Real-time electrophysiology in cognitive neuroscience : towards adaptive paradigms to study perceptual learning and decision making in humans

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ABSTRACT

Our personal history makes us what we are. This common sentence reflects the dynamical nature of the brain, which enables us to learn and optimize our decisions in an ever-changing environment. In cognitive neuroscience, the neuronal underpinnings of human learning and decision-making have been studied thoroughly using psychophysical measures as well as concurrent neuroimaging and electrophysiological observations. Perceptual decision tasks, like those used with animal models, are most often used to unravel the computational and physiological core processes at stake, which nevertheless remain largely unknown. Importantly, psychological as well as physiological models of such processes have recently become more biologically plausible, leading to more realistic (and more complex) generative models of psychophysiological observations. In parallel, the young but exponentially growing field of Brain-Computer Interfaces (BCI) already exploits the plastic properties of the brain but also provides new tools and methods to analyze (mostly) electrophysiological data online. The main objective of this PhD thesis was to explore how the BCI paradigm could help for a better understanding of perceptual learning and decision making processes in humans.

At the empirical level, I studied decisions based on tactile stimuli, namely somatosensory frequency discrimination. More specifically, I showed how an implicit sensory context biases our decisions, as predicted by a sequential Bayesian model of two-alternative forced choices. Moreover, using magnetoencephalography (MEG), I was able to decipher some of the neural correlates of those perceptual adaptive mechanisms. Using a dynamic causal modelling (DCM) approach, my results shed light on the dynamical involvement of frontal areas in implicit learning processes that subsume behavioral optimization. Together, these findings support the hypothesis that an internal perceptual-reference builds up along the course of the experiment.

At the theoretical and methodological levels, I propose a generic view and method of how real-time electrophysiology could be used to optimize hypothesis testing, by adapting the experimental design online. Using simulated data based on recent psychophysiological models of perception, I demonstrated the validity of this online adaptive design optimization (ADO) approach to maximize design efficiency at the individual level. I also discussed the implications of this work for basic and clinical neuroscience as well as BCI itself.

Keywords: brain-computer interfaces (BCI); electrophysiology; perceptual decision-making; contextual dependent learning; adaptive design optimization (ADO); hypothesis testing; generative models of brain functions; cognitive neuroscience

RESUME

Notre expérience passée nous façonne. Cette phrase résonne comme une évidence, elle reflète simplement la nature dynamique de notre cerveau, qui nous permet d'apprendre et de prendre des décisions dans un environnement en constante évolution. En neurosciences cognitives, les substrats neuronaux de l'apprentissage et de la prise de décision chez l'homme ont pu être étudiés à l'aide d'approches psychophysiques couplées à de la neuroimagerie et de l'électrophysiologie. Comme chez l'animal, ce sont le plus souvent des tâches de décisions perceptuelles qui ont été mises en œuvre pour élucider les processus psychophysiologiques sous-jacents, lesquels demeurent néanmoins en grande partie incompris. Récemment, les modèles computationnels de ces processus se sont raffinés et complexifiés pour prendre la forme de modèles génératifs des données psychophysiologiques de plus en plus réalistes d'un point de vue neurobiologique et biophysique. Dans le même temps, le nouveau champ de recherche des interfaces cerveau-machine (ICM) s'est développé de manière exponentielle et exploite déjà les propriétés plastiques de notre cerveau. Il apporte également de nouveaux outils et de nouvelles méthodes d'analyse des données électrophysiologiques en temps-réel. L'objectif principal de cette thèse était d'explorer comment le paradigme de l'électrophysiologie temps-réel peut contribuer à élucider les processus d'apprentissage et de prise de décision perceptive chez l'homme.

Au niveau expérimental, j'ai étudié les décisions perceptives somatosensorielles grâce à des tâches de discrimination de fréquence tactile. En particulier, j'ai montré comment un contexte sensoriel implicite peut influer sur nos décisions, comme prédit par un modèle Bayésien séquentiel de choix forcé à deux alternatives. De plus, grâce à la magnétoencéphalographie (MEG), j'ai pu étudier les mécanismes neuronaux qui sous-tendent cette adaptation perceptive. A l'aide de l'approche par modèle causal dynamique (DCM), mes résultats mettent en lumière l'évolution de l'implication des régions frontales au cours de l'apprentissage implicite, en lien avec l'optimisation de la performance comportementale dans ce type de tâche. L'ensemble de ces résultats renforce l'hypothèse de la construction implicite d'un a priori ou d'une référence interne au cours de l'expérience.

Aux niveaux théoriques et méthodologiques, j'ai proposé une vue générique de la façon dont l'électrophysiologie temps-réel pourrait être utilisée pour optimiser les tests d'hypothèses, en adaptant le dessin expérimental en ligne. En utilisant des données simulées et sur la base de modèles psychophysiologiques récents de la perception, j'ai pu fournir une première validation de cette démarche adaptative pour maximiser l'efficacité du dessin expérimental au niveau individuel. Je discute enfin les implications de ce travail en neurosciences fondamentales et cliniques ainsi que pour les ICM.

Mots-clés: Interface cerveau-machine (ICM); électrophysiologie; décision perceptuelles; apprentissage contextuel; expérience adaptative optimisée; test d'hypothèses; modèles génératifs de fonctions cérébrales; neurosciences cognitive

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PREAMBLE

It might be argued that the task of the neuroscientist, the task of understanding the behavior and capturing the hidden vagaries of human brain activities into cause-effect mechanical processes, is a more difficult one than that of any other scientist. Certainly the problem is enormously complex. However, a lot of progress has been made with the help of new technologies. Obviously neuroscience is a convergent science intimately related to diverse fields such as biology, psychology and physiology but also mathematics, computer science and engineering. Together, these fields are involved in the development of neuroimaging techniques which provide new tools to observe brain processes. Today, such improvements provide direct access in real-time to brain activity through brain-computer interface (BCI) devices. I claim that such developments will change the way of conducting neuroscience experiments in the laboratory, by providing the opportunity to investigate brain processes interacting with the environment in a controlled and optimized fashion. We know that the brain demonstrates an important adaptation ability through plasticity and learning mechanisms. Current scientific models describe brain processes, such as perceptual decision-making, while taking into account their dynamical aspect. Actually the neuroscience community needs dynamical models to refine hypothesis about brain function. At the same time, basic research requires adaptive and dynamical experimental tools to investigate efficiently such models.

The aim of my PhD thesis is to further the understanding about the dynamic of brain perceptual learning and to provide a proof of concept for a new approach to investigate the dynamical aspect of brain processes using recent developments in computer science and BCI. In the first chapter of this introduction, I describe how BCI research have led to a new interactive and dynamical experimental environment. Then in a second chapter, I show how empirical studies in cognitive neuroscience have led to recent models of perception and sensory contextual learning models that become more realistic and take into account the dynamical aspect of the brain-environment interaction. Considering that each of these chapters could represent a full research career, the reader should not expect to find a complete presentation of these topics, but rather an overview of my work's context. Finally in a third chapter, I present the objectives of my thesis and introduce the two main studies:

- an experimental study allowing us to refine assumptions behind the notion of contextual dependent perceptual learning

- and a theoretical study with simulated data in which I demonstrate and validate the benefits of using real-time electrophysiology to improve hypothesis testing about perceptual learning processes in cognitive neuroscience.

CHAPTER I. BRAIN COMPUTER INTERFACE (BCI)

The aim of the present chapter is to give an overview about brain computer interfaces. I will first try to give a general definition of what could be called a brain-computer interface (BCI), based on recent discoveries that participate to the history of the field. Second, I will illustrate several applications from the field and develop the recent use of real-time electrophysiology. Finally I will explain how BCI could provide an interesting way to conduct experiments in the laboratory. Such motivations and imagination of future applications were the first steps underlying the work described in this thesis.

1.1. DEFINITION AND APPLICATION OVERVIEW

1.1.1. DEFINITION

In a broad sense, brain-computer interfaces (BCIs) refer to direct communication between the brain and an external device, bypassing the usual sensory or motor pathways. Obviously the external device can take different forms, from a simple computer to a sophisticated robotic arm for instance. BCI research and development are an interdisciplinary challenge involving neurobiology, cognitive science, psychology, engineering, mathematics, computer science and medical science. Recently BCI has started to slowly infiltrate business market and novel actors are now part of the landscape: business managers, marketing managers, journalists and ethicists. Such a diversity of players raises important ethical issue, starting by a correct and clear definition of a BCI. A few years ago, a survey was proposed to 145 BCI researchers at the 4th International BCI conference, which took place in May–June 2010 in Asilomar, California (Nijboer et al., 2011). The authors assessed respondents' opinions about a number of topics. They investigated preferences for terminology and definitions relating to BCIs (see Figure 1). If the use of cerebral rhythms to control an external machine clearly belongs to the BCI field, others systems remain controversial. This survey showed how it is difficult to precisely define the broad family of BCI applications.

Over the past 20 years, productive BCI research programs have arisen encouraged by new understanding of brain functions and by the advent of powerful technical equipment. Obviously the first goal of BCI remains to provide augmentated communication and control technology for people with disabilities such as severe neuromuscular disorders, amyotrophic lateral sclerosis, brainstem stroke and spinal cord injury. Present-day BCIs determine the intent of the user from a variety of different electrophysiological signals (see Figure 2): slow cortical potentials (SCPs) (Kübler et al., 2001; Hinterberger et al., 2004), P300 potentials (Farwell and Donchin, 1988; Perrin et al., 2012; Mayaud et al., 2013), mu or beta rhythms recorded from the scalp (McFarland and Wolpaw, 2005;

Thomas et al., 2013) and cortical neuronal activity recorded from implanted electrodes (Donoghue et al., 2007; Hochberg et al., 2012). Future progress will depend on identification of these signals, whether evoked potentials, spontaneous rhythms, or neuronal firing rates, that reflect hidden mental intents.

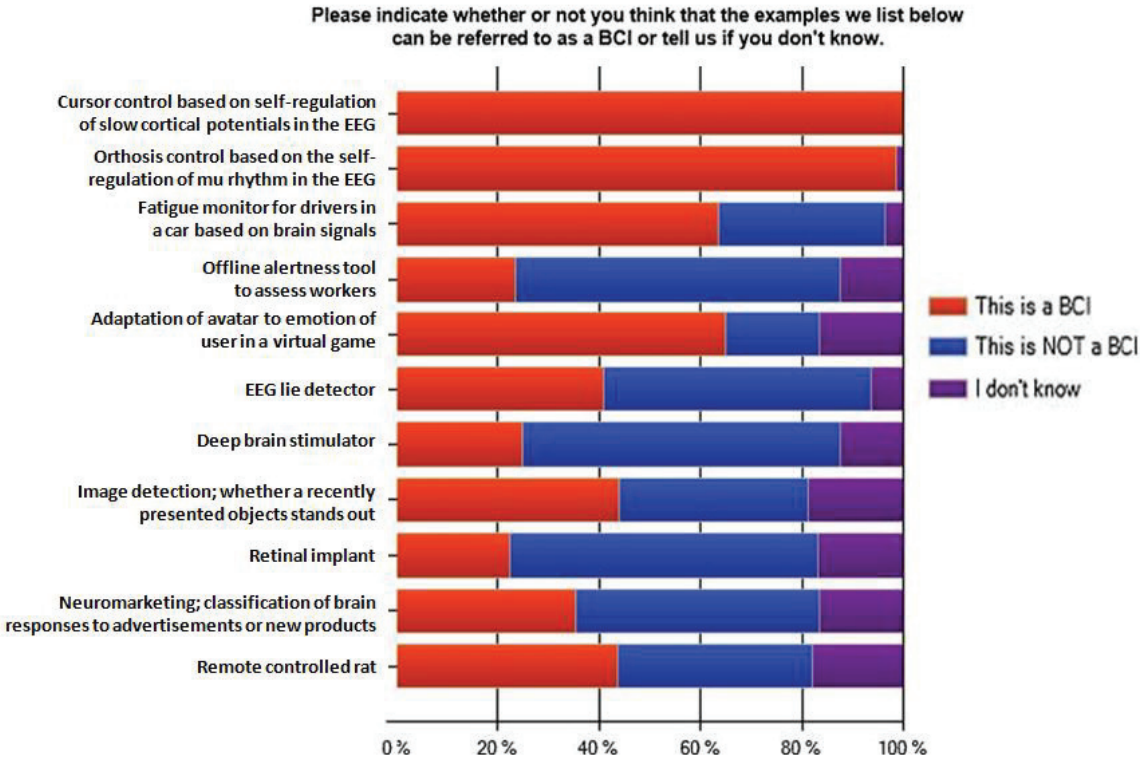


Figure 1: The percentage of people who did (*red*) or did not (*blue*) consider the listed example as a BCI or who did not know (*purple bar*). Adapted from Nijboer et al., 2011.

Thus a BCI is a system that can recognize a specific set of patterns in brain signals following five consecutive stages: signal acquisition, preprocessing (or signal enhancement), feature extraction, classification, and the control interface. The signal acquisition stage captures the brain signals and may also perform noise reduction and artifact processing (e.g. muscular activity, blink…). The preprocessing stage prepares the signals in a suitable form for further processing. The feature extraction stage identifies discriminative information in the brain signals. Once measured, the signal is mapped onto a vector containing effective and discriminant features from the observed signals. The classification stage classifies the signals taking the feature vectors into account. The choice of good discriminative features is therefore essential to achieve effective pattern recognition, in order to decipher the user's intentions. Finally the control interface stage translates the classified signals into meaningful commands for any connected device.

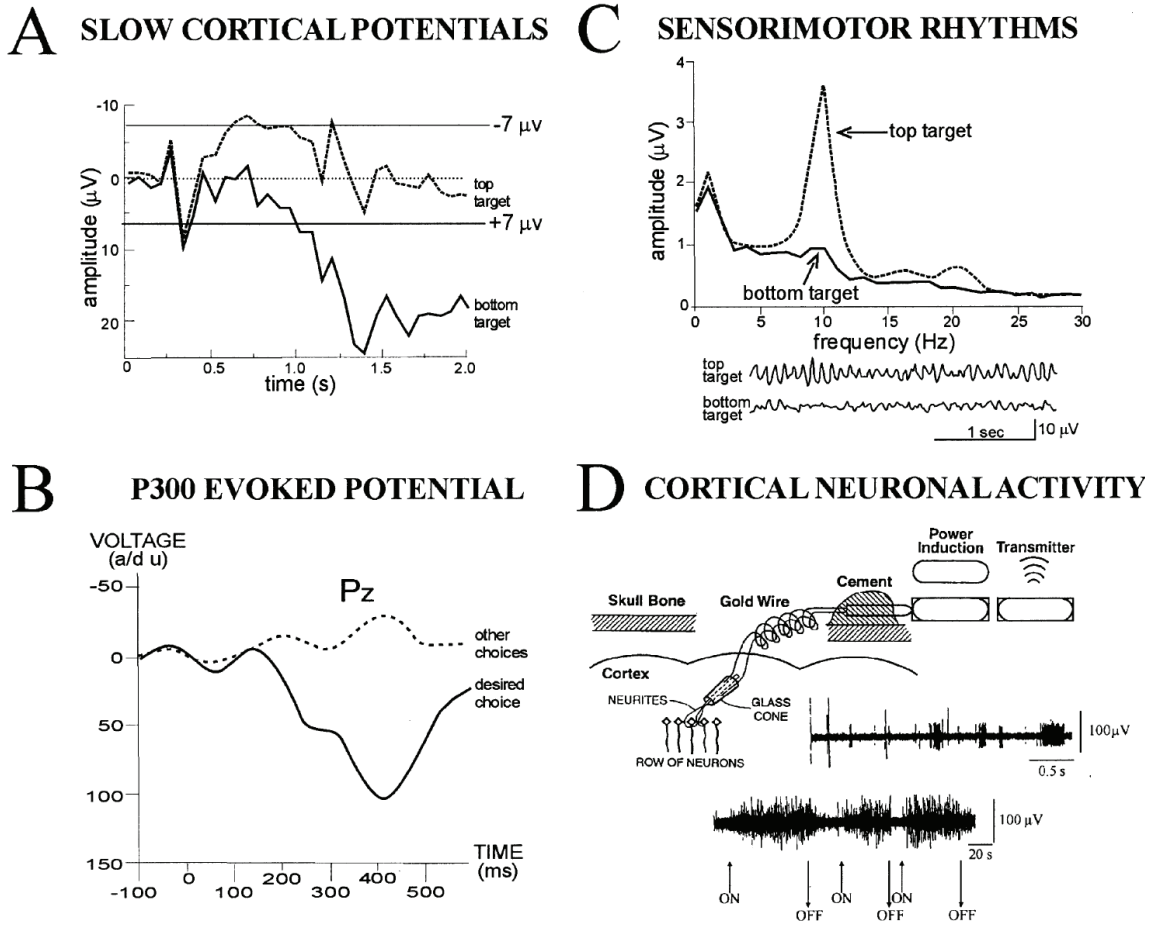


Figure 2: Human BCI electrophysiological signal types (from Wolpaw et al., 2002). A-C are non-invasive methods, D is invasive. **(A) SCP BCI**. Scalp EEG is recorded from the vertex. Users learn to control SCP to move a cursor toward a target at the bottom (more positive SCP) or top (more negative SCP) on a computer screen. **(B) P300 BCI**. A matrix of possible choices is visually presented and flash in succession while scalp EEG is recorded over the centroparietal area. Only the choice directly looked at by the user evokes a large P300 potential (i.e. a positive potential about 300ms after the flash). **(C) Sensorimotor rhythm BCI**. Scalp EEG is recorded over sensorimotor cortex. Users control the amplitude of a 8-12Hz mu and 15-25Hz beta rhythms to move a cursor to a target at the top or at the bottom of the screen. Frequency spectra show that control is allowed based on amplitude variation of sensorimotor rhythms (here clearly the mu-frequency band). **(D) Cortical neuronal BCI**. Electrodes implanted in motor cortex detect action potentials and local field potentials of multi-unit or single cortical neurons (traces). Users learn to control neuronal firing rate to move a cursor to select targets (letters or icons) on a screen.

Even if BCI applications seem to be quite recent, the idea of sampling in real-time cerebral activity is far from new and has fed several fantasies in 20th century movies. Hans Berger, the inventor of electroencephalography (EEG) already speculated in 1929 that someone could read the mind state based on the EEG signal using clever mathematical analyses (Berger, 1929). In the 1950s, Jose Manuel Rodriguez Delgado, a professor of physiology at Yale University, was a pioneer for implanting electrode arrays in cats, monkeys, bulls and even humans (Horgan, 2005). For instance his work was the first allowing external control of the activity of brain regions involved in motor function (Delgado et al., 1976), emotions (Delgado et al., 1956) or food intake (Delgado and Anand, 1953). However, Delgado limited his human research to implanted epileptic patients because the therapeutic benefits of implants were unreliable and highly subject dependent (Mahl et al., 1964). Even though his work was highly criticized by his contemporary researchers, Delgado opened the way for further

investigations (Horgan, 2005). Around the same time, Fetz and colleagues concluded that monkeys were able to learn to control neurons located in their primary motor cortices using a reinforcement conditioning technique (Fetz, 1969). For the first time these results revealed the ability of a living being to control the electrical activity of its own neurons. However, the specific term of "Brain Computer Interface" has its origin in the 1970s. The first scientific publications using this term are those of Jacques Vidal from the University of California Los Angeles (UCLA). The idea of a direct brain-computer communication emerges from the belief that electrophysiological data are not just composed of stochastic fluctuations but also contain a complex signal mixture providing information about cerebral functions and brain states (Vidal, 1973). A few years later, Niels Birbaumer's team showed the ability of human to voluntarily control slow cortical potentials (SCP) via neurofeedback (Elbert et al., 1980). Since the 1980s, a tremendous number of studies on humans or animals has focused on technical development for data analysis, in order to improve BCI efficiency for communication and control (Wolpaw et al., 2002).

The number of articles published in the BCI field has increased exponentially over the past decade (see Figure 3). Successful studies on brain signal phenomena have promoted these advances. The maturity of neuroimaging techniques and development of computer hardware and software has allowed more sophisticated online analysis, in such a way that interest goes now beyond the laboratory or the clinical environments. For instance, specialized companies such as Emotiv or Neurosky have already developed some initial applications oriented towards the general public. Today, several types of applications based on online data acquisition are already available and are being actively investigated.

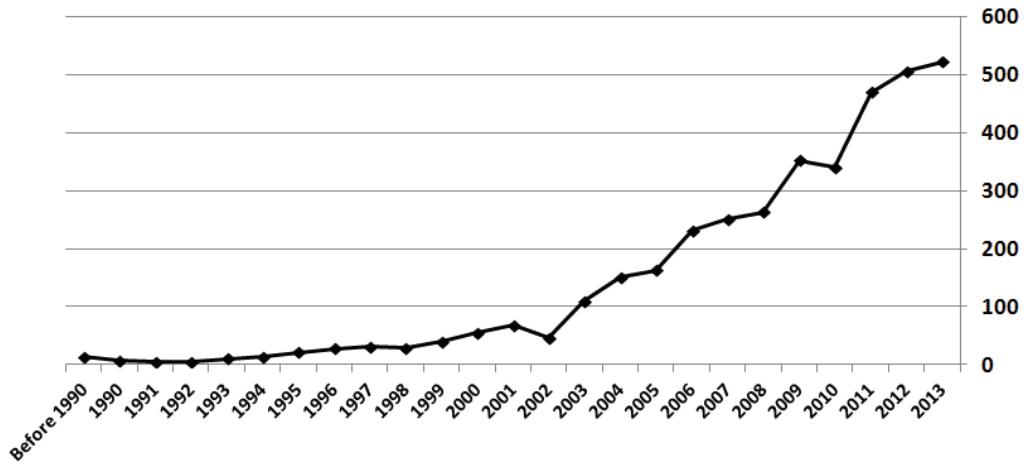


Figure 3: Number of publications referenced in PubMed with the keyword : "Brain Computer Interface".

1.1.2. CURRENT APPLICATIONS

Obviously BCI developments are mostly driven by clinical applications. Its use focuses on the rehabilitation of disabled people in relation to communication or movement. However, another clinical application is real-time feedback, used by the medical staff for diagnosis or for directly informing the patient about his brain activity. Furthermore, the BCI context could be used to improve the gaming experience. I will introduce and provide an overview of some of these applications.

Restorative BCI (Neuroprosthetics & Communication)

People live longer but an increasing number of people suffer from conditions that affect their capacity to communicate, to interact with their environment or limit their mobility (World Health Organization, 2011). Handicapped people suffering from disabilities due to stroke, neurodegenerative disorders, hereditary myopathies or traumatic injuries, would benefit most from assistive BCI technologies. The first big challenge for the field is to make some major progress in the development of assistive apparatuses for paralyzed people. As mentioned in the first paragraph, the idea is to use brain signals to directly control assistive machines. In most cases, disabled people can use residual movements recorded with the electromyogram (EMG) to control external devises. Unfortunately, a few disabled people do not have any residual movement, in which case a BCI could be the only way to provide rehabilitation of communication or movement. The main idea is then to use the activity of healthy motor brain areas, which in many cases of paralysis remain capable of generating motor commands despite being disconnected from the body's effectors (Mattia et al., 2009). Today, many studies on monkeys or humans have shown that invasive technologies, such as implanted multielectrode-arrays in motor cortical areas, allow fine control of external robotic arms (Hochberg et al., 2006, 2012; Donoghue et al., 2007). Using invasive recordings and stimulations, it is hoped that BCI could be used to restore complete sensorimotor functions of the paralyzed or absent limbs. Along this line, Miguel Nicolelis' group, at Duke University, published a monkey study in which invasive recording within the primary motor cortex was coupled with intracortical microstimulation (ICMS) of the primary somatosensory cortex (O'Doherty et al., 2011). This operation is called Brain-Machine-Brain Interface (BMBI) and improves the control learning ability of monkeys based on direct "tactile" feedback of virtual targets explored on a screen. These results suggest that clinical motor neuroprostheses might benefit from the addition of ICMS to generate artificial somatic perceptions associated with mechanical or robotic prostheses (Lebedev et al., 2011). Human ability to control a robotic arm or a wheelchair with motor imagery has also been investigated using several non-invasive techniques such as electroencephalography (EEG) (Galán et al., 2008), magnetoencephalography (MEG) (Buch et al., 2008) or functional magnetic resonance imaging (fMRI) (Lee et al., 2009). Such applications are based on the similarity in brain activity modulation during movement imagination and real execution (Pfurtscheller, 2000). Some studies propose to combine several types of markers (P300

and mu/beta rhythms) recorded with EEG to increase the number of possible commands or simply to increase the information gathered and therefore the accuracy of the BCI (Allison et al., 2010). Today, researchers and medical staffs are working together to find the best way to exploit brain signals and residual motor activity in order to combine them in a hybrid-BCI system (Allison et al., 2012). An important advantage of including other biosignals into BCI control relates to the improved reliability and usability in daily life, but also the degree of self-efficacy, a dimension that should not be underestimated in acceptance of such technology, but also in the context of restorative BCI training for example.

Such pathological context could imply a decrease or even an absence of higher motor or cognitive functions, such as language and other forms of basic communication (writing, pointing, yes/no answering…). Once again, the BCI field provides solutions based on electrophysiological signals. Rehabilitation of communication with EEG has already been successfully investigated for many years using the P300-speller (Farwell and Donchin, 1988). As its name suggests, it allows a participant to spell letters and words towards sentences. The very generic method is to select an item in a list based on a successive stimulation flash paradigm (see Figure 2 B). Today such BCI protocol can be optimized to improve speed and accuracy using clever adaptive methods and online automatic error correction (Perrin et al., 2012). Others spellers are based on different electrophysiological markers: sensorimotor oscillatory activities (Pfurtscheller et al., 1998), steady-state visual evoked potentials (SSVEP) (Müller-Putz et al., 2005), motion-onset visual response (N200 component) (Hong et al., 2009) or slow cortical potentials (SCPs) (Birbaumer et al., 1999). In addition, one recent invasive BCI study on a human volunteer suffering from locked-in syndrome (severe paralysis) reports a continuous decoding of neuronal activity in motor cortex during attempted speech, translated into auditory parameters for a real-time speech synthesizer (Guenther et al., 2009). This single case study highlights the feasibility of neural prostheses providing synthetic speech, although this study was limited to the volunteer's vowel productions. Another study using electrocorticography (ECoG) signals in humans suggests that it is possible to decode and also characterize the cortical substrates involved in the discrimination between distinct vowels and consonants (Pei et al., 2011). These findings demonstrate that ECoG signals associated with different imagined phoneme articulation can enable invasively-monitored human patients to control a one-dimensional computer cursor rapidly and accurately on a screen (Leuthardt et al., 2011). In that case, the authors suggest that the cortical network associated with speech could provide an additional cognitive and physiologic substrate for communication BCI operation. At the moment, the limitation of available reliable neural markers forces researchers to explore different cortical networks to decode subjects' intentions.

Clearly BCIs are not yet able to fly airplanes and are not likely to do so anytime soon. At least they can provide useful actions for highly disabled people, such as answering simple questions quickly, control the environment (e.g. lights, television…), perform slow word processing or even

operate a neuroprosthesis. Nevertheless, the future value of BCI technology will always depend on how much we understand brain function and on the reliability of the brain markers identified using the available recording techniques.

Diagnosis BCI

BCI developments based on neuroimaging and electrophysiology have provided a number of new tools for assessing patients who clinically appear to be in a vegetative state (a medical condition in which a patient shows sustained unresponsiveness and does not show evidence of awareness). To do this, one does not need a high information transfer rate. In that sense the real-time fMRI (rtfMRI) technique has provided some interesting results and perspectives (Christopher deCharms, 2008). For instance rtfMRI could potentially be used to communicate or to determine the state of consciousness of a patient in an apparently persistent vegetative state. In 2006, a study investigated the possibility of exploring the state of consciousness in a 23 year old woman who fulfilled all of the internationally agreed clinical criteria for the vegetative state (Owen et al., 2006). She was shown to be covertly aware and able to respond to commands by modulating her fMRI activity. The experimenters verbally instructed her to imagine either playing tennis or walking through her house, although it was unclear whether she could hear or understand them. Resulting activations in supplementary motor area (SMA) and parahippocampal cortices (PPA) lead the authors to conclude that she had performed the task. A few years later, different teams collaborated and tried to apply a similar technique in a study involving 54 patients with consciousness disorders (Monti et al., 2010). Their results showed that only 5 patients were able to willfully modulate their brain activity, reflecting some awareness and cognition and suggesting a potential reclassification of their state of consciousness. Obviously, to the patient or their family, even a single communication session could be of immense value. In spite of this apparent success in detecting covert awareness, performing fMRI on patients who are in vegetative state remains exceptionally challenging. Thereby several groups have sought to explore whether EEG can be used to detect level of consciousness at the bedside based on evoked response potentials (Fischer et al., 2008; Schnakers et al., 2008; Morlet and Fischer, 2013) or motor imagery tasks (Cruse et al., 2011, 2012). These studies reveal awareness and even allow rudimentary communication for some patients who remain entirely behaviorally non-responsive. The implication of such findings may extend the immediate clinical and scientific findings to influencing future legal proceedings (Fernández-Espejo and Owen, 2013).

Curative BCI (Neurofeedback)

Another applications of BCI is neurofeedback training which feeds back information about brain activity to allow for the training of voluntary regulation of brain activity. It has been known for a long time that people can voluntarily regulate some oscillatory activity produced by the brain (Paskewitz and Orne, 1973). Neurofeedback training has since been tested on different pathological

diseases such as attention-deficit hyperactivity disorder (Gevensleben et al., 2012; Lofthouse et al., 2012), epilepsy (Kotchoubey et al., 1999; Sterman and Egner, 2006) and depression (Schneider et al., 1992). Even if such BCI applications were primarily based on recordings using EEG, there is also a literature about rtfMRI used for neurofeedback exploiting the spatial precision of such acquisition (see for review: Weiskopf, 2012). Remarkably, neurofeedback training has been associated with improved behavioral or cognitive performance despite no clear pattern of changes in the EEG most of the time (Vernon, 2005). Such observations suggest that the direct effect of neurofeedback is unclear and motivate further investigation such as well-controlled "sham-neurofeedback" conditions in order to show whether the intention to control a moving bar could be sufficient to engage a brain network involved in cognitive control and produce positive effects (Ninaus et al., 2013).

Gaming BCI

The potential utilization of brain signal to send commands without any movement raises a lot of interest in the entertainment gaming context. Everyone can find on "BCI" games already available and commercialized the net some. Some of them suggest the exploitation of brain activity modulation to control a ball for instance (MindFlex from Mattel Inc.; Force Trainer from Lucas Inc.; Mindball from IP Productive Inc.). In this specific case, one may wonder whether such games, using a single frontal electrode acquisition, are not just based on muscular control and therefore far from the BCI definition. Despite some misconceptions in the use of BCI for gaming, the numbers of applications in the field is increasing. The BCI interaction in gaming can be formalized in two main parts. The interaction could be "explicit" when a participant uses the modulations of his brain activity to control the game, for instance using motor-imagery to control a pinball machine (Tangermann et al., 2008). In contrast, one could use "implicit" or passive BCI interactions to monitor less conscious brain activity modulation, for instance taking alpha band frequency (8-12Hz) as relaxation marker that is used to modify the appearance of a virtual avatar in the game (Nijholt et al., 2009; Bos et al., 2010). Beyond the interests of the general public, other studies investigate the implementation of BCI gaming environments dedicated to severely motor restricted end-users (Holz et al., 2013). For instance, the P300-speller communication interface has been modified to provide an artistic interface called "Brain Painting", enabling creative expression through painting pictures (Zickler et al., 2013). Besides entertainment, BCI-gaming could provide a new experimental environment where two people interact in a new way. Along these lines, our team has developed a P300-BCI version of the famous old fashioned game called "Connect Four" (Maby et al., 2012). Two players compete against each other using their brain activity only and provide an interesting context to study social interactions or effects of motivation. Finally, the involvement of the video game industry in the BCI fields should occur in collaboration with researchers. Nevertheless positive perspectives are expected given the large financial funds coming from the gaming industry for the future development of EEG acquisition system adapted to the constraints of BCI.

1.1.3. REAL-TIME ELECTROPHYSIOLOGY

As we have seen in the last part, BCI applications are diverse and essentially based on real-time interaction between the participants and an external device. The nature of such interaction varies from one application to another but still remains based on real-time acquisition (i.e. single trial processing). Large efforts are currently being made to develop and improve online analysis of brain activity. Additionally, we have seen that electrophysiology techniques are by far the most widely used in BCI, although fMRI has been used successfully in real-time (Christopher deCharms, 2008). One first reason is that is simply the most used technique: EEG is cheap, portable and non-invasive. Moreover, all electrophysiology techniques offer high temporal resolution allowing efficient investigation of the brain activity dynamics which is clearly an advantage for several BCI applications (Millán and Carmena, 2010).

BCI defined by this real-time interaction reacts like any communication or control system, with input (i.e. electrophysiological activity), output (i.e. feedbacks, device commands), components that translate input into output, and a protocol that determines timing and decision-making on the interaction. To understand how real-time acquisition and analysis operate in a same protocol it is necessary to describe the components that translate brain signal into feedback. Figure 4 shows these different elements and their interaction.

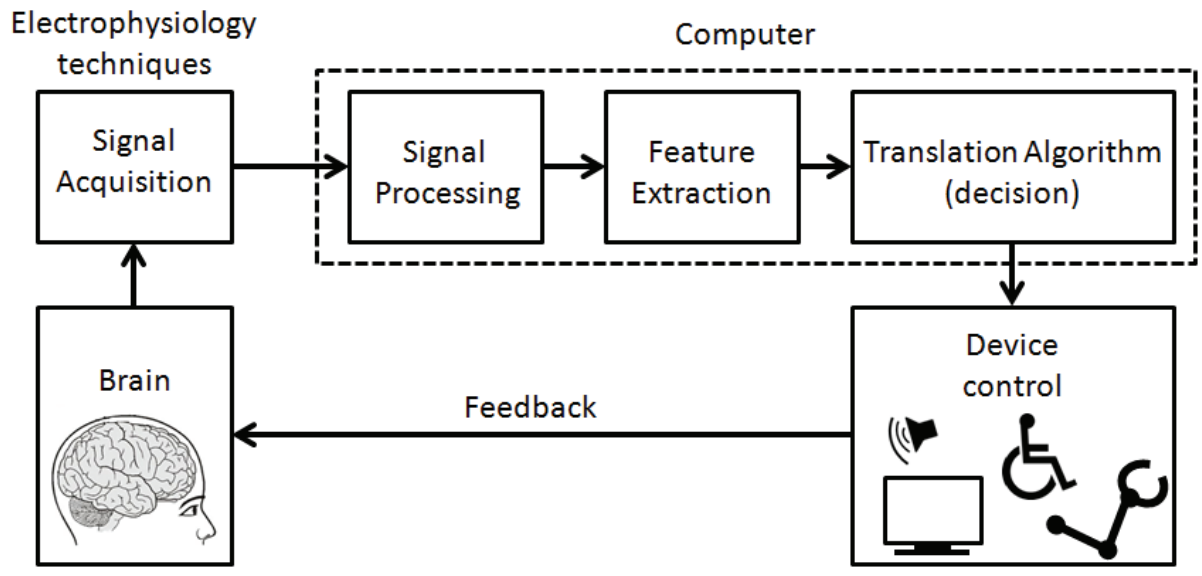


Figure 4: Typical loop operation of a brain-computer interface. The brain activity of the user is registered, physiological markers of interest are extracted, interpreted and translated into decision or numerical commands. A sensory feedback is usually provided to the user.

First, in the signal-acquisition part of BCI operation, the chosen input is acquired by the recorded electrodes, amplified and digitized given a certain sampling rate. The signal is then subjected to one or more of a variety of feature extraction procedures, such as spatial filtering or spectral analyses for instance. The main idea of this step is to extract the signal features that encode the user's commands, obviously based on several assumptions about relevance of spatio-temporal features of brain activity. We have seen that BCI can use signal features in the time domain (i.e. evoked potentials) or the frequency domain (i.e. mu or beta rhythm). This operation step is often made by automatic computation based on expectation-maximization methods in order to separate several classes in the signal and improve classification accuracy. Thus it is possible for a BCI protocol to use a set of autoregressive parameters that correlate with the user's intent but not necessarily reflect specific brain events. In other words, it may be difficult to ensure that the chosen features are not contaminated by EMG, electro-oculography (EOG) or other non-brain artifacts. Improving knowledge about these signal features or electrophysiological markers can help recognize and eliminate the effects of non-brain artifacts and thus guide future BCI developments. The next step is to translate these signal features into device commands-orders that carry out the user's intent. The general purpose is to change independent variables (data or features) into dependent variables (classes or commands). Numerous algorithms and methods have been proposed in order to achieve such data classification (Besserve et al., 2007). Basically, most standard classification methods can be described as a two-step procedure which consists first of a learning phase followed by actual estimation of unknown class labels. During the learning phase, a discriminant function is fitted to a portion of the data generally called the training data set and then, in the second phase, the trained model (achieving optimized separation on the training set) is used to discriminate between the classes from new data sets. In this thesis, we are not going into the details of all these effective algorithms but just pointing that they need to be adaptive. Actually translation algorithm used in BCI protocol must adapt to each user on different levels. First, the algorithm adapts to the user's signal features. In supervised BCI situation, the experiment starts with a training phase where the algorithm learns, based on an initial set of data, the feature distribution corresponding to different commands (different classes). Whether such a training phase is never repeated, the BCI system will continue to be effective only if the user's performance and the data features stay very stable. However, electrophysiological signals typically display variations linked to several hidden parameter (i.e. fatigue, illness, influence of recent events, immediate environment…). Thus, effective BCIs need to take into account such variations and provide translation algorithm with periodic or continuous online adjustments to infer and match as precisely as possible the user's current range of signal feature values to the available range of device command values. Finally the sensorial feedback closes the loop and gives the user information about the command executions. The output can take several forms starting from a simple visual feedback on a computer screen towards fine control of wheelchair or robotic arm. In BCI situations, the feedback is used by the brain to maintain communication, learn utilization and improve the accuracy and speed of the interaction.

The description of standard BCI protocol leads us to address the central fact of BCI interaction: there are two adaptive controllers, the Computer and the user's brain. Obviously the brain possesses a high level of adaptation and BCI signal features are modulated along the experimental time course. In that sense, BCI signal features will be affected by the device commands they are translated into: computer outputs will affect computer inputs. Hopefully, we could expect in the most desirable case that the brain will modify signal features so as to improve BCI operations. However adaptation coming from the computer must be well thought out and controlled because inappropriate adaptation could impair performance of BCI protocol. Because the BCI interaction involved these two adaptive controllers, the user's brain and the Computer system, its design is among the most difficult problems confronting BCI research.

Real-time electrophysiology remains the best opportunity to study such dynamical interaction with high time resolution. I want to describe how such technique can bring out new way to conduct experiments and has motivated recent applications. We argue that real-time electrophysiology techniques taken from the BCI field could reveal new and important modifications in the way that we conduct experiments in a laboratory context. In summary, BCI and real-time electrophysiology in particular provide an interesting context for experimentation in the laboratory due to its active and potentially adaptive environment.

1.2. REAL-TIME COGNITIVE NEUROSCIENCES: MOTIVATIONS AND APPLICATIONS

BCI and particularly real-time electrophysiology have not yet contributed to widespread long-term new therapies. A successful BCI using real-time electrophysiology would enable patients to recover social abilities, namely interacting, communicating, exchanging, and even playing with others. However, despite tremendous efforts and partial success, BCI research has not yet produced clear new therapies with such routine application. The reasons for this failure are not precisely known but clearly involve the difficulty to interpret brain activation from the electrode signal given the hidden neural code. Experts from the field were assembled to discuss the problems and potential solutions (Durand et al., 2014). Many important points were raised, in particular the need for a translation strategy taking basic research to the future BCI applications. Obviously, BCI field must pursue the development of robust techniques to access neural signals and improves the reliability of procedures for user interface. Large efforts are currently being made to develop and improve online analysis of brain activity. However it becomes increasingly evident that the lack of understanding of biological response remains a barrier for further developments. Such limitations motivate the improvement or the renewal of basic research about the brain. While cognitive neuroscience can inform the development of BCI, the reverse might also hold. In that sense, some ideas emerge about how real-time electrophysiology could be used in the laboratories to enhance the creation of new tools in order to investigate brain functions.

One more time, it is the result of a high level collaboration among neuroscientists, engineers and computational scientists, and it seems to provide a new field of research aiming at using real-time for basic neurocognitive investigation with non-clinical purposes. Thus BCI researches increasingly investigate alternative applications in healthy human subjects. Here, I present some examples of such new applications.

