not acquired on the same time point as the last acquired plane (the front of the head). A correction is applied by interpolating the time of the actual slice to a reference slice, often the time of the middle slice or the time of the first plane. It is discussed that longer TR’s (i.e. larger than 2-3 s.) have larger interpolation error (Henson, 2007, p. 199). In short this pre-processing stage results in the fact that the rows in the design matrix and in the response vector represent voxels $i$ on the time point $t$. The TR determines thus the speed at which a new volume can be collected and can thus be considered as the sampling rate in the design matrix.

Motion Correction Although subjects are asked to move as little as possible while being scanned, movement artefacts are inevitable. Since voxels are typically between 1-3 mm$^3$ small head movements can become a very disturbing source of error. As Lindquist (2008) notes, if subjects move too much, the signal becomes useless and the subject has to be removed from the dataset. Motion correction typically consists of aligning the acquired images with a target image. By using 6 parameters a rigid body transformation can be employed. This
permits a translation and a rotation of the 3 dimensions in order to match the target image \cite{Lindquist:2008}. In order to have a good motion correction an optimisation process has to be completed \cite{Friston:2007}. It should furthermore be noted that these 6 parameters for the motion correction are added to the design matrix. Although it should control and adjust for unwanted artefacts, this pre-processing step is not without criticism as it can create itself artefacts such as bogus activation \cite{Freire:2001}.

Co-registration and/or Normalisation fMRI scans are of lower spatial resolution than anatomical scans. Therefore, as noted in e.g. \cite{Lindquist:2008}, it is a common procedure to map the activation of the functional images on anatomically more detailed images. This is called the co-registration. This can e.g. be done by the above-mentioned rigid body transformation or other procedures. Furthermore, besides the individual level a common brain model to compare group results has to be applied on the data. After a continuous normalisation procedure to a template brain model, between-subjects inference can be conducted validly.

Spatial Smoothing The purpose of spatial smoothing is twofold. It copes with inter-subject functional anatomic variability, and it furthermore also improves the signal to noise ratio. The data are typically smoothed by a Gaussian kernel. In the literature, this is mostly characterized by the full width of the kernel at half its maximum height (FWHM). The values range from 4-12 mm typically \cite{Lindquist:2008} (e.g. 8 mm in \cite{Santens:2010} and 7 mm in \cite{VanOpstal:2008}). By the use of this symmetric kernel, most weight goes to the voxel itself and symmetrically decreases for voxels further away \cite{Reimold:2006}. As a consequence the activation patterns are thus spread over several voxels while the random noise is weighted down since it doesn’t show up consistently. However, smoothing is not without criticism as it might spread activations to regions functionally unrelated to the task execution.

1.2.3 Inference

By the construction of an accurate statistical model, valid inference can be conducted from the data gathered in fMRI experiments. Due to the complex structure of the data, the temporal and the spatial relationship have to be coped with. The first paragraphs will shortly introduce the General Linear Model as well as the modelling of the autocorrelation in fMRI data. We remind that the design matrix is a convoluted matrix \cite{Figure:3}.
**General Linear Model (GLM)** The GLM is a widely used, general framework with application in a broad range of fields. Although this model is straightforward in principle, it comes with several assumptions that have to be satisfied. For the analysis of the BOLD signal, voxel-wise GLM-models are fit. It should be noted that although the GLM approach is mostly used, alternative approaches do exist (see e.g. Friston, Glaser, Henson, Kiebel, Phillips, & Ashburner, 2002, for a Bayesian approach). In (1), the basic model is shown. We denote $Y_{it}$ as the BOLD-level in the voxel $i$ on time point $t$ with $t = 1 \ldots T$. $X_{it}$ is the respective design matrix and $\epsilon_{it}$ is the error term.

$$Y_{it} = X_{it}\beta + \epsilon_{it}$$ (1)

In order to have valid inference from linear models such as Equation 1 crucial assumptions concerning the error term $\epsilon_{it}$ have to be made. However, since the data consist of observations that are not fully independent because of the temporal relationships inherent to the procedure of acquisition, additional modelling of these relations has to occur in order to be able to yield valid inference.

Another property of the analysis of fMRI data is the application of a high-pass filter on the data, right before the inferential stage. This is a temporal filter for the reduction of irrelevant noise. Scanner drift is an important type of noise caused by the scanner. It is a common phenomenon that over time the signal intensity at a voxel decays systematically (Lazar, 2008c). For this source of noise a highpass filter aims to maximize the signal to noise ratio. The high-pass filter is described by a cut-off value for the frequency of the slowest signal that gets detected. Typical values for the highpass filter are between 120-128 s. This means that signal information with a slower frequency than once per 120-128s is discarded. In blocked paradigms, one has to assure that the duration of blocks is not interfering with the cut-off value, because otherwise information related to state (e.g. because of an enduring block) induced signal will get lost. The ability to reduce noise is thus strongly related to duration of the blocks.

Additionally, the analysis of BOLD signal differences, in absence of a pre-determined region of interest but also even within a pre-specified region, faces multiple testing problems. Because often the region of interest is larger in than one voxel, massive inference has to be conducted. Since thousands of voxels have to be taken into account in the worst case scenario (i.e. a search for signals in the entire brain), appropriate procedures to account for multiple testing have to be applied. It should however be noted that often a *mask* is applied to avoid searching in uninteresting regions.
1.3 Design optimization

Three reasons for the optimization of designs have already been mentioned: 1) The BOLD-signal change is no direct measure of neuronal activity; 2) in-scanner experiments have to cope with timing possibilities offered by the scanner and 3) the BOLD signal change is a relative measure of condition related brain activation. In this short section, three optimality criteria will be distinguished. We note again that the technical details can be found in the Method section.

The experimental procedure was already introduced. Although much of the design properties depend on the (psychological) theoretical background of the specific research question, the exact course and set-up of the experiment has to be determined in the design stage of the experiment. It is within these specifications that properties can be chosen that lead to poorly or well defined design. Due to the use of a GLM model for the data analysis and due to several properties of the scanning procedure, it remains challenging to optimally set a design especially within constraints.

It is often mentioned that the two major design types (blocked and event-related designs) are optimal for different purposes. It is then assumed that blocked designs are better for the detection of regional brain activation while event-related designs are advantageous in the estimation of the shape of the HRF \cite{Maus2010, Henson2007, Liu2004}, for example, makes a distinction between the estimation efficiency (i.e. the ability to estimate the HRF), the detection power (i.e. the ability to detect functional activation) and the conditional entropy, which can be defined as a measure of (perceived) randomness in the design while discussing optimal experimental design.

Although measuring the timing and the duration of the brain activity, has obvious links with the reaction time measurements in behavioural experiments \cite{Lindquist2007} and although the estimation of an accurate HRF is of major importance, most brain research concerns the magnitude of brain activity by using the canonical HRF (as in Figure 2). As a consequence, additional precision does not get modelled and is thus lost. Here we restrict the design optimization in terms of the ability to detect functional activation. This is also motivated by the fact that in the analysis of the two designs that we will optimize \cite{VanOpstal2008, Santens2010} no additional parameters of the HRF are estimated (because of the use of the already-modelled canonical HRF). By this restriction the estimation of the parameters in the GLM become most crucial in the determination of the efficiency. This will be discussed further-on in the Method section.

It should be noted that any design that satisfies some non-psychological optimality criterion, should be tested with a psychological reality. We would like to stress that cognitive-
psychological experimental design should thus be controlled for several factors depending on
the human being per se. We can thus not neglect the fact that monotone sequences of trials
induce fatigue, easy to predict sequences induce habituation, contrary to the optimality cri-
teron these can satisfy (see e.g. Kao et al. 2009). Several strategies have been developed
for the optimalisation of design taking these factors into account (e.g. Liu 2004). It should
additionally be stressed that every research question at itself often comes with a psychologi-
cal (behavioural) experimental task. This imposes additional restrictions on the optimization
process.

1.4 An introduction to the datasets.

1.4.1 Blocked design: Van Opstal et al. (2008)

The study of Van Opstal et al. (2008) deals with the learning of ordered sequences. More
precisely it is about a learning process known as transitive inference which concerns the
transition of previously learnt knowledge. For example if relations between A→B, B→C and
C→D are learnt, transitive learning took place if one can infer the correct relationship between
items not presented together: i.e. A→C?

In the study the authors were searching for the neural correlates of the mechanisms under-
lying these findings. In what follows the rather methodological properties of the experiment
will be given. There were 6 blocks within the scanning session. There were 5 blocks in which
the same material was presented and learning was supposed to occur. In the 6th block new
items were presented. This was done to disentangle arousing or habituation effects from learn-
ing effects. Table 1 shows the timing properties of the four phases per block. There was a
fixation phase in which the participants were made familiar with the stimuli (senseless char-
ters), next there was a learning phase followed by a test phase, at last there was a control
phase in order to disentangle sensori-motor and working memory effects from learning effects.
The trial duration in all phases was limited to set to 2.8s. Before each phase there was a
presentation of the instructions of the task that had to be performed during that phase, this
also took 2.8s. One block had a total duration of 118.6s.

Furthermore, the TR was set to 2.5 s and the highpass filter had a cut-off of 128s. As
mentioned before in this study the canonical HRF was used to model the course of the BOLD-
level. In total there were 19 categorical predictor variables: 6 times 3 phases per block and 1
for the moments considered as non-informative. This last predictor variable was set present
during the instructions. During the first 150s before block 1 and block 6 no predictor variables
were set active. The design matrix is concretized in the Method section.

16
<table>
<thead>
<tr>
<th>Phase</th>
<th>Composition</th>
<th>Duration</th>
<th>Number of repetitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixation Phase</td>
<td>fixation cross</td>
<td>15s</td>
<td>no repetitions</td>
</tr>
<tr>
<td>Learning Phase ($L_1$)</td>
<td>fixation cross, learning item, define hindmost (response)</td>
<td>0.2s, 0.2s, max. 2.4; min. 0.2s</td>
<td>10</td>
</tr>
<tr>
<td>Test Phase ($T_1$)</td>
<td>fixation cross, learning item, define hindmost (response)</td>
<td>0.2s, 0.2s, max. 2.6s</td>
<td>12</td>
</tr>
<tr>
<td>Control Phase ($C_1$)</td>
<td>fixation cross, control item, define if seen (response)</td>
<td>0.2s, 0.2s, max. 2.6s</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 1: Course of the experiment in Van Opstal et al. (2008) for 1 block. a: response registration time started from the presentation of the stimulus.

1.4.2 Event-related design: Santens et al. (2010)

The study of Santens et al. (2010) is about the non-symbolic representation of numerical information. The authors are especially interested in those processes that result in the activation of number-selective neurons. They focus thus on those processes responsible for the conversion between the input of a number of objects into a number-selective code.

In order to find the neural correlates of interests the authors used a design with following properties. In short, displays containing a number of dots (1-5) were presented to the participants and brain activity was measured. Furthermore, several parameters had to be controlled in order to distinguish non-numerical effects from numerical effects. For example, 5 dots on a screen create more light compared to 1 dot when the size of the dots is kept equal. Therefore a distinctions was made between intensive parameters such as individual item size or interitem spacing and extensive parameters such as cumulative area of the dots in the display, total luminance or total area spanned by the configuration. By the combination of these parameters the authors assured that the comparison between areas associated with a large amount of dots ($n_l$), intermediate amount of dot ($n_m$) and a small amount of dots ($n_s$) could only be attributed to the associated numerosity. The stimuli were presented on average every 5s. In this design there was a jittering factor on the ISI. As such the ISI varied from 3.4s to 6.6s. Additionally during the experiment 20% of the trials were null events and
in 12% of the trials a numerical control task was presented in order to ensure attention and numerical processing.

There were 5 runs of 102 trials in a pseudorandom order. The 5 event types (3 numerosities and 2 control tasks) were first-order counterbalanced. Each trial type was equally often followed by another trial type. Furthermore, again the canonical HRF was used to model the BOLD level. The cut-off of the highpass filter was set to 120.5s. It should be noted that here a motion correction was performed, resulting in additional parameters in the design matrix. Due to a loss of data only 4 blocks were analysed. In order to keep the results fully comparable, we will only optimize a design with 4 blocks. Per block there were 5 predictor variables and one additional constant, resulting in 24 parameters to estimate.

1.5 Research Goals

Throughout this section we shortly repeat the research questions. First of all, we want to determine how optimal the two studies are. Secondly, what is the impact of changing design parameters? The third research question is closely related to the second research question: are there feasible improvements without inevitable costs? We will examine this both for the design of Van Opstal et al. (2008) and for the first experiment in Santens et al. (2010). Like this we aim to cover an evaluation and optimization of the two major types of experimental designs in functional brain imaging techniques.
2 Method

For the optimization of the event-related and the blocked design the same optimization criterion is used. The specifications hereof are outlined in the first part of this section. In the second part, the design matrices of the study of [Van Opstal et al. 2008] and [Santens et al. 2010] are presented in order to give the estimated parameters an explicit interpretation. In the last part, the specific implementation of the design optimization is specified. Although a same basic optimization principle is the basis for the optimization of both design types, the exact specifications differ.

2.1 General formulation of the optimality-criteria

Before starting this section, we first introduce a general notation that will be used throughout this section. We denote $\xi_j$ as a specific design $j$ from the design space $\Xi$. Experimental design theory states that, given a specific statistical model of analysis (here the GLM), every design $\xi_j$, has an information matrix $M(\xi_j)$. These topics will be discussed subsequently. Once the information matrix is determined, optimality criteria are applied to find most optimal designs. A short note about the factors excluded from the optimization is given in the final part.

2.1.1 Detailed Statistical model of fMRI data

GLM (general case) For the determination of the information matrix of the statistical model for the analysis of the BOLD signal, we need to consider the properties of voxel-wise GLM-models. For the GLM, we define this information matrix as the variance-covariance matrix of the parameter vector $\beta$ (with $\beta^\prime = (\beta_0, \ldots, \beta_{p-1})$). We start with the general formulation of the information matrix in the GLM and specify it afterwards for the specific case for the analysis of fMRI data. Reconsider (1) here again presented in more detail:

$$y_i = X_i \beta + \epsilon_i$$

with $y_i^\prime = (y_{i1} \ldots y_{iT})$ is the BOLD-level vector for a voxel $i$ on with elements on the $t^{th}$ (with $t = 1 \ldots T$) scans. $X_i$ is the respective design matrix and $\epsilon_i$ is the error term. Further-on, the index $i$ will be dropped. The variance-covariance matrix of the Least Squares Estimator (LSE) of $\beta$ equals

$$\text{var} \hat{\beta} = \sigma^2 (X^\prime X)^{-1}$$

It is that the variance of a given $\beta_j$ (with $j : 0 \ldots p - 1$) is proportional to the diagonal elements of $(X^\prime X)^{-1}$. The covariance between $\beta_j$ and $\beta_k$ are proportional to the off-diagonal elements $(j, k)$. Since in the design stage the residual variance $\sigma^2$ is unknown and identical for every design, the value of $\sigma^2$ will not be taken into account.
Researchers are often interested in hypotheses concerning several particular combinations of parameters. Often a $t$ test statistic for a linear combination $c$ of $\beta$ is used

$$\frac{c'\hat{\beta}}{\sqrt{\text{var}(c'\hat{\beta})}}$$  \hspace{1cm} (4)

where $c$ is the contrast vector of length $p$ with a linear combination of the parameters of interest. An extension to an $F$-test statistic to test the significance of the hypothesis $H_0: \beta = \beta_{H_0}$ estimates can be made using

$$\frac{(\beta - \beta_{H_0})'(X'X)(\beta - \beta_{H_0})}{s^2(p - 1)}$$  \hspace{1cm} (5)

with $p$ the first degree of freedom of the $F$-test statistic and $s^2$ an estimate of $\sigma^2$. For the $F$ test statistic, a matrix $C$ can also be used. This is a $l$ by $p$ matrix, with $l$ the number of linear combinations of $\beta$.

**GLM (fMRI-analysis case)** Throughout this paragraph we will focus on fMRI-data specific adaptations of the GLM in order to be able to conduct valid inference, given the complex spatio-temporal structure of fMRI data. A GLM like (2) is straightforward in principle. Two inevitable complications arise and are described here. A first issue is the distribution of the error terms. Secondly there is a high-pass filter that is applied on the design matrix (and on the BOLD signal). In the final part of this paragraph a slightly adapted information matrix is presented.