Brain state monitoring

One of the big challenges to understand simple brain processes as perceptual decision-making is to establish a causal link between subjective behaviorally reported experiments and measurable brain activity. Traditional difficult sensorimotor or cognitive tasks like the detection of near-threshold stimuli, perceptual decisions in just-noticeable difference discrimination, or high-load memory tasks, revealed moment-to-moment fluctuations of behavioral outcome in reaction to the very same stimuli. There is currently a strong interest in how brain-state fluctuations can impact cognition. These state fluctuations are partly reflected by ongoing oscillatory activity and several studies have set out to find neuronal correlates that explain this variability (Linkenkaer-Hansen et al., 2004; Thut et al., 2006; van Dijk et al., 2008; Mazaheri and Jensen, 2010; VanRullen et al., 2011; Weisz et al., 2014). In particular, these studies that identify from prestimulus intervals in the ongoing EEG/MEG predictors of performance in the subsequent task are potentially relevant for establishing a causal link between brain activity and behavior. Monitoring of brain states and decoding of covert user states evoke a growing interest (Blankertz et al., 2010). Examples of these mental states are the levels of arousal, fatigue, emotion, workload or other variables, for which the brain activity correlates are (at least partially) accessible to measurement. However, identifying which aspects of neuronal activity form a brain state remains a complicated issue. Firstly, relevant brain states are present at multiple time scales (i.e. circadian rhythm, alpha oscillation phase…). Secondly, identification of brain state dynamics usually depends on the behavioral responses. Current methods used by researchers for capturing brain states are questionnaires, analysis of errors made by the participant, or video recording of the experiment. However, all of these methods present clear disadvantages. Questionnaires cannot determine the subject's mind set in real-time (during the execution of the task) but only after, and moreover they could interfere with the task and answers are often impacted by subjectivity. The analysis of error is a difficult method due to the high multi-factorial variability within and between subjects. Finally, video analyses only measure the external behavioral outcome of the subject, and potentially miss internal variation of mental state that would not affect clearly visible behavioral actions. Today, researchers aim to combine electrophysiological recording and real-time data analysis in order to provide a new way to investigate brain states (Blankertz et al., 2010), developing softwares dedicated to real-time MEG/EEG acquisition and analysis (Hartmann et al., 2011; Sudre et al., 2011). With these tools, the non-intrusive evaluation of mental states in real-time and on a single-trial basis, such as an online system with feedback, can be built. Analysis on a single-trial level is the only way to understand

moment-to-moment variability that may lead to a deeper understanding of brain functions. Moreover, this procedure provides information to send stimulations at a specific time based on real-time recording of brain state and depending on the final purpose of the investigation.

Brain State Dependent Stimulation (BSDS)

While, most of the time, participants are tested with a more or less preprogrammed sequence of stimuli (subject to some random factors), it becomes possible to adjust the presentation of stimuli to the momentary brain state of the subject (Jensen et al., 2011). The idea is to investigate the functional role of brain states by introducing stimuli in real-time to subjects depending on the actual state of their brain. Behind this exciting idea, several simple questions are hidden: what reliable brain activity markers could be used ? What kind of stimulation should be used and when ? And what could be the real advantage of choosing real-time stimulation ?

Actually, a few examples of attempt BSDS study are already available. Obviously, studies focused on clear and reliable brain signal easily (or less difficult) monitored in real-time. Such experiments focused on spontaneous brain activity and mostly investigate alpha ongoing oscillation (~8-12Hz) since it has a strong signal to noise ratio and it is associated to interesting functional cognitive hypothesis as covert attention (Thut et al., 2006; VanRullen et al., 2011) or active inhibition (i.e. sensory gating) (Klimesch et al., 2007; Jensen and Mazaheri, 2010; Haegens et al., 2011a) for instance. Driven by the aim of describing a causal relation between some cognitive hypothesis and pattern of reliable marker, researchers could manipulate stimuli presented to the subject depending on an online characterization of amplitude or phase of alpha oscillation. One example was the effect on phosphene induction of Transcranial Magnetic Stimulation (TMS) that depends on occipito-parietal alpha oscillation amplitude (Romei et al., 2008). It is the same observation for near-threshold perception: lateralized low alpha activity inversely correlates with phosphene or stimulation perception (see Figure 5).

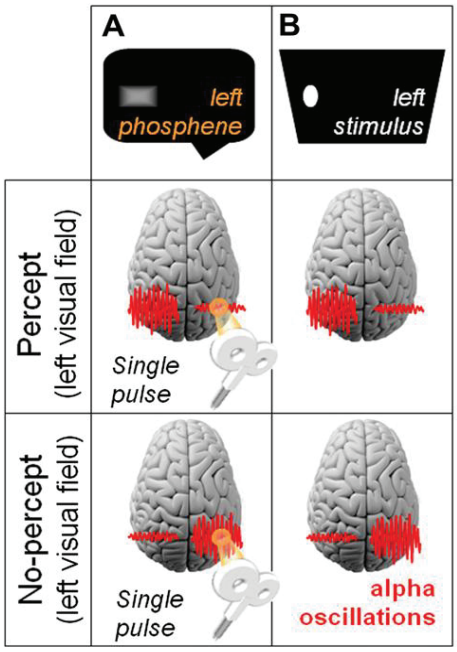


Figure 5: Illustration of brain oscillations prior to stimulus onset and their modulation in TMS/EEG research (extract from Taylor and Thut, 2012). Pre-stimulus alpha-oscillations over occipito-parietal sites (in red) co-vary (spontaneously) with **(A)** phosphene perception as probed via occipital TMS (Romei et al., 2008), and with **(B)** perception of veridical visual stimuli (e.g. Hanslmayr et al., 2007; van Dijk et al., 2008; VanRullen et al., 2011). Low alpha power is linked to high likelihood of detection and high alpha power with a low likelihood (depending on alpha-lateralization over the two hemispheres and visual field of presentation, note that examples are provided for left visual field stimuli only).

Thomas Hartman and colleagues tried to provide a causal, rather than a correlational, evidence and used a BSDS protocol under the ConSole environment to provide real-time recording and send TMS stimulation when alpha is either low or high (Hartmann et al., 2011). Even if they could validate the real-time acquisition protocol, they reproduced partially the results from (Romei et al., 2008), showing that on average trials in which no phosphene was perceived were preceded by higher alpha. However they were not able to show that pre-stimulus alpha power predicted the probability of seeing a phosphene by comparing the responses to high and low alpha trials. The authors proposed further hypothesis to interpret this unexpected result. This might be due to the small number of participants (6 subjects), but they also said that the "high" alpha category seems to be functionally more diverse than simply reflecting inhibitory state and that under certain conditions it may even favor a perception. This could indicate that the relationship between alpha power and behavior is not linear, as other authors previously assumed, but needs to be investigated in details. Actually, a more complex parabolic relationship between prestimulus alpha oscillatory activity and behavioral response has already been found in another context (somatosensory near-threshold detection), where very high and low amplitudes lead to the same performance level (Linkenkaer-Hansen et al., 2004). Thus even if BSDS provides an interesting way to conduct active and online experiment it is still not a guarantee of success for the hypothesis testing challenge.

Related to BSDS, the "double flash" illusion has also been used to investigate the function of ongoing oscillations (Gho and Varela, 1988). When two visual stimuli are flashed with a slight and fixed stimulus-onset asynchrony (SOA), they can either be perceived as two flashes or as a moving light depending on the phase of ongoing alpha oscillations (see Figure 6). In this EEG study the stimuli were delivered depending on the phase of the ongoing alpha activity. The findings demonstrated that the perception could be somewhat manipulated depending on the alpha phase. This result suggests that discrete components in visual perception can be related to brain oscillations. However, VanRullen and colleagues noted that their own attempt to replicate this result in 10 subjects using 600 trials per subject was unsuccessful: they could not find significant correlation between the phase of alpha activity and stimulus perception on a trial-by-trial basis (VanRullen and Koch, 2003). One more time, appears the difficulty to efficiently test functional hypothesis and the BSDS principle seems to be clearly necessary but not sufficient to challenge the investigation of brain ongoing activity and infer their complex causal relationship to behavioral outcomes.

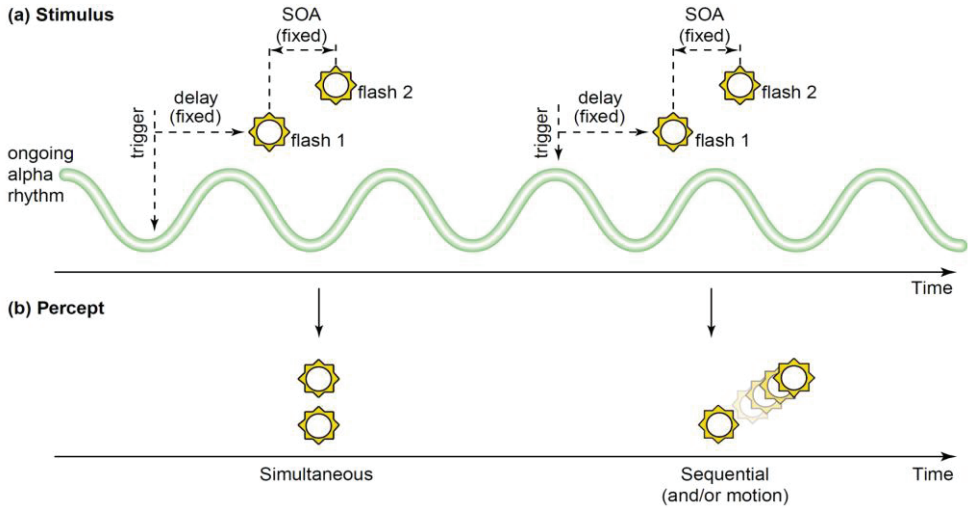


Figure 6: Perception and alpha phase. The perception of a given physical event can be influenced by the phase of the ongoing alpha EEG cycle at which this event takes place. For phases separated by 180°, the perception of two successive visual flashes goes from 'sequential' to 'simultaneous'. (Extracted from VanRullen and Koch, 2003)

In another study the relationship between alpha phase and evoked responses was addressed (Kruglikov and Schiff, 2003). The phase of the ongoing alpha activity was characterized online and the auditory stimuli were then presented as a function of phase. This allowed the authors to demonstrate that the magnitude of the positive evoked potentials at 30 and 50ms (P30 & P50) in response to the sound stimulations were influenced by ongoing alpha phase. Moreover they could extract these notoriously small signals with fewer trials than are customarily required. This study suggests that BSDS, when applied to phase-triggered evoked potential analysis, may in addition to

reducing the number of trials required for averaging, produce more robust neural signals and offer a novel approach for exploring cognitive physiology.

Spontaneous oscillations are not only observed at rest but also during sleep. Oscillations during sleep have been hypothesized to be involved in offline processing of information acquired during the day (Diekelmann and Born, 2010). For instance, it has been proposed that slow wave oscillations reflect the reactivation of recently acquired information. To test this notion, a recent study investigated the consequences of enhancing slow wave activity. During sleep, EEG was used to record the ongoing brain activity. When slow wave activity was detected, a device started to play sounds in phase with brain slow oscillations. These sounds served to enhance the slow wave activity (see Figure 7). The study demonstrated that such enhancement seems to promote sleep-dependent memory consolidation (Ngo et al., 2013). Using this type of BSDS, it was concluded that slow wave sleep is causally related to memory formation.

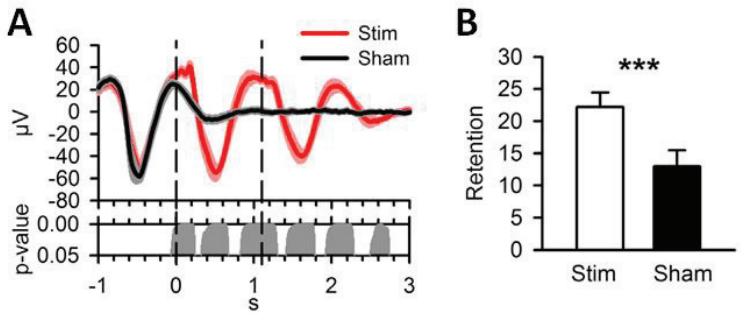


Figure 7: Auditory stimulation in-phase with slow oscillations induces trains of slow oscillations and enhances declarative memory (adapted from Ngo et al., 2013) **(A)** Mean (±SEM) EEG signal (at the Cz electrode) averaged (across subjects) time locked to the first auditory stimulus (t = 0 s) for the Stimulation (red line) and Sham (black) conditions. Bottom panel indicates significant differences between conditions. **(B)** Mean (± SEM) retention of word pairs across sleep for the Stimulation (Stim) and Sham conditions (***$p < 0.001$).

Now, several studies investigate the use of BSDS as a means to enhance the efficacy of repetitive TMS (rTMS) in the clinical context. For instance, rTMS based on EEG activity has been widely proposed as a treatment for major depression (Micoulaud-Franchi and Vion-Dury, 2011). Moreover, one attempt to personalize the rTMS stimulation based on EEG frontal alpha oscillations specific to each patient leads to an indication of a trend toward a greater antidepressant effect (Price et al., 2010). More recently, BSDS coupled with TMS stimulation was investigated in another clinical context. The study examined brain stimulation applied concurrently with motor-imagery of one patient with severe hand paresis to induce more specific use-dependent neural plasticity during motor training for neurorehabilitation. Authors suggested that coupling TMS pulses to ipsilateral sensorimotor desynchronization during motor-imagery significantly increased the excitability of the stimulated motor cortex, an effect not observed in non-BSDS protocols (Gharabaghi et al., 2014). This feasibility study provides a novel neurorehabilitation strategy for stroke patients lacking residual hand function.

However, further investigations on a larger number of patients are necessary before the utility of this novel approach for stroke rehabilitation can be recognized.

This set of studies illustrates how BSDS has been applied in order to gain new insight into the functional role of ongoing brain activity and sometimes in clinical context. Given the growing interest in the online stimulation based on brain states, BSDS is likely to become a more frequently used tool in cognitive neuroscience.

BCI context impacts and expands the way to conduct basic experimental research

We have seen that real-time electrophysiology close-loop protocols allow particularly interesting approach which could improve the way of choosing stimulation during experiment. Actually, the BCI field brings to us several new opportunities to investigate in details functional brain hypothesis. Broadly speaking, it pushes ourselves to refine and identify clear hypotheses about the mapping between brain signal and cognitive processes. First of all, BCI forces researchers to focus on the most robust task-dependent modulations of brain signals (Blankertz et al., 2010). This could serve to ensure that an empirical investigation does not get stuck on a working hypothesis pertaining to aspects of the data being relatively weak. Also when developing a BCI it is essential to control for various confounds such as task difficulty in order to get reliable signals. During this process one often stumbles on new experimental questions pertaining to fundamental aspects that might not have been addressed before. See for instance Bahramisharif et al. (2011) in which modulations of brain activity by covert attention prompted a question on how these changes were modulated by eccentricity. Additionally, due to the fact that BCI protocols like visual P300-Speller are very demanding tasks, it offers an interesting context to investigate human learning processes and motivational impact on feedback evoked responses (Perrin et al., 2012).

Regarding the BCI context, we could dissociate "explicit" interaction (when the subject is aware of the close-loop interaction) and "implicit" interaction (when the subject is unaware). The explicit BCI context remains a very exclusive and specific context of interaction in public mind, probably due to its quite new presence in the media. For instance in P300-speller context, when healthy subjects participate in a BCI experiment, sometimes they could try to challenge and test the reality of this interaction: I was told to spell this letter but if I select another one, what's going on? Is that the computer will do something different if I do mind wandering? What happens if I imagine a sound each time my letter flashes in place of counting?... Obviously, all of these could participate to the subject find his proper user strategy to practice the task, but it reveals the particular aspect of the interaction. In such case, the experimental set-up could be perceived as a second agent (clever or not), or as a mirror of participant performance (or even as a marker of his/her brain signal "quality"). As researcher it is important to be aware of such issues and provide sufficient explanation to avoid misunderstanding and potential bias in the participant behavior. Nevertheless such interaction relying

on explicit, real-time and closed-loop connections is an attractive context for innovative online experiment of social cognition (Schilbach et al., 2009). Actually in daily life our brain always interacts in real-time with the environment, in that sense BCI brings the experimental context to something as more natural and ecological situation. The brain processes are highly dynamical, in this respect model-based approaches need to be thought of as dynamical and adaptive methods. To improve co-adaptation of the BCI context interaction such computational models could also be used to provide clever artificial agents. This puts the BCI experimenter into a rather new situation. Instead of considering the BCI user's brain as a black box and instead of taking a static machine's perspective, the experimenter is forced to adopt a systemic view and to consider the human and artificial agents as a whole (Mattout, 2012). Moreover BCI set-up could be the third artificial agent that links together two real subjects interacting with each other using only their brain activity. Typically the BCI gaming version of the old fashion game "Connect Four", developed in our team, provides a particular and new competitive context to interact with another human (Maby et al., 2012).

BCI context could highly modify the way that we will conduct future experimental study, in the meantime it provides an extraordinary interesting dynamic environment for basic neuroscience at the laboratory. Such dynamical, interactive and complex situations call for computational models of psychophysiological functional mechanisms to ensure efficient investigation of electrophysiological markers involvement (Friston and Dolan, 2010). Uncovering and modeling the neural mechanisms of BCI context interaction will benefit to both basic and clinical real-time applications.

CONCLUSION

In conclusion, new approaches based on online analysis of ongoing brain activity are currently in rapid development. These approaches are amongst others informed by new insight gained from EEG/MEG/fMRI studies in cognitive neuroscience and hold the promise of providing new ways for investigating the brain at work. Thus, although the evolution of BCI is likely to remain driven by important clinical and practical goals, it will also offer a unique family of tools for challenging some of the most fundamental ideas of modern neuroscience (Mussa-Ivaldi and Miller, 2003). For instance, the use of real-time electrophysiology in basic research is starting to modify the way of thinking an experimental design. Actually, the opportunity to adapt stimulation according to brain state offers a new approach to infer brain functions. Moreover it is becoming increasingly obvious that specifying and refining hypotheses (models) about the relationship between electrophysiological markers and brain processes as perceptual decision-making remains necessary. Recently, psychological theories became more biologically plausible, leading to more realistic generative models of psychophysiological observations.

CHAPTER II. PERCEPTUAL DECISION-MAKING

We have seen that BCI research fields will continuously modify the basic research about brain functions and place the participant in interaction explicitly or implicitly with his experimental environment. It is increasingly of interest to focus on how our brain works in interaction with the environment. Numerous neurosciences studies investigated brain processes of such interaction. Regarding the complexity of brain functions, researchers often simplify the situation in the laboratory in order to infer dynamics and organization of the interactive brain. Simply speaking, experiments often investigate how our brain takes information from the external world and how it reacts in response to this information. The process by which information that is gathered from sensory systems is combined and used to influence how we behave in the world is referred to as perceptual decision-making (Heekeren et al., 2008). The aim of the present chapter is to introduce a short overview of the literature of perceptual decision-making. Knowing that this topic could be the subject of several PhD theses, I do not claim that the presentation that I make here is exhaustive. However, I want to give some taste of how empirical research, psychological theories and computational neuroscience are now intermingled in a more comprehensive and realistic model of psychophysiological phenomena behind the notion of perceptual decision-making.

2.1. PROCESSES AND NEURAL CORRELATES

From the time of the ancient philosophers through to the modern pursuits of cognitive neuroscience, it has been a human passion to comprehend the physical basis of what we experience subjectively and how we take decisions that lead to our actions. However, in this historical context, our generation is the first to have access to increasingly direct glimpses of the brain-environment interface, through the science of neuroimaging. It could be seen as our modern capabilities for mapping the physical substrates of our implicit mind mechanisms. Though perceptual decision-making is perhaps rather simplistic relative to the complex decisions we make everyday, understanding the neural processes governing even the most simple decisions will shed light on how we make decisions under uncertainty or contextual variations.

2.1.1. STATE OF THE ART & TYPICAL TASK

There is a vast research history and numerous papers that have investigated the processes by which our brain represents sensory information and how such representations give rise to perception, memory and decision-making (see review: Gold and Shadlen, 2007; Romo and de Lafuente, 2013). Today we know that perceptual decision-making is influenced not only by the sensory information,

but potentially by many others factors such as attention, task difficulty, learning, prior probability of the occurrence of an event and even the outcome of the decision (Shadlen and Kiani, 2013). Traditional psychological theories speculate that the perceptual decision-making process consists of components that act in an hierarchical manner, with serial progression from perception to action (Tversky and Kahneman, 1981). More recent neuroscientific findings indicate that some of the components of this process happen in parallel (van der Meer et al., 2012). Before the development of methods to monitor brain activity during behavior, physiological mechanisms could be inferred only from behavioral tests. When there were no physiological methods that enabled the objective recording of neuronal functions, sensory physiology had to rely essentially on the reporting of subjective percepts. Historically, psychophysical tasks and techniques have shaped the development of experimental cognitive research (Ehrenstein and Ehrenstein, 1999). Neurophysiological work in subjects (humans or non-humans) performing sensory discriminations, combined with computational modeling, have paved the way for neuroimaging studies that aim to understand perceptual decision-making processes in the brain. Today, psychophysical methods and tasks are still used in conjunction with the various neuroimaging and electrophysiological techniques (e.g. single-neuron recording, EEG, MEG, fMRI…) in order to provide neurophysiological findings. In such tasks, the basic principle is to link perceptual experience to physical stimuli. Stimulus characteristics are carefully manipulated and participants are asked to report their perception of the stimuli using simple actions (e.g. button press, eyes saccade movement…). In this context, the investigation of perceptual decision making requires the experimenter to formulate a question that is precise and simple enough to obtain from the participant a convincing answer. In simple perceptual decision-making tasks subjects are often faced with simple problems such as: "Did you perceive the stimulation ?" (e.g. near-threshold (NT) stimulation detection tasks), or: "Which of the two stimuli is larger (intensity, frequency, duration…)?" (e.g. sensory discrimination task). Generalizing the study of perceptual decision making across different species and paradigms can be challenging. Obviously, we can find numerous variations of paradigms in the literature targeting different sensory modalities (see Figure 8). I will quickly describe simple tasks that contribute substantially to the history of the field and that appear to engage perceptual decision mechanisms.

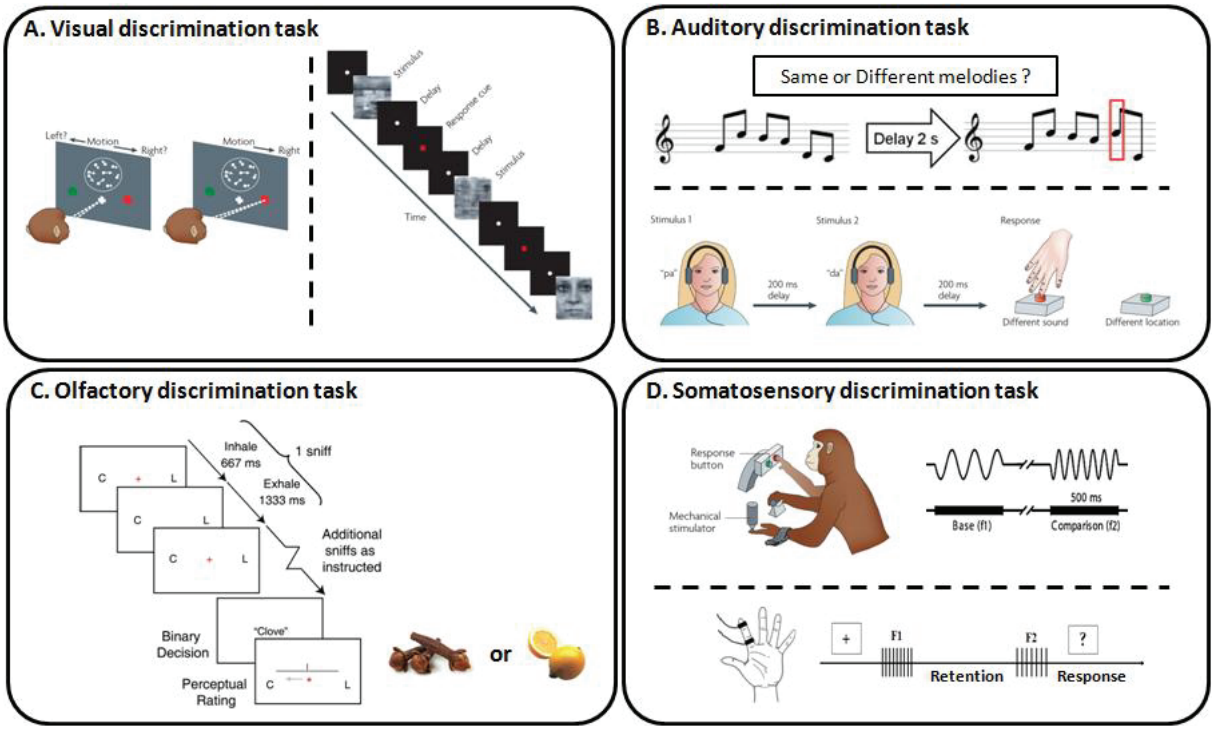


Figure 8: The general experimental approach to study perceptual decision making is to have study subjects (monkeys or humans) perform sensory discriminations. Examples of typical tasks used in different sensory modalities. **(A)** Visual discrimination task. Left panel: Random-dot motion (RDM) direction discrimination task; Right panel: face-house categorization task (adapted from Heekeren et al., 2008). **(B)** Auditory discrimination task. Up panel: melodic tones sequence discrimination (adapted from Albouy et al., 2013); Down panel: syllables discrimination as 2AFC task (Kaiser et al., 2007) in which participants had to decide whether two syllables were the same or different with respect to their identity ("pa" or "ba") or with respect to their perceived location (left or right) (adapted from Heekeren et al., 2008). **(C)** Olfactory discrimination task. 2AFC odor categorization task. Subjects inhaled were instructed to make a given number of sniffs of a mixture of odor composed by eugenol ("clove" odor) and citral ("lemon" odor) in different proportion and they have to decide which of the two percepts dominated the. Visual cues C and L (clove and lemon, respectively) were used to remind subjects which response button corresponded to which choice (adapted from Bowman et al., 2012). **(D)** Somatosensory discrimination task. Up panel: Monkeys subjects have to decide which of the two sequentially presented tactile flutter stimuli has higher frequency (adapted from Romo and Salinas, 2003). Down panel: adapted similar paradigm with electrical tactile frequency stimulation on fingertips of human subjects (adapted from Pleger et al., 2006; Sanchez et al., 2012).

To study perceptual decision making in the visual domain, many studies have used a random-dot motion direction discrimination task (Newsome et al., 1989; Gold and Shadlen, 2007) in which subjects have to decide whether the net motion of a noisy field of dots is in one direction or the opposite direction (for example leftward or rightward) and indicate their choice in most cases with a quick eye movement to the target appropriate side. Also in the visual domain, a frequently used task is a face-house categorization task (Heekeren et al., 2004; Philiastides et al., 2011) in which participants have to decide whether a noisy image presented on a screen was a face or a house and indicate their decision with a button press (see Figure 8A). Furthermore, perceptual decision making has also been investigated in the auditory domain, with researchers using a two-alternative forced choice (2AFC) task in which participants had to decide if two auditory stimulations presented sequentially were the same or different. Such paradigms were mostly used on humans with different auditory stimulation materials such as: syllables (Kaiser and Lutzenberger, 2005), simple sounds (Nahum et al., 2010) or even complete melodies (Albouy et al., 2013) (see Figure 8B). Finally, some studies have investigated

olfactory perceptual decision making using similar 2AFC task with odor stimulations in rats (Miura et al., 2012) or in humans (Bowman et al., 2012) (see Figure 8C).

Here I want focus on the description of one example of a simple task widely used with humans and non-human primates. An experimental paradigm that is well suited to both animal, human, and computational research: the tactile frequency discrimination task (see Figure 8D). It has several properties that make it highly suitable for use as a model system: a time sequential organization of processes involved, straightforward experimental designs that can be translated from animal to human research (or vice versa) with little change, simple and inexpensive experimental apparatus, and similar neural correlates in both humans and animal models (Bancroft and Servos, 2011). Historically, Mountcastle and colleagues pioneered this approach in the 1960s and made a number of important behavioral and electrophysiological observations (Mountcastle et al., 1967, 1969). The paradigm is fairly simple and requires the subject, typically a monkey, to compare the frequency of two tactile stimuli (f1 and f2), separated by a time interval. Subjects have to indicate whether the frequency of the second stimulus (f2 = comparison stimulus) was lower or higher than the frequency of the first stimulus (f1 = base/reference stimulus) (see Figure 9). The range of frequencies used (~10-50Hz) is called the flutter sensation and it has been shown that humans and monkeys have similar abilities for detecting and discriminating tactile stimuli delivered to the hands and in particular to the index finger (Talbot et al., 1968; Mountcastle et al., 1990).

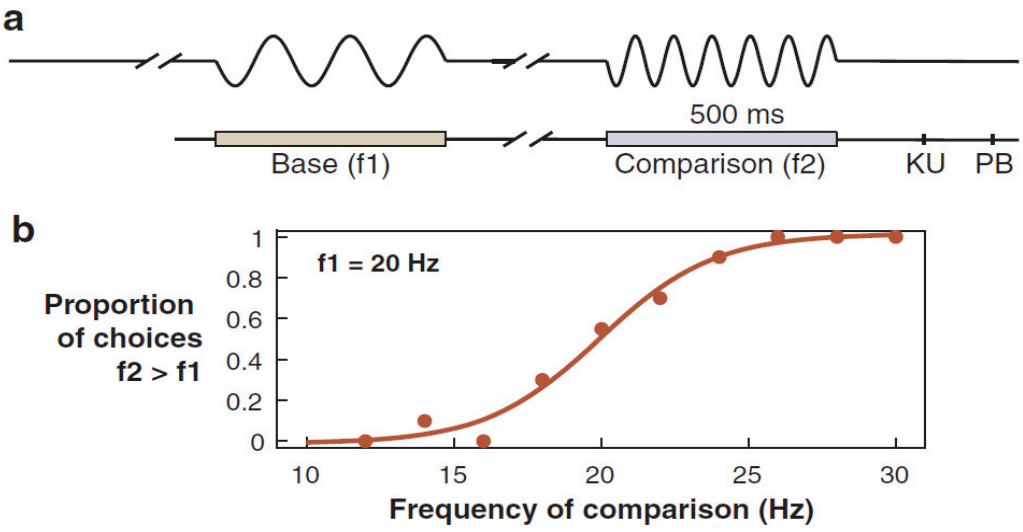


Figure 9: The tactile frequency discrimination task. **(a)** Testing paradigm. A first tactile stimulation is delivered to the finger at base frequency f1. After a delay period, a comparison tactile stimulus is delivered at frequency f2. Then the monkey must decide whether f2>f1, a decision it indicates by releasing a key (KU) and pressing a button (PB) with its free hand. **(b)** Psychometric function. The task is difficult when the base (20Hz) and comparison frequencies are similar (f2 ≈ f1). The task is easy when the difference between the two frequencies exceeds ~8Hz (adapted from Gold and Shadlen, 2007).

Interestingly, the task can be conceptualized as a chain of cognitive operations: encoding the first stimulus frequency (f1), maintaining it in working memory, encoding the second frequency (f2), comparing it with the memory trace that was left by the first one, and finally deciding to communicate the result of the comparison to the motor system (Romo and Salinas, 2003). Such paradigms were traditionally used and are still used to uncover principles of brain organization of how sensory inputs are converted into memories and decision motor reports. Actually, the tactile discrimination task has proven to be a valuable tool to study how behavioral actions are selected according to current and past sensory information (Romo and de Lafuente, 2013). By requiring the subjects to compare two stimuli separated by a delay period, the discrimination task makes it possible to uncover the neuronal mechanism underlying the comparison of working memory information with incoming sensory stimuli potentially modified by internal prior neural state (Carnevale et al., 2012).

2.1.2. KEY PROCESSES & NEUROPHYSIOLOGICAL MARKERS

Cognitive neuroscience is motivated by the precept that a discoverable correspondence exists between mental states and brain states. This precept seems to be supported by remarkable observations and conclusions derived from event-related potentials, oscillatory activity and functional imaging with humans and neurophysiology with behaving monkeys (Schall, 2004). Neuroimaging studies and data analysis methods that link perceptual decisions to brain signals lead to a new view about the neural basis of human perceptual decision-making processes.

A series of elegant single-unit recording studies has investigated perceptual decision-making in the somatosensory domain using the tactile discrimination paradigm (Romo et al., 2012). From these experiments, based on invasive recording of neuronal responses in a variety of cortical areas of awake monkeys, some important concepts of perceptual decision making have emerged. Today, it is well known that the representation, the integration of sensory evidence, and the decisional process involve different brain structures. Previous single-cell recording approaches used methods to determine when, where and how neurons carry information about stimulus frequency (Romo et al., 1999; Romo and Salinas, 2003; Luna et al., 2005; Hernández et al., 2010; Romo and de Lafuente, 2013). Firstly, as the task is based on somatosensory stimuli, neuronal responses in both primary (SI) and secondary (SII) somatosensory areas are of interest (Mountcastle et al., 1990; Salinas et al., 2000). Moreover researchers have identified a set of regions critical for tactile working memory and perceptual decision making: primary somatosensory cortex (SI), secondary somatosensory cortex (SII), prefrontal cortex (PFC) and medial premotor cortex (MPC) (Romo and Salinas, 2003; Romo and de Lafuente, 2013). Extensive single-cell recording work in macaques has been done by Romo et al., (1999) allowing the tentative assignment of roles to these regions: SI is believed to be involved in stimulus processing, SII in stimulus processing and decision-making, PFC in stimulus storage and

decision-making, and MPC in converting decisions into motor responses (Brody et al., 2002; Romo and de Lafuente, 2013).

Moreover, functional MRI (Pleger et al., 2006; Preuschhof et al., 2006; Li Hegner et al., 2010), EEG (Spitzer et al., 2010; Spitzer and Blankenburg, 2011), and MEG (Haegens et al., 2010; Sanchez et al., 2012) research in humans has produced results that are generally consistent with single-cell recordings in macaques, suggesting that there is substantial similarity between the neural correlates of tactile perceptual decision making mechanisms in human and non-human primates.

Taking some results from the tactile discrimination paradigm, in single unit recordings with monkeys studies and in global brain activity recordings with other non-invasive techniques in humans, I will try to describe some keys processes that conduct sensory information to decision making related to specific neurophysiological activity.

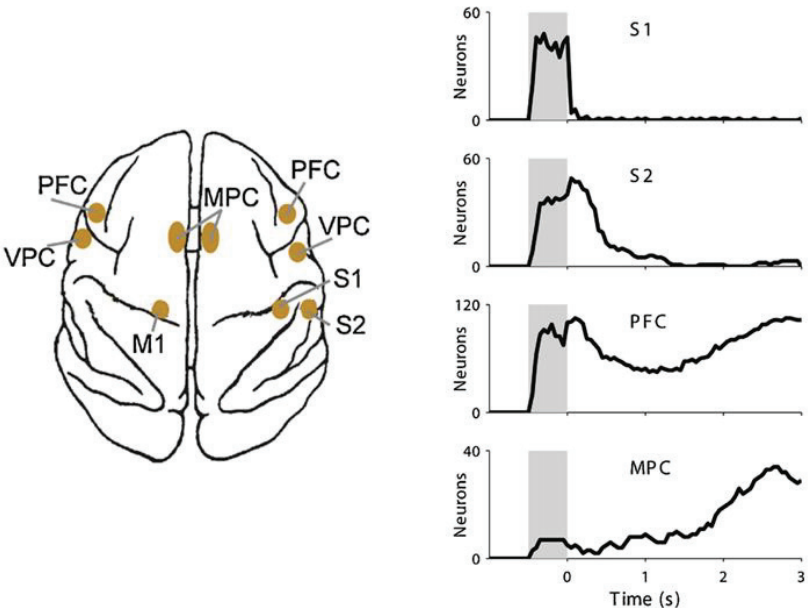


Figure 10: Tactile frequency discrimination task with monkeys.

Left: Top view of the monkey brain and the cortical areas recorded during perceptual discrimination (orange spots). Recordings were made in primary somatosensory cortex (S1) and secondary somatosensory cortex (S2) contralateral to the stimulated hand (right hemisphere) and in primary motor cortex (M1) contralateral to the responding hand/arm (left hemisphere). Recordings were made contralateral and ipsilateral to the stimulated fingertip prefrontal cortex (PFC), ventral premotor cortex (VPC), and medial premotor cortex (MPC).

Right: Neuronal responses observed during the first stimulation (f1) and delay period in four areas. Grey shape represents f1 duration. Black lines indicate the number of recorded neurons carrying a significant signal about the base stimulus (f1), as a function of time relative to the beginning of the delay period (fixed delay of 3s). S1, primary somatosensory cortex; S2, secondary somatosensory cortex; PFC, prefrontal cortex; MPC, medial premotor cortex.

(Adapted from Romo and de Lafuente, 2013)

Encoding sensory information

Tactile stimulation can drive neuronal populations in primary somatosensory cortex (Mountcastle et al., 1990; Salinas et al., 2000; Luna et al., 2005). Extracellularly recorded responses of neurons in cortical area SI have shown that the cells respond phasically to each tactile stimulation pulse (Hernández et al., 2010). These stimulus-evoked responses parametric to the frequency of the stimulation have been detected in the form of evoked somatosensory steady-state responses (SSR) in humans with EEG/MEG techniques (Tobimatsu et al., 1999; Nangini et al., 2006; Giabbiconi et al., 2007; Spitzer et al., 2010). The SI neurons carry information about stimulation in the temporal structure of their spike trains and their firing rate code seems to be associated with the animal's discrimination performance (Salinas et al., 2000). Moreover, interesting results arise from studies that directly stimulated SI using microstimulation or via tactile stimulation (Romo et al., 1999, 2012). Monkeys were able to discriminate the stimulus frequencies either delivered to the fingertips or artificially injected into a cluster of SI neurons. However, the response of the primary somatosensory area stops reflecting information about the stimulation immediately after the end of the stimulus (see Figure 10). SI neurons do not seem to store information about the stimulus during the delay period, therefore suggesting that they do not have the capacity to compare the two stimuli for the decision motor report (Lemus et al., 2010). This poses the question of where and how in the brain all these processes are implemented in order to solve this task. An obvious candidate in the ascending hierarchy is SII, as well as areas that receive inputs from SII. Actually other results from SII recording have shown that even cells in this area do not seem to carry information about the exact temporal structure, the average firing rate has stimulation-dependent responses that continue for a few hundreds of milliseconds after the end of f1 into the delay period (Brody et al., 2002; Romo and de Lafuente, 2013). Human electrophysiological experiments have shown that in addition to phase-locked activity such as SSR, others oscillatory markers suggest somatosensory area activations known as induced non-phase-locked responses such as mu-band (~8-13Hz) and beta-band (~15–25 Hz) evoked response desynchronisation (ERD) during stimulation, and a subsequent beta rebound after stimulus offset (Bauer et al., 2006; Haegens et al., 2010; Spitzer et al., 2010). Such induced responses in early sensorimotor areas are not modulated by the frequency of stimulation. Moreover, some studies also modeled the somatosensory networks involved in tactile perception using a dynamical causal modeling (DCM) approach to infer effective connectivity of primary brain regions (Auksztulewicz et al., 2012). They found that recurrent and forward-backward intimate connections explain stimulation processing to provide stimulation perception. Despite the close and dynamical interaction between somatosensory areas underlying perception and stimulus feature extraction (e.g. frequency in our case) activity in the somatosensory areas provides no evidence for a sustained representation of tactile frequency beyond a few hundred milliseconds after f1 (see Figure 10).

Maintaining sensory information

One of the key features of the discrimination task is that it requires short-term storage of information about the first stimulus. Where and how does this happen? So far, the clearest neural correlate of the working-memory component of the task has been found in the prefrontal cortex (PFC), an area implicated in working memory in numerous experiments (Romo et al., 1999; Miller et al., 2003; Kaiser and Lutzenberger, 2005; Gold and Shadlen, 2007; Heekeren et al., 2008; Hernández et al., 2010; Philiastides et al., 2011). The inferior convexity of the PFC contains neurons that increase their activity in a frequency-dependent manner during the delay period between base and comparison (Romo et al., 1999) (see Figure 10). In one non-invasive human study, researchers were able to extract the frequency of the base stimulus (f1) by observing modulations of beta-band (20–25 Hz) amplitude EEG activity in human PFC, specifically in the inferior frontal gyrus (IFG), during the delay in the tactile discrimination task (Spitzer et al., 2010; Spitzer and Blankenburg, 2011). This elegant result is in line with previous findings reporting stimulus-dependent neuronal activity in monkey PFC, suggesting that this might be the neural substrate of the subject's short-term memory for f1 during the delay period (Romo et al., 1999). Other results from humans have shown that the neural activity in the IFG plays a causal role in successful maintenance of somatosensory information (Auksztulewicz et al., 2011). In this latter study, the authors used an rTMS protocol to disrupt activity in the IFG and observed that the participants' behavioral performance was impaired during this tactile 2AFC working memory task. Thus, the analysis of prefrontal region activation revealed that neurons respond during the f1 stimulus period and during the delay period (Brody et al., 2002; Romo and de Lafuente, 2013) (see Figure 10). Is PFC the only cortical area involved in working memory during tactile discrimination? Certainly not, but given the results from causal investigation using rTMS stimulation, the PFC may play a crucial role.