**HRF parameter estimates and convolution of the design matrix** Since in both studies the canonical HRF was used, no additional parameters were estimated for the exact shape of the HRF. The typical shape of the HRF (see Figure 2) consists of two gamma functions. One of both represents the peak while the other represents the undershoot (Henson & Friston, 2007, p.181).

The design matrix, as was discussed earlier, is convoluted with this expected change in the BOLD signal. The SPM package (this is one of the most frequently used software packages for analysis of fMRI data: Wellcome Trust Centre for Neuroimaging, 2010) performs this at a resolution that is higher than the time scan (which depends on the TR). Typically, 16 time bins are created per scan such that stimulus/block onsets do not need to coincide with the scan onsets. From this higher temporal resolution there is a down-sampling to the sampling rate of the scans, i.e. the TR. Within the TR there is a time point T0 specified (typically this is the first scan) (Henson & Friston, 2007).
Modelling the autocorrelation  Due to the temporal relation of the subsequent observations \( y_{it} \) we cannot assume independent and identically distributed error terms \( \epsilon_{it} \). Indeed, we recognize that

\[
\epsilon_i \sim N(0, V \sigma^2)
\]  

where \( V \) is the autocorrelation structure of the data. Since incorrect modelling of this temporal relationships would result in invalid inference, this is an important step in the data analysis.

Several approaches for the modelling exist. These include the assumption of sphericity (and thus ignoring the variance-covariance structure) and the assumption of an AR(p) autocorrelation structure (see e.g. Gautama & Van Hulle, 2005, for a technical note on obtaining the correct order of an AR(p) model in the fMRI context.). In the more recent versions of the SPM software (Wellcome Trust Centre for Neuroimaging, 2010) a Restricted Maximal Likelihood estimation of an AR(1) covariance structure (Glaser & Friston, 2007) is conducted.

\[
AR(1) = \sigma^2 \begin{bmatrix}
1 & \rho & \rho^2 & \rho^3 \\
\rho & 1 & \rho & \rho^2 \\
\rho^2 & \rho & 1 & \rho \\
\rho^3 & \rho^2 & \rho & 1 \\
\end{bmatrix}
\]  

From (7) it is clear that this structure involves, besides the variance component \( \sigma \), also a correlation component \( \rho \). From (7) it is also evident that the further observations lie apart, the smaller the relation between the two observations is expected to be. It is furthermore assumed that the variance of the BOLD-signal remains constant over time since only the \( \sigma^2 \) appears on the diagonal matrix.

After the estimation of \( V \) a matrix \( A \) is constructed such that

\[
AVA' = I
\]

is satisfied. All elements of (2) are then multiplied with the matrix \( A \). This results in

\[
\tilde{Y}_i = \tilde{X}_i \beta + \tilde{\epsilon}_i
\]

with \( \tilde{Y}_i = AY_i \) and \( \tilde{X}_i = AX_i \)

The consequence of these multiplications is that error structure (6) becomes

\[
\tilde{\epsilon}_i \sim N(0, I \sigma^2)
\]

which is whitened. Because information of thousands of voxels is used to compute \( V \) (and hence \( A \)), an extreme precision is assumed that permits a pooling over voxels (Henson &
As such information of several voxels is used in order to obtain the covariance matrix estimate. It should at last be noted that it is thus tacitly assumed that all voxels share a common covariance structure.

High pass filtering  Also the analysis of the temporal high-pass filter has consequences for the statistical analysis of the BOLD-signal. Remember that the application of the high-pass filter might have unwanted implications: the removal of true signal (Henson & Friston 2007). However, it is common practice to remove signal with a frequency under the cut-off, which should be determined by the researcher. It has a standard value of 128s in the SPM software package (Wellcome Trust Centre for Neuroimaging 2010).

Often this filtering is applied just before the inferential stage in the analysis, and thus after the modelling of the autocorrelation. If filtering is applied before the estimation of the AR(1)autocorrelation structure this will cause inaccuracies since some relations between time points will not be captured (Smith, Jenkinson, Beckmann, Miller, & Woolrich 2007). This is because the filter then already has discarded the lowest frequencies possibly showing a relation between two time points.

From a technical point of view the highpass filter is implemented in a filter matrix $S$. This matrix consists of discrete cosine transforms with harmonic periods until the cut-off time (Henson & Friston 2007, p. 184). Consequently (9) becomes

$$S \tilde{Y} = S \tilde{X} \beta + S \tilde{\epsilon}$$  (12)

with $S = I - X_0X_0^+$, $X_0$ is the design matrix with the basis functions of the discrete cosine transformation included in the design matrix $X$ (as in equation (2)). $^+$ denotes the is the Penrose-Moore generalized inverse of the design matrix.

Contrasts of interest  The implementation of these adaptations to the GLM results in an information matrix similar to (3). $M(\xi_j)$ then becomes:

$$\text{var} \hat{\beta} = [X'S'A'VASX]^+\sigma^2$$  (13)

2.1.2 c-Optimality: minimal variance of the contrasts of interest

Optimality criteria  In Table 2 several optimality criteria are shown (this is not an exhaustive list). In fMRI research these three (taking $c$ and $C$ optimality as one criterion) criteria are most often used (see e.g. Maus et al. 2010, Kao et al. 2009, Liu 2004). We denote $\Psi$ the criterion to be optimized. These optimality criteria are all characterized by an inverse information matrix $M(\xi_j)$ . More efficient designs $\xi_j$, i.e. having smaller variance-covariance elements, will be considered more optimal. The specific implementation differs for
the criteria. For A-optimality, the average variance components are used to determine how optimal a design is. Designs are D-optimal if the logarithm of the determinant of the inverse information matrix is maximal.

We remind that the $c/C$ relate to contrast vector/matrix afore mentioned. As can be seen in (4), a single estimated contrast results in a $t$-test statistics. Multiple contrasts, defined by a matrix $C$, can be tested at once as well by means of an $F$-test statistic like (5). In $c$-optimal designs a linear combination elements of the information matrix has to be optimal. This can be seen as weighted combination of variance parameters. This can be extended to the case where several linear combinations have to be taken into account, i.e. $C$-optimality.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>$\Psi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>$\text{tr}M^{-1}$</td>
</tr>
<tr>
<td>$D$</td>
<td>$\log</td>
</tr>
<tr>
<td>$c$</td>
<td>$c'M^{-1}c$</td>
</tr>
<tr>
<td>$C$</td>
<td>$\text{tr}C'M^{-1}C$</td>
</tr>
</tbody>
</table>

**Table 2:** Optimality Criteria applied in designs of fMRI studies. $M(\xi_j)$ is compactly notated as $M$.

**Motivation for the $c/C$ criteria** We opt for the $c/C$ optimality criterion. The choice for this type of optimality was preferred above the two other criteria. In the context of design optimization in fMRI-studies, Maus et al. (2010) note that D-optimality is less frequently applied than A-optimality. But we note that in Kao et al. (2009) both are discussed and implemented.

This choice for the $c/C$ optimality criterion was furthermore motivated by the very ad-hoc approach here. Since the design optimization should be performed in the light of the specific research question, for which e.g. not all parameter estimates are of the same importance, this was preferred over other types of optimality that take into account more variance components, such as A and D optimality criteria. Thus, in the determination of the optimal design we only take into account 1) the variance of the parameters of interest 2) in a linearly weighted manner.

**General implementation** The $c$-optimality is implemented in the context of fMRI analysis by

$$\Psi_c = c'[X'S'A'VASX]^{+}c\sigma^2 \tag{14}$$
where $\Psi_c$ has to be minimized. $C$-optimality easily extends then to

$$\Psi_C = C'[X'S'\Lambda'\Lambda SX]^{-1}C\sigma^2$$

(15)

where $\Psi_C$ has to be minimized. We will however, when comparing designs, express their efficiency. We use the formulation of amongst others Kao et al. (2009). The efficiency is expressed by

$$E_C = \frac{1}{\Psi_C}$$

(16)

$$E_C = \frac{\text{rank} C}{\Psi_C}$$

(17)

where for the $C$-optimality the unicity of the information in the contrast is incorporated.

From the optimality criteria in Equation 14 and 15 it is clear that several elements will impact the optimality and hence the efficiency. We acknowledge 5 elements: 1) the contrast itself ($c$); 2) the design matrix ($X$); 3) the autocorrelation model ($A$ and $V$); 4) the filtering matrix ($S$) and 5) the residual variance ($\sigma^2$).