Integrating sensory evidence and deciding

During the tactile frequency discrimination task, in the medial premotor cortex (MPC), an area linked to motor output, a significant number of neurons respond to the base stimulus during the late part of the delay period (Romo and Salinas, 2003) (see Figure 10). Encoding of f1 could proceed in a serial and feedforward fashion from SI to SII, then to PFC and MPC but this is unlikely given feedback/recurrent communications between cortical areas (Lamme and Roelfsema, 2000; Auksztulewicz et al., 2012). Motor areas clearly receive some sensory information, and it has been shown that activity of motor regions can be related to evidence accumulation towards one decision or another (Donner et al., 2009). However the large overlap between sensory-, memory-, decision- and motor-related activity suggests that related areas of the brain are anatomically highly inter-connected (Rizzolatti and Luppino, 2001). In this connected network, SII is connected to SI and to frontal areas and is thus appropriately placed to integrate both bottom-up (sensory) and top-down (memory) information. It has been found that the responses of SII neurons are a function of both f1 and f2 during

and after the second stimulus and then change into responses that correlate with the monkey's decision (Romo et al., 2002). Also, decision-related responses have been observed in frontal areas such as MPC (Hernández et al., 2002) or PFC (Romo and de Lafuente, 2013). Motor area neuron recordings suggest that they could be related either to the end result of the comparison process or to the motor command that was associated with the output movement (Gold and Shadlen, 2000; Hernández et al., 2002). Thus, extensive study of the monkey somatosensory system with tactile frequency discrimination tasks shows that stimulus integration and comparison are widely distributed across cortical areas (Romo and de Lafuente, 2013). Recently, oscillatory analyses were applied on local field potentials (LFPs) recordings of the monkey sensorimotor system (Haegens et al., 2011b). These authors found that oscillatory activity in the beta band (12-26Hz) reflected the temporal and spatial dynamics of accumulation and processing of evidence leading to the decision outcome. This study was in line with the observation of fronto-parietal beta oscillations recorded in humans during a visual decision making task (Donner et al., 2007). Such results argue in favor of important interaction in local or large-scale cortical networks revealed by oscillatory activity and suggesting the distributed dynamics of perceptual decision-making (Siegel et al., 2011).

Models of perceptual decision-making

Perceptual decision-making research has lead to the development of mathematical models. At the behavioral level, linear diffusion models describe a wide range of experimental results (Smith and Ratcliff, 2004). In particular, sequential-sampling models such as diffusion models are widely used for fitting response-time and accuracy data in 2AFC tasks. There is a large variety of family models which vary according to parameter specification or the nature of the decision-making (i.e. two choices speeded decisions or complex decisions among different valued alternatives) (Smith and Ratcliff, 2004). Generally such models postulate that the information driving the decision process is accumulated continuously over time until a decision boundary is reached (see Figure 11A). More specifically, the information from a stimulus (the sensory evidence) is represented in a diffusion equation by the mean drift rate of the random variable. This random variable is accumulated over time from the starting point toward one or the other boundaries. The escaping through a given boundary corresponds to making a specific decision (see Figure 11B). Thus, signal detection theory and sequential analysis provide a theoretical framework for understanding how decisions are formed (Gold and Shadlen, 2007).

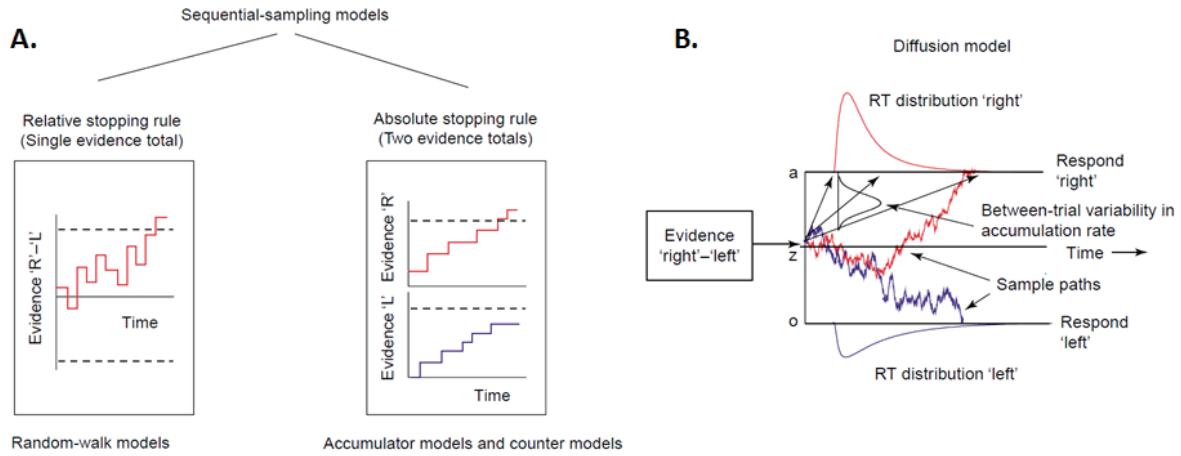


Figure 11: Sequential-sampling models for two-choice decisions. **A. The main model classes.** The models assume that decisions are made by integrating noisy stimulus information over time until a criterion amount of evidence needed for a response is obtained. In random walks, evidence is accumulated as a single total. Evidence for a right response ('R') increases the total; evidence for a left response ('L') decreases it. A response is made when the evidence for one response exceeds the evidence for the other by a criterion amount (a relative stopping rule). In accumulator models and counter models, evidence for the two responses is accumulated as separate totals. The response is determined by the first total to reach a criterion (an absolute stopping rule). Models are classified according to whether evidence accumulates continuously or at discrete time points, and whether the increments to the evidence totals are of variable size (continuously distributed) or occur in discrete units (e.g. counts). Random walks in continuous time are diffusion processes. **B. Diffusion model.** The sample paths represent moment-by-moment fluctuations in the evidence favoring right and left responses. The process starts at z and accumulates evidence until it reaches one of two criteria, o and a. If the upper criterion is reached first, a 'right' response is made; if the lower is reached first, a 'left' response is made. The moment-by-moment fluctuations in the sample paths reflect noise in the decision process. The mean rate of accumulation varies randomly from trial to trial because of variability in the quality of the stimulus information. This variability allows the model to predict errors that are slower than correct responses. Other behaviorally sources of variability are the location of the starting point of the accumulation process and the duration of the non-decision component of times for stimulus encoding and response time (RT). The first of these sources of variability allows the model to predict errors that are faster than correct responses; the latter allows it to describe the shape of the leading edge of RT distributions. (Extracted and adapted from Smith and Ratcliff, 2004).

However based on such phenomenological models it remains difficult to assign a biological meaning to the model parameters (Deco and Romo, 2008). In this sense, several non-linear and biologically plausible models emerge. Usually, the dynamics relevant for decision making in these nonlinear models depend on the stability of the spontaneous activity state disturbed once the stimulus is presented, to rapidly evolve towards one of the two decision states. Biologically realistic models complement diffusion models without losing their ability to explain behavioral data (Deco and Romo, 2008). Such non-linear models constitute an important literature expressing the needs for more biologically plausible models (see for review: Deco et al., 2013). Today, another way of modeling perceptual decision-making processes is based on Bayesian approaches (Daunizeau et al., 2010b). In short, Bayesian models allow the perceptual decision process to be interpreted in terms of predictive coding which postulates that decisions are based on a comparison of predicted and observed sensory inputs. The exact equivalence between Bayesian inference equations and the classically used drift-diffusion model was recently demonstrated (Bitzer et al., 2014). A major advantage of the Bayesian model is that it can be extended to incorporate prior knowledge about the sensory context into the decision process. In this sense, Bayesian schemes provide an interesting tool to take into account the updating of beliefs and learning during perceptual decision-making tasks.

Interim conclusion

To conclude, the tactile discrimination task is a paradigm that provides an interesting experimental environment within which to investigate the human, animal, and computational models simultaneously (Bancroft and Servos, 2011). Studies that combine behavior and neurophysiology, typically in monkeys, have begun to uncover how the elements of decision formation are implemented in the brain. Research translates well between human and non- human subjects, and tactile perceptual decision-making relies on a simple paradigm which involves an identified set of cortical regions, making it an ideal model system that can be studied using behavioral, imaging, and computational neuroscience. At the same time it is increasingly obvious that we need to take into account the dynamical aspect of the brain to widely understand the processes of perceptual decision-making. Current studies require biologically plausible and complex models of brain mechanisms in order to bridge the gap between the electrophysiological activity markers, behavioral outcomes and cognitive functions. Today advanced Bayesian theories allows us to consider the brain as a constructive or predictive organ that actively generates inferences from its sensory inputs using an internal or generative model (Friston et al., 2003). The present PhD thesis is embedded in this contemporary framework that considers the brain as a computational and dynamical system designed to make inferences about properties of a physical environment.

2.2. CONTEXTUAL DEPENDENT LEARNING

2.2.1. EVIDENCE FOR THE DYNAMICAL AND CONTEXTUAL DEPENDENT NATURE OF THE BRAIN

To survive in our complex environment, we have to adapt to changing contexts. Thankfully our brain is an highly dynamical adaptive organ. Every day we interact continuously with a complex, uncertain and moving environment but we are perfectly able to manage this more-or-less consciously and even sometimes we are able to find some regularity and similarity with past experienced events. Deep in your brain, dynamical mechanisms exhibit adaptability and plasticity that is almost limitless. One of the most telling examples is the discovery of the extraordinary ability of the sensori-motor cortex to reorganize the representation of the body within somatotopic maps after an amputation (Turner et al., 2001). Another example, experienced by more people, it is the fast modification of our body schema after a tool use (Cardinali et al., 2012). Moreover some results also reveal that one can easily have the illusional feeling of ownership of a "fake" external limb (i.e. a rubber hand or a fake body) integrated into one's own peripersonal space after seeing and feeling simple coherent and synchronized tactile stimulation both on our body and on the object: it is called the "rubber hand illusion" (Ehrsson et al., 2004). Such findings actively changed the way we see and investigate brain function by revealing the existence of strong and dynamical adaptive processes guiding the way we

perceive external reality. The brain has extraordinary abilities to integrate new information and to replace or update old beliefs with new observations. Our perception and our learning processes that depend on it, are intimately related and potentially modified by the context in which we find ourselves. Conceptually, one could see our permanent interaction with the environment as a succession of perceptual decisions with diverse contextual influences arising from variations of the external and internal states. For example, in a natural environment such as our house, searching for a given target object (e.g., our keys) might be guided by a variety of predictive cues generated by previously acquired knowledge, such as the target's characteristics (e.g., its color, size, and shape as defined by a top-down implemented search template). In addition, predictions can also be derived from contextual factors, such as the most probable location of the target (e.g., in our jacket), and its typical co-occurrence with other objects (e.g. our wallet) (Wolfe et al., 2011; Conci et al., 2012). Such a way of seeing and understanding brain mechanisms suggests that we are always engaged in implicit learning processes that contribute to the building-up of our beliefs about the external world and the shaping of our future perceptual decisions.

Nevertheless, the idea of a contextual influence is fairly vast and need to be define because it could be related to an emotional context (Wieser and Brosch, 2012), a social context (Engelmann and Hein, 2013) or even an economical context (Loewenstein et al., 2008). In our case we are interested in how the sensory context influences the perceptual decision-making processes. Actually every decision that we take is impacted more or less by our past perception. In a dynamic and continuous inference our brain is learning what to expect next (Series and Seitz, 2013). Broadly speaking, our brain must integrate and maintain a huge quantity of information about our sensory environment and this information is often complex and noisy. Thus in ambiguous situations, knowledge of the world guides our interpretation of the sensory information and helps us make decisions quickly and accurately, although this sometimes leads to illusions (Summerfield and Egner, 2009). The dynamics of such processes can be seen and investigated at the experimental time-scale level. Contextual sensory dependent learning are mostly investigated implicitly. A lot of studies focus on visual perception to uncover how our perception is strongly shaped by our expectations. One example is the priming effect during the bistable perception task where the presentation of some contextual prior will increase the probability that the participant perceives a specific interpretation of an ambiguous stimulation (see Figure 12 AB) (Brugger and Brugger, 1993; Series and Seitz, 2013). Other interesting examples of contextual implicit learning priors can be found in tasks where participants are asked to evaluate the direction of a Necker's cube (see Figure 12 C) and their choices are manipulated by spatial cue training (Haijiang et al., 2006). Moreover, such dynamical mechanisms are present in speech perception, for example expectation of certain words depends on the topic of the conversation, and on a shorter time-scale dynamic, on the immediately preceding words in the same sentence (Norris and McQueen, 2008; Lash et al., 2013). Obviously, sensory contextual-dependent learning is investigated in the typical

perceptual decision-making tasks that we presented in the last paragraph, namely 2AFC discrimination tasks. It has been known for a long time that performance depends on stimulation context over trials (Harris, 1948). Typically, psychophysical and neuroimaging studies have identified an astonishing bias during 2AFC discrimination tasks called the "time-order effect" (Preuschhof et al., 2011) or the "contraction bias" (Ashourian and Loewenstein, 2011) that underlies contextual implicit learning and shapes perception in several sensory modalities.

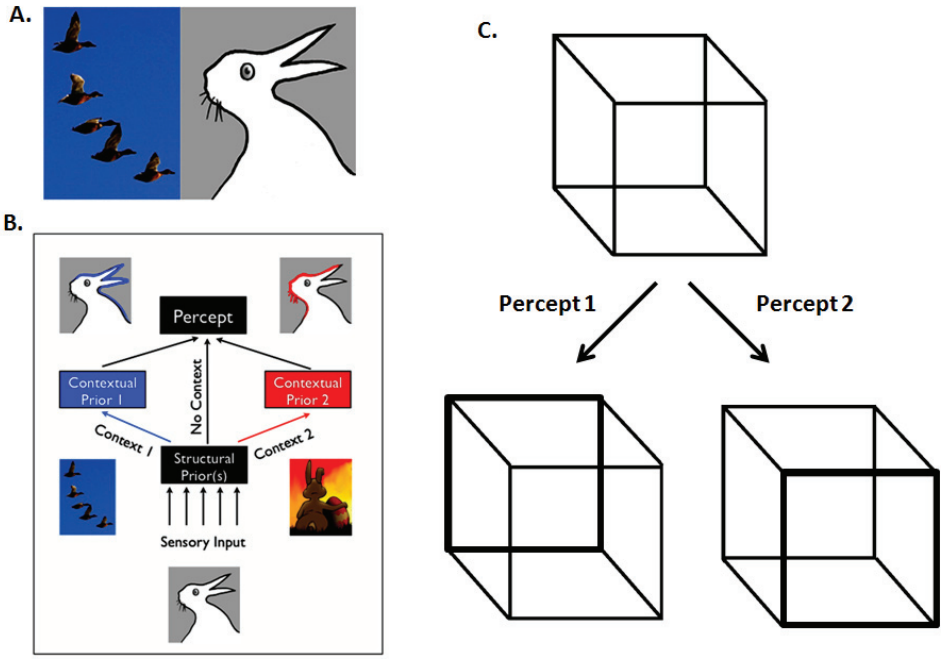


Figure 12: Contextual expectations and bistable percept. **A.** Example of a contextual expectation. What do you see in the drawing on the right: a rabbit or duck? This ambiguous and bistable percept can be influenced by the spatial context in which it is placed, e.g., having just seen a flock of ducks would make one more likely the perceive a duck. **B.** Different contextual priors can superseded initial structural priors (non-controlled individual priors) leading to different percept of a same stimulus. **C.** Necker's cube. One could see upper face in front (percept 1) or lower face in front (percept 2). (Adapted from Haijiang et al., 2006; Series and Seitz, 2013).

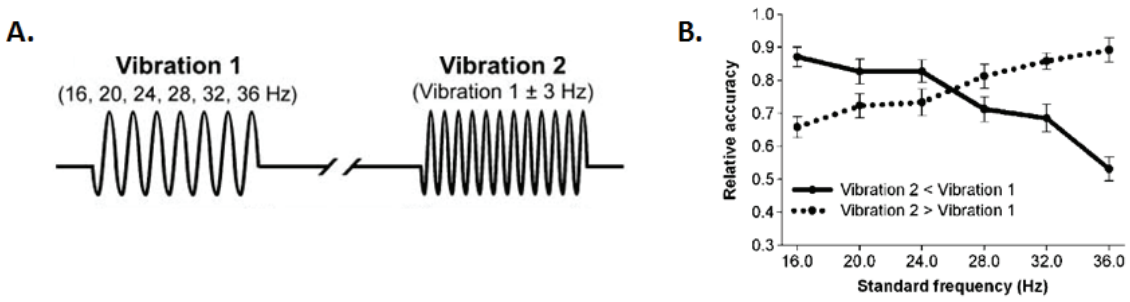


Figure 13: Tactile contextual dependent behavioral bias. **A.** Experimental design. Subjects stimulated on the right index fingertips had to decide whether the second vibration (f2) had a higher or lower frequency than the first vibration (f1). f1 had one of the six different frequencies (16, 20, 24, 28, 32, and 36Hz), f2 was either 3Hz higher (50% of the trials) or lower than f1. **B.** Time-order effect. Interaction between the frequency of the first tactile stimulus of a trial and the time order of presentation. Better performance for low frequencies when f2 was lower than f1 and worse performance when f2 was higher than f1. Reverse relationship for high-frequencies stimuli. (Adapted from Preuschhof et al., 2011).

Regarding the tactile frequency discrimination task, Preuschhof and colleagues have shown that such biases predict a large proportion of the variation in behavioral performance given equivalent difficulty in the situations (Preuschhof et al., 2011). As always, subjects have to judge which of the two stimuli had the higher frequency. However in that case in which f1 can be one of several frequencies centered around 26Hz, f2 frequencies depends on f1 and the difficulty remains constant (f2 = f1±3Hz) (see Figure 13). This study found an interaction between the stimulus-relevant characteristics (i.e. frequency) and the time order of stimulus presentation: the "time-order effect". For low-frequency stimuli, accuracy is high when f2 is of lower frequency than f1. Conversely, for high-frequency stimuli, accuracy is high when f2 is of higher frequency than f1 (see Figure 13). These results suggest that this behavioral pattern is a consequence of the effect of a general reference weighting process determined by the sensory context and background information (Seger and Peterson, 2013).

The customary explanation for the bias is that the perceived relevant characteristic of a stimulus (i.e. frequency) is a weighted combination of its veridical frequency and a reference frequency, such as an average of all contextually relevant stimuli, that serves as a general reference, hence the name of "contraction bias" (Ashourian and Loewenstein, 2011). Interestingly, fMRI analysis revealed that neural correlates of the encoding and the integration of sensory information in such protocols implicate brain areas similar to those observed in typical somatosensory discrimination tasks such as the somatosensory network (SI, SII) and frontal areas (IFG) (Preuschhof et al., 2011). Some monkey studies have investigated which cortical areas contain neuronal activity that correlates with behavioral bias (Hernández et al., 2010). Actually they noticed that during the decision the monkey could give different weights to both stimulation frequency representations. Except for neurons in SI, the authors found that a large fraction of neurons correlated with this behavioral bias. Moreover, this neural bias was more evident in the PFC than in SII. This is thus consistent with the fact that relevant stimulation characteristics (i.e. frequency) are integrated and represented in a dynamical network and when one of the two stimulus frequencies is more strongly represented than the other, it could bias the behavioral performance in the task. Furthermore, several cues in others sensory modalities (i.e. visual and auditory) strongly suggest that brain processes involving sensory and frontal brain regions could operate efficiently to implicitly guide perceptual decision-making toward a categorization task based on learned contextual sensory reference (Grinband et al., 2006; Summerfield et al., 2006; Nahum et al., 2010; Ashourian and Loewenstein, 2011). Today all these findings lead to understand perceptual decision-making as dynamical processes that provide brain's ability to create generalized representation continuously updated of a sensory context (Seger and Peterson, 2013). Indeed, contextual learning studies show that the brain continuously extracts and learns the statistical regularities of the environment, and can do so automatically and without awareness (Series and Seitz, 2013). A growing theory in neuroscience is that perceptual decision-making can be described using

Bayesian inference models and that the contextual dependent nature of the brain can be view as prior beliefs in a statistical inference process (Daunizeau et al., 2010b; Series and Seitz, 2013; Moutoussis et al., 2014).

2.2.2. CAPTURE THE DYNAMICAL AND CONTEXTUAL DEPENDENT NATURE OF THE BRAIN

Humans and others animals interact and operate in a world of sensory uncertainty. Our brain must deal with many factors that have a negative impact on the reliability of sensory information regarding the world: the mapping of 3D objects into a 2D image, neural noise in sensory coding, structural constraints on neural representations (e.g. density of receptors in the skin or in the retina) … etc. Actually we can perceive the relevant characteristics of any stimulation quickly and reliably despite the complexity and noise within the information gathered. We know that our perceptual decision can be influenced by our knowledge about the world. Indeed given the lack of sensory inputs with good signal-to-noise ratio, it has been suggested that our brain uses an internal representation of the world (i.e. internal model or hypothesis) to compute environmental data and to provide efficient perceptual decision-making. In other words, the brain infers the state of the external world based on prior knowledge about it. Seminal works from Helmholtz started to define perception as inference (Helmholtz, 1925). Helmholtz described the notion of "reality-as-hypothesis" with the view that we "attain knowledge of the lawful order in the realm of the real, but only in so far as it is represented in the tokens within the system of sensory impressions" (Westheimer, 2008). Researchers have begun to apply the concepts of probability theory rigorously to problems in biological perception and action (Knill and Pouget, 2004; Trommershäuser, 2009). Today Bayesian statistical decision theory formalizes Helmholtz's initial idea (Friston, 2010). This statistical framework is a powerful tool to capture and investigate the dynamic and contextual dependent nature of the brain.

Probabilistic generative models

One of the key features of Bayesian modeling is the probabilistic generative model. It is the generic approach used to infer how subjects make perceptual decision in the presence of uncertainty (Daunizeau et al., 2010b). Behavioral or electrophysiological responses generated by subjects during an experiment are based on perceptual inferences. Indeed the researcher's position becomes tricky because no one can have direct access to the subject's hidden internal and dynamical representations, only behavioral and neurophysiological data are available. Thus the experimental situation could be seen as: (i) one subject trying to infer the hidden state of the experimental context (e.g. difference between 2 stimulations, stimulation probability…) given his perceptual inference limited by noisy sensory gathering; (ii) the experimenter must infer the internal cognitive state of the subject based on other noisy data (e.g. reaction time, performance measures, evoked or induced neural activity…). This situation is called "Observing the observer" and is related to making inferences about inferences (i.e.

meta-inference) (Daunizeau et al., 2010a, 2010b). Interestingly, generative models allow the embedding of perceptual inference of decision-making in order to infer, as experimenters, the probabilistic representation of sensory contingencies and outcomes used by subjects. Such generative models aim to explain the causal relationship between experimental (e.g., cognitive) manipulations and the observed neurophysiological or behavioral responses. Mathematically speaking probabilistic generative models can describe how experimental manipulations (u) influence the dynamics of the subject's hidden (i.e. neuronal, hemodynamic or cognitive) brain states (x) then formalize how the system's hidden states map onto experimental measures (y) (e.g. reaction-time, performance, evoked potentials amplitude…). Typically, this is done by writing the following ordinary differential equations: the evolution equation (i.e. perceptual or neuronal model) and the observation equation (i.e. response model). In a generic way, u corresponds to experimental control variables, that is, exogenous inputs to the system that might encode changes in experimental condition (e.g., frequency of tactile stimulation, or visual stimulation-type like face *vs.* house) or the context under which the responses are observed (e.g., sleep *vs.* awake). Thus in their general form generative models are defined by a pair of assumptions $\{f, g\}$ (see Figure 14).

Evolution equation: $f(\cdot)$

The first component, f, is the evolution function, which prescribes the evolution or motion of hidden (unobservable) neuronal or psychological states x, such that:

$$\dot{x} = f(x, \theta, u) \tag{1}$$

where $\dot{x}$ is the rate of change of the system's states x and θ is a set of unknown evolution parameters (e.g. learning rate, strength of neural connection …).

Observation equation: $g(\cdot)$

The second component, g, is the response function and prescribes the mapping from hidden states to observed neurophysiological, metabolic or behavioral responses, such that:

$$y = g(x, \varphi, u) + \varepsilon \tag{2}$$

where g is the instantaneous non-linear mapping from the system's (i.e. brain) states to observations and φ is a set of unknown observation parameters (e.g. individual reaction-time distributions, source localization parameters…). ε indicates random fluctuations or noise that corrupt the observed data.

Note that θ and φ represent fixed, but unknown, values that parameterize the evolution and observation functions, respectively. These values might differ from one subject to another or, for the same subject, from one experimental condition to the next. Thus they will be estimated based on y (i.e. the recorded data).

Referred to as "observing the observer" problem, this approach can involve the embedding of a subject's (the observer) dynamic causal model of the environment ($M_s = \{f_s, g_s\}$) into an experimenter's (another observer observing the subject) dynamic causal model of the subject ($M_e = \{f_e, g_e\}$). Further, assuming that the subject implements an optimal online Bayes inference to invert the duplet $\{f_s, g_s\}$ and infer the hidden states of the environment, the evolution (perception) function, f_e, incorporates this inference and learning process, while the observation (response) function, g_e, defines the mapping between the hidden subject's internal states (the inferred or posterior estimates of the environment hidden states) onto behavioral or physiological responses. This is why this approach is also referred to as a meta-Bayesian approach (Daunizeau et al., 2010b). Importantly, in this context, we explicitly model the link between the precise sequence of presented sensory inputs and the subject's evolving beliefs about the state of the world.

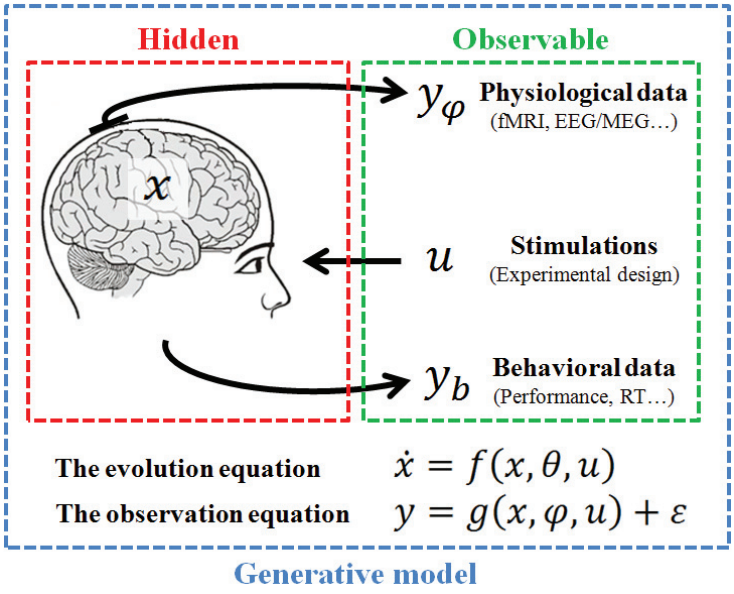


Figure 14: Generative models that provide formal constraints on the way the data were generated. The hidden mental state $\boldsymbol{x}$ evolution is observed through behavioral or physiological data and is modulated by the experimental design. The evolution and the response functions formalize an generative model (hypothesis) that describes how the hidden system's state evolves and that predicts how such evolution of the hidden state maps into the observed data. (Inspired from Daunizeau et al., 2011b)

Finally these models are embedded in a Bayesian statistical framework, which allows one to deal with complex (e.g., probabilistic) models by introducing prior knowledge about unknown model parameters. It is particularly powerful in conjunction with model comparison methods such as random-effects Bayesian model selection (Stephan et al., 2009) and model families space (Penny et al., 2010). Given competing models of learning and inference, Bayesian model inversion and comparison can be used to infer the nature of the underlying process and its relationship to the measured responses. The resulting posterior model probabilities assess each model's relative explanatory power in a way that balances fit and complexity such that the comparison between any two models is valid irrespective of their relative complexity.

Modeling neurophysiology: Dynamical Causal Modeling (DCM)

While seminal concepts in cognitive neuroscience have considered that cognitive and perceptual systems in the brain are supported by isolated brain areas, recent theories go beyond this view notably by considering that brain functions are supported by highly hierarchically organized functional systems that involve dynamic interactions between brain areas. Interestingly today dynamic models referring to Bayesian statistical modeling are available and describe, in terms of ordinary differential equations, the motion of hidden neurophysiological states and the mapping from these hidden states to observed brain signals (Friston et al., 2003). Such dynamical causal modeling (DCM) aims to explain, quantitatively and mechanistically, how observed neurophysiological responses are generated (i.e. DCM for fMRI signal see for review: Stephan and Friston, 2010; DCM for EEG/MEG signal see: Kiebel et al., 2009). Moreover, DCM is the method of choice for estimating effective connectivity between different brain areas (i.e. sources or regions of interest (ROIs)) (Stephan et al., 2010). The simple idea behind DCM is to formulate one or more models about how recorded data are caused in terms of a network of distributed sources. These sources talk to each other through parameterised connections and influence the dynamics of hidden states that are intrinsic to each source. Bayesian model inversion provides conditional densities on their parameters (i.e. extrinsic or intrinsic connection strengths parameters). These conditional densities are used to provide the probability of the data given the model, namely the "model evidence" (see for technical review: Friston et al., 2007) and are used for model comparison (Penny, 2012).

Typically, DCMs for electromagnetic data (EEG and MEG) are based upon neural-mass models of interacting neuronal populations (David et al., 2006; Kiebel et al., 2009). Each source of electromagnetic activity is modeled as an equivalent current dipole (or ensemble of small cortical patches) whose activity reflects the depolarization of three populations (i.e. one inhibitory and two excitatory). Interestingly, one can embed any neural-mass model into DCM. The most commonly used is based on the Jansen model (Jansen and Rit, 1995). This neural-mass model emulates the electromagnetic activity of a cortical source using three neuronal subpopulations. A population of excitatory pyramidal (output) cells receives inputs from inhibitory and excitatory populations of interneurons, via intrinsic connections (intrinsic connections are confined to the cortical sheet). Within this model, excitatory interneurons can be regarded as spiny-stellate cells and receive forward connections. Excitatory pyramidal cells and inhibitory interneurons occupy agranular layers and receive backward inputs. All the three layers receive lateral inputs. Using these connection rules, one can construct hierarchical cortico-cortical network models of several cortical sources using intrinsic, forward, backward and lateral connection assumptions (David et al., 2006) (see Figure 15).

Actually, DCM as neuronal network models can be used as forward models to explain MEG/EEG data. Moreover this is an interesting framework that embeds realistic biophysical models of neural dynamics into statistical data analysis tools that target experimental neuroscientific questions

about brain functions. Currently there is a growing body of literature using DCM applications to infer perceptual brain processes related to electrophysiological signal recordings for basic or even clinical neuroscience (e.g. Garrido et al., 2008; Boly et al., 2011; Auksztulewicz et al., 2012; Albouy et al., 2013). DCM seems to be the most suitable framework within which to assess the context-specific effects of an experimental manipulation on brain dynamics and connectivity. This is because it is based upon a probabilistic generative model that describes how experimental manipulations induce changes in hidden neuronal states that cause the observed measurements. Note that the interested reader could refer to (Daunizeau et al., 2011a) for a critical review on the biophysical and statistical foundations of the DCM framework.

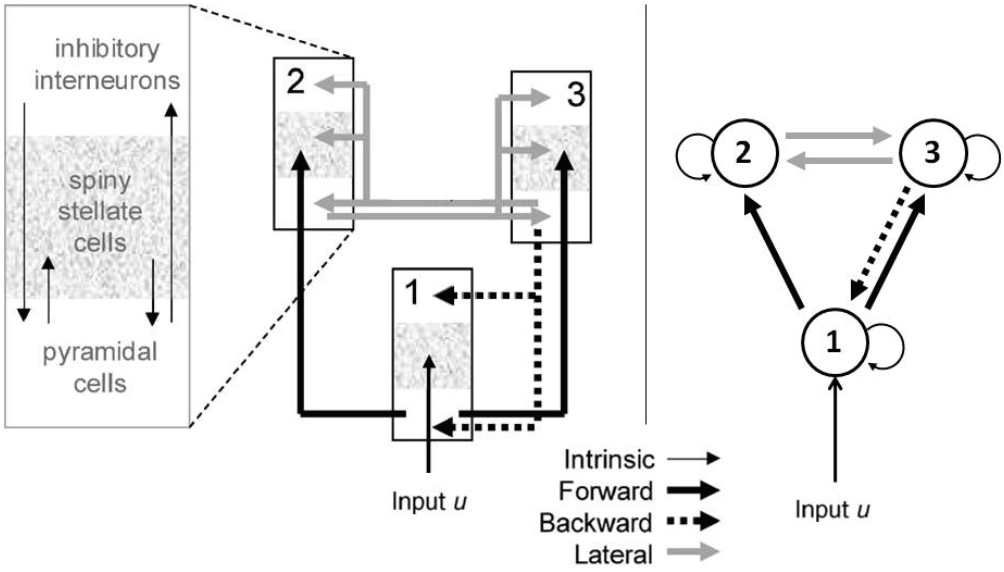


Figure 15: Example of a typical DCM hierarchical network composed of three cortical areas. Each node (source) is modeled with three subpopulations (pyramidal, spiny-stellate and inhibitory interneurons) and targeted by different connections types (i.e. intrinsic, forward, backward and lateral). Extrinsic inputs (u) evoked transient perturbations around the resting state of the lower sources in the hierarchy. Interactions among different regions are mediated through excitatory connections with specific organization defining model structure. Right panel is a more usual schematic representation of the same DCM three nodes structure. (Adapted from David et al., 2006).

Modeling behavior: Bayesian Brain

There is a growing body of literature suggesting that the brain follows Bayes' rule to interact with the environment, it is called the "Bayesian Brain hypothesis". Models based on the Bayesian brain hypothesis propose that, at each moment in time, our brain uses implicit knowledge (i.e. beliefs) of the world to infer properties of future events (i.e. stimulation) from ambiguous or complex situations (Friston et al., 2013a; Series and Seitz, 2013; Shadlen and Kiani, 2013; Moutoussis et al., 2014). In mathematical terms, to say that a system performs Bayesian inference is to say that it updates the posterior probability $P(H|D)$ that a hypothesis H is true given some data D by executing Bayes' rule:

$$P(H|D) = \frac{P(D|H).P(H)}{P(D)} \quad (3)$$

The likelihood $P(D|H)$ measures how expected the data are under the hypothesis H. The prior $P(H)$ corresponds to prior expectations about the probability of the hypothesis H before (or independent of) data observation. $P(D)$ is termed the marginal likelihood and is the same for all possible hypotheses considered, this factor does not enter into determining the relative probabilities of different hypotheses. In such a way that we can say that posterior probability $P(H|D)$ is proportional to likelihood times prior:

$$P(H|D) \propto P(D|H).P(H) \quad (4)$$

The process of perception could be seen as a Bayesian inference where the final perception of a sensory event is affected by prior contextual knowledge. Priors should reflect previous experience with the sensory world and serve to interpret data in situations of uncertainty (Series and Seitz, 2013). The more uncertain the data, the more the prior influences the interpretation. Moreover, in an iterative Bayesian inference schema, posterior probabilities become priors for the next inference. In this way priors are updated after each Bayesian computation of a sensory event. The underlying idea is that the brain has a model of the world that it tries to optimize using sensory inputs (Adams and Mamassian, 2004; Kersten et al., 2004; Friston, 2010; Brown et al., 2013).

The brain could be understood as an inference machine that predicts and explains its sensations (Brown et al., 2013; Friston et al., 2013a). Bayesian framework offers quantitative tools to investigate and formalize how our brain can generate predictions against which sensory samples are tested to update beliefs about their causes using probabilistic models. Perception then becomes the process of accessing the posterior probability of the percept given sensory data. Interestingly one could see the importance of prior expectation on perceptual interpretation (Conci et al., 2012). Given the strong influence of priors when uncertainty or sensory noise are high, behavioral bias during perceptual decision-making could be explained by a tendency to be biased toward internal priors. Today, the statistical inference remains an interesting and useful conceptual framework to understand and quantitatively investigate behavior in typical perceptual experiments (Gold and Shadlen, 2007).

From an clinical perspective, Bayesian perception theory has recently provided new insight for studying neurodevelopmental pathology with abnormalities in sensation and perception such as autism (Pellicano and Burr, 2012). These authors proposed that perceptual experience of autistic people could be explained by an attenuation of Bayesian priors that could lead to a tendency to perceive the world more accurately rather than modulated by prior experience. Currently this hypothesis is debated, however only the way to interpret the Bayesian inference over posterior computation leading to a more precise perception is discussed and not the Bayesian accounts of autistic perception (Brock, 2012; Friston et al., 2013b; Van Boxtel and Lu, 2013).

To conclude, the Bayesian framework provides a generic and adaptive tool to model behavioral and cognitive brain processes (Tenenbaum et al., 2011). In particular, perceptual decision-

making and learning mechanisms are currently investigated using such statistical inference models in basic or clinical research.

2.2.3. CURRENT TRENDS IN DEFINING MODELS OF PERCEPTUAL DECISION MAKING

As we have seen before, neuroscientists possess the mathematical means to challenge the brain functions investigation. Generative models and the Bayesian statistical framework are powerful tools to describe and predict behavioral and neurophysiological data then to compare them with empirical data in order to uncover hidden brain mechanisms. In this part I want to shortly present a few examples of how computational models could be used to better understand and measure perceptual bias or contextual implicit learning processes.

Computational models (cognitive models)

Contextual implicit learning could take the form of behavioral bias in 2AFC discrimination tasks namely "the contraction bias" or "time-order effect" (Ashourian and Loewenstein, 2011; Preuschhof et al., 2011). An elegant study showed how Bayesian perception theory could encompass such a bias using a simple Bayesian inference model in which noisy representations of visual stimuli are combined with prior knowledge about the stimulation context in order to bias behavioral responses (Ashourian and Loewenstein, 2011). In this simple visual discrimination task subjects had to decide which of two successive horizontal bars (L1 and L2) presented on a screen was longer. The difference in length between the two stimuli varied between -30% and + 30%, moreover on 50% of the trials the lengths of the first and the second bars were equal (L1=L2). The authors focused on such impossible trials to reveal the contraction bias where subjects tended to report "L1>L2" depending on the bar length (see Figure 16). They argued that the contraction bias emerged because brain uses Bayes' rule to combine noisy information about the lengths of the bars with prior contextual knowledge about the history of stimulations.

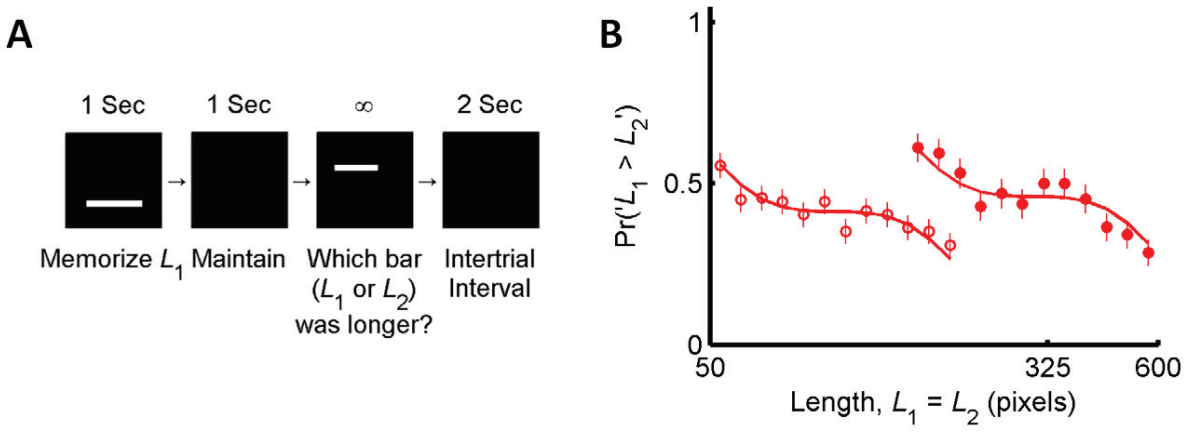


Figure 16: The 2AFC visual discrimination task and subjects' performance. **A.** Schematic standard trial. Subjects viewed a horizontal bar (L1) for 1sec and memorized its length. After a 1sec delay, subjects viewed a second bar (L2) and were instructed to report which of the two bars was longer. Unbeknownst to the subjects, on 50% of the trials, the lengths of the two bars were equal (L1=L2). **B.** Effect of the prior on the response during impossible trials (L1=L2). Two group of subjects performed the task for two overlapping different sensory context, bars could take lengths between 50 and 200 pixels in the first group (open circles) and between 150 and 600 pixels in the second group (filled circles). The figure represents the fractions of times in which subjects reported "L1>L2" on the impossible trials plotted as a function of bar length. For a given group (one sensory context), subjects overestimated the length of the memorized L1 bar when the bars were small and underestimated L1 where they were long, consistent with the contraction bias. This effect is the same for both group and depends on the actual sensory context (range of stimulation). Given that the physical range of stimuli is changed from group 1 (open circles) to group 2 (filled circles), small bars become long bar for instance, we observed a lateral shift in the prior and so in the contraction bias too. (Adapted from Ashourian and Loewenstein, 2011).

They defined L_i as the length of bar i (in logarithmic scale to accord Weber's law: see Deco et al., 2007) and R_i as its neural representation. Their model assumes that this representation is noisy such that:

$$R_i = L_i + \varepsilon_i$$
$$with\ \ \varepsilon_i \sim N(0, \sigma_i^2) \tag{5}$$

Then, assuming an uniform prior distribution of bar lengths $P(L_i)$, they combined it with the likelihood function denoted $P(R_i|L_i)$ using Bayes' rule:

$$P(L_i|R_i) \propto P(R_i|L_i).P(L_i) \tag{6}$$

Given a pair of neural representations (R_1, R_2) of the lengths of the first and second bars, the probability that L_1 is longer than L_2 is:

$$P(L_1 > L_2|R_1, R_2) = \int_{-\infty}^{\infty} P(L_1|R_1) \int_{-\infty}^{L_1} P(L_2|R_2)\, dL_2\, dL_1 \tag{7}$$

They reproduced the contraction bias for simulation with impossible trials where $P(L_1 > L_2|R_1, R_2) = 0.5$ using the assumption that $\sigma_1 > \sigma_2$ reflecting the fact that L_1 has to be stored in memory that may contribute to additional noise to the representation of L_1 compared to L_2 (see Figure 17). Finally, authors provided a normative and quantitative interpretation of the contraction

bias using Bayesian statistical framework. This type of finding is consistent with the literature showing that the brain uses Bayesian rules to perceive sensory input leading to contextually dependent cognitive biases.