The contrasts of interest play an important role, these can however not be easily modified. The design matrix itself, however, can be modified more easily. The information on the rows (i.e. the trial order, the duration, the onsets, ...) will impact the efficiency. We exclude however the auto-correlation model from the efficiency calculations. This is motivated in the next section together with other factors excluded from the optimization. At last, the high pass filter settings (i.e. the cut-off value for the lowest acceptable frequency) will impact the efficiency because it modifies the design matrix.

2.1.3 Factors excluded from the optimization

First, the autocorrelation modelling ($A$ and $V$) will be left out of the calculations since the procedure for estimating the covariance structure is based on the data at hand. The size of this effect can thus not be predicted beforehand. It should furthermore be noted that this will have an impact on the data. We note that others (Maus et al., 2010) let the $\rho$ parameter vary in the interval $[0, 0.5]$. Kao et al. (2009) set a standard value of the $\rho$ of 0.3. As this value might as well be an underestimation or an exaggeration of the true temporal correlation matrix we opted to not include this. The modelling of the temporal correlations is furthermore not without criticism (Gautama & Van Hulle, 2005).

Secondly, a similar argument holds for $\sigma^2$. It is estimated from the data at hand. Furthermore it will impact the optimality for all contrasts at the same degree since it is assumed to be constant. Thirdly, motion correction is performed by the construction of additional predictor variables in the design matrix. This can also not be predicted beforehand. Intuitively
lots of translations and rotations should introduce undesired additional variance reducing the optimality. Fourthly, we exclude the estimation of the HRF parameters. Since in the original studies the canonical HRF was used, only the detection power needs to be optimized. Finally, we didn’t change the sampling rate in the design matrix as this would artificially increase the power. It should however be noted that a smaller TR implies more scans in the same time. However, the consequence is that the quality of the images decreases. We opted however to follow the choice of the original researchers in this matter.

2.2 Design matrix and statistical model of Van Opstal et al. (2008) and Santens et al. (2010).

Design matrix of Van Opstal et al. (2008)  In the design of Van Opstal et al. (2008) there were 1235 scans. The design matrix consisted of 20 columns: 19 predictor variables and 1 intercept. In $X_{\text{junk}}$ the onset information about the instructions, and the familiarisation prior to block 1 and block 2 was stored. In $X_L$, the onset information about the learning blocks was stored. In $X_T$, the onset information about the testing blocks was stored and in $X_C$, the onset information about the control blocks was stored. The number indices refer to the respective order in which the blocks occurred. $X_{\text{int}}$ stores the intercept. This matrix is compactly presented in (18).

$$
X_{1235 \times 20} = 
\begin{bmatrix}
X_{\text{junk}} & X_{L1} \ldots X_{L6} & X_T \ldots X_T & X_{C1} \ldots X_{C6} & X_{\text{int}} \\
1235 \times 1 & 1235 \times 6 & 1235 \times 6 & 1235 \times 6 & 1235 \times 1 \\
x_{1,j} & x_{1,L1} x_{1,L2} \ldots x_{1,L5} x_{1,L6} & x_{1,T1} x_{1,T2} \ldots x_{1,T5} x_{1,T6} & x_{1,C1} x_{1,C2} \ldots x_{1,C5} x_{1,C6} & x_{1,\text{int}} \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
x_{1235,j} & x_{1235,L1} \ldots x_{1235,L6} & x_{1235,T1} \ldots x_{1235,T6} & x_{1235,C1} \ldots x_{1235,C6} & x_{1235,\text{int}}
\end{bmatrix}
$$

The 1032 by 24 design matrix of Santens et al. (2010) In the design of Santens et al. (2010) there were 1032 scans, or 258 scans per run. The design matrix consisted of 24 rows. There were 20 predictor variables and 4-run specific intercepts. In $X_S$, $X_M$, and $X_L$ the onset information about respectively the small, medium and large number condition was stored. In $X_{\text{int}}$, the run-specific intercepts were stored. These were also pre-averaged. Their value was thus 0.25. In $X_{CI}$ and $X_{Cr}$, the onset information about the control task with respectively a right and a left expected response was stored. The number indices refer to the respective run in which the conditions occurred. This matrix is compactly presented in Equation 19.

---

1 Although in their paper a total number of 1248 scans is reported, the reconstruction of the design matrix only yielded 1235 scans. This is because the scanner registered some additional time after the last control phase (Van Opstal, personal communication).
Although in this study a motion correction procedure was conducted, this is not inserted in this design matrix. The original design matrix thus consisted of 6 more parameters for a rigid body transformation.

\[
X_{1032 \times 24} = \begin{bmatrix}
X_{S1}X_{M1}X_{L1}X_{C11}X_{Cr1} & \ldots & \ldots & X_{S4}X_{M4}X_{L4}X_{C14}X_{Cr4} & \ldots & \ldots & X_{S1032}X_{M1032}X_{L1032}X_{C1032}X_{Cr1032}
\end{bmatrix}
\] (19)

2.3 Implementation of design optimization in Van Opstal et al. (2008) and Santens et al. (2010)

2.3.1 Design optimization of Van Opstal et al. (2008)

Contrasts of interest The study of Van Opstal et al. (2008) postulated 2 contrasts of interest. The first contrast, shown in (20), consisted of the comparison between testing condition of the best learnt items in the block 5 \((T_5)\) and the testing condition of blocks 1 and 6 \((T_1\) and \(T_6)\), controlling for other effects by taking into account the respective control conditions. The other contrast, shown in (21) is a control contrast for the difficulty in the items between the test conditions in the first, second and third block versus the control conditions in these blocks (respectively \(T_{1-3}\) and \(C_{1-3}\)).

\[
\text{Contrast1} : \quad -\frac{1}{2}(\beta_{T_1} + \beta_{T_6}) - \beta_{C_5} + \frac{1}{2}(\beta_{C_1} + \beta_{C_6}) + \beta_{T_5} = 0 \quad (20)
\]

\[
\text{Contrast2} : \quad -\frac{1}{3}(\beta_{T_1} + \beta_{T_2} + \beta_{T_3}) + \frac{1}{3}(\beta_{C_1} + \beta_{C_2} + \beta_{C_3}) = 0 \quad (21)
\]

As can be seen, the main focus of these contrasts lies on the testing blocks and on the control blocks. By means of (16) the efficiency will be calculated for both of these contrasts.

Restrictions in manipulatable design parameters As argued in section 1.3, any design can be improved such that it has maximal mathematical efficiency. In Van Opstal et al. (2008), since the design type stems from a well-know psychological paradigm, i.e. the transient learning paradigm, several general restrictions are imposed on the design. As a consequence we restrict a number of factors to vary in our manipulation.

The first restriction is the order of the blocks. Since by nature, first learning has to occur in order to test this, the learning phase always has to precede the test phase. Also the control phase cannot be intermixed with the test phase since a change in this order will induce additional complexity. This confound occurs because of the fact that in the situation where the control phase precedes the test phase, the learnt items have to be remembered on
a later moment than before. Furthermore, we do not change the number of blocks per condition in order to be able to compare the results of a new design with the results of the current design. For example, creating additional blocks would change the amount of learning that took place in block 5, which occurs in the contrasts of interest. So, 6 blocks will occur for every condition as in the original study.

Also considerations can be made about the number of trials in the learning condition of one block. This will nevertheless be varied. Although the learning per se was not of main interest in this study, this learning might become asymmetric within a block between the items if an odd number of learning trials occurs. This is because only adjacent pairs of items are presented in the learning phase (for 6 items 5 adjacent pairs were presented twice in the original study). It might be argued that less than 10 trials in the learning phase will result in insufficient learning per block. This has to be evaluated by researchers familiar in the field. We can however make a distinction in the best designs based on the number of trials in the learning phase: the overall best design, the best design with exactly 10 trials in the learning phase and the best design with more than 10 items. In the latter case the learning is still asymmetric but each pair will be presented at least twice with 6 items.

The number of trials in the test and control phase was in the original study equal, these amounts were also kept equally.

Furthermore as maximizing would imply infinite scanning we restrict the number of scans to be within the range of 120 scans from the original design (i.e. 1235 scans). With a TR of 2500ms this results in an additional scanning time of 5 of the original scanning time. This makes the range of the scanning procedure in time from about 47 minutes to about 57 minutes. This is still within the range of a feasible effort for the participants in the experiment if the scanning time would be maximal.

**Protocol** First we will manipulate the manipulatable parameters over a range of values. Next, we will look at those factors playing a role in both contrasts in those designs with a higher efficiency than the original design. This will be done visually by inspection of general trends of each manipulated factor. This visual procedure should result in a set of sub-optimal designs. The final optimal design settings should then be chosen after the application of an appropriate high-pass filter. It should be noted that the cut-off value of the high-pass filter cannot be lower than the total duration of one block because that will result in the loss of block-related signal.

In the first step, we will manipulate: 1) the *fixation* time from 13s to 17s (by 1s); 2) the *instruction* time from 2.4s to 3.2s (by 0.1s); 3) the *trial* duration from 2.4s to 3.2s (by 0.1s); 3) the *number* of trials in the *learning* phase (8 to 14); 4) the *number* of trials in the *testing* phase (8 to 14).
and control phase (8 to 14). This will result in 25515 different designs. These designs are then subjected to the length restriction (i.e. from minimally 1115 to maximally 1355 scans).

In a second step those designs with higher efficiencies on both contrasts separately will be selected. Furthermore, if components are not considered as influential we will set these back to their original values as in Van Opstal et al. (2008). The specifications of this design are shown in Table 3. This should restrict the pool of designs considerably again. Afterwards the above argumented distinction between the number of trials in the learning condition will be made (i.e. > 10, 10 and no restriction). For the determination of the best design we will apply an average highest efficiency. However, we will control for the meaninglessness of the efficiency values by taking into account the order of the designs. This order will be determined on the c-efficiencies separately for both contrasts.

At last, an appropriate highpass filter should be applied to the data, keeping in mind the consequences of this filter. This will again be done visually by showing the efficiencies per contrast (expressed in percentage relative to the original contrast) for a range of cut-off values.

<table>
<thead>
<tr>
<th>t Trial</th>
<th>n Learning</th>
<th>n Test/Control</th>
<th>t Fixation</th>
<th>t Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8s</td>
<td>10</td>
<td>12</td>
<td>15s</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Table 3: Design properties of the original design of Van Opstal et al. (2008).

R-code references For the construction of the separate designs a function called design_a_matrix was created. In this matrix the blocks are implemented in a matrix with a length in tenths of seconds. This matrix will then be cut into scans (by means of the function couper). These functions can be found in the file support_functions.R. Afterwards this matrix will be convoluted based on the spm_hrf function of the spmR package (Rosseel 2010). The actual manipulation and the further selection of optimal designs can be found in manipulationBlocked.R. The dataset with the design properties for the designs that satisfy the length restriction are stored in length_corrected.Rdata. At last the efficiency was calculated with the function eff also stored in support_functions.R.

It should be noted that the way of composing this blocked design is performed rather raw. This is because we had no actual onset times at the time of the manipulation. Moreover, we stress that the efficiencies of the original design matrix highly resembles the efficiencies obtained by this reconstruction process. This can be found in the file blocked.R. This served as the basis for the design_a_matrix function. The original design matrix is stored in design_unfil.txt. The files are stored on a CD-ROM.
2.3.2 Design optimization of event-related designs

Contrary to the design optimization procedure of the design of Van Opstal et al. (2008), the search for an optimal design in event-related designs is somewhat more difficult since an almost infinite number of random or pseudorandom event consequences can be generated for e.g. two conditions that have to be contrasted by means of an event-related design. This is why the search for an optimal design for 5 conditions (3 numerical and 2 control-task related) gets complicated, especially if the order (or total design) has to be subject to several restrictions. Examples of restrictions are: 1) the proportion of trials types; 2) counterbalancing and 3) the spread of the conditions throughout the experimental procedure. Fortunately, some search algorithms are constructed to guide the search for an optimal event-related fMRI design. Throughout this paragraph we focus on the recent implementation of Kao et al. (2009) that incorporates elements of an older optimization procedure of Liu (2004) and Wager & Nichols (2003). The multi-objective (MO) approach of Kao et al. (2009) will be depicted in the next paragraphs.

Multi-objective In their search of an optimal design, the authors include four criteria. These criteria then get weighted and an optimal design is based on this weighted criterion. They included two objectives for the analysis of fMRI data: i.e. the detection power and the estimation efficiency. These criteria refer, respectively to the power to detect task related signal changes and the efficiency to estimate the parameters for the HRF. Additionally they also incorporate a counterbalancing controlling objective and a sub-design objective. The latter objective assures that over the entire experimental procedure there is an equal spread such that every condition appears equally often. These four criteria form a weighted MO optimization criterion. For the determination of the estimation efficiency and the detection power the authors give the choice for the A or D optimality criterion. We however adapted this to the \( c \)-optimality criterion for the two single contrasts.

Genetic Algorithm (GA) search algorithm The general principle of Genetic Algorithms is extensively described in the work of Holland (see e.g. Holland 1992). In short the basic principle is to use good solutions as a basis for the generation of better solutions. Kao et al. (2009) use several fMRI design types (blocked designs, m-sequence, fully random designs and their combinations) for an efficient search over the design space \( \Xi \). For the outline of the procedure we mainly make use of the structure and notation of (Kao et al., 2009, p. 851). Figure 4 graphically represents the stage of the initial designs, the evaluation of these initial designs and the cross-over stage.

Step 1. The creation of initial designs. This results in the creation of G initial designs of
three kinds and their combination: fully random event-related, m-sequences (which is event-related in sequences of m events) and blocked. The MO-criterion is then used to evaluate the fitness of these initial designs.

**Step 2.** The second step is called the crossover step. With probability proportional to the initial fitness, draw with replacement G/2 pairs of designs to crossover. A random point has to be chosen to let the exchange find place between the two designs. As such a fraction of design material can be exchanged between the two designs. Note that in this point there is a random component. See Figure 4.

**Step 3.** This step is called the mutation step. Here a random selection of q% trials from the G offspring designs is made. These trials are replaced by randomly generated ones. A trial can represent a stimulus or a rest.

**Step 4.** In this immigration step another I designs are added to the design population. These I designs are drawn from the random designs, the block designs and their combinations.

**Step 5.** Here the fitness of all designs is again determined of the offspring designs (created in Step 2) and of the immigrants.

**Step 6.** Imitating the principle of natural selection, here only the best G designs are kept. The designs are evaluated based on their fitness. These will form the base for the next generation of designs. The other designs are discarded.

**Step 7.** Steps 2 through 6 are repeated until the stopping rule (i.e. after 10,000 iterations) is encountered. Best designs are kept track of, over generations.

### 2.3.3 Design optimization of Santens et al. (2010)

**Contrasts of interest** As mentioned in 1.4.2, the study of Santens et al. (2010) also postulated 2 contrasts of interest. The contrasts are outlined in (22) and (23). It is clear that the three conditions are represented in these contrast. Here again, by means of (16) the efficiency will be calculated.

Contrast1:  
\[-\beta_{S_1} - \beta_{S_2} - \beta_{S_3} - \beta_{S_4} + \beta_{S_1} + \beta_{M_2} + \beta_{M_3} + \beta_{M_4} = 0\]  \quad (22)

Contrast2:  
\[-\beta_{M_1} - \beta_{M_2} - \beta_{M_3} - \beta_{M_4} + \beta_{L_1} + \beta_{L_2} + \beta_{L_3} + \beta_{L_4} = 0\]  \quad (23)

**Restrictions in manipulatable design parameters** Since in this design the order of the events (and hence conditions) is more freely adjustable than the design of Van Opstal et al. (2008) we opted to keep the proportions of condition in the different runs fixed here.
Fig. 3. Comparison of actual data for 10 subjects collected at 3 T (A) to predicted response in a linear system (B). Flickering checkerboard stimuli (120 ms) were presented, and motor responses were collected, once per second in a series of 1, 2, 5, 6, 10, or 11 stimulations, with a 30-s rest interval following the series. Data in (A) show percentages of signal change in series of each length. Linear predictions (B) were constructed by convolving a canonical HRF, normalized to the observed response height of a single checkerboard stimulation, convolved with the stimulus delta function for each series. Actual responses to long series peaked at approximately two times the height of the single stimulation response, whereas the linear convolution predicts responses over five times greater.

Fig. 4. Schematic showing the stages in GA operation. Design vectors are transformed to model matrices, which are tested for fitness. Selected designs undergo crossover, and the resulting "children" are retested iteratively until the algorithm is stopped.