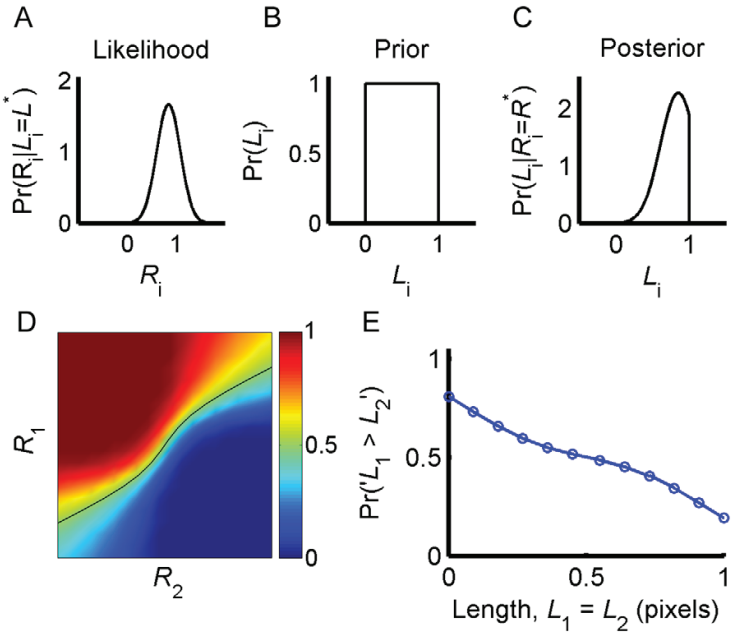
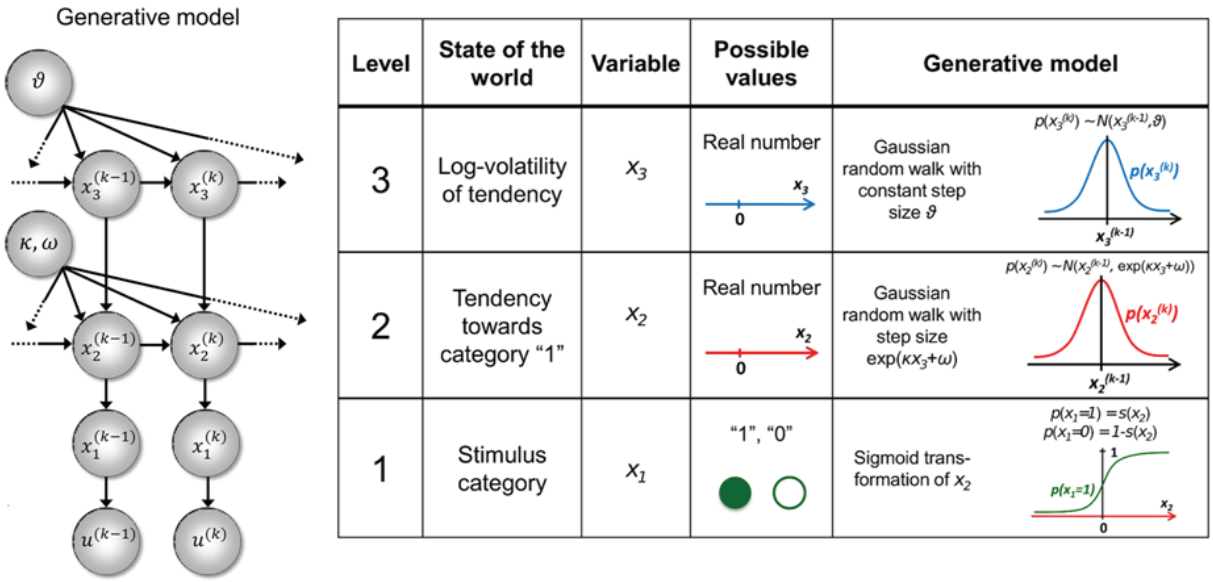


Figure 17: Bayesian model of behavioral response of the visual discrimination task. **A.** The likelihood of a representation $\boldsymbol{R_i}$ given a particular length (here $\boldsymbol{L_i = 0.85, \sigma_i = 0.24}$). **B.** The uniform prior distribution of bar lengths. **C.** The posterior distribution of $\boldsymbol{L_i}$ given a particular measurement (here $\boldsymbol{R_i = 0.85}$) calculted using Bayes' rule. **D.** The probability that $\boldsymbol{L_1 > L_2}$ for different values of $\boldsymbol{R_1}$ and $\boldsymbol{R_2}$ such that $\boldsymbol{P(L_1 > L_2 | R_1, R_2) = 0.5}$ (black line) with $\boldsymbol{\sigma_1 = 0.24}$ and $\boldsymbol{\sigma_2 = 0.13}$. **E.** Response curve of the model on the impossible trials $\boldsymbol{L_1 = L_2}$ reproducing the behavioral contraction bias.

Others examples of a recent attempt to formalize contextual perceptual learning introduces a generic hierarchical Bayesian framework for individual learning under uncertainty (i.e. environmental volatility and perceptual noise) (Mathys et al., 2011; Vossel et al., 2013). Actually, even when stimuli are presented with a very high signal-to-noise ratio, many aspects about the state of the world (i.e. the cause of sensory inputs) remain nontrivial to infer such as its probabilistic structure: the rules that relate causes of stimuli to each other. Underlying this idea, the goal of the brain mechanisms is to minimize surprise about sensory inputs and thus underwrite homeostasis, either by updating model-based predictions or by eliciting actions to sample the world according to prior expectations. Notably, it has been proposed that perception and action optimize a free-energy bound on surprise (Friston et al., 2007; Friston, 2009, 2010). Based on this free-energy principle considering the brain as a Bayesian inference machine, Mathys et al. (2011) introduced an extension of a dynamical generative model developed previously (Daunizeau et al., 2010a) and that exploited the information given to the subject about the task. To model learning in general terms, one has to imagine an agent who receives a sequence of sensory inputs $u^{(1)}, u^{(2)}, \dots, u^{(n)}$. Given the generative model of how the environment

generates these inputs, probability theory describes how the agent can use the inputs and prior information to predict the next input $u^{(k)}$. This study presents a computational hierarchical learning model assuming Gaussian random walks of states at different levels, with the step size determined by the next highest level (see Figure 18). This general model that can deal with discrete or continuous inputs, was presented in a simple situation where the agent is interested in a single (binary) state of its environment (e.g. whether it is a standard stimulation or a deviant one).



Level	State of the world	Variable	Possible values	Generative model
3	Log-volatility of tendency	x_3	Real number	Gaussian random walk with constant step size ϑ
2	Tendency towards category "1"	x_2	Real number	Gaussian random walk with step size $\exp(\kappa x_3+\omega)$
1	Stimulus category	x_1	"1", "0"	Sigmoid trans-formation of x_2

Figure 18: Overview of the hierarchical generative model. (Adapted from Mathys et al., 2011)

Left: schematic representation of the generative hierarchical Bayesian model. $\boldsymbol{x_1^{(k)}, x_2^{(k)}, x_3^{(k)}}$ are hidden states of the environment at the time point $\boldsymbol{k}$. They generate $\boldsymbol{u^{(k)}}$, the input at time point $\boldsymbol{k}$, and depend on their immediately preceding values $\boldsymbol{x_2^{(k-1)}, x_3^{(k-1)}}$ and the parameters $\boldsymbol{\vartheta, \kappa, \omega}$.

Right: Table summary for each level. The probability at each level is determined by the variables and parameters at the next highest level. These levels related to each other by determining the step size (variance) of a random walk. At the first level $\boldsymbol{x_1}$ determines the category of the input $\boldsymbol{u}$. At the second level, $\boldsymbol{x_2}$ is a real parameter of the probability that $\boldsymbol{x_1 = 1}$, using a sigmoid (softmax) function ($\boldsymbol{s(\cdot)}$) . The values of $\boldsymbol{x_2}$ change with time as a Gaussian random walk and is normally distributed around its value at the previous time point $\boldsymbol{x_2^{(k-1)}}$. The third level $\boldsymbol{x_3}$ determines the dispersion of the $\boldsymbol{x_2}$ random walk (i.e., the variance: $\boldsymbol{exp(\kappa x_3 + \omega)}$) as well the parameters $\boldsymbol{\kappa}$ and $\boldsymbol{\omega}$ (which may differ across agents). The third state determines the log-volatility of the environment (e.g. Behrens et al., 2007). In this case authors stop at the third level setting the variance of $\boldsymbol{x_3}$ to $\boldsymbol{\vartheta}$ (which may differ across agents) but note that further levels can be added on top of the third.

This generative model offers an interesting possibility to assign meaning to the parameters about how the agent could infer environmental probability. While the second level state x_2 refers to the environmental events probability tracking, the third one x_3 refers to the confidence about the agent's estimate of environmental volatility (Behrens et al., 2007). For instance one could reduce the agent's learning rate of environmental probability by reducing the parameter ω (variance of the second level random walk independent from the third level): this corresponds to an agent who pays little attention to new information. Another example, when variance parameter ϑ is reduced (variance of the

third level random walk), the generative model is overly confident about its prior estimate of environmental volatility and expects to see little change, this leads to an agent who has higher-level beliefs that remain impervious to new information without modifying the second level learning rate (Mathys et al., 2011). Recently such a generative model has been applied to the analysis of saccadic reaction times in a location-cueing visual paradigm with a volatile probabilistic context in order to probe Bayesian theories of perceptual inference (Vossel et al., 2013). These authors inferred subject-specific learning parameters from empirical behavioral responses using this type of hierarchical Bayesian learning model. The authors' findings showed that there is considerable interindividual variability within the group of healthy subjects who participated in the experiment. They concluded that in the future it is necessary and important to relate this variability to neurobiological factors.

Neurophysiological models (neurocognitive models)

We have seen that perception can be modeled under the Bayesian brain hypothesis, as the process of computing a posterior distribution over causes using a generative model and sensory inputs, while perceptual learning could be explained as the updating of the brain's representations of the prior distribution based on the inferred posterior distribution (Friston et al., 2003; Ashourian and Loewenstein, 2011; Mathys et al., 2011). Focusing on neurophysiological data, it has been suggested that Bayesian mechanisms are encoded by neuronal populations whose responses to novel sensory inputs are interpreted as dynamics induced by the violation of prior expectations (Rao and Ballard, 1999; Garrido et al., 2008). Typical electrophysiological signal or brain markers of this violation are EEG/MEG novelty responses such as the mismatch negativity (MMN) or the P300 evoked potential (Näätänen et al., 2011; Morlet and Fischer, 2013). Such markers can be found using simple experimental paradigms where EEG or MEG are used to measure event-related responses to violations of expectancy or learned regularities. Traditionally, such responses are recorded during oddball experiments or more recently during roving paradigms (see Figure 19) in several sensory modalities. Precisely, the MMN can be found by subtracting the event-related potential (ERP) elicited by "standards" (i.e. frequent and regular stimuli) from the ERP elicited by "deviants" (i.e. stimuli that perturb the regularity). Such electrophysiological markers promote theories about how the brain could implement probability learning and compute surprise in response to unexpected stimulation.

Actually, a mathematical definition of surprise under the Bayesian brain hypothesis has already been proposed namely the Bayesian surprise (Baldi and Itti, 2010). Broadly speaking, the idea is to measure the amount of surprise in the data for a given observer (agent) by looking at the changes that take place in going from the prior to the posterior distributions. In others words, from the general Bayes rule (see equation (3) the effect of D (i.e. data) is clearly to change $P(M)$ (i.e. prior over a set $\mathcal{M}$ of possible models (or hypotheses)) to $P(M|D)$ (i.e. posterior over $\mathcal{M}$) and one way to estimate the surprise is to determine information carried by D by measuring the distance between the prior and the posterior distributions. The Kullback-Leibler divergence is typically used to compute the distance (or

dissimilarity) between probability distribution (Penny, 2001) and can be used to formalize Bayesian surprise (BS) (Baldi and Itti, 2010):

$$BS(D, \mathcal{M}) = KL\big(P(M), P(M|D)\big) \tag{8}$$

An elegant study has shown that in a somatosensory mismatch paradigm Bayesian surprise signals are encoded by multiple cortical regions of somatosensory and frontal networks involving SI, bilateral SII, bilateral IFG and medial cingulate cortex (Ostwald et al., 2012). These authors tested a roving experiment where electrical stimuli of two amplitudes (high and low) were delivered to the median nerve (see Figure 19). To relate single-trial source activity to Bayesian perceptual learning, the authors formalized a model that assumes the brain implements a trial-by-trial Bayesian parameter learning scheme with an exponential forgetting time window of stimulus observations in the distant past history, then is able to compute Bayesian surprise as the Kullback-Leibler divergence between prior and posterior parameter probability distribution at the single trial level. They found that Bayesian surprise can provide a better explanation for source-reconstructed single-trial EEG signals than conventional model such as the "linearly modulated stimulus change model" (less complex model implementing a linear relationship between the expression of evoked source activity and the number of standards preceding a deviant stimulus).

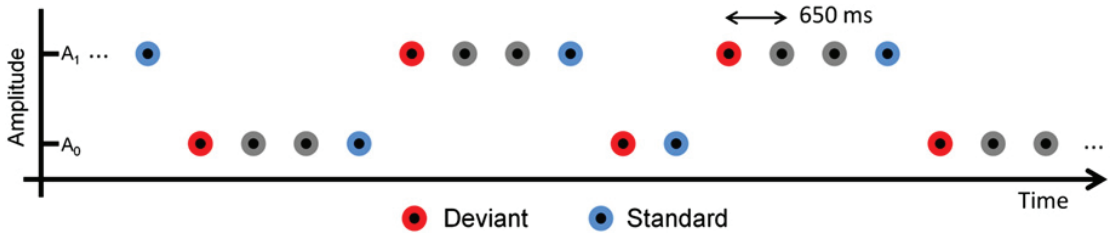


Figure 19: Somatosensory mismatch **e**xperimental paradigm. High (A_1) and low (A_0) amplitudes electrical stimuli were delivered to the median nerve with an inter-stimulus interval of 650ms. Trains of identical stimuli comprised 2, 4, 8 or 16 stimuli. The first stimulus in each train of identical stimuli was labeled a deviant. To compare deviant (red) and standard (blue) responses based on the same number of trials, only those stimuli immediately preceding a deviant stimulus were labeled standard. (Adapted from (Ostwald et al., 2012) and based on a previously established roving paradigm for the somatosensory domain (Baldeweg et al., 2004))

Because the mismatch negativity (MMN) potential remains an easily recordable and a non-invasive electrophysiological measure of the neural response to regularity violation by sensory stimuli, it is widely studied for understanding neurophysiological and computational processes underlying statistical learning and the prediction of future events in the brain. However, the algorithmic nature and the underlying neurobiological implementation of such processes remain controversial and debated. Recently, a study investigated different conceptual hypotheses about the computational quantities indexed by MMN responses by formalizing models from distinct theories (Lieder et al., 2013). These authors tested these generative models by comparing their ability to explain empirical

trial-by-trial changes in MMN amplitude from eight healthy subjects in an auditory roving oddball experiment. Models based on the free-energy principle provided more plausible explanations of trial-by-trial changes in MMN amplitude than models representing the two more traditional theories (change detection and adaptation). Such findings suggest that the MMN reflects Bayesian learning of sensory regularities. Moreover the authors introduced in this paper recent attempt to formalize traditional and modern competing theories of an electrophysiological response (MMN) by implemented neurocognitive models using the probabilistic generative model framework.

In the future, such modeling approaches will lead to greater understanding of contextual perceptual learning. Furthermore, the link between single-trial electrophysiological potentials and perceptual inference can be currently studied using such plausible and realistic models of how the brain generates neurophysiological signals given its ability to learn the probabilistic structure of the environment.

CONCLUSION

Perceptual decision making has been widely studied in different experimental set-ups and sensory modalities because it underlies processes that tell us how the brain interacts with the world. Today it is increasingly obvious that we have to take into account the dynamical aspect of such mechanisms. Thankfully recent developments from computational modeling and Bayesian statistics offer a framework and an interesting opportunity to quantitatively investigate the dynamical interaction between the brain and a changing environment. All these models formalize how the brain learns and deals with the uncertainty using dynamical generative models. Such models can describe the intimate relationship between sensory input (i.e. stimulation) in a controlled context (i.e. experiment) and the brain's ability to apprehend the probabilistic structure of complex environments (i.e. hidden structure of experimental design) at the single trial level. These findings constitute a necessary and useful computational apparatus in order to imagine future perspectives for designing an experiment in order to test alternative generative models (i.e. hypotheses) about brain function.

CHAPTER III. HYPOTHESES AND OBJECTIVES

This chapter introduces the main objectives of my PhD thesis. On the one hand, we have seen that brain-computer interfaces (BCIs) emphasize the need for online data acquisition techniques as well as methods for making and adapting decisions online. On the second hand, recent efforts in the field of perceptual decision making have yield more biologically plausible models account for the dynamical nature of learning mechanisms. In other words, psychological theories have become more biologically plausible, leading to more realistic generative models of psychophysiological observations, while the active field of BCI has fostered the development of real-time data processing. Given the recent and important advances in both fields, neuroscientists may now use them as an opportunity to explore new and more efficient ways of experimentally testing basic or clinical hypothesis.

Information seeking in humans and monkeys, is driven by natural sampling and experience based learning (Nelson et al., 2010; Shadlen and Kiani, 2013). Many situations require careful information selection. For instance, visual perception requires performing specific eye movements towards the informative parts of the visual scene. In a completely different context, carefully sequentially selected clinical tests may optimize the diagnosis and the ensuing decision about the most appropriate treatment. Very similarly, some experimental designs (e.g. what stimulation to present) are more efficient than others in the aim of disentangling between competing scientific hypotheses. This analogy resonates with the view of human actions as a mechanism to fulfill perceptual predictions which derives from an internal model of the world (Friston et al., 2013a). Hence, in experimental science, choices of parameters could be seen as some action oriented towards fulfilling the prior expectation that the outcome of the experiment should tell the initial alternative hypothesis apart. In other words, as prior beliefs influence perception and ensuing actions, researchers prior assumptions motivate a specific experimental design and drive the interpretation of the data to eventually conclude in favor of the winning hypothesis. Following this analogy, one may formalize a computational way of optimizing experimental designs online, in the same way recent mathematical models formalize human perception and decision making. The later typically rest on both Bayesian inference and Bayesian decision theory. The state of the art described in Chapter I & II motivated this work, aiming at innovating in the way one investigates the brain mechanisms that subsume perceptual learning and decision-making.

HOW COULD WE REFINE HYPOTHESES ABOUT THE DYNAMICAL NATURE OF PERCEPTUAL DECISION-MAKING?

In the previous chapter we saw that behavioral and neural correlates of perceptual decision-making have been established through a number of different experimental studies, in humans or monkeys. Interestingly, empirical findings point towards the involvement of a distributed network of brain regions. Several important sub-processes have been investigated including: stimulation encoding, maintenance of information in working memory and decision-making based on past sensory evidence. These processes have been associated with specific signals, originating from specific brain areas. However, the functional role of markers in of perceptual decision-making remains uncovered. In order to unravel further, we decided to study the evolution of those markers over time, as behavioral response evolves due to the implicit influence of the experimental context. In line with recent attempts to explain perceptual-decision biases (e.g. time-order effect or contraction bias), we aimed at studying such adaptive processes in a well-known and simple discrimination task. We focused on tactile frequency discrimination since such protocols have been extensively studied in humans and monkeys, and have been shown to possibly reflect a decision bias (Preuschhof et al., 2011). We hypothesized that such a bias reflects the build-up of a contextual prior, as it has already been suggested in the visual domain (Ashourian and Loewenstein, 2011). This hypothesis fits with the wider framework of the Bayesian brain hypothesis. It suggests that the brain learns about the environment by computing some statistics which will optimize its predictions or prior expectations (Knill and Pouget, 2004; Moutoussis et al., 2014). Even in the context of low level, simple sensory discrimination, this suggests that some contextual parameters are implicitly learned, which raises several outstanding questions. What are the neural correlates of contextual adaptation during a typical perceptual-decision task? Could some new contextual prior be implicitly learned and interfere with the previous context set?

The first objective of my PhD work was to decipher the behavioral and neural correlates of implicit contextual-dependent learning during perceptual decision-making, by investigating these processes in a typical tactile frequency discrimination task. This was the aim of the study using magnetoencephalography (MEG) together with behavioral measures (see Study 1). In this study, I first showed how behavioral responses are impacted by the context of stimulation (previous stimuli) using a simple behavioral paradigm that can be used to quantify the contraction bias. In a companion experiment using MEG, I investigated the neural correlates of implicit context-based adaptive processes. Relevant signal features include evoked fields, oscillatory activities and steady-state responses. Taking advantage of the relatively good spatial resolution of MEG, I used classical source reconstruction as well as dynamical causal modeling to infer the cortical network and the modulations of effective connectivity in that network that subsume the observed behavior. Namely, I have been able to investigate the initial phase of the experiment where the implicit learning takes place.

COULD REAL-TIME ELECTROPHYSIOLOGY PROVIDE NEW INSIGHTS INTO PERCEPTUAL DECISION MECHANISMS?

Apprehending perceptual decision-making as a dynamical process that involves contextual adaptation leads to questioning the importance of the influence of the recent history of experimental events or trials in current decisions. Given this realistic hypothesis, one then has to envisage that any choice or modification in the experimental design might trigger some learning process which will impact future perceptual decisions. Such a causal relationship makes it even more difficult to investigate the hidden neural correlates of perceptual decision-making. In turn, it also raises important questions regarding the functional meaning of the electrophysiological markers that accompany such implicit mechanisms. Over the past few decades, researchers have efficiently explored the electrophysiological correlates underlying perceptual decisions. This has led to models whose most recent form include explicit attempts to capture their dynamical nature and hence the over-trials dependencies. However, optimizing the experimental design in order to disentangle such advanced models has become challenging (Daunizeau et al., 2011b). Hopefully the BCI field together with the Bayesian framework offer efficient tools and opportunities to conceive adaptive experiments that could yield the optimization of dynamical, non-linear, hypothesis testing. Thus, the second aim of this thesis was to validate the usefulness of real-time electrophysiology in offering a new and active way to conduct neurocognitive experiments for the investigation of dynamical neurophysiological mechanisms and cognitive processes.

Intuitively, useful experiments are those for which plausible competing theories make the most contradictory predictions. Such questions about experimental efficiency were discussed before. People soon realized that they could take advantage from online data acquisition to inform and optimize future observations. This was first referred to as sequential hypothesis testing. Initially, the concept of sequential hypothesis testing originated in the field of quality control, which draws on statistical inference from sequential samples of data. In the middle of the 20th century, Abraham Wald began to use such efficient data sampling for industrial purposes as a way to decide whether batches of munitions were of sufficient quality to ship. He developed the sequential probability ratio test as the optimal procedure to test a hypothesis against its alternative, using the minimal number of samples (i.e. a speed versus accuracy tradeoff) (Wald, 1945). Generally speaking, finding the optimal way to collect data is crucial for decision. Deciding which piece of information to acquire or attend to is fundamental to perception, as well to medical diagnosis and scientific inference (Nelson et al., 2010; Shadlen and Kiani, 2013). Obviously, it would be better if we could have an online access to the information gain after each data collection. However in most cognitive experiments, data are collected according to a design that is finalized before the experiment begins. Thus the key solution is to provide adaptation and flexibility within experimentation. As research on perceptual decision making has

grown more sophisticated during the last century, new adaptive methodologies have been developed to increase efficiency of measurement. Such procedure are known as adaptive design optimization (ADO) (Myung et al., 2013). Such new methodology provides a way to run an experiment with dynamical modification of the design in response to observed data (Cavagnaro et al., 2009a). In psychophysics, where changes in stimulus strength or other characteristics are associated with changes in the ability to detect or discriminate the stimuli, simple adaptive testing approaches have already been proposed (e.g. the stair-case procedure to estimate a sensory threshold) (Leek, 2001). Because of its flexibility and efficiency, the use of adaptive designs has become popular in many fields of science. In the fields of experimental psychology and electrophysiology, recent forms of ADO have been applied to estimating psychometric functions (Kujala and Lukka, 2006), to optimizing the comparison of computational models of memory retrieval (Cavagnaro et al., 2009b) and to optimizing the duration of the experiment when comparing alternative neuronal models (Lewi et al., 2009). Now taking advantage of real-time electrophysiology, we envisage that online data acquisition will provide an optimal way to compare neurocognitive hypothesis. This call for the same online tool that the BCI community is developing for the online analysis of electrophysiological brain signals (Millán and Carmena, 2010). Besides, interpreting complex generative models of those data online calls for efficient and robust computational approaches that can deal with statistical model comparison, such as approximate Bayesian inference schemes (Daunizeau et al., 2011b, 2013). With ADO and in contrast with standard (non-adaptive) experiments, the total number of trials is not set in advance, nor is the nature of the stimulation at each trial or stage of the experiment. Moreover, one does not wait until the end of the data acquisition process to proceed with data analysis and statistical inference. Instead, at each trial, the appropriate data features are extracted in order to up-date our (the experimenter's) information about the model parameters and to assess the model plausibility itself.

In a second theoretical study (see Study 2), I introduced, illustrated and validated the principle of ADO in the aim of improving hypothesis testing in the domain of perceptual learning. This first validation study is based on simulation only. In terms of models, I used recent advances in Bayesian models of human learning in an uncertain environment, from sequential observations. This fits common task situations such as the well-known and simple oddball paradigm where no behavioral response is required (Ostwald et al., 2012). Importantly in this context, models have been proposed to explain both the underlying dynamical mental process and its trial-wise neurophysiological correlates (Mathys et al., 2011; Lieder et al., 2013). Finally, in a last and short opinion paper, I discuss more broadly how ADO could benefit our understanding of brain signals in generalizing the principle of brain-state dependent stimulations (Jensen et al., 2011), and how it should benefit classical BCI applications in return by accelerating scientific discovery in brain function for basic and clinical purposes.

CHAPTER IV. STUDY 1: BEHAVIOR AND MEG

4.1. INTRODUCTION OF THE ARTICLE

Previously I showed how tactile frequency discrimination tasks have been widely used to study working memory and perception, particularly in monkeys (Romo and de Lafuente, 2013), and in humans using non-invasive electrophysiology (Haegens et al., 2010; Spitzer and Blankenburg, 2011). The experimental set-up was rather simple: participants had to discriminate between two stimulations presented at higher or lower frequency, which allowed the investigation of dynamical processes related to perceptual decision-making. Actually, this specific research led to identification of reliable brain activity markers and brain regions related to specific mechanisms in this simple task such as: stimulus encoding, working-memory, comparison and decision-making. However, some studies in various sensory modalities showed that implicit contextual learning during a discrimination task could lead to bias behavioral responses (Nahum et al., 2010; Ashourian and Loewenstein, 2011; Preuschhof et al., 2011). These findings suggested a brain tendency to use sensory context internal reference based on stimulation history, in order to switch from a real discrimination strategy (i.e. where two stimulations are compared) to a simpler categorization strategy (i.e. where stimulation is categorized according to the average of sensory context) (Nahum et al., 2010; Seger and Peterson, 2013).

I have studied behavioral and neural correlates of the sensory contextual influence on the performance. Using two experimental procedures, I have tried to describe the dynamical mechanisms that lead to contextual learning. I have used a protocol where the first stimulation frequency remained the same along the experiment. A stable relevant characteristic of stimulation is known to influence implicit processes of contextual adaptation (Harris, 1948). Focusing the analysis on the reference stimulation, I aimed to investigate the progressive mechanisms that lead to context-dependent behavioral bias centered on the reference frequency. Using MEG, I intended to reveal brain regions and activities involved in the adaptive process that are linked to a better performance and a sensory context learning during the task.

4.2. ARTICLE: BUILD-UP OF AN INTERNAL REFERENCE DURING TACTILE FREQUENCY DISCRIMINATION: A BEHAVIORAL AND MEG STUDY.

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(Paper in preparation)

ABSTRACT

Exploring behavioral responses and MEG signals, we studied neural correlates of perceptual decisions in a two-alternative forced choice paradigm consisting in tactile frequency discrimination based on electrical stimulations. Perceptual decision-making is often investigated with tactile frequency discrimination tasks. Such protocols usually operate after extensive training, when human or non-human subjects have reached a plateau of performance. In this study instead, we focus on the learning or adaptation phase compared to the plateau of performance. We show behavioral and physiological evidence of such transition which suggests an implicit strategy shift from discrimination to classification, yielding an improvement in both accuracy and reaction time. The first stimulus was a reference frequency that must be retained and compared to a second variable stimulus. At the behavior level, results allowed us to distinguish a learning part where performance increased reflecting contextual learning that bring participants to bias their decision-making. After participants were exposed to a specific stable experimental context around 30Hz stimulation we tested for perturbation of this contextual learning based on time-order effect (also called contraction bias) evaluation. We found the first three sessions are sufficient to promote buildup of an internal perceptual reference which could perturb shortly a new contextual learning. Using MEG in another experiment, we focused on the study of neural correlates involved in the buildup of an internal reference based on the first stimulation perception. Stimulations elicited steady-state evoked fields, which were source-localized in primary somatosensory cortex. Focusing on the amplitude of this neural response for the first stimulation, we have found significant correlation with performance discrimination during the first part of the experiment. Moreover, amplitude for late evoked activity to the first stimulation increased for correct trials during the first part of the experiment, source localization of this effect suggested involvement of inferior frontal gyrus (IFG). We performed dynamical causal modeling to elucidate effective connectivity between the somatosensory network and these frontal regions. Interestingly, it reveals the crucial role of bilateral IFG. During the first part of the experiment, these results seem to reflect active mechanisms oriented towards the buildup of a perceptual internal reference frequency based on first stimulation stability. Finally, the dynamics of these response

modulations, that vanished during the second part of the experiment, highlight the shift from a comparison strategy to an implicit classification mechanism.

INTRODUCTION

The ability to actively maintain representations of sensory information, flexibly update it, reorganize this information and use it for guiding actions and decisions are essential parts of human behavior (Romo and Salinas, 2003). Perceptual decision making is the act of selecting one possibility or sequence of action from a set of alternatives on the basis of accessible sensory evidence. Consequently, when such decisions occur, sensory information in all sensory modalities must be interpreted and decoded into behavior. However it is known that perceptual learning occurs and including automatic unconscious mechanisms which could bias decision-making in a difficult choice situation (Galdi et al., 2008). Most studies use two-alternative forced choice paradigm (2AFC) to investigate perceptual decision making processes, asking participants to discriminate between sequentially presented stimuli about features difference (i.e. frequency, density, magnitude, etc.). Recently, Nahum and colleagues have found that the perceptual system actively attempts to bypass comparisons between two recently presented stimuli and replace them with a task-related classification ("high" or "low") based on an internal reference whereas participants remained unaware about this process modification (Nahum et al., 2010). Moreover it is known that perceptual context could influence future decision-making (Ashourian and Loewenstein, 2011).

In order to elucidate this implicit and automatic mechanism we studied the neural correlates of perceptual decisions in a specific 2AFC protocol. The task consisted in tactile frequency discrimination based on electrical stimulations. Basically subjects discriminate the second stimulus based on sensory evidence which represent a reference frequency of the first stimulus stored in memory. The sensory context in this task could modify the future decision, and subjects base their decisions on a perceptual global experience. In other words, previous trial history and perceptual implicit memory could play an important role in the decision outcome. Interrogations emerge about the processes that necessarily contribute to building and maintenance of such prior perceptual information and therefore conduct to the comparison process evolution.

This study investigated the neural correlates and cerebral areas involved in implicit tactile perceptual contextual learning. Subjects could form an internal representation of the first base stimulation frequency (F1) and compare the second stimulus (F2) to a combination of this implicit representation and real F1 frequency. It would mean that subjects have developed an integrated representation of the standard stimulus, and that they based their future decision on a comparison between the sensation evoked by F2 with the relatively constant internal reference. When F1 varies, this internal reference tends to become closer to the average of different F1 frequencies as prior bayesian up-dating process and this phenomenon biases performance depending on the time order of

stimulus presentation: known as time-order effect (Preuschhof et al., 2011) or contraction bias (Ashourian and Loewenstein, 2011).

Firstly we tested how the existence of an internal reference could be reveal after a progressive and implicit contextual learning using a behavioral task. In this first experiment we examined how such slow building mechanisms based on contextual information could be disturb regarding behavioral contraction bias observation. Secondly using a MEG experiment with a fixed reference first stimulation and looking at modulation of evoked and induced activities across the experiment, we study the build-up of a such internal perceptual reference. To go further in explaining this progressive implicit phenomenon we used dynamical causal modeling to elucidate early perceptual somatosensory processing evoked by the first stimulation based on recent findings that have studied in details the basic somatosensory processing in a detection task with this method (Auksztulewicz et al., 2012). We asked whether these electrophysiological markers provide insight concerning the localization and the dynamic of this specific mechanism leading perceptual system towards build-up of an internal reference.

MATERIAL AND METHODS

Subjects

Forty (mean age: 21±1.75 years, range: 18-28 years, 20 males) and twenty (mean age: 24±3.5 years, range: 19-36 years, 10 males) healthy right-handed subjects participated at the first behavioral experiment and at the second MEG experiment respectively. All participants had normal or corrected-to-normal vision, reported normal tactile sensitivity and had no history of neurological or psychiatric disorders. Participants gave written informed consent before the experiment.

Stimuli and behavioral task

Non painful electrical stimulation of the left index finger was delivered by a constant current stimulator (GRASS Technologies). Constant stimulation intensity was adjusted in each subjects to 2.5 times the sensory threshold level (Pleger et al., 2006) as individually established prior to the MEG recordings (mean : 0.86±0.17mA; range : 0.52-1.3mA).

Subjects performed 6 sessions of a two-alternative forced-choice frequency discrimination task. During the task, participants were instructed to fixate a small cross located at the centre of the screen. Meanwhile, they had to discriminate between the frequency of two electrical stimuli (F1 and F2) applied sequentially. Each trial was preceded by a 1500ms baseline period followed by a 500ms first stimulation (F1). The first stimulation was followed by a 2s-long retention interval after which the second stimulation (F2) was delivered for another 500ms (see Fig. 1).Subjects had to indicate whether the first or the second frequency was higher by pressing a button with their right (non-stimulated) hand (Left button with index finger : F1>F2; Right button with major finger : F2>F1). After the second

stimulation a "?" replaced the fixation cross until the participant pressed the button. Subjects had 4s to respond prioritizing accuracy over the speed and were asked to always respond. Then a black screen separate each trials and lasting for 1500ms. No feedback was given. Subjects could practice the task briefly (15 trials) before starting the actual recording. The complete experiment was programmed and run using the software package Presentation (Neurobehavioral Systems).

First experiment (behavior only): three groups of subjects performed 6 sessions of the same task as in the first study, except for sessions 4 and 5, where F2 was always 2Hz higher or lower than F1. During those two sessions, in group 1 (N = 20), F1 varied and ranged between 25 and 35Hz (F1 = 25, 27, 29, 31, 33 or 35Hz; mean=30Hz). In group 2 (N = 10), F1 ranged between 21 and 31Hz (F1 = 21, 23, 25, 27, 29 or 31Hz; mean=26Hz). In group 3 (N = 10), F1 ranged between 29 and 39Hz (F1 = 29, 31, 33, 35, 37 or 39Hz; mean=34Hz).

Second experiment (with MEG acquisition): F1 consisting of a train of electrical pulses delivered at a frequency of 30Hz. 17 different frequency values were considered for F2, ranging from 22 to 38Hz. Hence the absolute frequency difference between the two stimuli (F1 and F2) varied between 0 and 8 Hz (ΔF). All frequencies were equally represented in each session (balanced design), in a randomized manner. In each session, a total of 5 events were presented for each ΔF, resulting in 85 trials. After the MEG session, participants' subjective reports regarding their strategies were collected. However, participants remained unaware of the constancy of the reference stimulation.

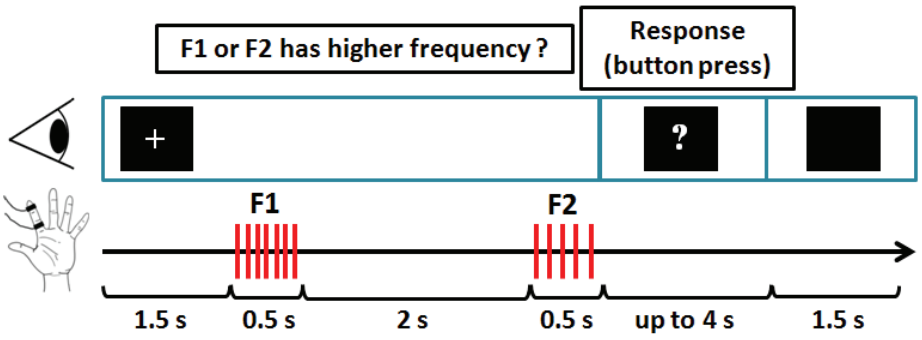


Figure 1: Schematic drawing of one trial.

Behavioral analysis

A psychometric function was estimated for each subject by plotting the percent (P) of stimulus F2 that were identified as higher in frequency than stimulus F1, as a function of the actual difference in frequency (ΔF). Logistic functions of the form $f(x) = \frac{1}{1+e^{-(B1.x+B0)}}$ were fitted to the data using an iterative Newton-Raphson scheme. Hence behavioural responses are determined by two parameters: (1) the psychometric slope (B1), and (2) the intercept (B0) (Fig. 1).

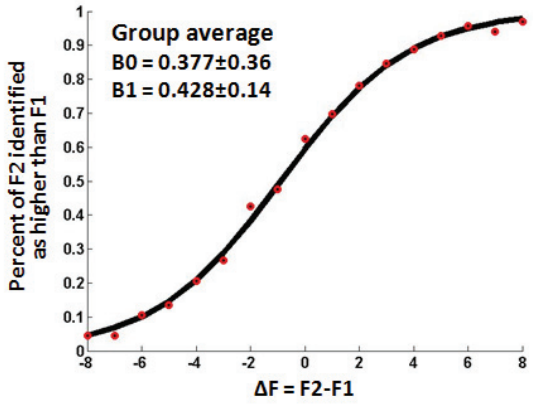


Figure 2 : Logistic function of group average performance results.

Therefore, we defined "difficult trials" based on individual psychometric curves for which percent probability to respond "F2>F1" laid between 0.3 and 0.7. The rest of the trials are defined as "easy trials". For further analyses of reaction times (RT), outliers (more than 2 standard deviation above or below the mean) were rejected based on a Gaussian fit of the log-RT for each subject and performance condition (correct and incorrect). Non-parametric Wilcoxon signed-ranks tests were performed to evaluate performance evolution across sessions.

MEG recordings

MEG signals were recorded on a CTF Omega 275 channel whole head system (VSM MedTech Ltd., Canada) with continuous sampling at a rate of 600 Hz, and a 0–150 Hz filter bandwidth. Vertical electrooculogram (EOG) and electrocardiogram (ECG) were acquired with bipolar montages. Subjects were placed comfortably lying down within a magnetically shielded room. They were instructed not to move and to keep their eyes open during the experiment without blinking too much. Three fiducial coils (nasion, left and right pre-auricular points) were placed for each subject to determine the head position within the MEG helmet, and to provide co-registration with the anatomical MRI images. Head position was checked at the beginning and end of each block to ensure that head movements did not exceed 0.5 cm (this was confirmed by additional offline checking before the data analyses).

Data Analyses

MEG data were analyzed in sensor and source spaces using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK; Friston et al., 2008; Litvak et al., 2011) and custom MATLAB code (Mathworks Inc., Natick, MA, USA). The analyses reported here focused on steady-state and transient evoked fields evoked and oscillatory activities induced by F1, i.e., during the encoding and memorization of the reference somatosensory pattern. Signals were off-line bandpass filtered (0.1 – 20 Hz) for evoked responses or highpass filtered (0.1Hz) for steady-state responses and other oscillatory activity. The MEG data were corrected for eye movements and cardiac artifacts using independent

component analysis. Trials with remaining artifacts (muscles activity) were excluded from analysis by careful visual inspection. The artifact-free MEG data were segmented into 600 ms epochs ranging from 100 ms before F1 stimulus onset to 500 ms after offset. A -100 to 0 ms interval was used for baseline correction. Spectral analysis was performed on 5500ms epochs ranging from 1500ms before first (F1) stimulus onset to 1000ms after comparison (F2) stimulus offset. A time-frequency power analysis between 2 and 45Hz was performed using fast Fourier transform (FFT) multitaper approach using a single Hanning taper with sliding adaptive time windows of four cycles length. Evolution of spectral power over time was expressed as logarithmic transformation of power changes relative to a prestimulus baseline period (1000-500ms before F1).

Sensor level analysis

Using averaged trials where the first stimulus frequency was equal to the second one (30-30Hz trials), we identified, at the group level, emerging responses in term of sensor regions of interest (ROI) and time-windows, using one-sample SPM t-tests compared to baseline. Family-wise errors (FWEs) in time–frequency space were controlled using random field theory (RFT). Each ROI was defined according to emergent activity threshold corrected for family wise error. Statistical parametrical maps were thresholded at $p_{FWE\text{-}corrected} < 0.05$, using RFT on the cluster level to control for FWE. We identified emerging MEG activity ROIs and time period for transient, steady-state response (SSR) and oscillatory event related synchronisation/desynchronisation (ERS/ERD).