These are shown in Table 4. Furthermore, the number of trials/events per run was also kept constant: i.e. 102 events per run. Additionally, since a jitter interval was introduced with a uniform distribution of 400, 800, 1200, 1600 more or less than the average event duration of 5000ms. As in the original study the counterbalancing order was again set to first order counterbalancing, ensuring that every trial was equally predictive (and hence non-predictive) for a next trial. Furthermore, the proportion of trial types was as in the original study and is shown in Table 4.

<table>
<thead>
<tr>
<th>Trial type</th>
<th>Run 1</th>
<th>Run 2</th>
<th>Run 3</th>
<th>Run 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>small</td>
<td>24/102</td>
<td>27/102</td>
<td>25/102</td>
<td>26/102</td>
</tr>
<tr>
<td>medium</td>
<td>23/102</td>
<td>23/102</td>
<td>27/102</td>
<td>26/102</td>
</tr>
<tr>
<td>large</td>
<td>28/102</td>
<td>26/102</td>
<td>24/102</td>
<td>24/102</td>
</tr>
<tr>
<td>control (l)</td>
<td>10/102</td>
<td>12/102</td>
<td>12/102</td>
<td>12/102</td>
</tr>
<tr>
<td>control (r)</td>
<td>85/102</td>
<td>88/102</td>
<td>88/102</td>
<td>88/102</td>
</tr>
</tbody>
</table>

Table 4: Proportions of the trial types in the original study of Santens et al. (2010).
**Protocol**  Several parameters have to be set in the search algorithm. As mentioned in the Introduction section, we aim to look for the efficiency determined by the detection power. Consequently in the MO criterion the weight given to the estimation efficiency was set to zero. We opted to increase the weight of the counterbalancing criterion and the detection power criterion. Also the subdesign objective was accounted for. So starting from a standard setting for which all objectives are given equal weight (i.e. 0.25), we changed this to the situation where only 3 objectives are accounted for. The weights in the MO-criterion are 0.375 for the detection power and the counterbalancing and 0.25 for the subdesign properties. The counterbalancing was set to first order counterbalancing (as in the original study). Unless stated differently we let the algorithm run for 10,000 cycles for all runs. This is the standard stop rule in [Kao et al.](2009). Furthermore, the number of a generation was to 20, the number of immigrants was set to 4 and the rate of mutation was set to 0.01. These are again the standard values.

First the average duration of the trials will be determined. This will be conducted for each run separately while setting the proportion of events per condition to the respective proportions per block as in Table 4. Since manipulations of the ISI can only be performed with a unit-increase of 1 s this will be performed at the durations of 4, 5 and 6 s. We remind that in the original study the ISI was on average 5 s. Next, we let the algorithm run for all runs during 10,000 cycles in order to determine the best order per run taking into account the event probabilities per run as in the original study. Afterwards, we will compare the designs with the original design.

After having determined the trial order, the jitter properties had to be determined. This will be done in an intuitive manner. We will use the jitter timing of the original study. This can be found in Table 5. In order to determine the efficiency over jittering time we will sample 200 random jittering time orders and calculate the efficiencies for different high-pass filter properties.

**MATLAB® - and R-code references**  Two sequence of computation were used in here. First, optimal sequences were obtained by the use of the implemented search algorithm of [Kao et al.](2009). However, we changed some parts of their code. First the type of optimality was changed to the average \(c\)-optimality in the file AmpEfficiency.m. Secondly the number of trials in a run was forced to be the identical number of the original study, this was done per run in the file getcBal.m. The second manipulation is motivated by the empirical finding that the algorithm tended to underrepresent the number of events in the created op-

\[^2\text{Since the control condition consisted of on average 5 trials per task, this resulted in computational problems in the procedure. That is why the two control tasks were combined and later-on randomly split.}\]
<table>
<thead>
<tr>
<th>Jitter time</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ms</td>
<td>22</td>
</tr>
<tr>
<td>400 ms</td>
<td>20</td>
</tr>
<tr>
<td>800 ms</td>
<td>20</td>
</tr>
<tr>
<td>1200 ms</td>
<td>20</td>
</tr>
<tr>
<td>1600 ms</td>
<td>20</td>
</tr>
</tbody>
</table>

Average= 786ms

**Table 5:** Distribution of the jittering times in Santens et al. (2010).

The optimal order. The other parameter settings can be found in the file Par_Assign_FINAL.m. The files are in the folder fMRI_matlab.

Once the event/trial orders were determined these were imported in R (see file manipulation_event.R), the control condition were randomly divided into the left and the right control task and the design was convoluted. The order of the trials is stored in best_runs.txt. The composition of the blocks done by the function spm_fMRI_design of the spmR package (Rosseel, 2010). The other used functions are identical to the manipulation of the blocked design.
3 Results

3.1 The design of Van Opstal et al. (2008)

3.1.1 Efficiency original design

For the first contrast of the original design the efficiency was 18.86, for the second contrast this was 85.48. After the application of the high-pass filter (with a cut-off of 128s) these values became 13.31 and 81.35. Furthermore the numerical values of the efficiency have no clear meaning and should thus per se be considered as relative with respect to other designs.

3.1.2 5 Suboptimal Designs for 3 situations in the learning phase

From the 25515 designs, only 12218 were kept because of the length restriction. Next, we selected those designs having a higher efficiency for both contrasts separately (without high-pass filter). This resulted in a further reduction to 4800 designs. From Figure 5 and Figure 6 it is clear that the manipulation of the number of trials in respectively the test and control phase and in the learning phase plays an important role as there are clear trends. It is apparent that on average an increasing number of trials in the test/control phase has a positive effect on the efficiency for both contrasts. Contrary to this positive relation, an increasing number of trials in the learning phase results in lower efficiencies on average. The duration of the fixation period and the duration of the instruction had no considerable effect (see Figure 12 and Figure 13 in Appendix section A.1).

By means of the colour indication for the trial durations we furthermore find that the trial duration tends to be influencing the efficiency as well since longer trial durations seem to have higher efficiencies. This pattern arises clearly in Figure 5. In Figure 6 this pattern is however less clear.

As outlined in the protocol for this optimization process we set the non-impacting factors back to their original value. The fixation phase and the duration of the instruction were thus set back to respectively 15s and 2.8s. As a consequence of the latter restriction only 102 designs remained. From these designs the average rank order of the efficiencies and the average efficiency over the two contrasts were calculated. Consequently a distinction was made between an overall best design, a best design with 10 trials and one with more than 10 trials. Table 6 shows the properties of the 5 overall best designs. It can be seen that these 5 designs have quite distinct properties. Furthermore, mind the fact that more scans does not always imply a better efficiency as the design with most scans (ID 12805) is only the fifth best design.
Figure 5: The efficiency per trial duration with respect to the number of trials in the test and control phase of those designs being more efficient than the original design.

Table 6: Design properties of the 5 overall best designs.

<table>
<thead>
<tr>
<th>ID</th>
<th>t Trial</th>
<th>n Learn.</th>
<th>nT/C.</th>
<th>Eff. C1</th>
<th>Eff. C1</th>
<th>n scans</th>
<th>Av. Eff.</th>
<th>Av. order</th>
</tr>
</thead>
<tbody>
<tr>
<td>12734</td>
<td>2.8</td>
<td>8</td>
<td>15</td>
<td>23.5289</td>
<td>105.6972</td>
<td>1343</td>
<td>64.6131</td>
<td>101.5</td>
</tr>
<tr>
<td>12609</td>
<td>2.6</td>
<td>8</td>
<td>16</td>
<td>23.5562</td>
<td>105.1683</td>
<td>1320</td>
<td>64.3622</td>
<td>101.5</td>
</tr>
<tr>
<td>12618</td>
<td>2.6</td>
<td>9</td>
<td>16</td>
<td>22.9848</td>
<td>103.6447</td>
<td>1344</td>
<td>63.3147</td>
<td>100.0</td>
</tr>
<tr>
<td>12796</td>
<td>2.9</td>
<td>8</td>
<td>14</td>
<td>22.7747</td>
<td>102.4443</td>
<td>1323</td>
<td>62.6095</td>
<td>99.0</td>
</tr>
<tr>
<td>12805</td>
<td>2.9</td>
<td>9</td>
<td>14</td>
<td>22.6696</td>
<td>102.2132</td>
<td>1351</td>
<td>62.4414</td>
<td>98.0</td>
</tr>
</tbody>
</table>

For the situation where the number of trials in the learning phase was restricted to 10 only 16 designs remained. The properties of the 5 best designs are shown in Table 7. For the situation where the restriction was that more than ten trials had to be in the learning phase 37 designs remained. The 5 best designs of this restriction are shown in Table 8. Notice here again that the length of the designs is not the sole determining factor.
Figure 6: The efficiency per trial duration with respect to the number of trials in the learning phase of those designs being more efficient than the original design.

Table 7: Design properties of the 5 best designs with exactly 10 trials in the learning phase.

<table>
<thead>
<tr>
<th>ID</th>
<th>$t$ Trial</th>
<th>$n$ Learn.</th>
<th>$nT/C.$</th>
<th>Eff. C1</th>
<th>Eff. C1</th>
<th>$n$ scans</th>
<th>Av. Eff.</th>
<th>Av. order</th>
</tr>
</thead>
<tbody>
<tr>
<td>12564</td>
<td>2.5</td>
<td>10</td>
<td>16</td>
<td>22.3358</td>
<td>100.7118</td>
<td>1329</td>
<td>61.5238</td>
<td>16.0</td>
</tr>
<tr>
<td>12751</td>
<td>2.8</td>
<td>10</td>
<td>14</td>
<td>21.9764</td>
<td>98.6639</td>
<td>1343</td>
<td>60.3202</td>
<td>14.5</td>
</tr>
<tr>
<td>12626</td>
<td>2.6</td>
<td>10</td>
<td>15</td>
<td>22.2254</td>
<td>98.3941</td>
<td>1320</td>
<td>60.3098</td>
<td>14.5</td>
</tr>
<tr>
<td>12501</td>
<td>2.4</td>
<td>10</td>
<td>16</td>
<td>21.5359</td>
<td>96.9662</td>
<td>1289</td>
<td>59.2511</td>
<td>13.0</td>
</tr>
<tr>
<td>12813</td>
<td>2.9</td>
<td>10</td>
<td>13</td>
<td>21.2517</td>
<td>95.4625</td>
<td>1323</td>
<td>58.3571</td>
<td>12.0</td>
</tr>
</tbody>
</table>

3.1.3 Application of the High-Pass filter in the suboptimal designs

The application of the high-pass filter is shown graphically. Furthermore, to increase interpretability, this is shown relative to the efficiency of the respective contrasts in the original design. Figure 7 shows the efficiency of the 5 overall best designs and of the original design. As can be seen, the application of the high-pass filter shows that the better designs only become more efficient when a higher cut-off value and thus a lower boundary is chosen for
Table 8: Design properties of the 5 best designs with more than 10 trials in the learning phase.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>12573</td>
<td>2.5</td>
<td>11</td>
<td>16</td>
<td>22.3369</td>
<td>100.7171</td>
<td>1353</td>
<td>61.5270</td>
<td>37</td>
</tr>
<tr>
<td>12635</td>
<td>2.6</td>
<td>11</td>
<td>15</td>
<td>21.6523</td>
<td>97.6506</td>
<td>1344</td>
<td>59.6515</td>
<td>36</td>
</tr>
<tr>
<td>12510</td>
<td>2.4</td>
<td>11</td>
<td>16</td>
<td>21.5082</td>
<td>96.9715</td>
<td>1312</td>
<td>59.2398</td>
<td>35</td>
</tr>
<tr>
<td>12519</td>
<td>2.4</td>
<td>12</td>
<td>16</td>
<td>21.3905</td>
<td>96.1990</td>
<td>1335</td>
<td>58.7947</td>
<td>34</td>
</tr>
<tr>
<td>12697</td>
<td>2.7</td>
<td>11</td>
<td>14</td>
<td>21.1723</td>
<td>95.4438</td>
<td>1332</td>
<td>58.3081</td>
<td>33</td>
</tr>
</tbody>
</table>

The high-pass filter. It can be seen that the overall best design and the second best design are almost identical, with the second best design peaking faster. It is also clear that at the original cut-off value none of the better considered designs outperforms the original design. This will be discussed in the Discussion section.

Figure 7: The efficiency percentage (relative to the efficiency of the respective contrasts on the original high-pass filter settings) for the 5 suboptimal designs and for the original design.

In Figure 8 the best designs for 3 amounts of trials in the learning phase are presented.
Here again it is clear that, in order to obtain a higher efficiency, a higher cut-off (and thus a lower frequency boundary) has to be chosen. This phenomenon is shown for the 5 overall best designs. From Figure 8 it is clear that in order to have a higher efficiency than the original design higher cut-off value has to be chosen. This phenomenon will be further described in the Discussion section.

In order to pick out one best design, one should thus take into account the lower High-pass filter cut-off. But as the designs are up to 40 to 60 % more efficient it is hard to assess the impact of the noise that will not be discarded. Furthermore the exact settings of the high-pass filter cut-off differ for the two contrasts of interest. We recapitulate the 3 best designs. For the overall best design this is design with ID 12734, for the design with exactly 10 trials this is design with ID 12564 and for the design with more than 10 trials this is the design with ID 12573.

![Graph](image)

**Figure 8:** The efficiency percentage (relative to the efficiency of the respective contrasts on the original high-pass filter settings) 3 optimal designs and for the original design for a limited range of high-pass filter cut-off values.
3.2 The design of Santens et al. (2010)

3.2.1 Efficiency original design

For the first contrast this efficiency was 0.2822, for the second contrast this efficiency was 0.2838. Note that these values are without the application of a high-pass filter. After the application of the high-pass filter (with a cut-off of 120.5s) these values became 0.2510 and 0.2619.

3.2.2 Optimization process

For the determination of the average ISI there seemed to be no apparent differences between an ISI of 4.5 or 6s. Over $1000^3$ iterations in 2 runs better efficiency at the 6s average ISI was obtained and 2 runs better efficiency at the 4s average ISI. We thus opted to keep the original ISI of 5s because no clear advantage of the 4s or the 6s average ISI condition could be demonstrated. In Table 9 the $F^*$ denotes the multi-objective criterion (which incorporated the averaged $c$-optimality value, the counterbalancing and the sub-design characteristics), whereas the $F_d$ denotes the detection power efficiency measured by the $c$-optimality criterion as an average for both contrasts. Furthermore the trial proportions per run were defined as in Table 4.

<table>
<thead>
<tr>
<th>run</th>
<th>av ISI (s)</th>
<th>$F^*$</th>
<th>$F_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>0.67440</td>
<td>0.13175</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.67373</td>
<td>0.12966</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.67503</td>
<td>0.13341</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0.67697</td>
<td>0.13859</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.67553</td>
<td>0.13476</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.67590</td>
<td>0.13573</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>0.67631</td>
<td>0.13683</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.67420</td>
<td>0.13119</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.67621</td>
<td>0.13655</td>
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<td>4</td>
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<td>0.13793</td>
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<td></td>
<td>5</td>
<td>0.67548</td>
<td>0.13461</td>
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<tr>
<td></td>
<td>6</td>
<td>0.67604</td>
<td>0.13611</td>
</tr>
</tbody>
</table>

Table 9: Results for the $F^*$ criterium and the $F_d$ criterium for 1000 iterations in the search algorithm of Kao et al. (2009).

3$^3$ This was lowered for computational purposes.
In Figure 9 the effects of the application of a random jittering factor are shown for an optimal design yielded by the search algorithm. The 95% prediction intervals for the efficiencies of the two contrasts are based on 200 permutations of the jittering times from Table 5. The prediction intervals are based on the 5th and the 95th quantiles of the efficiencies of the contrasts at the respective high pass filter cut-offs. As can be seen, an optimal sequence of trials can increase the efficiency with about 10% (at the same high-pass filter cut-off), even without the application of a jittering factor (orange lines). Furthermore, the application of the jittering factor results for 95% of the 200 random permutations of the jittering intervals in an increase of the efficiency from about 6 to 14%, even for different high-pass filter cut-offs.

**Figure 9:** The efficiency percentage (relative to the efficiency of the respective contrasts on the original high-pass filter settings) per contrast for an optimal design with the application of a jitter factor.
4 Discussion

Throughout this master thesis, a search for optimal designs in fMRI studies was conducted. For two exemplars of the most frequently used design types (i.e. event-related and blocked designs) more optimal designs were found. We showed that for the two particular cases the design could be optimized, albeit not without taking into account (several) restrictions. The results for the two cases are discussed throughout this section.