Source level analysis

We performed landmark-based co-registration of MEG data and MRIs using the locations of nasion and preauricular points (Mattout et al., 2007). Based on these response amplitude emerging time periods the sources of MEG activity were modeled using source reconstruction as implemented in SPM8 using the multiple sparse prior (MSP) model (Friston et al., 2008). For each participant, a forward model was constructed, using a 20484 vertex template cortical mesh coregistered to the individual head positions via three fiducial markers. The lead field of the forward model was computed using the multiple sphere MEG head model available in SPM8. Individual inverse solutions were obtained using the empirical Bayesian approach implemented in SPM8 (Mattout et al., 2006). The averaged time periods of 30-30Hz trials were inverted to identify cortical ROIs. SSR were source localized using data filtered (bandpass [29 31]Hz) restricted to this response time duration (150-500ms to stimulus onset, to avoid the evoked transient response). Each cortical ROI was defined according to emergent source activity threshold corrected for family wise errors ($p_{FWE\text{-}corrected} < 0.05$). Limited to this cortical ROI, steady-state evoked amplitude responses were calculated on sinusoidal fit of the source time-course. Five 300ms sliding time-windows centered to one pulse stimulation onset were averaged restricted to the steady-state duration (150-500ms to stimulus onset). Therefore, we performed single trials inversion in order to extract the source time-course of each ROI cluster. Then single trial SSR amplitudes were estimated based on sinusoidal fit for each ROI. The mean amplitude of the entire ROI

cluster fit was used as single trial SSR amplitude. Trial-by-trial data were then extracted for each subject, on which ANOVA and post-hoc analysis were performed with R (mixed model).

The localization of contrast was performed on the difference for each averaged condition (Localization of difference (LoD) = correct difficult trials - incorrect difficult trials) and for the specific time-window identified on 30-30Hz trials ([180 210ms]). Finally, oscillatory activities were inverted using data specific frequency filtered restricted to time period of interest and baseline period separately. LoD and oscillatory activity source emergence results were presented according to threshold corrected for family wise error ($p_{FWE\text{-}corrected} < 0.05$).

Dynamic causal modeling

DCM for ERP explains ERP as a resultant of stimulus-related changes in the activity of neuronal populations (David et al., 2006; Kiebel et al., 2009). Each cortical source is represented by three interconnected populations (pyramidal cells, excitatory interneurons, and inhibitory interneurons) representing different cortical layers. Different sources are connected by long-range connections conforming to physiological connectivity rules. Differences in interregional effective connectivity afford changes in the shape of ERP between conditions. The models and their constitutive sources are first specified according to functional hypotheses of interaction across brain structures of interest. Second, model parameters are inferred from the ERP and the evidences of models are computed using Bayesian procedures. Finally, Bayesian model selection (BMS) is applied to define the most plausible model (Stephan et al., 2009) or family of models (Penny et al., 2010). It computes the expected probability of obtaining a given model for any randomly selected subject in the group, and the exceedance probability, which is the belief that a particular model is more likely than any other model (of all models tested), given the group data. The BMS procedure takes into account not only the goodness of fit of the data, but also the complexity of the models (i.e., number of free parameters) to avoid overfitting the data.

We used DCM to infer hidden parameters of neuronal models from the epoched MEG data from 0 to 500ms according to the first stimulus onset (F1). Data were bandpass filtered between 0.1 to 45Hz in order to preserve transient and steady-state responses. DCM explains the data by a network model with a few dynamically interacting sources. The sources, here implemented as equivalent current dipoles, can be (1) connected in a fixed manner, modeling context-independent effective connectivity between regions, (2) exerting context-dependent influence on one another, representing modulatory connections, and (3) receiving direct driving input. All structural models in the subsequent analyses were specified for the same architecture including a single contralateral (here right) SI dipole (cSI), a symmetrical SII dipole pair (cSII and iSII) (Auksztulewicz et al., 2012) and a symmetrical IFG dipole pair (cIFG and iIFG). We used the position of maximum group activity source distributed localization as prior for each dipole position. The models contained a bilateral structural connection

between cSI and cSII, a bilateral connection between cSII and iSII and potentially bilateral structural connection between cSII, iSII and cIFG, iIFG respectively. The models differed with respect to the presence of connections to IFG sources and the number of individual extrinsic connection strengths modulated by condition, i.e., allowed different subsets of connections to change the strength of coupling between regions depending on discrimination performance (correct vs. incorrect). Peripheral input was assumed to be directly received only by cSI.

RESULTS

Behavioral data

First experiment

Performance tends to increase over sessions during the three first sessions (=PART 1) (Wilcoxon signed-ranks; $Z = -2.86$, $p < 0.01$ for session 1 compared to session 6), concomitantly reaction time decreases (Wilcoxon signed-ranks; $Z = -5.33$, $p < 0.01$ [session 1]; $Z = -4.48$, $p < 0.01$ [session 2]; $Z = -3.13$, $p < 0.01$ [session 3] compared to session 6) and together reach an optimal behavioral response (minimum reaction time and maximum performance) at the session 6 (PART2). Regarding PART 1 and last session 6, on average 83.7±5% of the stimulus pairs were correctly discriminated. The average response time (RT) was 602±230ms after second stimulus offset. During the two time-order sessions (4 and 5) the average accuracy was 68.8±5% and the mean RT was 648±257ms. These sessions present a global decrease of performance in terms of accuracy (Wilcoxon signed-ranks; $Z = -5.51$, $p < 0.01$ [session 4]; $Z = -5.52$, $p < 0.01$ [session 5] compared to session 6) and reaction time (Wilcoxon signed-ranks; $Z = -5.37$, $p < 0.01$ [session 4]; $Z = -4.93$, $p < 0.01$ [session 5] compared to session 6) due to the fixed 2Hz difficulty (see Fig. 3 A). Moreover these sessions were analyzed in the three groups of participants. Knowing that the PART 1 presented a stable context of stimulation around 30Hz, we expected perturbation of the time order effect (or contraction bias) for the two groups where participants performed the task in a different stimulation context (mean F1 = 26Hz or 34Hz) compared to the control group where the context remained stable (mean F1 = 30Hz). At the very beginning of session 4 for 26Hz and 34Hz groups, we have found the time-order effect (contraction bias) is not centered around the mean (F1) but shifted towards 30Hz, due to the previous three sessions (PART 1). This effect quickly disappears to elicit the expected bias at 26Hz or 34Hz (see Fig. 4A). Indeed, we observe an imbalance in the probability to respond F2>F1, depending on the context or mean frequency F1. This imbalance reflects the contraction bias that operates in a reverse fashion for groups with 26Hz and 34Hz contexts. Importantly, this imbalance is not observed for control group (30Hz) in which the mean frequency does not change between PART 1 and time-order sessions 4 and 5 (see Fig. 4B). The contraction bias is predicted by a sequential Bayesian model of two-alternative forced choices (see Appendix B of this study).

Second experiment

On average, 83.3±4% of the stimulus pairs were correctly discriminated. The average response time (RT) was 590±176ms after the second stimulus offset. Behavioral results show an increase in performance along sessions (higher accuracy and shorter RTs), distinct between the two parts of the experiment. This result is in line with what we have found in the first experiment. A session-by-session analysis showed that performance in the first two sessions differed significantly from that in the three last sessions (Wilcoxon signed-ranks; $Z = -3.6$, $p < 0.01$ and $Z = -2.05$, $p<0.05$ for session 1 and 2 respectively). A session-by-session analysis showed RT in the first three sessions that differed significantly from that in the three last sessions (Wilcoxon signed-ranks; $Z = -3.8$, $p < 0.01$ [session 1]; $Z = -3.1$, $p<0.01$ [session 2] and $Z = -2.9$, $p<0.01$ [session 3]) (see Fig. 3 B).

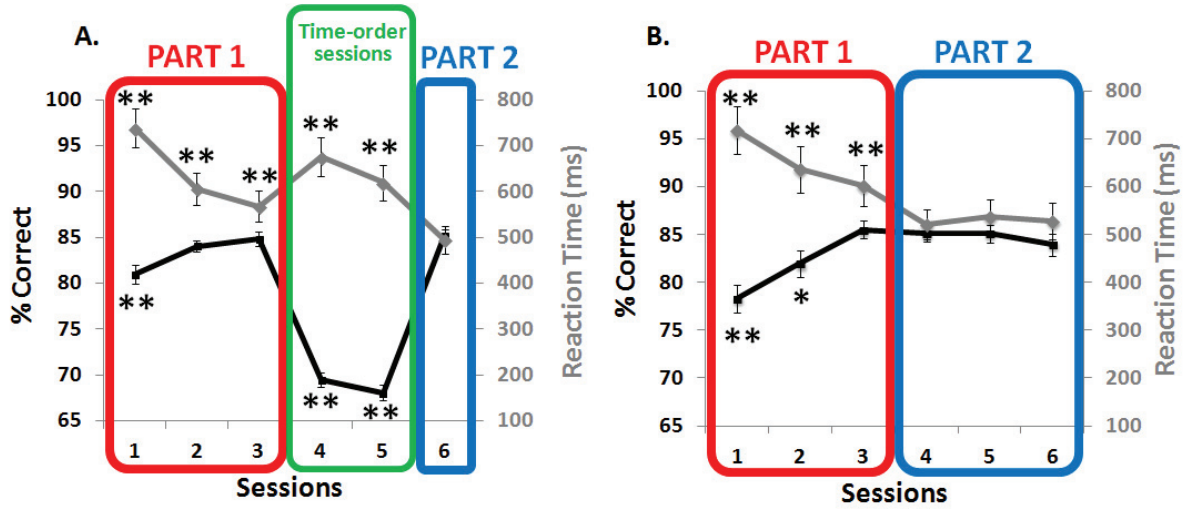


Figure 3: Behavioral global performance for the two studies. Average performance rate over sessions: black line = accuracy (% Correct) and grey line= reaction time (ms); **A) First experiment** : time-order sessions (green frame): decrease of performance due to the fixed 2Hz difficulty. **B) Second experiment** : the experiment can be split up in two parts according to the performance evolution. Same performance evolution as the study 1 during PART 1. Error bars indicate the standard error of the mean. (Wilcoxon non parametric pairwise comparisons to the PART 2 performance: * $p<0.05$; ** $p<0.01$).

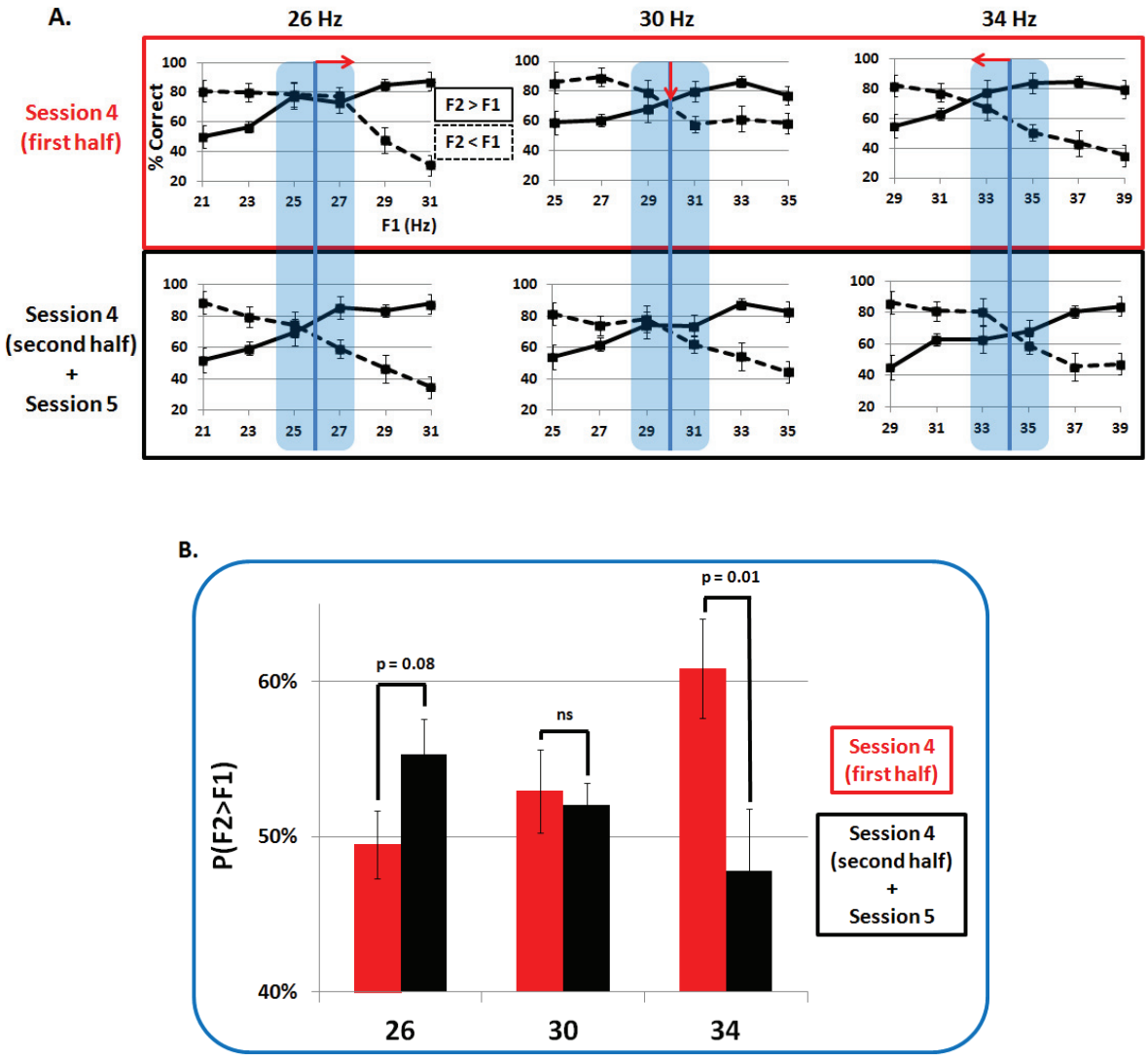


Figure 4: Behavioral analyze of time-order effect for each specific groups (mean F1 = 26Hz, 30Hz or 34Hz). When ΔF1 (ΔF1= F1 - mean[F1]), is positive participants tend to report that F1 is lower than F2. When ΔF1 is negative participants tend to report that F1 is higher than F2. Contraction bias : the perceived frequency of a stimulus is a weighted combination of its actual frequency and a reference frequency (internal reference), such as the average of all relevant stimuli. **(A)** Average performance rate (% Correct) depending of the group and session time (Upper panel framed in red: average of accuracy during 48 first trials of session 4; Bottom panel framed in black: mean accuracy during 48 last trials of session 4 and all trials of session 5). Red arrows represent expected PART1 effect on time-order effect perturbation (cross center location in this representation). The blue frame represents selected data (trials where F1 is around the contextual mean) for the next figure in B. **(B)** Percentage of response F2>F1 depending of the group and session time. Error bars indicate the standard error of the mean. (p values: Wilcoxon non parametric pairwise test).

Electrophysiological Data

Stimulus-evoked responses

Figure 5 illustrates the group averaged F1 (30 Hz) stimulus-evoked MEG activity at sensors located over somatosensory areas. Time period and channels regions of interest were defined based on one-sample emergence SPM t-tests restricted to 30-30Hz trials average compared to baseline [-100 0]ms to first stimulus onset ($p_{FWE\text{-}corrected} < 0.05$). Regions of interest significantly different from baseline were localized using SPM source reconstruction (see the supplementary Table in the Appendix A).

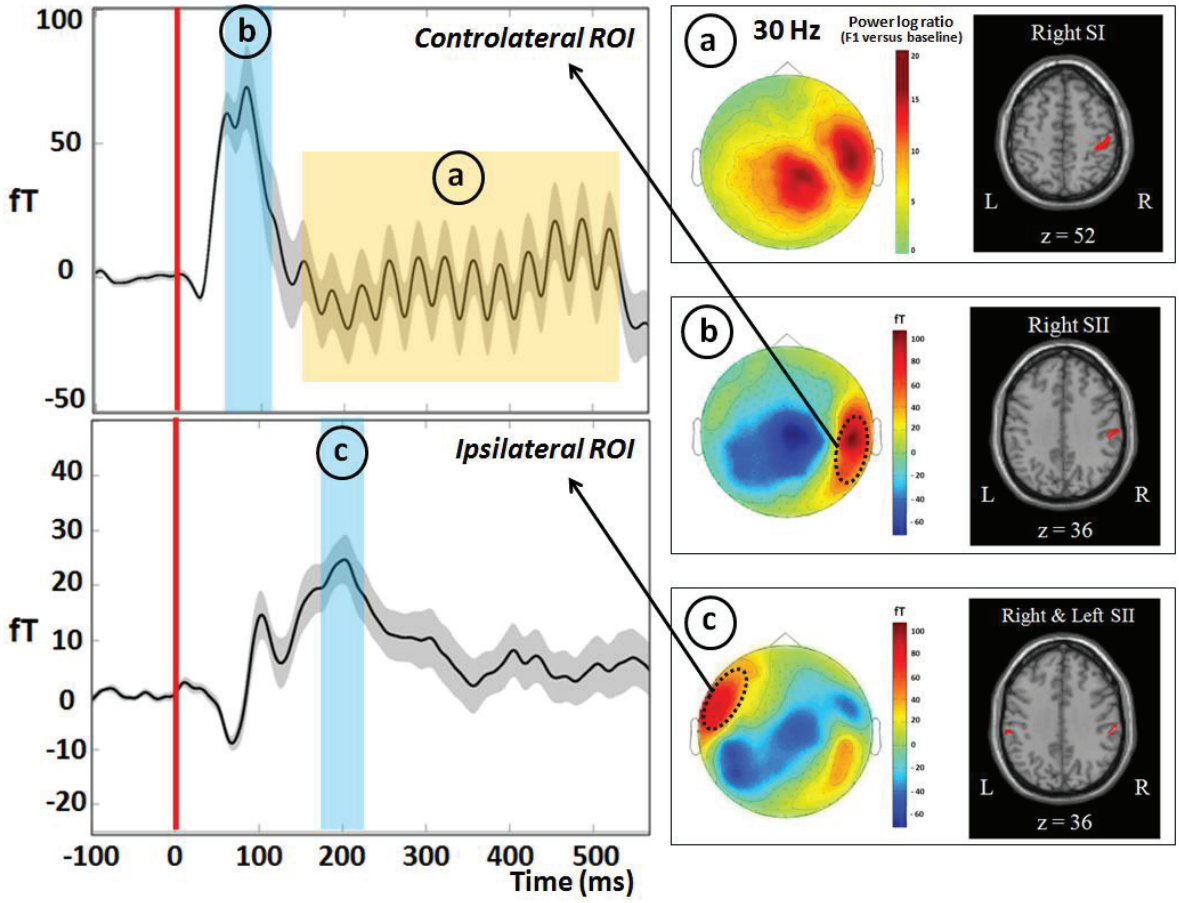


Figure 5: Left: Overview of averaged evoked response observed after first stimulus onset (red line). For illustration, data were pooled over two sets of channels contralateral (black dashed area in the topography '**b**') and ipsilateral (black dashed area on the topography '**c**') to the tactile stimulation. These channels were chosen because they showed significant emergent response sensors and time periods (blue shaded areas) based on SPM t-tests ($p_{FWE\text{-}corrected} < 0.05$) performed on 30-30Hz trials. Right: **(a)** Topography and SPM source reconstruction of the steady-state response on the controlateral primary somatosensory cortex (cSI) (peak activity MNI location, cSI: [50 -24 52]). This analysis was performed for bandpass filtered [29 31]Hz data and inversion was restricted to emerging time period of the steady-state response (orange shaded area). **(b)** Topography and SPM source reconstruction of 70-110ms transient response on the controlateral secondary somatosensory cortex (cSII) (peak activity MNI location, cSII: [58 -24 36]). **(c)** Topography and SPM source reconstruction of 180-210ms transient response on bilateral SII (peak activity MNI location, SII: [±58 -24 36]). Transient response analysis and inversion were performed on bandpass filtered [0.1 20]Hz data and restricted to their specific emergent time period (blue shapes). All plots of source reconstruction are showing emergent nodes related to SPM statistical threshold ($p_{FWE\text{-}corrected} < 0.05$).

Steady-state response amplitude :

Electrical stimulation evoked prominent frequency-specific "steady-state" responses, which were source-localized focally in primary somatosensory cortex (SI) contralateral to the stimulated hand (Fig. 5a). We examined to what extent the steady-state evoked responses to the reference stimulation were related to subjects' performance in the frequency discrimination task. Figure 6 illustrates for each parts of the experiment subsets of correct and incorrect discrimination trials (based on behavior) the source average sinusoidal fit amplitude activity evoked (see Material and Methods) by the reference frequency (F1). Statistical analysis showed that the steady-state responses evoked by the reference (F1) were significantly stronger for correct than for incorrect trials in part 1 ($F(1.9103)=3.9$; $p<0.05$), but not in part 2 (Fig. 6a). Performance was better for high amplitudes of SSR response to F1. Moreover, SSR amplitude is correlated with performance rate over subjects only during the first part of the experiment (Fig. 6b). The larger the SSR amplitude average to F1, the greater is the global performance in the first part of the experiment. Unfortunately, we were not able to analyze SSR to F2 which present a low signal-to-noise ratio due to few trials in each frequency condition.

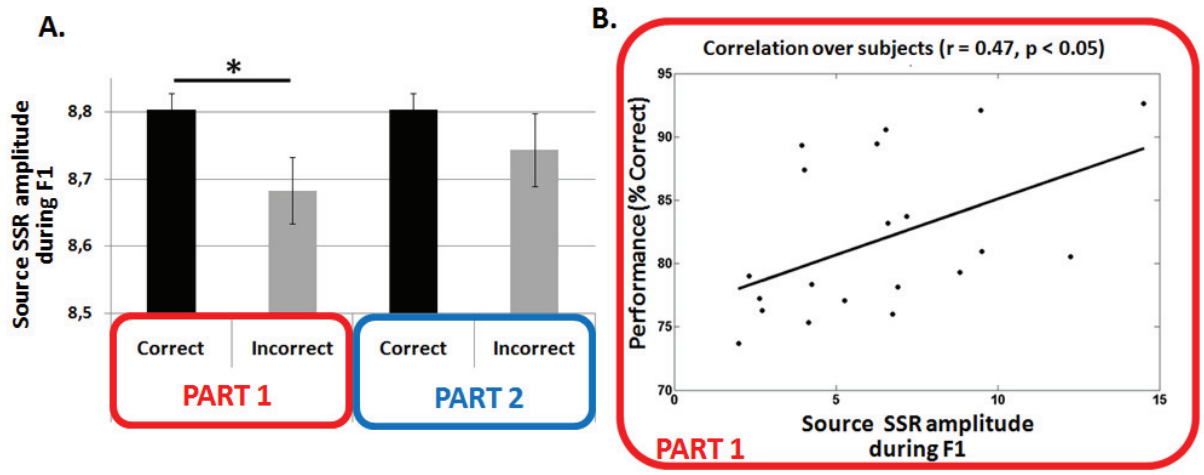


Figure 6: Steady-state source amplitude results during F1 with respect to performance across the two parts of the experiment. **(A)** Average of SSR sinusoidal fit amplitude for each condition. Error bars indicate the standard error of the mean. (Pairwise comparisons Bonferroni corrected: * $p<0.05$). **(B)** Graph showing SSR amplitude averaged during part 1. Each point represents one subject. SSR source amplitude ($x.10^4$ fT^2) evoked to F1 during the first part significantly correlate with part 1 performance (Pearson, $r = 0.47$, $p<0.05$).

Transient responses amplitude :

The following analyses were limited to the difficult trials that allowed balancing the number of correct and incorrect trials. In the controlateral evoked MEG activity were clearly observed transient responses 70-110ms after the onset of F1. These transient responses showed source distribution over controlateral secondary sensorimotor cortex (Fig. 5b) but were unrelated to frequency discrimination performance. However mean ROI sensor amplitudes for the late evoked transient response MEG activity (0.1-20 Hz bandpass filter) 180-210ms after the onset of F1 revealed several effects. Regarding the evolution of the mean amplitude (merging correct and incorrect trials) across the sessions compared to the group performance of discrimination, we observed a tendency for inverse parametric relation. When performance increases, the transient response amplitude decreases (Fig. 7). Moreover, we found significant performance effect (correct vs. incorrect) during PART 1 ($F(1.2365)=5.2$; $p<0.05$) and significantly decreased during PART 2 ($F(1.2365)=3.9$; $p<0.05$) (Fig. 8a). This transient response around 200ms was source localized over bilateral SII (Fig.5c). Therefore, in order to localize specifically the performance effect we performed the localization of difference (Henson et al., 2007) between the two conditions (PART 1 limited to difficult trials: Correct - Incorrect). The effect of accuracy on evoked responses was source localized in the bilateral inferior frontal gyrus (IFG) (Fig. 8b).

To pursue in details the analysis about the interaction between these several regions we are interested in this network effective connectivity with dynamical causal modeling on F1 evoked response according to performance differences during PART 1.

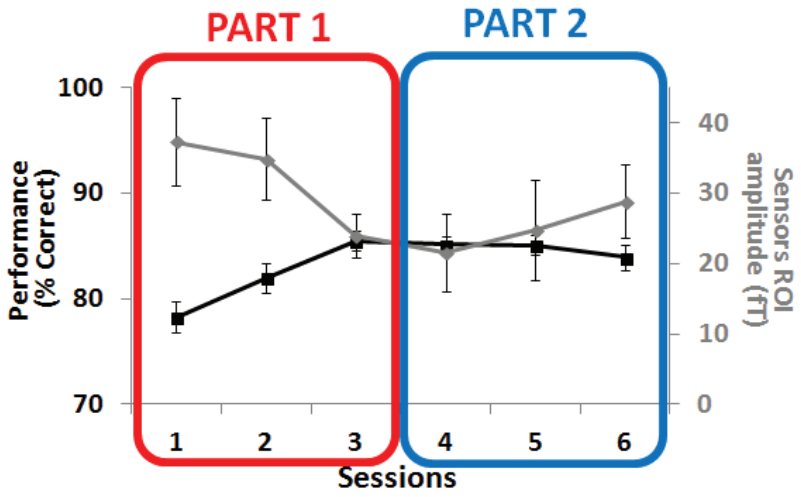


Figure 7: Transient response 180-210ms amplitude restricted to difficult trials (grey line) and behavioral group performance (black line) across the sessions of the experiment. Tendency for parametric evolution of the electrophysiological response and the performance rate. Error bars indicate the standard error of the mean.

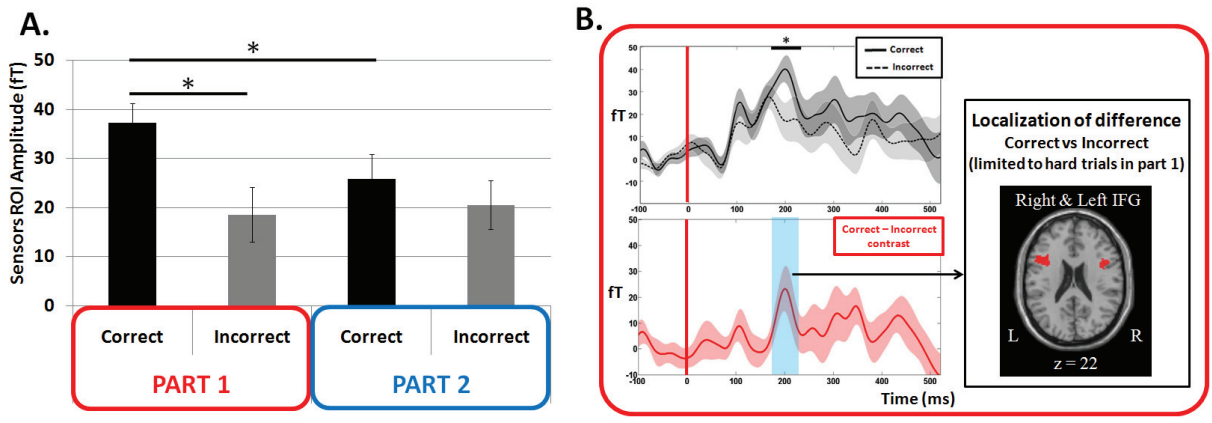


Figure 8: Transient response 180-210ms amplitude results with respect to performance restricted to difficult trials across the two parts of the experiment. **(A)** Average of sensors amplitude for each condition based on left ROI identified on 30-30Hz trials (Fig. 4c). Error bars indicate the standard error of the mean. (Pairwise comparisons Bonferroni corrected: * $p<0.05$). **(B)** Grand average evoked time course during part 1 for correct (solid black line) and incorrect (dashed black line) with standard error of the mean for each time point (grey shapes). We performed difference contrast between these conditions (red solid line) and localized the performance effect (localization of difference : LoD) in bilateral inferior frontal gyrus (IFG) [MNI location (±42 16 22)]. Source reconstruction shows emergent nodes related to SPM statistical threshold ($p_{FWE\text{-}corrected} < 0.05$).

Dynamical causal modeling

The architecture of the network involved in the generation of somatosensory responses has been studied recently in a detection task (Auksztulewicz et al., 2012). Authors applying dynamical causal modeling to electroencephalographic (EEG) data from human in a somatosensory detection task have shown that EEG components were well explained by a recurrent model. Within this model, controlateral primary and bilateral somatosensory cortex are fully connected with feedforward and feedback connections. Based on this recurrent somatosensory full-connected model, we decided to add IFG sources from our contrast localization results (Fig. 8 B) in order to test new model structures and effective connectivity in our task.

In the first step, to identify which network structure is the most probably involved in our task, we performed dynamical causal modeling on evoked response data restricted to 30-30Hz trials during first stimulation time period [0 500]ms. Four structural family models fully connected with variation in inputs parameters, number of nodes or IFG side were compared. The model with bilateral IFG (five nodes) showed the highest log evidence across all input parameters variations, and therefore this structural pattern was chosen as optimal for subsequent analyses (Fig. 9).

In the second step, to identify the most likely modulation pattern that could explain the significant difference in the difficult trials evoked response, we performed a group-level Bayesian model. Contrast test examined difference between correct and incorrect difficult trials during PART1 with correct discrimination performance treated as baseline. Five-node fully connected models with variation in inputs parameters and varying possibility of modulations for all connections strength were compared. Bayesian model selection (BMS) compared 10 families of models (group level, N = 20,

Random effect) with all somatosensory connections modulated, which differed in the direction of modulation of connections toward IFG (Fig. 10A). Random effects Bayesian model selection showed that feedforward modulations of both IFG connections (family model 7) had the greatest evidence to explain difference of evoked response between correct and incorrect discrimination during PART1 (Fig. 10B). Another contrast test was performed to examine difference between PART1 and PART2 difficult correct trials with PART1 treated as baseline. Random effects Bayesian model selection showed that forward-backward modulations of ipsilateral IFG connections (family model 9) had the greatest evidence to explain difference of evoked response between PART1 and PART2 correct discrimination (Fig. 10C).

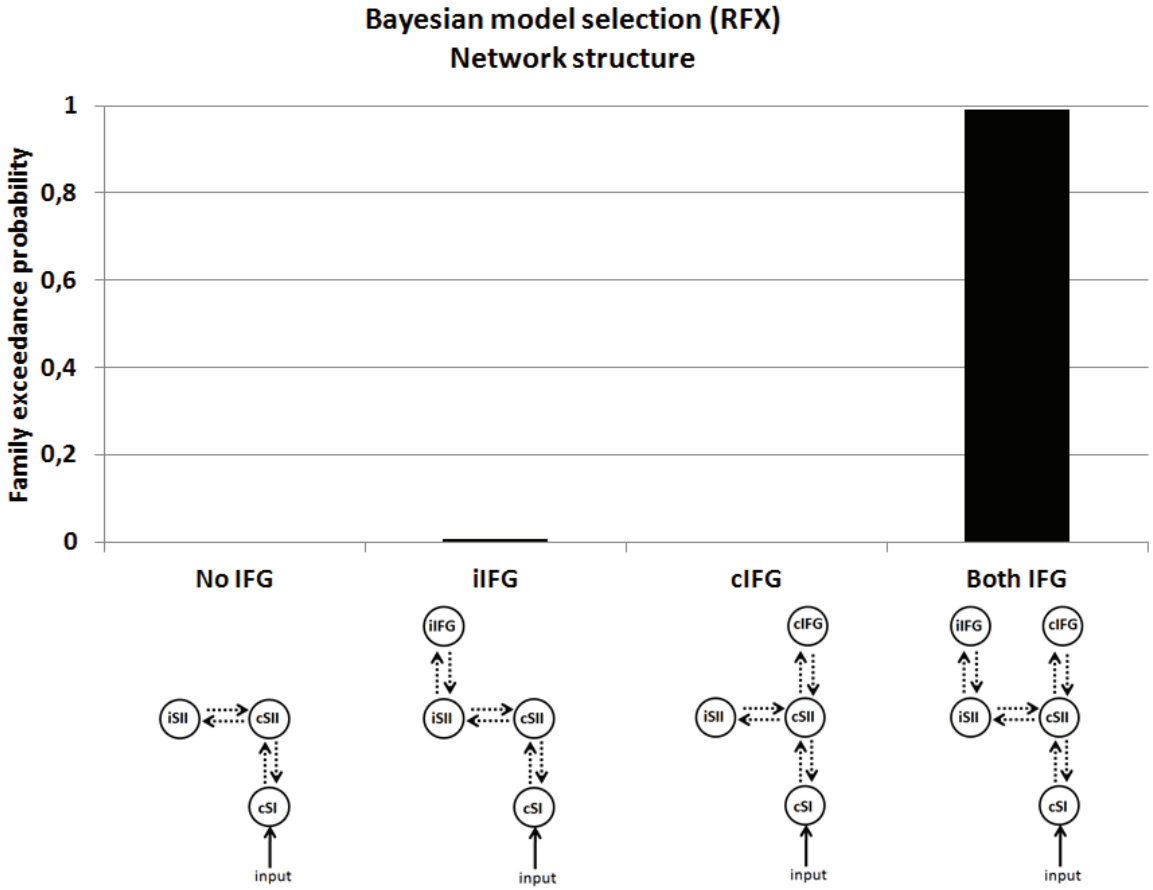
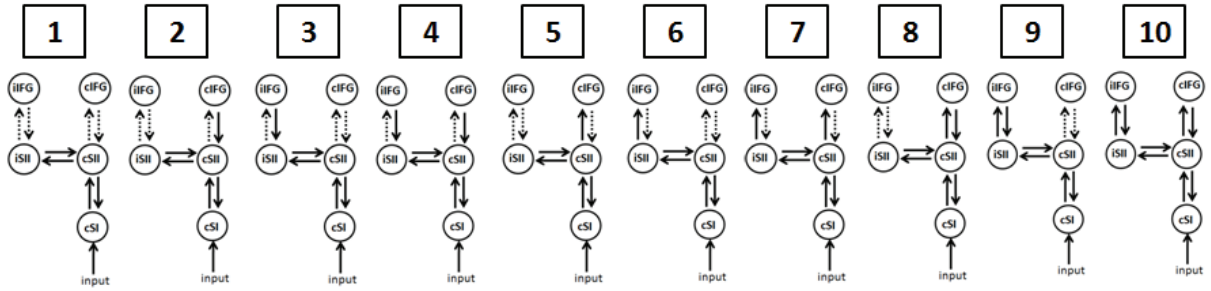


Figure 9: DCM. Results from bayesian model selection associated to schematic representation of structural DCMs : individual dipole locations representing cSI, cSII/iSII and cIFG/iIFG were used to construct a structural model. Dashed arrows indicate fixed connections. Familywise Bayesian model selection was used to establish the network architecture based on control trials (30-30Hz trials): the best models included both frontal region.

A.



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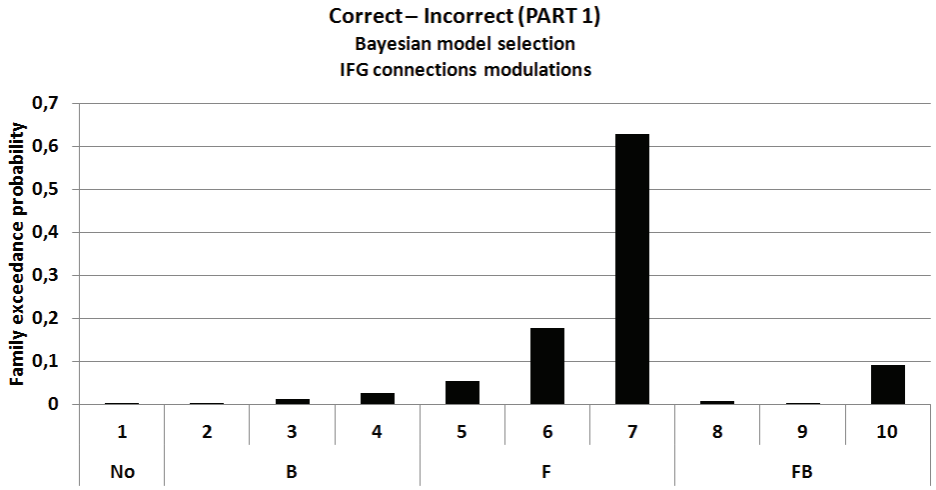


C.

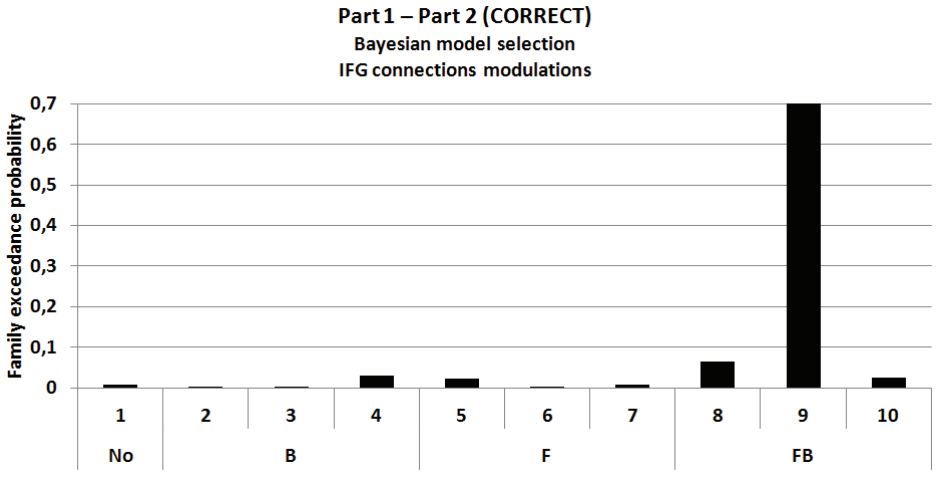


Figure 10: DCM. Results from bayesian model selection associated to schematic representation of structural DCMs : individual dipole locations representing cSI, cSII/iSII and cIFG/iIFG were used to construct a structural model. **Dashed arrows indicate fixed connections and solid arrows indicate modulated connections**. **(A)** Family-wise Bayesian model selection was used to establish the most likely modulation connectivity strength toward frontal regions (B = backward; F = forward; FB = forward/backward). **(B)** Contrast difficult trials PART 1 [Correct - Incorrect] : the best models included feedforward connections modulation toward both IFG (family model 7). **(C)** Contrast difficult correct trials [PART1 - PART2] : the best models included forward-backward connections modulation toward ipsilateral IFG (family model 9)

Oscillatory activities

We compared the stimulus induced activity to the baseline period ($t_{baseline}$ = -1000 -500ms). Typically, we observed that beta (15-25Hz) and mu (12-14Hz) activity decreased significantly over bilateral somatosensory areas ($p_{FWE\text{-}corrected} < 0.05$) during stimuli presentation. We could also detect a significant increase of occipital alpha (8-12Hz) activity during the whole trial time course ($p_{FWE\text{-}corrected} < 0.05$) (Fig. 11). No significant performance effect between correct and incorrect trials has been found in the beta and the mu band sources activities. However, significant positive correlation has been found between occipital alpha band activity and reaction time (Fig. 12a). Moreover, alpha band power difference between the two parts of the experiment was negatively correlated to the gain in performance in part 2 compared to part 1 over subjects (Fig. 12b). The more occipital alpha power increases during part 2, the smaller was the subject specific performance gain between the two parts of the experiment.