4.1 The optimization of the blocked design of Van Opstal et al. (2008)

For the design of Van Opstal et al. (2008) we defined three design configurations that are more optimal in terms of the \(c\)-optimality criterion for both contrasts separately. Since we allowed in our protocol for an increase or a decrease in time, keeping the TR constant, the more optimal designs had a longer scanning duration than the original design.

Optimization within strong restrictions During the search for an optimal design of the study of Van Opstal et al. (2008) we anticipated to possible criticism from a learning perspective. This anticipation is important as more optimal fMRI designs can only be optimal if, besides a numerical optimality criterion, they are also psychologically valid. This might seem ad-hoc, it is nevertheless interwoven with psychological theorizing. Furthermore because we aimed to have comparable results with respect to the original design of Van Opstal et al. (2008), the basic order of the blocks was maintained. Of course it should be added that blocked designs do not have to be that restrictive. In that case, several other design parameters can be changed (see e.g. Maus et al., 2010, for the optimization of this kind of designs).

As a consequence of this anticipation, 3 optimal designs were found for 3 amounts of trials in the learning phase. By setting the cut-off time of the high-pass filter of these designs low enough (longer cut-off period) more efficient designs were obtained. We repeat that an increase up to 60 % can be achieved. However, this is at the price of a reduced ability to remove low frequency noise such as drift. Of course, increasing the cut-off period also implicates the efficiency of the original design. So, designs are only better if they outperform the original design, taking into account the changing efficiency because of the change in high-pass filters.

For the optimal designs (see Table 10) this starts at about 130s for the first contrast and from about 140s the designs are optimal for both contrasts.

The higher cut-off time The higher optimal high-pass filter cut-off should come from the fact that the blocks become different (since we allowed in the protocol for a longer scanning period). By lowering the cut-off of the high-pass filter one thus cuts in the frequency signal
of the occurrence of the blocks. The signal solely related to the block might thus get lost in that case. This results in the fact that for the optimization with the high-pass filter settings identical to the original study, the original study appears to be the optimal. This raises the question whether it would have been possible at all to detect a better design at the same high-pass filter cut-off.

In Table 10 we present again the design graphically represented in Figure 10. We add however one design to control for the high-pass filter cut-off. This design consists of 1235 scans and has further minimal changes compared to the original design. The only change is the reduction in trials in the learning condition. These trials are recuperated in the test/control phase, and thus increasing the efficiency since the contrasts only involve the test/control phases. From Figure 10 it follows that better designs at the original high-pass filter cut-off can be constructed, even within the additional restriction where the length was kept identical. The need for a higher cut-off seems thus to be the consequence of the protocol we utilized as we allowed for more scanning moments and thus the possibility of longer blocks.

<table>
<thead>
<tr>
<th>ID</th>
<th>Trial</th>
<th>n Learn.</th>
<th>nT/C.</th>
<th>Eff. C1</th>
<th>Eff. C1</th>
<th>n scans</th>
<th>Av. Eff.</th>
<th>Av. order</th>
</tr>
</thead>
<tbody>
<tr>
<td>12734</td>
<td>2.8</td>
<td>8</td>
<td>15</td>
<td>23.5289</td>
<td>105.6972</td>
<td>1343</td>
<td>64.6131</td>
<td>101.5</td>
</tr>
<tr>
<td>12564</td>
<td>2.5</td>
<td>10</td>
<td>16</td>
<td>22.3358</td>
<td>100.7118</td>
<td>1329</td>
<td>61.5238</td>
<td>16.0</td>
</tr>
<tr>
<td>12573</td>
<td>2.5</td>
<td>11</td>
<td>16</td>
<td>22.3369</td>
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<td>1353</td>
<td>61.5270</td>
<td>37</td>
</tr>
<tr>
<td>12732</td>
<td>2.8</td>
<td>8</td>
<td>13</td>
<td>20.3684</td>
<td>91.9642</td>
<td>1235</td>
<td>56.1663</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>2.8</td>
<td>10</td>
<td>12</td>
<td>18.8637</td>
<td>85.4759</td>
<td>1235</td>
<td>52.1698</td>
<td></td>
</tr>
</tbody>
</table>

Table 10: Design properties of the 3 best designs, the design with 1235 scans (as in the original design) and the original design.

**The implications of the unequal length** By allowing for a cost in scanning duration, which resulted in designs with more scanning moments, we increased the design space $\Xi$. We motivated this because of the numerous imposed restrictions. Of course, one can argue that more is always better, from the results presented in Table 6, Table 7, and Table 8 we demonstrated however that more optimal designs do not automatically involve more scans. We furthermore remark that this will impact the effects of the autocorrelation model. This was however not investigated here as the model of the autocorrelation was not taken into account in the search for more optimal designs.
4.2 The optimization of the event-related design of Santens et al. (2010)

We demonstrated that by means of the implemented search algorithm of Kao et al. (2009) a more optimal trial order can be found. This is a first step in improving the optimality of the design. We remind that the average c-optimality is a meaningless number because both cannot be compared as they represent different contrasts. However, since the algorithm of Kao et al. (2009) needs one numerical value (for the numerical optimality criterion) to optimize we preferred this. We acknowledge that an alternative approach might have been the implementation of a $C$-optimality criterion. However, as the contrasts were not tested jointly in the original study, this was not preferred. Moreover, as the entire design space is not determined at every step it is unfeasible to determine the rank order of the designs. Consequently, we considered the average as the most appropriate measure.

We only demonstrated that one optimal trial order, better than the one at hand, can be achieved. The search algorithm can easily be run for every subject separately, so different pseudo-random but optimal trial orders can be determined. Afterwards, the most efficient jitter consequence can be determined. We consider it better to pick the jitter consequence yielding the most efficient designs. Consequently, an ingenious choice of the jitter can further
optimize the optimal trial order.

We furthermore acknowledged that the trial order differed per participant in the original study. This means that the reference design here is not fully representative but rather an exemplum. Moreover, we could not incorporate the variability due to randomness of the trial order as we only had the data of one participant. However, the variability due to the jitter interval could be plotted by means of a prediction interval similar to Figure 9. This is depicted in Figure 11. As can be seen, it should be noted that the jitter settings used in the original study for this particular subject is one of the better jitter orders. The average efficiency of the 200 random jitter orders is still more than 10 % lower than the average jittering order original trial order. This holds for both contrasts.

\[\text{Figure 11: Effects of the jittering interval on the high-pass filter cut-off value.}\]
5 Conclusions

In sum, we determined the efficiency of the original designs and improved manipulatable design factors so that more optimal designs emerged for the two study designs. For the blocked design of Van Opstal et al. (2008), we determined 3 designs as more optimal. However, taking into account the various design restrictions, we found that due to our protocol a higher cut-off for the high-pass filter was needed. With the application of a higher cut-off we found designs that are up to 50% better than the original design (with the application of the high-pass filter cut-off). Additionally we demonstrated that, even for a design with an equal length a more efficient design could be found. In the optimization of this study design it is nicely illustrated that optimization can be performed. It is nonetheless also a search for the right balance between numerical efficiency and psychological feasibility the design.

For the event-related design of Santens et al. (2010) we found that after the application of the optimal design search algorithm of Kao et al. (2009) a more efficient trial order could be determined. We furthermore demonstrated that with a clever choice of the jittering additional improvements could be made. This resulted in a trial order that was up to 15% better than the original design (with the application of the high-pass filter cut-off).

We conclude that for both design types improvements could be have been made, albeit with caution. We believe that it is however worth the effort to search for more optimal designs as these designs will have less unwanted variance. Moreover, as many of the tool are already (partly) implemented, the efficiency can easily be determined prior to the study. For event-related designs we suggest the use of the already implemented genetic search algorithm of Kao et al. (2009). Additionally, it is important to search for the application of jittering settings that further optimize the design.
A Appendix

A.1 Additional Figures

**Figure 12:** The efficiency with respect to the duration of the familiarisation period per trial duration.

**Figure 13:** The efficiency with respect to the duration of the instruction time per trial duration.
A.2 R and MATLAB® code

See CD-ROM.
References


Wellcome Trust Centre for Neuroimaging, . (2010). SPM 8. URL [http://www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)