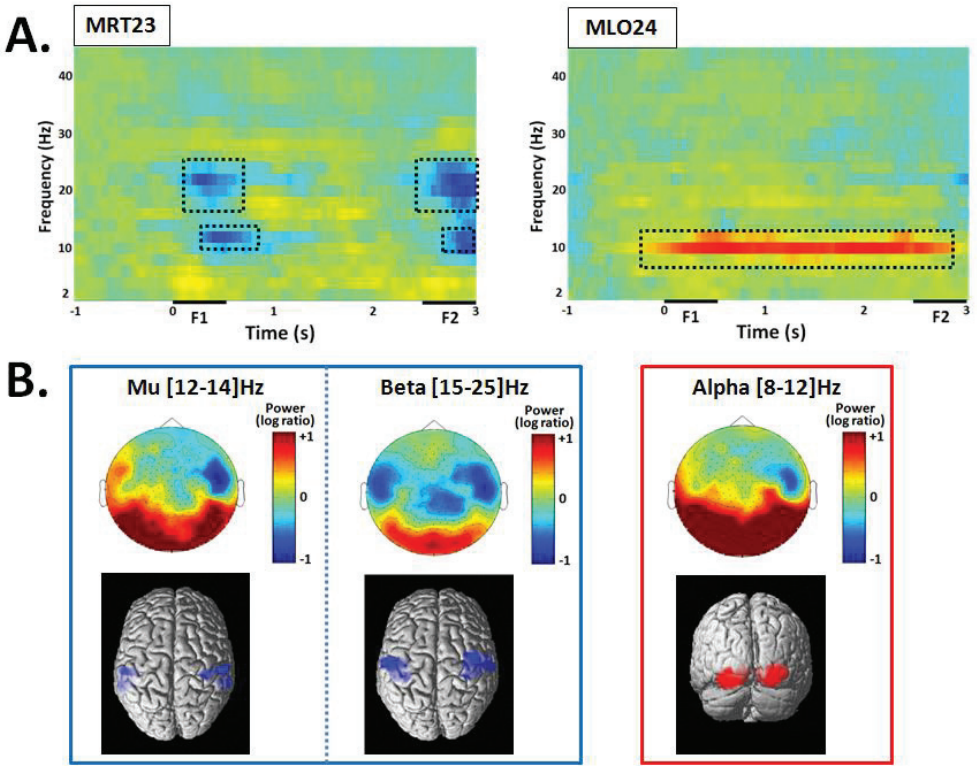


Figure 11 : Overview of oscillatory responses observed during the task. **(A)** Grand average power for 30-30Hz trials on two representative channels (Controlateral to the stimulation side: MRT23; Posterior sensors with maximal alpha power intensity: MLO24). Color scale is the same as topography map in B. The dashed rectangles highlight the time-frequency windows of the significant event-related beta and mu desynchronisation (left) or alpha synchronisation (right). **(B)** Scalp topographies and SPM source reconstructions for the TF windows outlined in A. Blue indicates a decrease and red indicates an increase in source power relative to prestimulus baseline (t: -1000 -500ms) ($p_{FWE\text{-}corrected} < 0.05$).

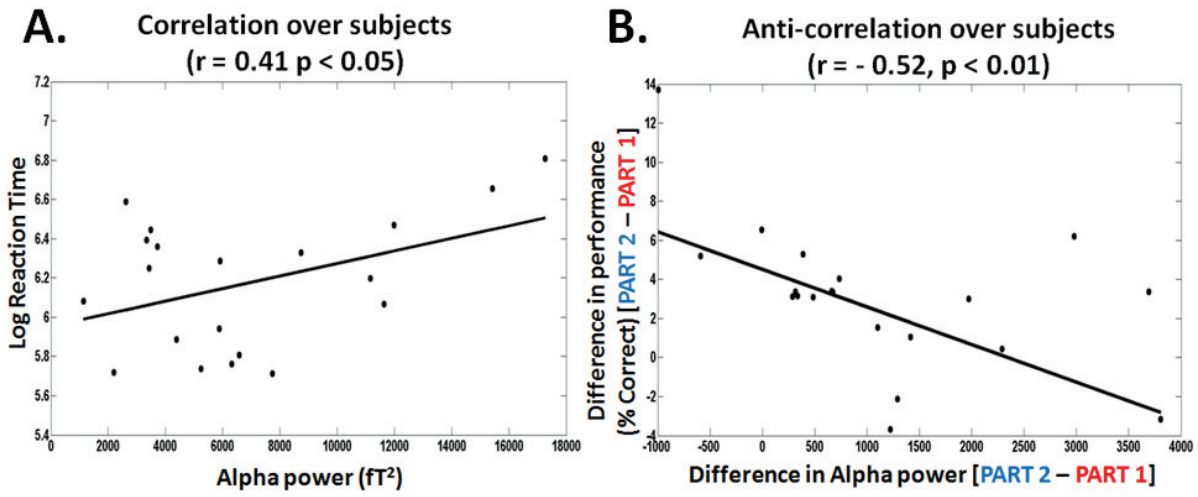


Figure 12 : Alpha band activity modulated by task reaction time and performance over parts. Graph showing alpha band power averaged without baseline correction, during all trial time (t: [0 3000]ms to F1 onset) over significant occipital channels ROI. Each point represents one subject. **(A)** Alpha power during the task significantly correlates with reaction time (Pearson, $r = 0.41$, $p<0.05$). **(B)** Difference between part 2 and part 1 averaged alpha power negatively correlates with performance gain (difference between part 1 and part 2 percentage of correct discrimination) (Pearson, $r = -0.52$, $p<0.01$).

DISCUSSION

We investigated neural correlates of a simple perceptual decision-making task. The central finding of the present study is the evidence for an implicit shift of a perceptual decision-making process conditioned by the context of stimulation due to buildup of an internal reference. Regarding our behavioral results of the first experiment analysis, we suggest the existence of implicit mechanisms that drive perception to be bias due to an implicit contextual learning. We observed perturbation of time-order effect during the first part of session 4 oriented towards the stimulation context learned before around 30Hz (during the PART1). This perturbation could be due to the progressive buildup of an internal frequency reference that prior future perception in a way that is consistent with Bayesian inference (Ashourian and Loewenstein, 2011). Therefore using time-order effect or contraction bias observation we showed that the learned reference does bias tactile decision making when the task set is modified. In the second experiment we identified two parts highlighting that subjects became faster and better over sessions until they reached a plateau. We focused on the PART1 which is similar to behavioral results found in the first experiment. This progressive increase of performance could support mechanisms that promote the buildup of a such internal reference. In this part of the experiment, results revealed that performance is linked to SSR amplitude modulation to F1. Performance was better for high amplitudes of SSR response to F1. Moreover, during this first part, SSR amplitude is correlated with performance over subjects. Regarding transient response in difficult trials, our results showed significant performance effect concerning amplitude of the 200ms evoked component. We were able to localize this effect in the inferior frontal gyrus. We have studied modulations of effective coupling at the cortical level using dynamic causal modeling. First, primary

and secondary somatosensory areas are not sufficient to explain the effect: the implication of bilateral IFG is needed. Precisely, modulations of connections from somatosensory cortices to IFG, account for the accuracy effect (correct vs. incorrect) during PART 1 and the PART effect (PART1 vs. PART2) regarding correct trials. This highlights an involvement of bilateral IFG as part of the performance optimization process. IFG has already been shown to be linked to frequency discrimination (Romo and Salinas, 2003; Spitzer and Blankenburg, 2011). Here we demonstrate its early involvement in the buildup of an optimal strategy. Finally, regarding PART 2, transient and SSR performance effects have disappeared. In addition, alpha power over occipital areas increased in the delay period and correlated negatively with behavioral performance gain. These results suggest a global decrease of vigilance during the second part. However performance of discrimination (accuracy and RT) during this second part is the highest of the whole experiment as if participants could perform the task while idling mechanisms are involved. Altogether, those results suggest a shift of strategy from a costing one needed to reach the plateau of performance to an automatic one. Some study suggest participant possibility to switch from a real comparison to a classification strategy to perform the discrimination in this type of protocol where the first stimulation remains (Nahum et al., 2010). Regarding our results from PART 1 analyses, we suggest the existence of mechanisms that aim at building-up an internal reference based on the first constant stimulus processing. In this way, during PART 2, participants seem to classify one stimulation, the varying one, as either high or low by comparing it to a buildup reference.

Despite this clear effect of the protocol on discrimination performance evolution, participants remained unaware of the constancy of the reference stimulus. As a recent similar study driven by Nahum and colleagues in the auditory modality (Nahum et al., 2010), in our study participants reported that they perceived F1, retained it in memory, perceived F2, and then compared the two. Authors have shown that humans have difficulties using retain-and-compare mechanisms and implicitly use classification based on an internal reference of base stimulus when possible as that was demonstrated for monkeys studies (Talbot et al., 1968; Mountcastle et al., 1990). Results of our study allow us to observe a specific evolution of behavioral and neurophysiological markers from comparison to classification strategy due to a few discrimination training trials before recording. The main conclusion is that we identified the progressive and implicit electrophysiological markers evoked by F1 that lead to building-up the frequency reference based on the first stimulation.

We propose that the protocol allow perceptual system to switch from interstimulus comparison to classification, which is based on comparison of a single stimulus, typically an internal reference. The dramatically improved performance stems from the greater accuracy of the classification mechanism. Focusing on physiological events related to the reference stimulation we tried to elucidate variations of brain response that highlight this implicit behavioral strategy switching.

Attention modulation

Other MEG studies have also shown steady-state signals in somatosensory cortex in response to electrical stimuli (Pollok et al., 2002). It is known that such responses are generated in primary somatosensory areas. Actually, properties of such tactile evoked steady-state responses have been described in detail previously (Tobimatsu et al., 1999; Nangini et al., 2006). Moreover, oriented and sustained spatial attention was found to be mediated by amplitude of SSR (Giabbiconi et al., 2004). Typically in part 1 of our experiment regarding the positive correlation over subjects, such attentional modulation reflected by reference stimulus-locked activity seems to be crucial to perform correct discrimination. This performance related difference (correct vs incorrect responses) is based on the assumption that the strength of steady-state evoked responses in SI is modulated by attention (Giabbiconi et al., 2007). During the part 2 SSR amplitude remained high but inter-trial modulation no longer affect discrimination performance. Importantly this result could reflect a necessary process to buildup an internal reference as a sensory representation based on F1 (Morgan et al., 2000) and highlight the initial involvement of primary somatosensory cortex activity in working memory mechanisms that support the memory trace of the first stimulation (Harris et al., 2002).

In addition oscillatory activity as alpha band power over occipital areas showed modulation of attentional/motivationnal engagement necessary to perform the task. Interestingly the majority of the participants showed increase in alpha activity during the task. Contrary to previous work we found negative correlation over subject between such posterior alpha activity and performance seems to reflect a drop in alertness (Pfurtscheller et al., 1996) rather than a specific inhibition of irrelevant areas (Klimesch et al., 2007; Haegens et al., 2010; Spitzer et al., 2010). This could be explained by the relative facility to reach an optimal and automatic behavior in our protocol due to presence of the reference frequency. This is in line with an automation of our task that highlights the implicit ability to use a constant reference stimulus when it is presented in every trials (Harris, 1948; Nahum et al., 2010).

Somatosensory working memory : IFG involvement

In the present study, we found a transient response performance effect linked to inferior frontal gyrus involvement. The consistent reports of the IFG being involved in working memory processing of somatosensory information (Kostopoulos et al., 2007; Auksztulewicz et al., 2011) are in accordance with the persistent activity found in macaque lateral prefrontal cortex in similar task (Romo et al., 1999). The IFG has further been shown to be crucially involved in human somatosensory processing (Pleger et al., 2006; Spitzer et al., 2010). In a recent study, Auksztulewicz and colleagues provide novel evidence for a causal involvement of the IFG in the somatosensory working memory function using repetitive transcranial stimulation (rTMS). Actually they managed to impair participant discrimination performance applying rTMS on the IFG during the interval between the two stimuli presentation (Auksztulewicz et al., 2011). The present study yields evidence for a more transient

involvement of the IFG linked to secondary somatosensory areas toward higher order processing of the first stimulation. The IFG can therefore be considered a candidate region whose activity may encompass the neural substrates of somatosensory working memory maintenance (Romo et al., 2002). The presence of this effect restricted to first part of the experiment seems to reflect a transient electrophysiological modulation in line with the strategy shifting. Actually, it could reflect transient and effective interaction of somatosensory areas with frontal areas necessary to build up a frequency internal reference based on F1 characteristic. Interestingly, this effect disappears in the second part reflecting a modulation of the network related to working memory processes. A recent fMRI study proposes that the role of inferior frontal regions in somatosensory memories lies in its functional interaction with SII cortex for the disambiguation of tactile information retrieval (Kostopoulos et al., 2007). Our DCM results show that network restricted to somatosensory areas is not sufficient to account for stimulation processing. We assume that modulation in the effective connectivity between these somatosensory areas and frontal regions could reflect internal mechanisms involved in the buildup and retrieval of F1 sensory representation, that could be called the internal contextual reference.

Conclusion

In sum, we used a simple task where high performance could be reached due to the presence of a reference frequency stimulation in every trial. Our results suggest that stimulus-locked MEG responses relate to early stages of tactile frequency processing in SI cortex and specific modulation of working memory networks between SII and inferior frontal gyrus can reflect implicit and progressive buildup of an internal sensory reference. The findings complement previous evidence for strategy shift from discrimination to classification and promote the study of effective connectivity modulation between somatosensory and frontal regions that operate memory processing in human subjects.

APPENDIX

A. Supplementary Table

ERP	PST window	Regions	MNI coordinates	p values (FWE corrected)	p values (No FWE corrected)
SSR	**150-500ms**	**Controlateral primary somatosensory area (cSI)**	**50 -24 52**	**< 0.01**	< 0.0001
Transient SEP	**70-110ms**	**Controlateral secondary somatosensory area (cSII)**	**58 -24 36**	**< 0.05**	< 0.0001
		Ipsilateral secondary somatosensory area (iSII)	-60 -28 36	0.08	< 0.0001
		Ipsilateral frontal gyrus (iIFG)	-42 22 18	0.1	< 0.0001
Transient SEP	**180-210ms**	**Controlateral secondary somatosensory area (cSII)**	**58 -24 36**	**< 0.05**	< 0.0001
		Ipsilateral secondary somatosensory area (iSII)	**-58 -24 36**	**< 0.05**	< 0.0001
		Ipsilateral frontal gyrus (iIFG)	-42 22 18	0.2	< 0.0001
		Controlateral frontal gyrus (cIFG)	42 16 24	0.2	< 0.0001
Contrast Part 1 Correct - Incorrect	**180-210ms**	**Ipsilateral frontal gyrus (iIFG)**	**-42 22 18**	**< 0.01**	< 0.0001
		Controlateral frontal gyrus (cIFG)	**42 16 24**	**< 0.01**	< 0.0001

In this table, we report all regions where activity was significantly different from baseline ($p<0.0001$ no-FWE corrected). Different evoked response potential (ERP) were localized: the steady-state response (SSR), transient somatosensory evoked response (Transient SEP) and the performance effect (Contrast Part 1 Correct - Incorrect). For each analysis, data of the post-stimulus time window (PST window) of interest were averaged across all participants to determine the coordinates of the cortical vertex showing the highest peak amplitude. Coordinates correspond to the vertex with maximal amplitude within each region (coordinates are in MNI space).

For the dynamic causal modeling (DCM) analysis, we used the position of maximum group activity source distributed localization with $p < 0.05$ (FWE-corrected) as prior for each dipole position of the DCM network (coordinates in bold in the table).

B. Sequential Bayesian model of two alternative forced choice

We formalized a Bayesian model of two alternative forced choice inspired from (Ashourian and Loewenstein, 2011). According to the Bayesian brain hypothesis, the time-order effect (or contraction bias) emerges because participants use Bayes' rule to combine noisy information about the frequency of the tactile stimulation with implicit prior information depending on the perceptual context. In this section, we formalize and describe our model.

In accordance with Weber's law, the frequencies of the stimuli are encoded in logarithmic scale. Let F_i and R_i be the frequencies of the tactile stimulation (i) and its neural representation, respectively. We assume that the probability of a neural representation R_i for a given stimulation frequency F_i is noisy and defined by likelihood function $P(R_i|F_i)$ with mean μ_i and variance σ_i :

$$P(R_i|F_i) \sim N(\mu_i;\ \sigma_i) \tag{1}$$

The internal prior distribution on frequencies $P(F_i)$ is also normally distributed with mean m_i and variance v_i :

$$P(F_i) \sim N(m_i;\ v_i) \tag{2}$$

Bayes' rule provides a method for combining information from the prior distribution with the likelihood in order to compute the posterior distribution $P(F_i|R_i)$, from which the percept derives:

$$\begin{aligned} P(F_i|R_i) &= \frac{P(R_i|F_i).P(F_i)}{P(R_i)} \\ where\ P(R_i) &= \int_{-\infty}^{\infty} P(R_i|F_i) \cdot P(F_i) dF_i \end{aligned} \tag{3}$$

After each stimulus presentation, the prior updates into the posterior. However, this learning might depart from optimal Bayes rule in practice and be more realistically modeled by implementing some forgetting whose kinetics can be fully prescribed by one parameter w:

$$w = \exp\left(-\frac{1}{\tau}\right) \tag{4}$$

w is defined by τ such that the further back in time the stimulation, the less its influence on current stimulus prediction. Accounting for this forgetting effet yields the following up-dating rules for the prior variance and mean, respectively:

$$\begin{aligned} v_{i+1} &= \frac{1}{\frac{w}{v_i} + \frac{1}{\sigma_i}} \\ m_{i+1} &= v_{i+1} \cdot \left(\frac{w \cdot m_i}{v_i} + \frac{\mu_i}{\sigma_i}\right) \end{aligned} \tag{5}$$

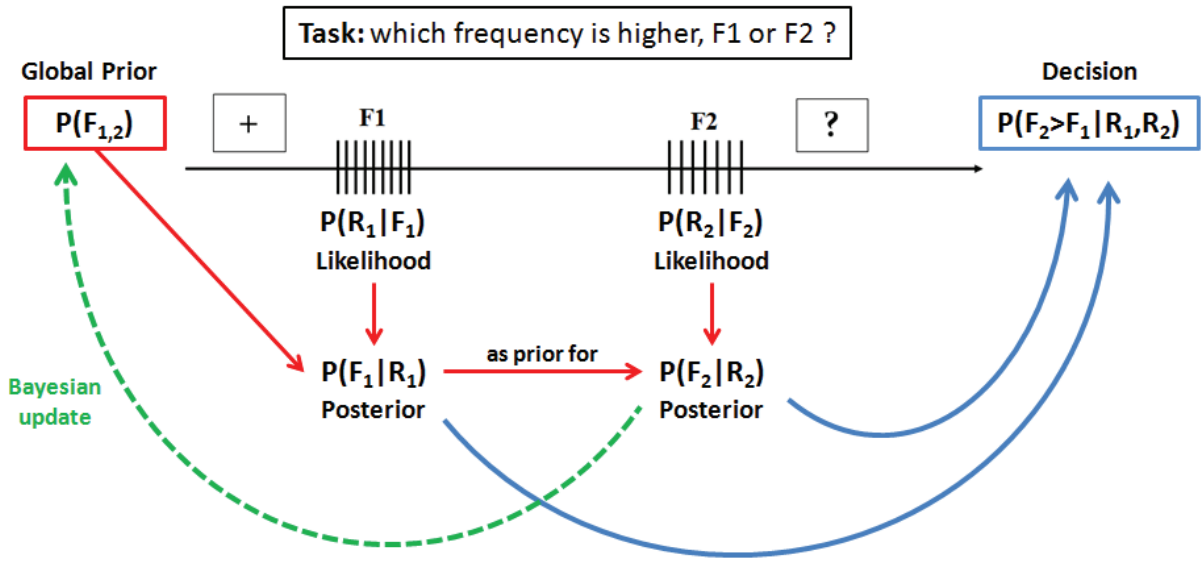
Given a pair of stimulation F_1 and F_2 (i.e. the frequency of the first and second tactile stimulation within a trial), we assumed that the first (F_1) perceived frequency (prescribed by posterior: $P(F_1|R_1)$) is computed by mixing the learned prior $P(F_1)$ with likelihood function $P(R_1|F_1)$, while the second (F_2) perceived frequency (prescribed by posterior: $P(F_2|R_2)$) is computed by mixing the posterior of the first stimulation that is maintained in memory $P(F_1|R_1)$ with likelihood function $P(R_2|F_2)$. In other words, the prior on the second frequency derives from the posterior (or percept) associated with the first frequency. But in order to model the effect of memorization over the delay period, the variance is increase by a multiplicative factor parameterized by γ such that:

$$P(F_2) = P(F_1|R_1)$$
$$with\ v_2 = \gamma \cdot v_1 \tag{6}$$

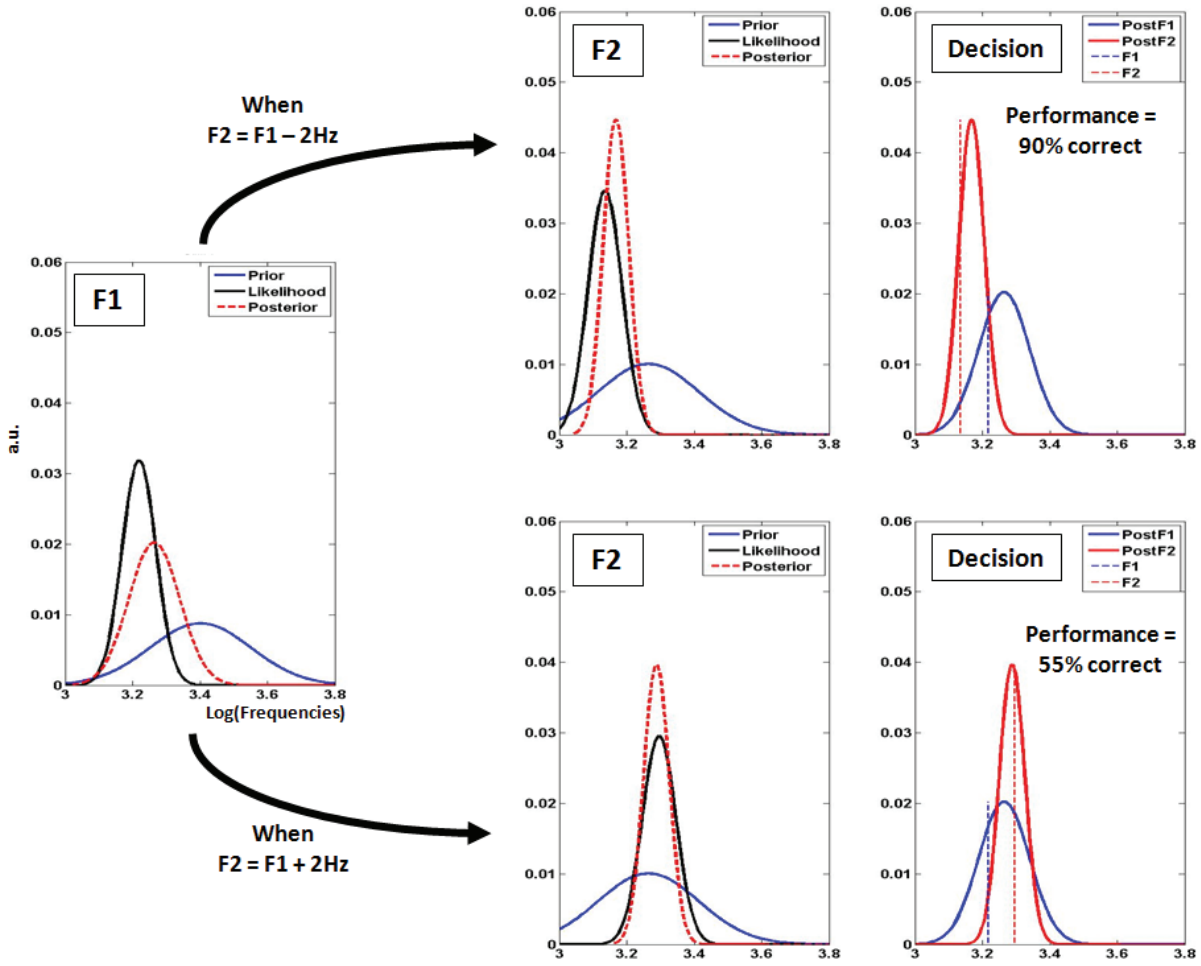
Then, the probability that the first frequency F_1 is higher than the second frequency F_2 is given by:

$$P(F_1 > F_2|R_1, R_2) = \int_{-\infty}^{\infty} P(F_1|R_1) \int_{-\infty}^{F_1} P(F_2|R_2)\, dF_2\, dF_1 \tag{7}$$

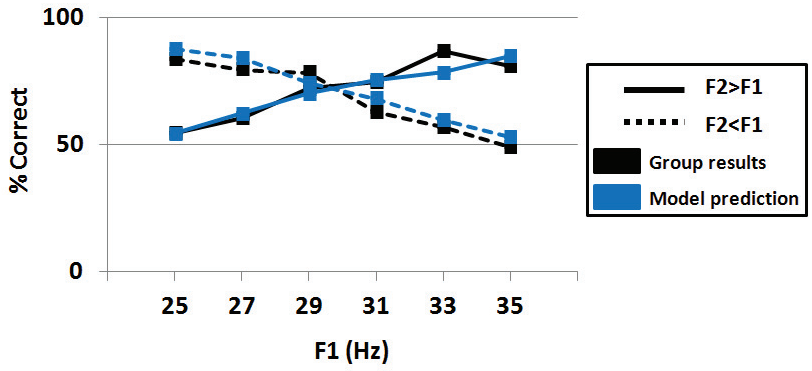
The decision and eventually the reaction time is based on this probability. After each trial, the posterior porbability associated with the second stimulation frequency is used to update the global prior according to equations (5). This model is sequential since it operates over trials and depends upon the history of stimulation. (see Figure 1 and 2 below). We used this model to fit the behavioral data reflecting the contraction bias in study (see Figure 3 below).



Appendix Figure 1: Schematic representation of the sequential Bayesian model for one trial.



Appendix Figure 2: Model predictions when F1 = 25Hz and F2 = F1 ± 2Hz. All frequencies are in logarithmic scale. **First**, F1 posterior is calculated based on a general prior (blue Gaussian) centered here around 30Hz, then this posterior is used as prior over F2 after increasing the variance according to parameter (γ) in order to take into account the loss of information due to the retention period. **Second**, F2 posterior is calculated and the final decision is based on both stimulation posteriors. **Finally**, as the right panels show, F1 and F2 final posteriors (blue and red Gaussians) are different from the veridical stimulation frequency (blue and red dashed lines). Thus, we observe that when F2 is higher than F1 by 2Hz, the respective posterior distributions do overlap much more than when F2 is lower than F1 by 2Hz. This asymmetry yields the contraction bias effect.



Appendix Figure 3: Time order effect (contraction bias) - Behavioral results and model predictions for the 30Hz context group (N=20). The first stimulation (F1) could take 6 different frequencies (25, 27, 29, 31, 33 or 35Hz) and after a delay period the second frequency (F2) was always 2Hz higher or lower than F1.

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CHAPTER V. STUDY 2: ADO WITH SIMULATIONS

5.1. INTRODUCTION OF THE ARTICLE

Brain computer interfaces are based on closed-loop interaction between direct real-time brain signals acquisition and feedback from external devices. Previously I have described how such close relationship and real-time access towards ongoing brain activities have led to a rethinking of the classical way to conduct experiments in the recent neuroscience literature. In particular, real-time electrophysiology could be used to choose the precise characteristics and timings of stimulation based on hypotheses about the brain state namely Brain-state dependent stimulation (BSDS) (Hartmann et al., 2011; Jensen et al., 2011). However a brief review of these studies revealed that the BSDS experiments share a common trait: online data processing could be used to optimize hypothesis testing. This points towards the importance of conceiving and implementing adaptive paradigms, where experimental design parameters are optimized online. Recent advances in Bayesian inference and decision theory provided an efficient way of implementing this approach and enabling comparison of alternative models of brain function. Online data acquisition in order to inform and optimize future stimulation (or sampling) choices has been primarily used to industrial purposes and called sequential hypothesis testing (Wald, 1945). Recently, the basic principle was formalized and named adaptive design optimization (ADO) (Myung et al., 2013). Mainly, the procedure has been evaluated on behavioral data (Cavagnaro et al., 2009b). Nevertheless recent development of Bayesian inference methods adapted to design optimization prior to data acquisition revealed interesting tools available to motivate future applications for cognitive neuroscience experiments (Daunizeau et al., 2011b).

The aim of this study was to demonstrate and validate the principle of ADO in a simulated perceptual learning experiment using real-time single trial acquisition. Firstly, I validated the principle of ADO based on a behavioral example used by Myung and colleagues (Myung et al., 2013). Secondly, I extended the approach toward real-time electrophysiology application using current models of perceptual learning as a proof of concept to investigate the gain of ADO compared to classical offline experiments. In other words, this study provided a new and original way to conduct a cognitive neuroscience experiment, based on real-time data acquisition. Since this principle approach seeks to optimize hypothesis testing, it would benefit to our understanding of brain signals and it should also benefit to classical BCI applications in return.

5.2. ARTICLE: TOWARD A NEW APPLICATION OF REAL-TIME ELECTROPHYSIOLOGY: ONLINE OPTIMIZATION OF COGNITIVE NEUROSCIENCES HYPOTHESIS TESTING

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ABSTRACT

Brain-computer interfaces (BCIs) mostly rely on electrophysiological brain signals. Methodological and technical progress has largely solved the challenge of processing these signals online. The main issue that remains, however, is the identification of a reliable mapping between electrophysiological measures and relevant states of mind. This is why BCIs are highly dependent upon advances in cognitive neuroscience and neuroimaging research. Recently, psychological theories became more biologically plausible, leading to more realistic generative models of psychophysiological observations. Such complex interpretations of empirical data call for efficient and robust computational approaches that can deal with statistical model comparison, such as approximate Bayesian inference schemes. Importantly, the latter enable the optimization of a model selection error rate with respect to experimental control variables, yielding maximally powerful designs. In this paper, we use a Bayesian decision theoretic approach to cast model comparison in an online adaptive design optimization procedure. We show how to maximize design efficiency for individual healthy subjects or patients. Using simulated data, we demonstrate the face- and construct-validity of this approach and illustrate its extension to electrophysiology and multiple hypothesis testing based on recent psychophysiological models of perception. Finally, we discuss its implications for basic neuroscience and BCI itself.

Keywords: brain-computer interfaces; real-time electrophysiology; adaptive design optimization; hypothesis testing; Bayesian model comparison; Bayesian Decision Theory; generative models of brain functions; cognitive neuroscience

1. INTRODUCTION

1.1. On Common Challenges in BCI (Brain-Computer Interfaces) and Cognitive Neurosciences

Brain-computer interfaces (BCIs) enable direct interactions between the brain and its bodily environment, as well as the outside world, while bypassing the usual sensory and motor pathways. In BCI, electroencephalography (EEG) is by far the most widely used technique, either with patients or

healthy volunteers, simply because it offers a non-invasive, direct and temporally precise measure of neuronal activity at a reasonable cost [1]. BCI research is still mostly driven by clinical applications, and in this context, EEG has been used for a variety of applications. These range from replacing or restoring lost communication or motion abilities in patients suffering from severe neuromuscular disorders [2–4] and devising new therapies based upon neurofeedback training [5], to active paradigms in disorders of consciousness to better diagnose non-responsive patients [6] and possibly to communicate with those in a minimally conscious state [7]. Interestingly, common to most of these BCI objectives, but also to the ones in basic and clinical neurosciences, is the refinement of our understanding of the functional role of electrophysiological markers and their within- and between-subject variations.

In this paper, we would like to further promote the idea that BCI and cognitive neuroscience researchers can help each other in pursuing this common goal. In short, the BCI paradigm puts the subject in a dynamic interaction with a controlled environment. From the perspective of cognitive neuroscience, this is a new opportunity to study normal and pathological brain functioning and to test mechanistic neurocognitive hypotheses [8]. In turn, BCI can benefit from progress in neurocognitive models for decoding mental states from online and single-trial electrophysiological measures [9]. Taking BCI outside the laboratory for daily life applications with patients or healthy people raises tremendous challenges, one of which is the need to decode brain signals in real time. This means one has to be capable of making efficient and robust inference online based on very limited, complex and noisy observations. Large efforts have recently been put into developing and improving signal processing, feature selection and classification methods [10–12], as well as acquisition hardware techniques [13] and dedicated software environments [14,15]. However, the main BCI bottleneck consists in the identification of a reliable mapping from neurophysiological markers to relevant mental states. This unresolved issue advocates for tight collaborations between BCI developers, electrophysiologists and cognitive neuroscientists.

Thankfully, a recent trend (and one that is increasingly catching on) has been to increase the permeability of the border between the BCI and cognitive neuroscience communities. New applications have emerged that rely on both disciplines and, thus, bring short-term benefit to both. One example is the so-called brain-state-dependent stimulation approach (BSDS) [16], the principle of which is to use BCI as a research tool for cognitive neuroscience, namely to study causal relationships between brain state fluctuations and cognition. In the BSDS, the functional role of a brain state is studied by delivering stimuli in real time to subjects, depending on their brain's actual physiological state. Other examples illustrate the reverse direction of this putative multidisciplinary cross-fertilization, showing how advances in cognitive neuroscience may improve BCI performance. An example is connectivity model-based approaches to neurofeedback, as demonstrated recently using fMRI (functional Magnetic Resonance Imaging) [17]. It is to be noted that such emerging applications

tend to extend the usefulness of BCI and real-time data processing to non-invasive techniques other than EEG, such as fMRI and MEG (Magnetoencephalography), which have similar overall principles, but might be even more effective for answering some of the cognitive neuroscience questions.

In this paper, we extend and formalize the BSDS approach by showing that our ability to process neuroimaging data online can be used to optimize the experimental design at the subject level, with the aim of discriminating between neurocognitive hypotheses. In experimental psychology and neuroimaging, this is a central issue, and examples range from stair-case methods to estimating some individual sensory detection or discrimination threshold [18], to design efficiency measures to optimize the acquisition parameter or the stimulus onset asynchrony (SOA) in fMRI studies [19]. The former operates in real time in the sense that the next stimulation depends on the previous behavioral response and is computed in order to optimize model fitting. The latter operates offline, prior to the experiment, and its aim is to optimize model comparison.

1.2. Adaptive Design Optimization

We introduce a generic approach in which real-time data acquisition and processing is aimed at discriminating between candidate mappings between physiological markers and mental states. This approach is essentially an adaptive design optimization (ADO) procedure [20]. The origins of ADO stem back to sequential hypothesis testing methods [21], whose modern forms have proven useful in human, social and educational sciences, where typical experiments involve a series of questions to assess the level of expertise of a particular subject [22]. The general principle is fairly straightforward. Figure 1 illustrates its application in the context of human electrophysiology and neuroimaging. In contrast with standard (non-adaptive) experiments, in ADO, the total number of trials is not set in advance, nor is the nature of the stimulation at each trial or stage of the experiment. Moreover, one does not wait until the end of the data acquisition process to proceed with data analysis and statistical inference. Instead, for each trial, the appropriate data features are extracted in order to up-date our (the experimenter's) information about the model parameters and to assess the model plausibility itself. Based on these estimates, a decision is made regarding some relevant design parameters for the next trials. The decision criterion should reflect the scientific objective of the experiment, e.g., a target statistical power for parameter estimation. This implies that some threshold can be met that would terminate the current experiment. In other words, ADO behaves like classical approaches, except that it operates online, at each trial. In turn, incoming trials are considered as future experiments, whose design can be informed by past observations or simply become unnecessary. At the level of a single subject, ADO can be used to improve on three problems: (i) model parameter estimation; (ii) hypothesis testing *per se*; (iii) the duration of the experiment. In the fields of experimental psychology and electrophysiology, recent forms of ADO have been applied to estimating psychometric functions [23], optimizing the comparison of computational models of memory retrieval [24] and optimizing the duration of the experiment when comparing alternative neuronal models [25]. However, optimizing

parameter estimation and hypothesis testing do not call for the same criteria and might not be possible simultaneously. In this paper, we focus on ADO for optimizing model comparison, which appears to be of primary interest in cognitive neuroscience. This is because, over the past decade, dynamic and non-linear computational models of neuroimaging and behavioral data have been flourishing [26]. In particular, established control theoretic approaches now rely upon biologically and psychologically plausible models of fMRI, electrophysiological or behavioral data (see, e.g., dynamical causal models (DCMs); [27–29]). Such generative models aim to explain the causal relationship between experimental (e.g., cognitive) manipulations and the observed neurophysiological or behavioral responses [30]. In particular, such tools have now been used to compare alternative models of learning and decision making in humans [28]. Importantly, these models are embedded in a Bayesian statistical framework, which allows one to deal with complex (e.g., probabilistic) models by introducing prior knowledge about unknown model parameters. Note that statistical inference can be made quick and efficient through the use of generic approximation schemes (*cf*. variational Bayes approaches; [31]). To extend ADO to dynamical neurocognitive models of electrophysiology data, we bring together such variational Bayesian approaches (which can be used in real time) and recent advances in design optimization for Bayesian model comparison (which can deal with complex models; [32]).

This paper is organized as follows. In the Theory and Methods section, we first describe the class of dynamical models that we compare. To make this paper self-contained, but still easy to read, we provide an appendix with a comprehensive summary of the variational Bayesian inference approach (see Appendix A1) and the design efficiency measure (see Appendix A2) that we rely on, in this new instantiation of ADO. We also emphasize how this compares with the recent pioneering approach for ADO in experimental psychology [20,24]. In the second part of the methods section, we introduce our validation strategy, which consists first of a demonstration of the face and construct validity of our approach by considering the same behavioral example as in [20]. Continuing to use synthetic data, we then demonstrate the extension of our approach to comparing variants of recent dynamical models of perceptual learning. In particular, by simulating several subject datasets, we illustrate how ADO compares with classical designs and how it optimizes hypotheses at the individual level. The next section presents the results of this validation. In the last section, we discuss these results, the perspectives they offer, as well as the challenges we now face to put ADO into practice.

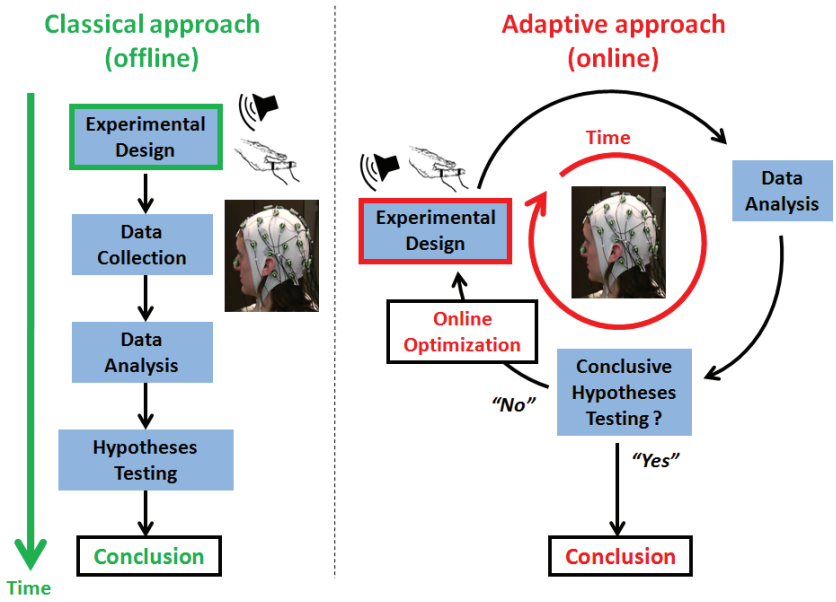

Figure 1. A schematic illustration of the adaptive *versus* classical experimental design approaches. The classical approach (*left*) is characterized by a sequential ordering of the main experimental steps: experimental design specification occurs prior to data acquisition, which is followed by data analysis and hypothesis testing. In contrast, the adaptive approach (*right*) operates in real time and proceeds with design optimization, data acquisition and analysis at each experimental stage or trial. The online approach enables hypothesis testing to be optimized at the individual level by adapting the experimental design on the basis of past observations. This is the general principle of adaptive design optimization (ADO), which can be extended to advanced computational models of electrophysiological responses thanks to brain-computer interface (BCI) technology, with the aim of optimizing experimental conclusions and the time-to-conclusion in cognitive and clinical neuroscience.

2. Theory and Methods

2.1. Dynamic Causal Models (DCMs)

In this section, we briefly introduce the very general type of complex generative models for which the proposed ADO procedure is most appropriate. In their general form, such models are defined by a pair of assumptions $\{f, g\}$. The first component, f, is the evolution function, which prescribes the evolution or motion of hidden (unobservable) neuronal or psychological states x, such that:

$$\dot{x} = f(x, \theta, u) \tag{1}$$

The second component, g, is the observation function and prescribes the mapping from hidden states to observed neurophysiological, metabolic or behavioral responses, such that:

$$y = g(x, \varphi, u) + \varepsilon \tag{2}$$

θ and φ are the model parameters. They represent fixed, but unknown, values that parameterize the evolution and observation functions, respectively. These values might differ from one subject to

another or, for the same subject, from one experimental condition to the next. ε indicates random fluctuations or noise that corrupt the observed data. Finally, u corresponds to experimental control variables, that is, exogenous inputs to the system that might encode changes in experimental condition (e.g., visual stimulation-type, like face *vs.* house) or the context under which the responses are observed (e.g., sleep *vs.* awake). Instantiations of such models have been proposed to explain the generation and the effect of experimental modulations in fMRI data [27] and various electrophysiological features in EEG, MEG or intracranial (*i.e.*, local field potentials (LFP)) data, such as evoked [33], induced [34] or steady-state responses [35].

More recently, a related dynamical-system based approach has been derived to model psychological states, their evolution over time and their mapping onto observable behavioral measures (e.g., choices, reaction times) [28] or physiological observations [36]. However, referred to as "observing the observer", this approach differs from the above classical DCMs, because it involves the embedding of a subject's (the observer) dynamic causal model of the environment ($M_s = \{f_s, g_s\}$) into an experimenter's (another observer observing the subject) dynamic causal model of the subject ($M_e = \{f_e, g_e\}$). Further, assuming that the subject implements an optimal online Bayes inference (see Appendix A1) to invert the duplet $\{f_s, g_s\}$ and infer the hidden states of the environment, the evolution (perception) function, f_e, incorporates this inference and learning process, while the observation (response) function, g_e, defines the mapping between the hidden subject's internal states (the inferred or posterior estimates of the environment hidden states) onto behavioral or physiological responses. Bayesian inference applies to the experimenter's model in order to compare pairs of models $\{M_s, M_e\}$ and infer those model parameters (see Appendix A1). This is why this approach is also referred to as a meta-Bayesian approach [28]. Importantly, in this context, we explicitly model the link between the precise sequence of presented sensory inputs and the evolving subject's beliefs about the state of the world.

2.2. Online Optimization of Model Comparison

Most of the generative models that are used in cognitive neuroscience fall into the class of nonlinear Gaussian models. Our approach combines two recent methodological advances and brings them online for ADO. First, we use a Bayesian framework to invert and compare such generative models [28] (see Appendix A1). Second, we use a previously proposed proxy to the model selection error rate [32] as a metric to be optimized online through the appropriate selection of experimental control variables (see Appendix A2). Under the Laplace approximation [37], this metric (the Chernoff bound) takes a computationally efficient analytic form, which is referred to as the Laplace–Chernoff bound. In [32], the authors disclosed the relationship between the Laplace–Chernoff bound and classical design efficiency criteria. They also empirically validated its usefulness offline, in a network identification fMRI study, showing that deciding whether there is a feedback connection between two

brain regions requires shorter epoch durations, relative to asking whether there is experimentally-induced change in a connection that is known to be present.

For the online use of the same criterion in order to optimize the experimental design for model comparison, at the individual level, we simply proceed as illustrated in Figure 1 in the adaptive scenario. At each trial or experimental stage, it consists of:

(i) Running the variational Bayes (VB) inference for each model, M, given past observations and experimental design variables;

(ii) Updating the prior over models with the obtained posteriors;

(iii) Computing the design efficiency or Laplace-Chernoff bound for each possible value of the experimental design variable, u;

(iv) Selecting the optimal design for the next trial or stage.

Finally, the online experiment will be interrupted as soon as some stopping criterion will have been met. Typically, the experiment will be conclusive as soon as one model is identified as the best model, for instance, when its posterior probability will be greater than 0.95. If this is not the case, when an *a priori* fixed number of trials would have been reached, the experiment will be considered as inconclusive in selecting a single best model for the given subject.

2.3. Validation

We now turn to the validation of the proposed approach. We describe two studies based on synthetic data. The first one demonstrates the face and construct validity of the approach by reproducing the simulation example in [20]. The second study illustrates how our approach extends to a realistic online scenario, whose aim is to compare more than two nonlinear models of perceptual learning based on electrophysiological responses only.

2.3.1. First Study: Synthetic Behavioral Data

In order to illustrate our approach for ADO and to provide a first demonstration of its face and construct validity, we reproduce results from Cavagnaro and colleagues [20,38]. These authors showed how an optimal design might look in practice, considering the example of a typical behavioral experiment designed to discriminate psychological models of retention (*i.e.*, forgetting). The experiment consists of a "study phase", in which participants are given a list of words to memorize, followed by a time interval (lag time), followed by a "test phase", in which retention is assessed by testing how many words the participant can correctly recall from the study list. The percentage of words recalled correctly typically decreases with the time interval. A model of retention is the function that can fit this relationship between retention and lag time. These authors considered two retention models: power and exponential forgetting [38].

Model power (POW):

$$p = a(t+1)^{-b} \tag{3}$$

Model exponential (EXP):

$$p = ae^{-bt} \tag{4}$$

In each equation, the symbol, p, denotes the predicted probability of correct recall as a function of lag time, t, between the study and test phase, with model parameters a and b.

As in [38], we simulated data under the (true) model POW, considering plausible values for model parameters. Note that the retention interval or lag time is the design variable whose value is being experimentally manipulated. For a given lag time, t, each model predicts the number of correctly recalled items:

$$y = n.a.(t+1)^{-b} \tag{5}$$

where $n = 30$ is the number of presented items at each trial.

The observable data, y, in this memory retention model formally follows a binomial distribution and (conjugate) Beta priors on parameters (a, b) are usually used. In our case, we used a normal approximation to the priors on parameters (a, b). As n increases, according to the central limit theorem, the binomial distribution tends to a normal density with matched moments, and a normal approximation to the likelihood function is appropriate. We simulated the responses from 30 participants, by drawing 30 pairs of parameter values a and b, considering $a \sim \mathcal{N}(0.8,0.5)$ and $b \sim \mathcal{N}(0.4,0.5)$.

For each simulated participant, ADO was initialized with the same priors over model parameters: $a \sim \mathcal{N}(0.75,2)$, $b \sim \mathcal{N}(0.85,2)$ for POW and $a \sim \mathcal{N}(0.9,2)$, $b \sim \mathcal{N}(0.15,2)$ for EXP; and the same prior for each model: $p(\text{POW}) = p(\text{EXP}) = 1/2$. Similar to what Cavagnaro and colleagues did, we compared ADO against two classical (non-adaptive) experimental designs. The first one, called "Random Design", is a complete random fashion design, where the lag time at each trial was chosen randomly between 0 and 100 s. The second one, called "Fixed 10 pt Design", presents, in a random order, each lag time from a fixed set of lag times concentrated near zero and spaced roughly geometrically: 0, 1, 2, 4, 7, 12, 21, 35, 59 and 99 s. The latter design is closer to the set of lag times used in real retention experiments [39]. We considered 10 trial-long experiments and computed the true (POW) model posterior after each trial, for each design. Only ADO is adaptive in the sense that, at each trial, the most efficient lag time is selected based on the updated posteriors over parameters and models, and the ensuing Laplace-Chernoff bound for each possible lag times. The results are presented in Section 3.1.

2.3.2. Second Study: Synthetic Electrophysiological Data

To demonstrate how our new instantiation of ADO extends to nonlinear dynamic causal models, which are of increasing interest in cognitive neuroscience, we now turn to a second series of original simulations. We therefore consider recent models of human perceptual learning in a changing environment [40–43] and combine them with recent works on how these models might predict single-trial EEG evoked responses [36,44]. These models can be thought of as a specific instantiation of the Bayesian brain and predictive coding hypotheses [45]. The former hypothesis postulates that the brain uses Bayesian inference for perception and perceptual learning. In other words, these processes rely upon an internal generative model, *i.e.*, probabilistic assumptions of how external states cause changes in sensory data (the sensory signal likelihood) and prior beliefs about these causes [46]. In addition, the predictive coding hypothesis [47] suggests that electrophysiological activity that propagates through neural networks encodes prediction (top-down) and prediction error (bottom-up) messages, whose role is to explain away sensory surprise by updating beliefs about hierarchically deployed hidden causes. Evoked electrophysiological responses that are reminiscent of such mechanisms were first established using so-called "oddball" experimental paradigms, where one category of rare stimuli (deviants) is intermixed with a second category of frequent stimuli (standards). The ensuing "mismatch negativity" (MMN) EEG evoked potential is then interpreted in terms of the response of the system to a violation of its prior expectations [48]. These responses have been observed in various sensory modalities, but are mostly documented in the auditory [49] and somatosensory domains [44]. Below, we expose the perceptual (evolution) and response (observation) models we considered for simulating MMN-like responses.

2.3.2.1. Perceptual Learning Model

We considered a simplified version of the perceptual learning model proposed in [43] to model perception in a volatile environment (see also [50]). This perceptual model (Figure 2) comprises a hierarchy of 3 hidden states (denoted by x), with States 2 and 3 evolving in time as Gaussian random walks. The probability of a stimulation category appearing in a given trial (t) (represented by State $x_1^{(t)}$, with $x_1 = 1$ for deviant and $x_1 = 0$ for standard stimuli) is governed by a state, x_2, at the next level of the hierarchy. The brain perceptual model assumes that the probability distribution of x_1 is conditional on x_2, as follows:

$$p(x_1|x_2) = s(x_2)^{x_1}\big(1 - s(x_2)\big)^{1-x_1} = Bernoulli\ \big(x_1; s(x_2)\big) \tag{6}$$

where $s(\cdot)$ is a sigmoid (softmax) function:

$$s(x) \stackrel{\text{def}}{=} \frac{1}{1 + exp(-x)} \tag{7}$$

Equations (6) and (7) imply that the states $x_1 = 0$ and $x_1 = 1$ are equally probable when $x_2 = 0$.

The probability of x_2 itself changes over time (trials) as a Gaussian random walk, so that the value, $x_2^{(t)}$, is normally distributed with mean $x_2^{(t-1)}$ and variance $e^{\kappa x_3^t + \omega}$:

$$p\left(x_2^{(t)} \middle| x_2^{(t-1)}, x_3^{(t)}\right) = N\left(x_2^{(t)};\, x_2^{(t-1)}, exp\left(\kappa x_3^{(t)} + \omega\right)\right) \tag{8}$$

Setting the parameter κ to 0 effectively means assuming that the volatility of x_2 is fixed over time. In all other cases, the magnitude of changes in x_2 over time (trials) is controlled by x_3 (the third level of the hierarchy) and ω, which can be regarded as a base (log-) volatility. The state, $x_3^{(t)}$, on a given trial is normally distributed around $x_3^{(t-1)}$, with a variance determined by the constant parameter, ϑ. The latter effectively controls the variability of the log-volatility over time.

$$p\left(x_3^{(t)} \middle| x_3^{(t-1)}, \vartheta\right) = N\left(x_3^{(t)};\, x_3^{(t-1)}, \vartheta\right) \tag{9}$$

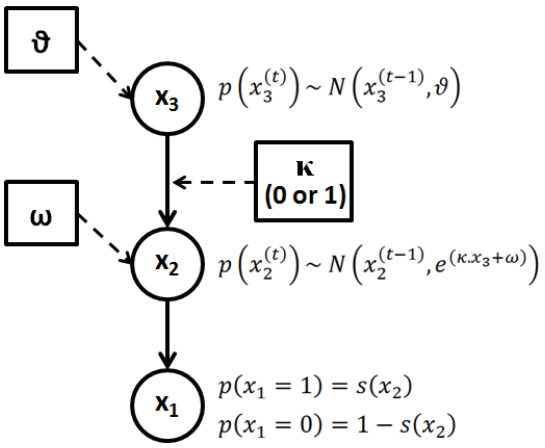

Figure 2. Graphical illustration of the hierarchical perceptual (generative) model with States x_1, x_2 and x_3. The probability at each level is determined by the variables and parameters at the level above. Each level relates to the level below by controlling the variance of its transition probability. The highest level in this hierarchy is a constant parameter, ϑ. At the first level, x_1 determines the probability of the input stimulus: standard (0) or deviant (1). The model parameters, ω and ϑ, control the agent's belief update about State x. Note that setting $\kappa = 0$ effectively truncates the hierarchy to the first two levels. In the diagram, squares represent fixed parameters, while circles represent state variables that evolve in time.

2.3.2.2. Electrophysiological Response Model

One can quantify the novelty of sensory input using Bayesian surprise. In what follows, we assume that EEG response magnitudes encode the Bayesian surprise induced by the observation of sensory stimuli at each trial. This is in line with recent empirical studies of the MMN in oddball paradigms [36,44].

Recall that, at any given trial, the Bayesian surprise is simply the Kullback–Leibler divergence between the prior and posterior distribution [51]. It indexes the amount of information provided by sensory signals at each level of the hierarchy. We simulated trial-by-trial EEG response magnitudes by

adding random noise to the (weighted) Bayesian surprise (BS) at the second level of the perceptual learning model:

$$y_t = h * BS\left(p\left(x_2^{(t)}\middle|u_t\right), p\left(x_2^{(t)}\right)\right) + \epsilon$$
$$\epsilon \sim \mathcal{N}(0, \sigma) \tag{10}$$

Note that under the Laplace approximation, BS has a straightforward analytic form (see [52]). In the current simulations, we fixed the weight parameter, h, to −10 and the noise precision or inverse variance to 100. We considered the problem of comparing five different perceptual models given simulated EEG data (see Table 1). M1 is a "null" model with no learning capacities. The four other models form a 2 × 2 factorial model space. Contrary to M4 and M5, M2 and M3 have no third level ($\kappa = 0$). They are unable to track the volatility of the environment. Orthogonal to this dimension is the base learning rate at the second level, which is controlled by the parameter, ω. In brief, M2 and M4 predict slower learning than M3 and M5.

Table 1. Five alternative models used and compared in simulations.

Models	ω Values	κ Values (If $\kappa = 0$, No Third Level)	ϑ Values	Ability to Track Events Probabilities	Ability to Track Environmental Volatility
M1	−Inf	0	-	No	No
M2	−5	0	-	Low learning	No
M3	−4	0	-	High learning	No
M4	−5	1	0.2	Low learning	Yes
M5	−4	1	0.2	High learning	Yes

We simulated 75 experiments in total, corresponding to 15 different synthetic subjects simulated under each model type as the true model. Each experiment consists of 350 trials. ADO was compared with the two following classical designs. The "stable" classical design has a fixed probability of the occurrence of a deviant ($p(u = 1) = 0.2$). The "volatile" classical design starts with 100 trials with a stationary sensory signal distribution ($p(u = 1) = 0.2$), followed by 150 trials with a volatile sensory signal distribution (which alternates 50 trials with $p(u = 1) = 0.1$, 50 trials with $p(u = 1) = 0.3$ and 50 trials with $p(u = 1) = 0.1$), followed by a stable period similar to the initial one. Results are presented in Section 3.2.

2.4. Software Note

Simulations in this work were performed using the VBA toolbox [53], which is under open-source GNU General Public License (v2) and freely downloadable from the toolbox's internet wiki pages [54].

3. RESULTS

3.1. First Study: Behavioral Synthetic Data

In brief, ADO chooses, at each stage, the lag time that maximizes the difference between model predictions and then updates model probabilities based on the model evidences. For example, in Stage 3 of the simulated experiment depicted in Figure 3, the optimal time lag was around 9 s. At this time lag, EXP predicts a higher percentage of correct responses than POW (*cf*. heat maps). When 39% of correct responses are observed (an outcome that is much more likely under POW than under EXP, *cf*. white arrows in Figure 3), POW's posterior probability is increased from 0.83 to 0.98 in Stage 4. Instead, EXP's posterior probability decreases from 0.17 to 0.02. As the experiment unfolds, the models' predictions converge towards the observed outcomes and the posterior probability of the true model (POW) approaches 1.

In line with Cavagnaro *et al.*, we compared ADO with two random classical designs. Figure 4 shows the distribution of lag time presentations for ADO and for both random designs (simulations with group size = 30). One can see that ADO selects lag times that lie at the extremes of the permitted range, or between 10 and 20 s. Given those distributions, the expected mean lag time per stage for each design is: ADO: 19.2; fixed 10 pt design: 24; and random design: 49.3.

Finally, Figure 5 shows the group mean of posterior probability for the true model (POW) as a function of stage depending on the design. On average (over the 30 subjects), ADO reaches a posterior model probability of 95% after about three stages. On average, the random design was still inconclusive after 10 stages (the posterior model probability is still below 95%). The fixed 10 pt design reaches a posterior model probability of 95% after seven stages, which corresponds to experiments twice as long as with ADO.

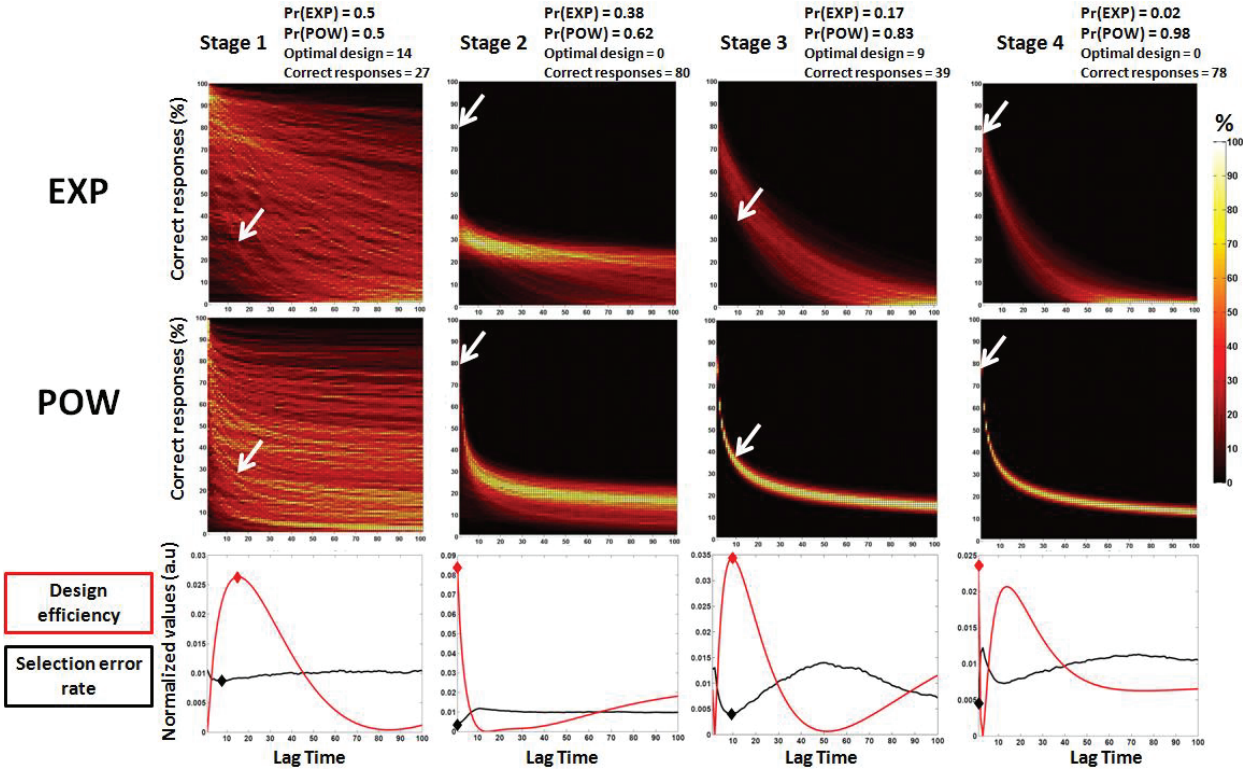

Figure 3. Predictions of the power (POW) and exponential (EXP) models in the first four stages of one simulated experiment and the landscape of selection error rate across lag time. The predictions are based on the prior parameter estimates at each stage. The text above and inside the graphs provides information about the prior probabilities of each model, the optimal designs for discriminating the models and the observed outcomes (correct responses) at each stage of the simulated experiment. Arrows denote the percentage of correct responses at the optimal lag time. For the heat maps of models predictions (*top* and *middle* panels), yellow colors indicate regions of higher probability. (*Bottom*) The bottom panel, represents the error selection rate for each possible lag time (normalized values of arbitrary units, *black line*), as well as the estimated efficiency (*red line*), which is our main criterion. At each stage, we choose the maximum of our criterion (*red diamond*), which mostly coincides (because of the approximation) with the minimum of the error selection rate (*black diamond*).

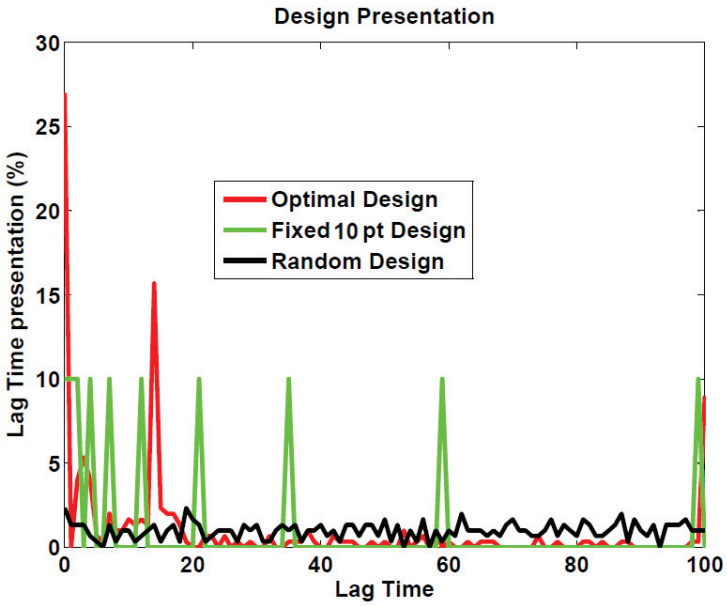

Figure 4. Lag time distribution for each experimental design (over the 30 simulations).

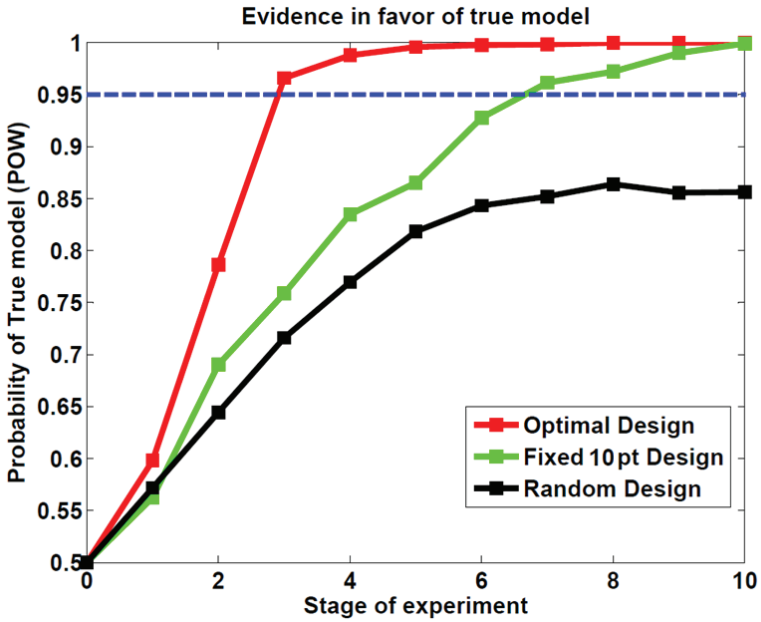

Figure 5. Posterior probabilities of the true (POW) model at each stage (average over 30 simulations).

In brief, our analysis reproduces the results of Cavagnaro *et al* [38]. Note that here, the optimal design was easily found using the direct calculation of the minimum model selection error rate (the black line in Figure 3). Although this may render our results rather anecdotic, our intention was simply to validate the approach on a simple case. In what follows, we generalize our results to a much more complex (and realistic) design optimization problem in which the direct calculation of the minimum model selection error rate is impossible.

3.2. Second Study: Electrophysiological Synthetic Data

Here, we assess ADO's ability to discriminate between complex (computational) models. Figure 6 presents an example of a simulation for each of the five models described in the results section (see Table 1). Under the "null" model (M1), fluctuations in the data are explained by measurement noise. One can see early differences in simulated data under models with high (M3 and M5) or low (M2 and M4) learning rates (the ω parameter). However, differences between three- (M4 and M5) and two- (M2 and M3) level models only appear when the sensory signal distribution becomes volatile.

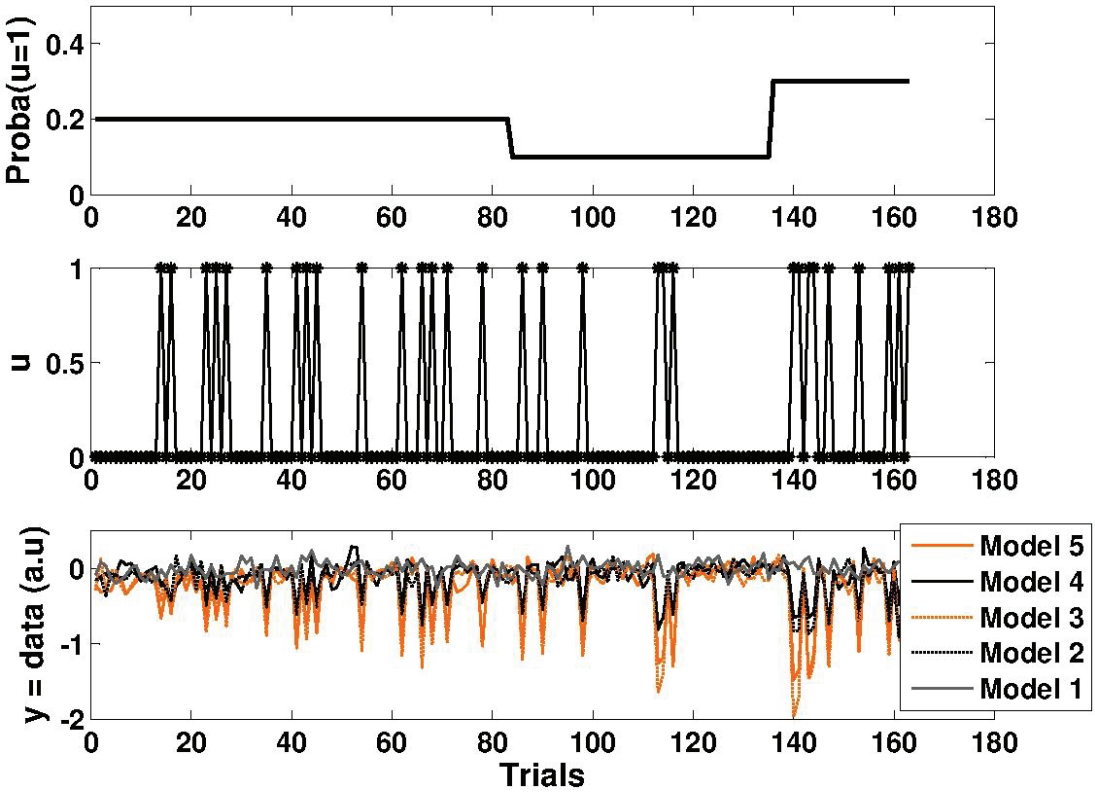

Figure 6. Simulated data for five Bayesian learning models (defined in Table 1). (*Top*) The dynamics of true deviant probability. (*Middle*) The sequence of sensory stimuli u (0 or 1). (*Bottom*) The dynamics of (noisy) Bayesian surprise (simulated electroencephalography (EEG) response magnitudes over trials).

As in the previous Section 3.1, we assessed the designs' ability to discriminate between the candidate models. Figure 7 summarizes the results over 75 simulations (with equal proportions of datasets simulated under each model). We considered that an experiment was conclusive when the posterior probability in favor of the true model reached or exceeded the threshold of 0.95 (after 350 trials). The simulation is labeled "non-conclusive" otherwise. We observed that almost half of the simulations (49.3%) were labeled non-conclusive when we used the stable classical design. The volatile classical design was much more efficient (14.7% of non-conclusive experiments), but less than ADO (2.7% of non-conclusive experiments). When focusing on conclusive experiments, we observed differences in

the number of trials needed to reach the 95% posterior model probability threshold. In brief, ADO yields faster experiments than both the volatile and stable classical designs (see Figure 7).

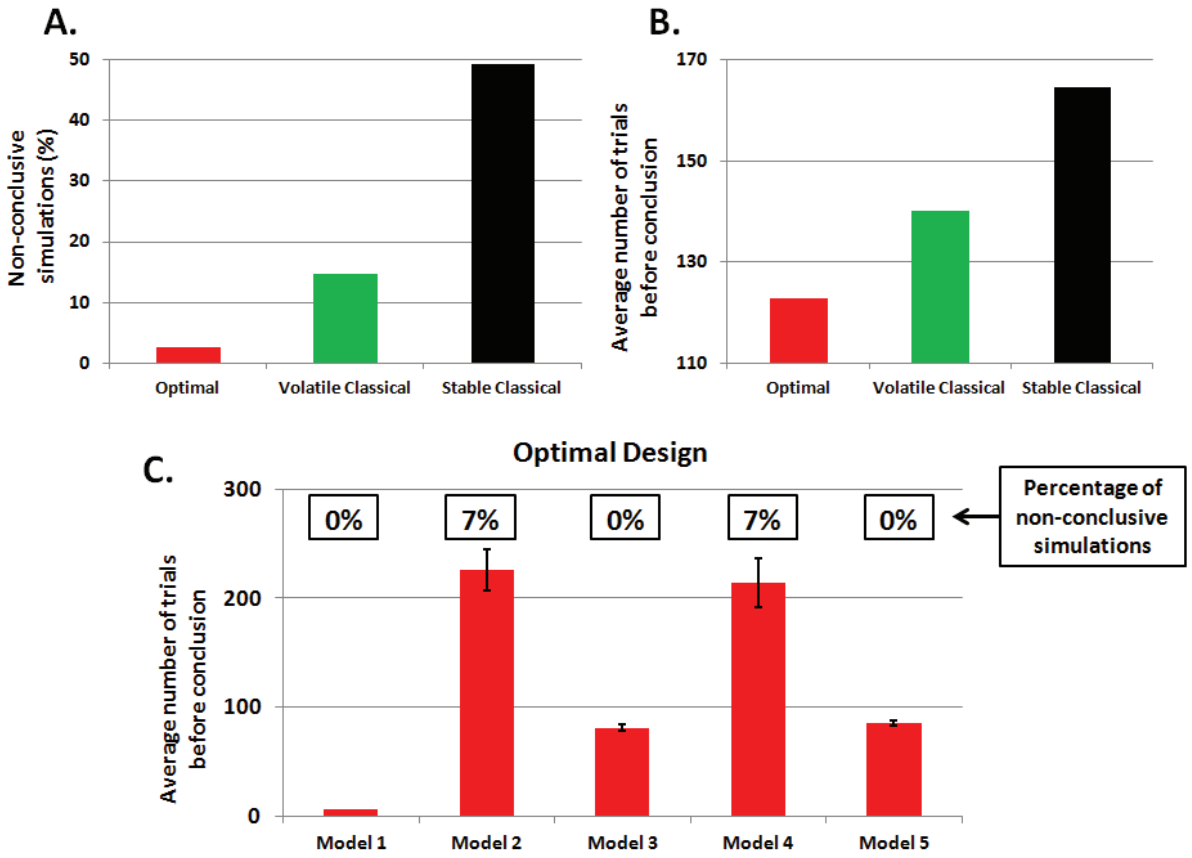

Figure 7. Adaptive design optimization (ADO) with learning models: simulation results. Note that a simulated experiment is deemed "conclusive" whenever the true model posterior probability is equal to or greater than 95%. (**A**) The number of non-conclusive experiments for each design; (**B**) the average number of trials needed to reach the 95% threshold in conclusive simulations; (**C**) the average number of trials before the conclusion and the percentage of non-conclusive simulations (note that in our case, 7% means one non-conclusive experiment over 15).

Figure 8 shows the average dynamics of model posterior probabilities, as a function of the true model. Note that M1 was discarded by all designs after about 10 trials (not shown). One can see that only ADO can select models with low learning rates (M2 and M4), given the 95% model posterior probability requirement. Note that models with higher learning rate (M3 and M5) take fewer trials to be selected, although the stable classical design only reaches the 95% threshold at the very end of the experiments for M3.

In conclusion, ADO performs better than classical designs, yielding fast and efficient experiments for all the models considered. The last point is important, since this implies that ADO does not induce biases in model selection.

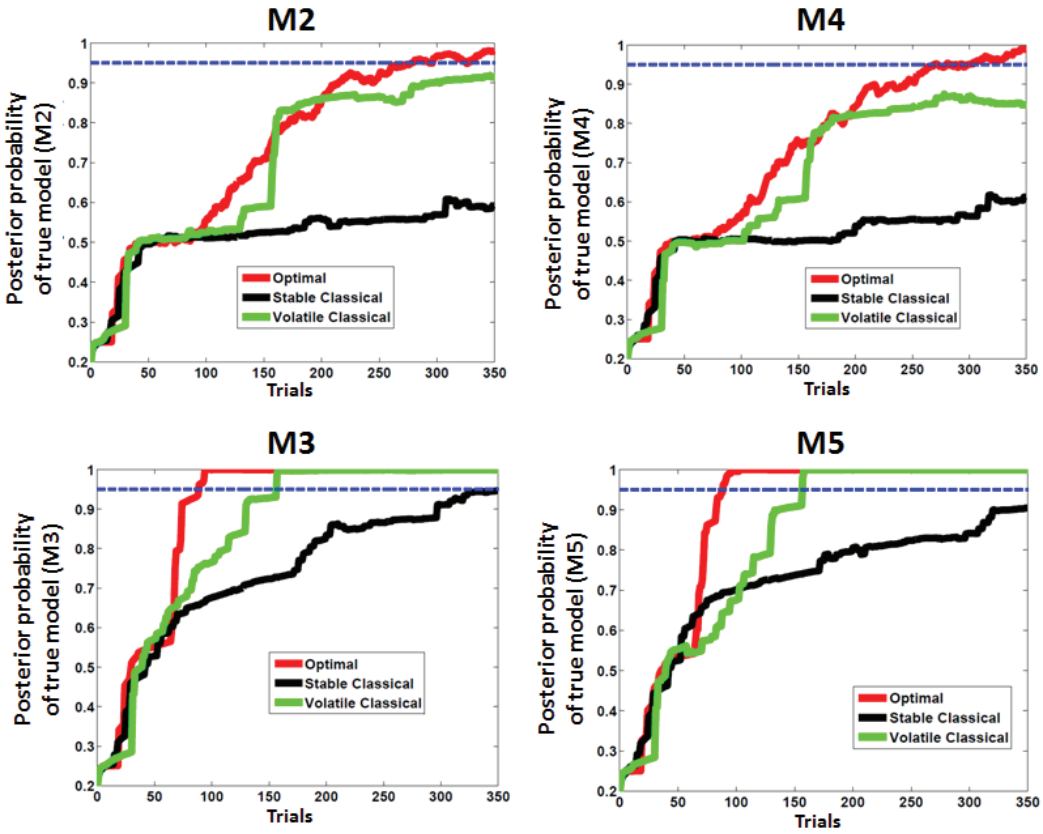

Figure 8. Posterior model probabilities at each trial in our simulated experiment: the average over 15 simulations for each model.

4. DISCUSSION

In this paper, we demonstrate the added-value of real-time acquisition and BCI loops, when applied to the aim of performing online design optimization. This work follows recent advances in Bayesian decision theoretic approaches to design optimization in experimental neuroscience [32]. We first validated our approach in the case of simple psychological models of memory retention [20,24,38]. We then extended our approach to more realistic and complex multi-model comparisons, given electrophysiological data. In brief, ADO outperforms classical (offline) designs, irrespective of the true generative process. This means we expect ADO to be most useful in experimental settings whose optimality cannot be known in advance, *i.e.*, when comparing complex models given low quality data (e.g., a low sample size and SNR (Signal-to-Noise Ratio)).

4.1. Current Limitations

First, ADO's performances depend upon the accuracy of prior information regarding model parameters. In fact, non-informative priors are unacceptable, because they induce flat predictive densities for all models, which prevents any design optimization procedure [32]. A solution to this issue would be to start with a classical (offline) design, perform model inversions given the first few data samples and then use the ensuing posterior distributions as priors in ADO.

Second, real-time processing of electrophysiological data remains challenging, because of data contamination by high-magnitude artifacts (*i.e.*, muscle activity, head movements, eye blinks, *etc.*). This means one may have to deal with missing data. This may be problematic when dealing with dynamical models that assume some continuity in the processes underlying experimental data (e.g., belief update in learning experiments).

Third, ADO cannot be used to optimize the experimental design and to select relevant data features (e.g., EEG markers) at the same time. This implies that admissible data features have to be identified prior to the experiment.

4.2. Perspectives

A promising application of ADO is differential diagnosis, whereby one seeks to discriminate between alternative pathological mechanisms. One such example is the inference of patients' mental states from electrophysiological makers in coma and related disorders [55–57]. Beyond such diagnostic objectives, ADO could prove useful in model-based predictions of individual treatment responses. Lastly, although BCI applications are often evaluated with respect to their clinical utility, we would like to emphasize that ADO (when combined with real-time electrophysiology) could find a wide range of practical applications in basic neuroscientific research.

4.3.. Conclusion

Our paper aims to provide a proof of concept of an original way to conduct basic research experiments. Using simulations, we demonstrated robust advantages of optimal design when the ADO procedure was compared with classical designs in behavioral or electrophysiological experiments. We envisage that the present paper could pave the way for future BCI applications in both basic and clinical research.

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Conflicts of Interest

The authors declare no conflict of interest.

APPENDIX A

A1. Bayesian Inference

In this Appendix, we briefly describe how approximate Bayesian inference applies to dynamic causal models, with a particular emphasis on Bayesian model comparison.

In the Bayesian framework, defining model M amounts to defining the likelihood and prior densities, respectively $p(y|x,\theta,\varphi,u,M)$ and $p(x,\theta,\varphi|M)$. Solving Bayes rule then produces the posterior density, $p(x,\theta,\varphi|y,M)$, and the model evidence or marginal likelihood, $p(y|M,u)$. The former enables inference on model parameters, while the later enables model comparison and selection. However, for complex non-linear models, such as DCMs, exact computation of those two quantities becomes intractable. Variational Bayes (VB) then offers a convenient and efficient approximate inference method, which operates iteratively and furnishes analytic forms to the posterior and model evidence. In short, it maximizes a lower bound to the model log-evidence, called the (negative) free energy, which writes:

$$F = log\ p(y|u,M) - KL\big(q(x,\theta,\varphi)\big|p(x,\theta,\varphi|y,M)\big) \tag{11}$$

where KL is the Kullback–Leibler divergence between an approximate posterior, q, and the true posterior. Since KL is always positive, F is a lower bound to the model log-evidence and maximizing F amounts to minimizing KL, such that q gets closer to the true posterior, while F gets closer to the model log-evidence. At the convergence of the VB process, F is used for model comparison, and the approximate posterior, q, for the winning model is used for inference on the parameters. Importantly, it can be easily shown that the free energy criterion forms a trade-off between model accuracy and model complexity [59]. In other words, it implements the parsimony principle, or Occam's razor, to prevent overfitting [60]. For a more detailed description of the VB approach and an exemplar application in neuroimaging, we refer the interested reader to [31] and [61], respectively.

In the Bayesian framework, comparing Model M_1 with Model M_2 rests upon computing the Bayes factor:

$$BF_{12} = \frac{p(y|M_1,u)}{p(y|M_2,u)} \tag{12}$$

which simply corresponds to the ratio of the two model evidences. Like in classical inference, where decisions are made based on so-called *p*-values, similar decisions can be made based on Bayes factors [62]. Hence a BF (Bayes factor) greater than 20 (or a log-BF greater than three) is considered as strong evidence in favor of Model M_1 (equivalently, to a *p*-value lower than 0.05 (=1/20)). When the

dimension of the model space is larger than two, a convenient quantity is the model posterior, which can easily be derived from the Bayes rule as follows:

$$p(M|y,u) = \frac{p(y|M,u)p(M)}{p(y|u)} \tag{13}$$

where:

$$p(y|u) = \sum_{M} p(y|M,u)p(M) \tag{14}$$

Under equiprobable priors over models, this boils down, for Model M_k, to:

$$p(M_k|y,u) = \frac{1}{1 + \sum_{M_i \neq M_k} BF_{ik}} \tag{15}$$

Then, a natural decision criterion is to select as the best model the one that obtains a posterior probability greater than 0.95.

A2. Design Efficiency: A Decision Theoretic Criterion

In this Appendix, we summarize the decision theoretic approach introduced in [32] to optimize design efficiency for the comparison of non-linear models of the sort described in Section 2.1.

In Section 2.1, we saw that model selection in a Bayesian framework involves evaluating model evidence. The reason why $p(y|m,u)$ is a good proxy for the plausibility of any model, M, is that the data, y, sampled by the experiment is likely to lie within the subset of Y that is highly plausible under the model that makes predictions most identical to the true generative process of the data. However, there is a possibility that the experimental sample, y, would end up being more probable under a somewhat worse model. This "model selection error" could simply be due to chance, since y is sampled from a (hidden) probability distribution. The inferential procedure of Bayesian model selection should then be designed to minimize (in expectation) the above model selection error. The probability, P_e, of selecting an erroneous model depends on both the data, y, that will be sampled and the experimental design, u, that will be used. It is given by:

$$P_e = 1 - \max_{M} p(M|y,u) \tag{16}$$

The task of design optimization is to reduce the effect of the data sampling process upon the overall probability of selecting the wrong model. In other words, the design risk we want to minimize corresponds to the marginalization of the above probability over the whole sample space, Y. Our optimal design, u^*, thus writes:

$$u^* = arg\min_{u} E_{p(y|u)}[P_e] \tag{17}$$

with:

$$E_{p(y|u)}[P_e] = 1 - \int_Y \max_M [p(M)p(y|M,u)]dy \tag{18}$$

Unfortunately, the above integral has no analytical close form and will be difficult to evaluate in most cases. As proposed in [32] instead, we minimize an information theoretic criterion, $b(u)$, which yields both upper and lower bounds to the above error rate. $b(u)$ is known as the Chernoff bound [63] and is such that:

$$\frac{1}{4(N_M - 1)} b(u)^2 \leq E_{p(y|u)}[P_e] \leq \frac{1}{2} b(u) \tag{19}$$

with:

$$b(u) = H\big(p(M)\big) - D_{JS}(u) \tag{20}$$

where N_M is the cardinality of the model comparison set, $H(\cdot)$ is the Shannon entropy and $D_{JS}(\cdot)$ is the Jensen–Shannon divergence [64], which is an entropic measure of dissimilarity between probability density functions (see Appendix A3). As shown in Appendix A3, this approximate criterion is very similar and brings a new perspective to the one initially proposed by [20].

A3. Comparison of the Chernoff bound with the Other Criterion

In this Appendix, we disclose the relationship between the Chernoff bound we use for online design optimization and the criterion proposed in the seminal work by Myung, Pitt and Cavagnaro [20]. The Chernoff bound writes (see Appendix A2):

$$b(u) = H\big(p(M)\big) - D_{JS}(u) \tag{21}$$

Minimizing this bound to the model selection error rate, with respect to design variable u, is equivalent to maximizing the Jensen–Shannon divergence:

$$D_{JS}(u) = H\left(\sum_M p(M)p(y|M,u)\right) - \sum_M p(M)H\big(p(y|M,u)\big) \tag{22}$$

Simply unfolding Shannon's entropy and applying Bayes rule yields:

$$\begin{aligned} D_{JS}(u) &= -\sum_M p(M) \int_Y p(y|M,u) \log p(y|u) - \sum_M p(M) \int_Y p(y|M,u) \log p(y|M,u) \\ &= \sum_M p(M) \int_Y p(y|M,u) \log \frac{p(y|M,u)}{p(y|u)} \\ &= \sum_M p(M) \int_Y p(y|M,u) \log \frac{p(M|y,u)}{p(M)} \end{aligned} \tag{23}$$

$= I(M; Y|u)$

where $I(M; Y|u)$ is the mutual information between the data and model spaces, given experimental design u. This conditional mutual information is the information theoretic criterion derived and maximized by Myung and colleagues.

The Jensen–Shannon divergence, or equivalently, the above conditional mutual information, is the relevant terms of the Chernoff bound to the model selection error rate. For simple models, such as the memory retention models compared here and in [20], the model selection error rate can easily be computed with high precision using Monte-Carlo simulations. However, when comparing nonlinear models, such as the learning models considered in this paper, the appeal to the approximate design efficiency provided by the Jensen–Shannon divergence is required. Importantly for such models, under the Laplace approximation, this criterion takes a simple analytic form, which can be computed online efficiently [32].

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CHAPTER VI. DISCUSSION

6.1. SUMMARY

6.1.1. AIM OF THE THESIS

Recent research has significantly contributed to uncovering the dynamics of brain processes. The computational mechanisms and neural correlates of context-dependent perceptual learning have started to be empirically deciphered. Besides, advanced developments in online brain signal processing have become available thanks to the growing BCI field, and real-time electrophysiology protocols may change the way neuroscientists stimulate the brain during experiments. These technical advances provide interesting tools to further understand the dynamics of brain function. Indeed, neuroimaging and cognitive neuroscience have largely moved from correlational analysis to the testing of causal hypothesis on how neurophysiological and behavioral reponses are related and generated. Moreover, thanks to the Bayesian framework in particular, such psychophysiological models of brain function have gain realism and biological plausibility. They have become non-linear and dynamical to account for learning and decision-making processes or for the modulation of effective connectivity in neuronal networks. As a consequence, for a given experiment, alternative hypothesis to compare might become more and more complex and numorous. One central idea I explored in this work was to take advantage of real-time electrophysioloigy in order to optimize this hypothesis testing. What real-time offers is the possibility to adapt the experimental design online, as we gain evidence over the model space of interest. Finally, this is an interesting paradigm shift, which moves from classical (static) experimental designs to adaptive (dynamical) ones. I believe this change offers new opportunities to investigate the link between brain mechanisms and resulting behaviors.

In the present thesis, this is why I focused on tasks where dynamical aspects of brain processes are emphasized and can be investigated. I refined our understanding of implicit adaptive processes involved in a typical perceptual decision-making task. I then provided the proof-of-concept in the use of real-time electrophysiology to optimize hypothesis testing in the context perceptual inference and learning. Two questions motivated the present research:

- What are the psychological and physiological underpinnings of context-dependent perceptual decision making?

- Could we improve our empirical investigation of such processes by combining real-time electrophysiology with advanced modelling and decision-theoretic approaches, for adaptive design optimization?

6.1.2. MAIN RESULTS

The results obtained in each study have already been summarized in each chapter's discussion. This discussion section will be used to set this work into a broader context and to discuss how our research could improve cognitive neuroscience hypothesis testing and particularly the understanding of perceptual learning processes.

In the first study, I investigated implicit adaptive processes underlying contextual dependent learning in a classical perceptual decision-making experiment, namely a tactile frequency discrimination task. With the aim of refining the dynamic and neural correlates of brain processes involved in this typical task, I presented findings that suggest the early and crucial involvement of frontal areas as a part of the performance optimization process that might contribute to the contraction bias when the task set is modified. Relevant markers of brain activity dissociate the two parts of the experiment: alpha oscillatory power increases over occipital regions in the delay period and negatively correlates with accuracy suggesting a drop of alertness towards task automation rather than an active inhibitory mechanism of irrelevant areas (i.e. visual areas in this case), the amplitude of evoked steady-state somatosensory responses in primary sensory cortex (SI) correlates and predicts performance only during the first part of the experiment. Moreover, the models analysis of effective connectivity modulation (using dynamic causal modeling) suggested an early involvement of the bilateral inferior frontal gyrus (IFG) in the performance optimization process and in the buildup of an internal reference stimulation frequency. Together, these findings shed light on both the psychological and physiological dynamic processes that take place in this kind of task, which have been suggested to reflect Bayesian optimal perception (Ashourian and Loewenstein, 2011) and hence a switch from discrimination to classification facilitated by the buildup of an internal reference (Nahum et al., 2010).

In the second study, I focused on perceptual learning from a theoretical perspective models in order to validate our principled approach for adaptive design optimization (ADO). The principle of ADO has been already demonstrated on behavioral data (Myung et al., 2013) as well as with single-neuron recordings (Lewi et al., 2009). However, our instantiation of ADO extended the previous approach by enabling the comparison of dynamical models of behavior and/or physiological responses. This was made possible thanks to the approximate optimization criterion previously proposed (Daunizeau et al., 2011b). I first validated this approach by replicating the findings of a previous behavioral application (Cavagnaro et al., 2009b), and then extended the demonstration using simulated data from recent generative models of perceptual learning in a an oddball paradigm. The proposed approach revealed two main advantages compared to classical experimental designs: the duration of the experiment could be shortened, while its conclusion would be more accurate (i.e. less prone to error). In other words, for a single subject, ADO enables to minimize the risk of concluding in favor of a wrong hypothesis, and requires fewer trials to conclude.

However, several bridges need to be crossed before this theoretical findings could apply empirically, namely to test generative models of perceptual learning processes. In particular, the framework proposed in the second study (Chapter V) has not yet been applied to paradigms and models inspired by the first study (Chapter IV). Moreover, ADO calls for online experiments for complete validation. Therefore future technical developments and basic research will be necessary to pursue this approach and ultimately test ADO online, with real data, based on hypotheses (generative models) inspired by our tactile MEG study.

6.2. IMPLICATIONS FOR PERCEPTUAL DECISION-MAKING

This section revisits the empirical results obtained in the first study in an attempt to elaborate refined hypotheses on the dynamics of perceptual decision-making. These hypotheses may pertain to the neurophysiological findings and/or to the behavioral contraction bias and its modelling with sequential Bayesian learning.

6.2.1. NEURAL CORRELATES OF CONTEXT-DEPENDENT PERCEPTUAL INFERENCE

As presented in the introduction, some theories and empirical results establish a strong link between the sensory context and perceptual decision biases (Ashourian and Loewenstein, 2011; Preuschhof et al., 2011). Data from study 1 suggest that the encoding and maintenance of frequency information from short tactile stimulations lead to the buildup of a contextual sensory reference. Using MEG recordings during a classical tactile frequency discrimination task where the first stimulation remains constant, we observed modulations of brain signals related to the encoding of the reference stimulation. Based on the optimization of behavioral performance over time, we distinguished two parts in the experiment that suggest an evolution in the dynamical learning process. The brain regions recruited during the encoding of the tactile stimulation involved the contralateral primary (SI) and bilateral secondary (SII) somatosensory cortices, as well as bilateral inferior frontal gyrus (IFG). These results are convergent with numerous studies (Harris et al., 2002; Romo and Salinas, 2003; Spitzer et al., 2010; Romo et al., 2012), suggesting that the IFG plays a general role in memory. Notably it is supposed to maintain relevant information and trigger active low-level encoding strategies in sensory areas. This is consistent with our findings on the modulations of effective connectivity in this network. Our data suggest that causal interactions between bilateral IFG and bilateral SII underlie the performance optimization process during the first part of the experiment. This observation is in agreement with the contemporary hypothesis in neuroscience suggesting that both perception and memory processes are supported by dynamic interactions between different areas (Friston et al., 2003; Garrido et al., 2008; Siegel et al., 2011; Albouy et al., 2013). Moreover, our results complement previous findings on somatosensory perception. Using TMS stimulation, Auksztulewicz et al., (2012)

proposed that tactile stimulus detection is characterized by feedforward connections and recurrent processing between somatosensory areas (SI and bilateral SII). Interestingly the same team also showed that the involvement of frontal regions such as IFG is necessary to preserve performance in a discrimination task compared to a simple detection task (Auksztulewicz et al., 2011). In accordance with this idea, the winning generative model that we proposed in study 1 requires the involvement of frontal regions coupled with feedforward connections of somatosensory areas during the encoding stimulation phase of the tactile frequency discrimination task (see Dynamical causal modeling).

We observed SI activity during the first part of our experiment, as reflected by of the amplitude of the steady-state evoked response. In this encoding phase and in this first phase only, this activity is predictive of performance. Interestingly, this finding together with our results on effective connectivity are in line with previous observations and interpretations. A previous study revealed that primary somatosensory regions may have a transient role in the maintenance of somatosensory information in tactile frequency discrimination tasks (Harris et al., 2002). These authors used TMS pulses over controlateral SI, not during the stimulus period but at different timings in the retention interval (i.e. inter-stimulus interval). They found that performance was significantly impaired when pulses were delivered early in the retention interval but not if delivered in the last part of the retention interval (i.e. just before the second stimulation) (see Figure 20).

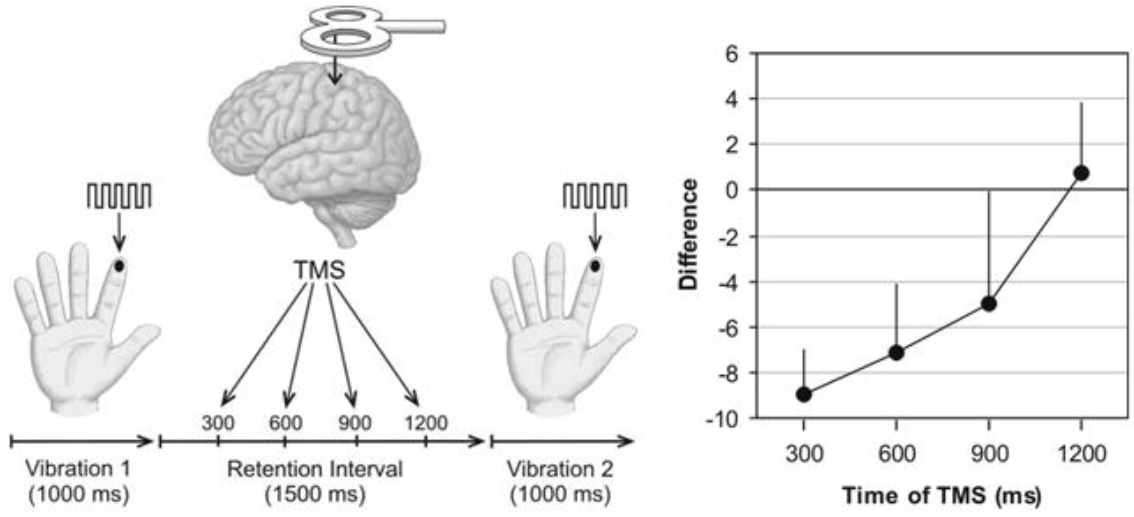

Figure 20: Experimental procedure and behavioral result for tactile discrimination task with TMS. Left: Experimental design. Participants received a single TMS pulse during the retention interval that separated the two tactile stimulations. TMS was delivered 300, 600, 900 or 1200 ms after the end of the first stimulation. TMS was applied to the left or right SI, thus on half the trials TMS was applied to the SI controlateral to the stimulation presented to the left index. Right: Effect of TMS on discrimination performance. The figure shows the mean difference in accuracy between trials in which TMS was applied to the controlateral SI and trials in which TMS was applied to the ipsilateral SI. The score is significantly below zero when TMS was delivered at the beginning of the retention interval. Error bars indicate SEM. (Adapted from Harris et al., 2002)

The authors concluded that controlateral SI may act as a potential transient storage site for information that contributes to working memory. They proposed that during the stimulus presentation the frequency is encoded by the primary and secondary somatosensory cortices. Then the memory trace could be supported initially by activity in both SI and SII and in frontal regions during the first part of the retention interval, but at the end of the retention interval the memory trace might no longer be held in SI. Such results and interpretation seem to be in disagreement with previous monkey studies that did not observe sustained activity among neurons in SI (see 2.1.2. Key processes & Neurophysiological markers), leading them to conclude that neurons in SI do not participate to the maintenance of tactile working memory traces (see for review: Romo and de Lafuente, 2013). However, this difference could arise from procedural differences. The monkeys studied by Romo and colleagues were trained for several months on the discrimination task, whereas the human subjects in our experiment (as in Harris and colleague's experiment) were given no previous training (or just few trials). In that respect, our results refine the neural correlates of such adaptive processes, highlighting the involvement of bilateral IFG in connection with the somatosensory network. The dynamic modulation of these connections appear to be involved in this performance optimization process, which has been suggested to rely on the buildup of an internal reference (30Hz in our case). If so, this reference should bias behavior as early as after three sessions of practice. This is what we tested in a purely behavioral task. Actually, our behavioral results showed that a learned general reference frequency (i.e. sensory context around 30Hz during the first part of the experiment) biases tactile decision making as shown by the subjects' performance in subsequent time-order sessions. Our findings reflect the context-dependent contraction bias previously observed in somatosensory discrimination (Preuschhof et al., 2011), like in the visual sensory modality (Ashourian and Loewenstein, 2011).

Performance optimization associated with the learning of the reference stimulation frequency may express as an implicit strategy shift from discrimination to categorization, as previously observed when one stimulation (i.e. the reference) remains stable (Nahum et al., 2010). This is supported by the correlation between the decrease in amplitude of the late evoked response to the reference stimulation and behavioral performance, which proved significant only in the first part of the experiment. Indeed, in the second part, subjects could use prior knowledge about the reference frequency they had learned, in order to categorize the second stimulation frequency. This might be reflected by the electrophysiological activity in the frontal region during the encoding phase of the first stimulation decreases. Such interpretation are in line with the idea that general representations related to implicit perceptual learning could influence decision-making leading to such categorization strategy (Seger and Peterson, 2013).

6.2.2. *BAYESIAN PERCEPTUAL INFERENCE AND LEARNING*

In Chapter II, we mentioned that the brain can be understood as an inference machine that predicts and explains its sensations (Brown et al., 2013; Friston et al., 2013a). Today, the Bayesian framework offers quantitative tools to formalize how our brain can generate percepts and update contextual prior beliefs using probabilistic models. Perception then becomes the process of accessing the posterior probability of hidden environmental causes given sensory data. In our case, perception would thus results from the combination of a noisy sensory encoding distribution (the likelihood) and a learned prior distribution about stimulation frequency (the prior), as prescribed by Bayes' rule (see Figure 21 & B. Sequential Bayesian model of two alternative forced choice).

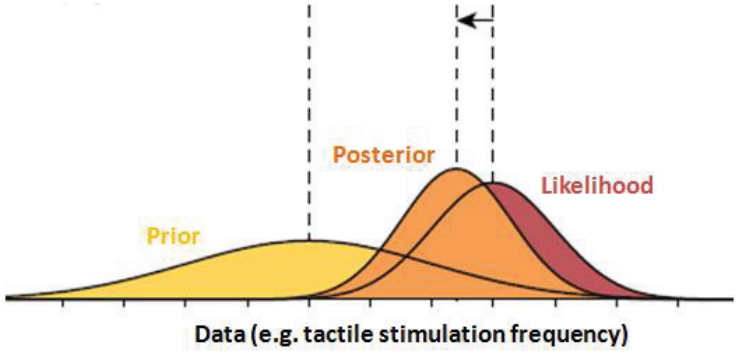

Figure 21: Bayesian perception. A noisy sensory observation (red Gaussian) is combined with the prior (yellow Gaussian) to produce a posterior distribution (orange Gaussian). The optimal estimate represented by the mean of the posterior distribution, is shifted towards the prior as indicated by the arrow. Thus the final perception could be different from the veridical initial data value.(Inspired from Brock, 2012)

Based on the Bayesian brain hypothesis and our neurophysiological findings, I intend to situate within a neurophysiological context the perceptual learning process during the tactile decision-making task (see Figure 22). First, since sensory integration is related to the interaction between primary and secondary somatosensory areas (Yamashiro et al., 2009; Wühle et al., 2010; Auksztulewicz et al., 2012; Romo et al., 2012), this part of the hierarchical network may be encoding the likelihood probability of the incoming noisy sensory information. Prior information about sensory context can be maintained in frontal regions (Spitzer et al., 2010; Auksztulewicz et al., 2011; Haegens et al., 2011b; Romo and de Lafuente, 2013) which may then provide a top-down predictions to somatosensory areas (Haegens et al., 2011a). Furthermore, the position of secondary somatosensory areas between top-down and bottom-up influences may facilitate the Bayesian computation in this region (Romo et al., 2002; Romo and de Lafuente, 2013). Finally, the maintenance of prior information in frontal areas might come from bottom-up message passing from lower areas that convey prediction errors or, in other words, up-dates of the priors into posteriors according to Bayes' rule. This process would subsume the dynamics of perceptual learning over trials, which influences or biases perceptual inference, within each trial. Obviously, further investigations are needed to refine

those hypothesis and the underlying neurophysiological mechanisms. Nevertheless, previous studies have shown that oscillations in the beta frequency located in IFG have an amplitude parametric relationship with the first stimulation frequency during the delay period (Spitzer et al., 2010; Spitzer and Blankenburg, 2011). Using a contraction bias experimental set-up that provides a modification of the sensory context (e.g. by modifying the range of stimulation frequencies between blocks), one could test whether beta activity located in the IFG regions correlates with the posterior bayesian estimation of the stimulation frequency rather than with the true stimulation frequency.

Finally, Behavioral Bayesian models and electrophysiological generative models provide distinct but complementary views allowing investigation of implicit perceptual learning processes. Incorporating these tools into interactive models addressing both the behavioral and neural mechanisms of perception is an exciting challenge for the future.

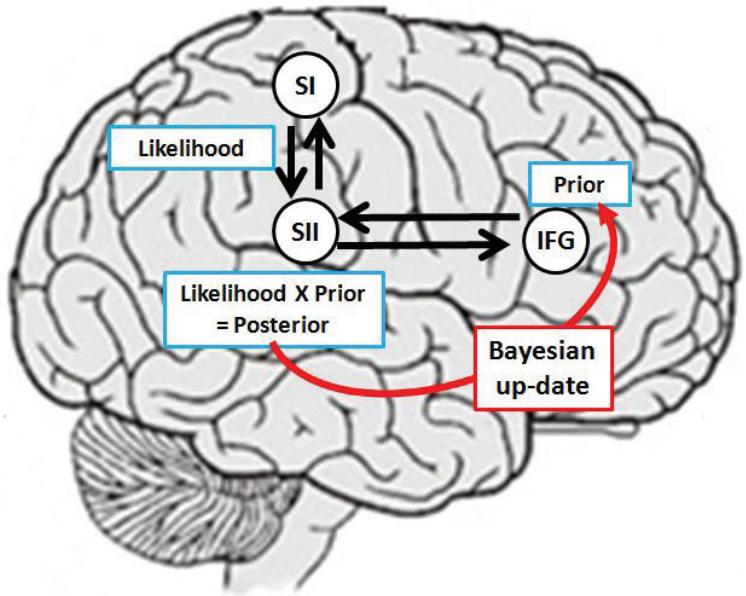

Figure 22: Schematic speculative representation of Bayesian inference hypothesis about somatosensory perceptual learning. This representation is restricted to the right brain hemisphere (controlateral to tactile stimulation of the left hand). White circles represent the network sources involved in somatosensory perceptual learning: controlateral primary (SI), bilateral secondary (SII) somatosensory areas and bilateral inferior frontal gyrus (IFG). Black arrows represent the effective connectivity in this identified network based on dynamical causal modeling analysis from the first study of this thesis. SI and SII sensory area could extract and encode frequency stimulation information as a likelihood probability density that is associated to prior information stocked in frontal regions by top-down influence. The neural representation of the stimulation frequency (i.e. the percept) results from the Bayesian computation of posterior probability density that will be maintained in working memory and will update prior information.

6.3. IMPLICATIONS FOR BCI

An optimized experiment is one in which data collection is efficient and the results are maximally informative. In other words, it is one in which plausible competing theories or models make contradictory predictions. Today, due to the complexity of psychophysiological models as a result of them becoming more biologically realistic, this goal can be difficult to achieve because of uncertainties about the consequences of design decisions on models predictions. In study 2, I demonstrated the success of a Bayesian framework dedicated to adaptive design optimization (ADO) when comparing models of perceptual learning with simulated electrophysiological data. Compared with two different classical (non-adaptive) methods, ADO distinguished the models efficiently with fewer trials.

In order to present and discuss the second study implications towards a novel BCI application, I will present the following short paper at the 6th International Brain-Computer Interface Conference 2014 in Graz (Austria).

6.3.1. A PRINCIPLED APPROACH FOR CROSS-FERTILIZATION BETWEEN BCI, BASIC AND CLINICAL NEUROSCIENCES

Authors: Gaëtan Sanchez & Jérémie Mattout

Abstract

Real-time electrophysiology and neuroimaging have developed tremendously with the advent of Brain-Computer Interfaces (BCI). Most BCI applications are still driven by clinical or other, much applied, objectives (e.g. video games). However, a few original studies have highlighted the potential interest of processing brain activity in real-time, for the purpose of targeting specific fundamental questions in cognitive neuroscience. A brief review of the main motivations behind these studies reveals strikingly that they share a common basic principle: online data processing could be used to optimize hypothesis testing. This simple principle points towards the importance of conceiving and implementing adaptive paradigms, where experimental design parameters are optimized online. Recent advances in Bayesian inference and decision theory provide an efficient way of implementing this approach and enabling formal comparison of alternative models of brain function. Early numerical evaluations suggest that, in the long term, this could be used to refine, optimize, and shorten emerging neuroimaging-based diagnostic procedures. Finally, since it would benefit our understanding of brain signals, it should also benefit classical BCI applications.

Context and Motivations

BCI research is mostly driven by clinical applications, which rely on decoding the user's mental state from brain activity. In that respect, BCI rests on basic research that tries to establish a link between cognitive functions and specific neurophysiological markers. In the recent years, there has been a rapid development of brain imaging and electrophysiological protocols to address neurocognitive questions. However, one can reasonably argue that a major limitation to efficient BCI is the lack of reliable mappings from neurophysiological markers to targeted mental states. Although often considered aside from basic and clinical neurosciences, BCI do share the need for a better understanding of brain signals. Interestingly, real-time protocols might contribute to this endeavor.

An empirical approach: Brain-State Dependent Stimulation (BSDS)

There have been early attempts to exploit real-time technologies in original cognitive neuroscience paradigms. For example, Gho and Varela presented visual stimulations depending on the phase of ongoing alpha activity [1]. The authors reported a causal relationship between the phase of alpha oscillations at the time of stimulus presentation and the ensuing conscious percept. However, other authors could not reproduce those findings, thus highlighting the technical and maybe methodological limitations of this early approach [2].More recently, another team wanted to demonstrate the causal role of alpha power modulations in gating phosphene induction by Transcranial Magnetic Stimulation (TMS) [3]. Although the authors could validate their real-time protocol, they only partially reproduced previous correlation findings from classical protocols [4]. Among possible explanations for this failure, the authors raised the hypothesis of a complex (non-linear) dependency between alpha power and perception. Those examples have in common the use of real-time EEG in order to test some hypothesis about the causal influence on behavior of a specific electrophysiological marker. This approach has been coined Brain-State Dependent Stimulation [5]. While the above partly inconclusive results might be attributable to technical weaknesses, the strong intuition behind BSDS remains promising. To make this empirical approach efficient, we suggest it should be both: (i) acknowledged for what it really and exactly adds to classical experiment; (ii) formalized in a generic and optimal fashion. A fairly straightforward answer to the first issue is optimization of neurocognitive hypothesis testing. Then to fulfill this objective explicitly and address the second issue, we propose to appeal to a modern extension of sequential hypothesis testing: Adaptive Design Optimization (ADO) [6].

A theoritical framework: Adaptive Design Optimization (ADO)

ADO implies to depart from classical studies where experimental designs are set in advance, prior to the beginning of data acquisition. In contrast, it aims at exploiting our ever improving ability to process complex, multidimensional and noisy data in real-time, as an opportunity to up-dating our beliefs about model parameters and model evidences online. This is all the more meaningful now that psychological theories have become more biologically plausible, leading to more realistic generative

models of psychophysiological observations [7]. In particular, some of these models formulate a quantitative account of implicit learning processes, resulting from the dynamical nature of the interaction between a human subject and its (controlled) environment. Besides being very much relevant to BCI, such models render prior design of optimal hypothesis testing paradigms particularly difficult if not impossible [8]. ADO offers a generic solution to this optimization problem, be it applied to models of behavioral responses, neurophysiological responses or both. In nature, ADO is a tailored approach which yields a different experiment (sequence of stimuli) for each and every subject. Its optimality is such that it should yield faster, more conclusive and less error prone experiments than the ones based on classical (static) designs. The general principle of ADO is summarized in Figure 1 (right panel). Importantly, this approach is also particularly relevant to clinical practice, since diagnostic procedures amount to discriminating between alternative hypotheses (pathological mechanisms) in a single patient (observing his symptoms and biological markers). Using numerical simulations, we have shown how ADO could further improve this kind of investigation using advanced quantitative and dynamical causal models of perceptual learning and how they affect single-trial evoked responses [9]. This early validation and its main results are summarized below.

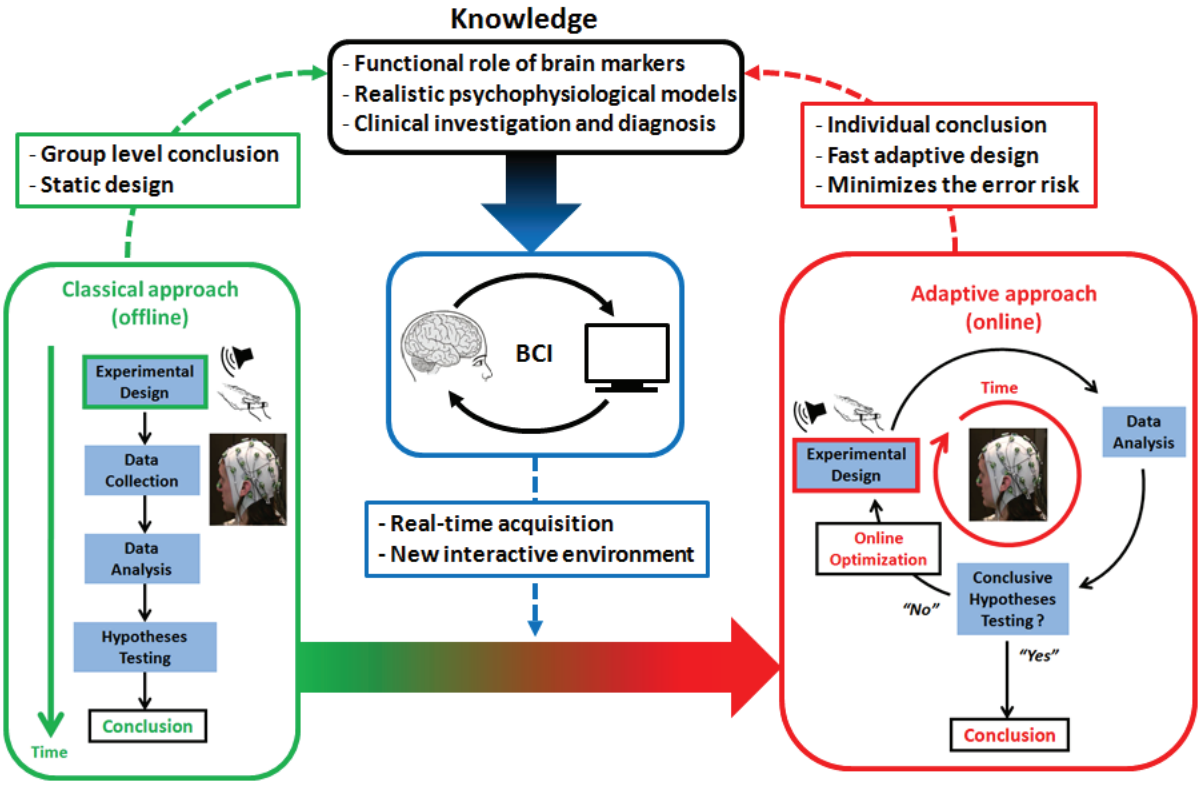

Figure 1: General principles of adaptive (right panel) versus classical (left panel) designs and illustration of the expected mutual benefits between the former and Brain-Computer Interfaces.

Methods and early results

To apply ADO to dynamical neurocognitive models of electrophysiology data, we rely on a recent approach by Daunizeau et al. [8], which brought together a meta-Bayesian framework to infer the subject's or patient's internal model of the environment [10] and a Bayesian decision theoretic criterion to optimize design efficiency and better disentangle between such alternative models. In practice, ADO then consists in two sequential steps applying at each trial or stage:

(i) Updating our belief over each model parameters and model evidence, using variational Bayes inference given recent past observations and experimental design variables;

(ii) Selecting the (predicted) most efficient experimental design parameters for the next trial.

Finally, the online experiment will be interrupted as soon as some stopping criterion will have been met. Typically, the experiment will be conclusive if one model can be identified as the best model (e.g. if its posterior probability is greater than 0.95). If this is not the case, when an *a priori* fixed number of trials would have been reached, the experiment will be considered as inconclusive. To face validate and illustrate ADO, we used recent generative models of human perceptual learning in a changing environment [11] and combined them with recent works on how these models might predict single-trial EEG evoked responses [12]. We considered the problem of comparing different perceptual models (i.e. learning profiles) given simulated EEG data. Therefore, we simulated an auditory oddball paradigm, where one category of rare stimuli (deviants) is intermixed with a second category of frequent stimuli (standards). The design variable to be chosen in each trial is simply the stimulation type (deviant or standard). The ensuing "mismatch negativity" (MMN) evoked potential is then interpreted a brain response to the violation of prior expectations [13]. ADO was compared with two classical designs: "volatile" and "stable", in order to disentangle between five perceptual models: a non-perceiving (null) model, two models enabled to learn the deviant's probability with different speed and the two same models endowed with the additional ability to track changes over time of this probability (volatility) with different speed (see [9]). As summarized on Figure 2, we observe that ADO yields more conclusive and faster experiments than the two other designs.

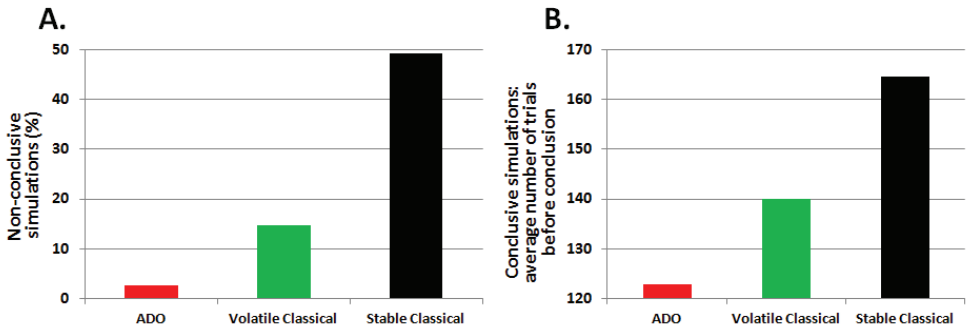

Figure 2: Summary of simulation results. (A) Number of non-conclusive experiments for each design; (B) Average number of trials needed to reach the 95% threshold in conclusive simulations.

Conclusion

In this paper, we discussed the added-value of BCI to cognitive and clinical neuroscience (see Figure 1). We identified that in the general aim of testing hypothesis on the relationship between neurophysiological activities and mental states or behavioral outputs, real-time data processing could be useful to optimize the experimental design in an adaptive fashion. This is the principle of ADO which we extended recently to cover realistic models of brain functions. As optimization applies at the individual level, ADO could be used to improve EEG-based clinical diagnosis. Using numerical simulations, we demonstrate the expected advantages of ADO. However, to obtain similar results in a real setting, substantial efforts should be put on methods for online artefact detection and correction.

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6.3.2. ADO: A GENERIC APPROACH

In this thesis, I have proposed a general method for optimizing the experimental design to maximize the sensitivity of Bayesian model selection. This method is very general and is applicable to any generative model of observed data (e.g., brain activity, behavioral responses or both). This principled approach relies on the definition of a statistical risk, in terms of an approximate information theoretic bound on the model selection error rate (i.e. the use of the Jensen-Shannon divergence for design optimality) (Daunizeau et al., 2011b). It generalizes to non-linear dynamical models the previously proposed criterion based on the maximization of mutual information (see the study 2 Appendix A3. Comparison of the Chernoff bound with the Other Criterion). Such powerful statistical adaptive tools benefit from the online acquisition of data. In our case, we focused on models underlying electrophysiological data and we formalized the way of using real-time electrophysiology to adapt experimental stimulations. This proof-of-concept highlights the potential of BCI in optimizing cognitive neuroscience experiments.

First, I mentioned that brain-state dependent stimulation (BSDS) methods provide online stimulation choices based on ongoing activity. However, such methods seem to suffer from the absence of a fine prior hypothesis. In that respect, BSDS have been more used in an exploratory manner so far, rather than constructed as a full hypothesis driven approache. ADO is explicitely designed in order to optimize the comparison of multiple models or model families.

Second, for simple models, such as the memory retention models (Cavagnaro et al., 2009b), the model selection error rate can easily be computed with high precision using Monte-Carlo simulations. Previous results based on behavioral data suggest that ADO's success is partly due to its flexibility in adjusting to individual differences (Cavagnaro et al., 2010). However, the behavioral model used in this study did not take into account any dynamical process. When comparing dynamical models, such as the learning models considered in the second study of this thesis, the appeal to the approximate design efficiency provided by the Jensen–Shannon divergence is required. Importantly for such models, under the Laplace approximation, this criterion takes a simple analytic form, which can be computed efficiently online (Daunizeau et al., 2011b). While previous online implementation and validation of ADO are restricted to non-dynamical generative models, our procedure extends online adaptive design optimization to dynamical non-linear models. Dynamical generative models describe how dynamical brain processes evolve over time depending on the influence of external inputs (i.e. stimulation). With the final aim of using real-time acquisition during electrophysiological experiments, such improvements of ADO were necessary. The ADO procedure proposed in this thesis completes and formalizes the current attempt to use real-time recordings to extend the power of experimental protocols.

Generally speaking, using real-time electrophysiology as a mean to efficiently sample data space implies some rethinking of the way we conduct model-based experiments. Design optimization and data modeling are complementary techniques that are embodied in ADO to provide a clear answer to the question of interest. The adaptive nature of this methodology controls for individual differences and makes it well suited for studying the most common and often largest source of variance. This procedure leads to individual conclusions because the algorithm optimizes the design and thus the data gathering for each participant. This capability also makes ADO ideal for studies in which few participants can be tested (e.g., rare memory or language disorders). Thus, the efficiency of ADO has begun to attract attention in various disciplines. It has been used for designing experiments in neurobiology (Lewi et al., 2009), adaptive estimation of contrast sensitivity functions of human vision (Kujala and Lukka, 2006), conducting sequential clinical trials (Wathen and Thall, 2008), and adaptive selection of stimulus features in human information acquisition experiments (Nelson et al., 2010). I hope that the present work will lead to an extension of the use of this approach towards model-based cognitive neuroscience experiments.

6.3.3. COMMON PERSPECTIVES TO THE TWO STUDIES IN THIS THESIS

Works presented in this thesis form two main parts that are fairly independent and may even appear unrelated. The empirical study allowed us to investigate relevant hypotheses about the link between stimulation context, and behavioral and electrophysiological observations. Using source reconstruction and dynamical causal modeling techniques I found that the early involvement of frontal regions and the somatosensory network reflects the performance optimization processes related to the buildup of an internal reference. The methodological part provided first a validation of the use of real-time electrophysiology to optimize hypothesis testing in an adaptive fashion. Using simulated data of a simple oddball paradigm, I found a clear advantage of adaptive design optimization to disentangle generative models of perceptual learning at the individual level. Thus, the first validation of our principled approach toward the use of real-time electrophysiology to optimize hypothesis testing was done with a different simulated paradigm because previous recent studies have validated the generative models that we used to infer brain mechanisms in our simulation (Mathys et al., 2011; Ostwald et al., 2012; Vossel et al., 2013).

However based on the findings from the first study we can imagine applications of ADO to investigate implicit perceptual learning in the context of tactile frequency discrimination task.

Predictive models of behavioral data tested with ADO

Regarding the behavioral effect, our study shows a contraction bias that is consistent with a Bayesian inference process of the context of the task created by the history of all frequencies of tactile stimulation presented to the subject. This Bayesian model describes the implicit perceptual learning

process with a leaning parameter (τ) defining a forgetting kinetic (see B. Sequential Bayesian model of two alternative forced choice) inspired from Ostwald et al. (2012). One could formalize different predictive models based on variations of this learning parameter, leading to different expressions of the contraction bias dynamics. Interestingly, in some preliminary investigations, we were able to generate a contraction bias using only two different frequencies in the first stimulation (see Figure 23). Thus, an experimental context can be set using only a couple of first stimulation frequencies alternating across trials. It follows that of the sensory context based on different F1 frequency couples would be the stimulation parameter that ADO could optimize in a behavioral experiment in order to disentangle alternative hypothesis about the perceptual learning dynamics of one single subject (i.e. through its contraction bias). Intuitively, the duration of a specific sensory context should be crucial to optimize in order to test the different predictions on the contraction bias made by the alternative models that differ from each other because of their contextual learning rate. In comparison to classical design where number of trials for a given context (i.e. F1 frequency couples) is set in advance, ADO procedure would optimize it.

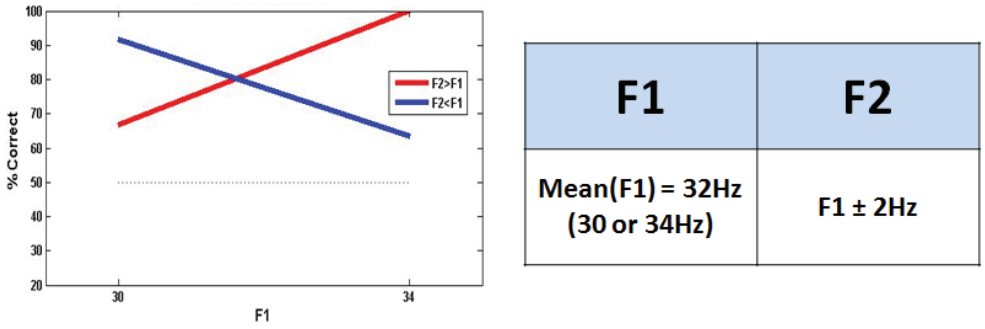
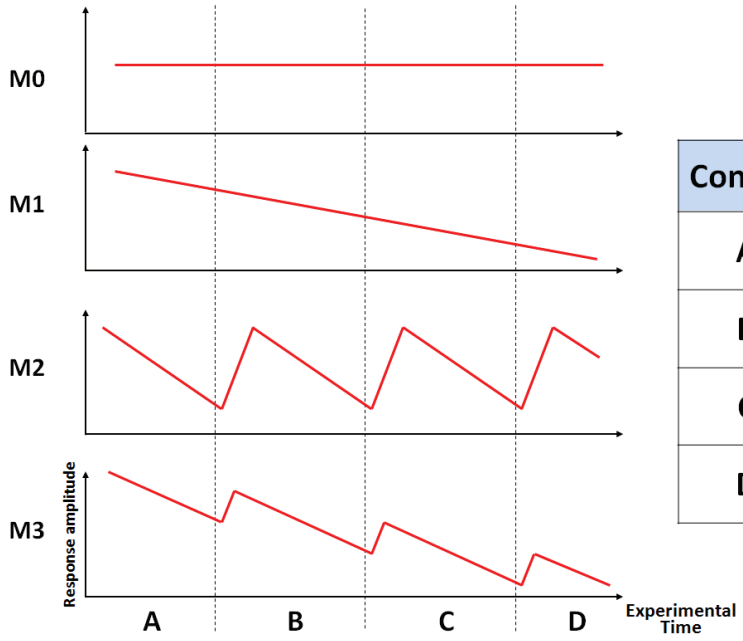


Figure 23: Behavioral performance reflecting the time-order effect (contraction bias) during a simplified version of the frequency tactile discrimination task. Similarly to previous task the participant has to decide which stimulation has higher frequency. **Left:** results from one subject average performance of discrimination over 100 trials (% of correct responses) depending on the first stimulation frequency (F1). **Right:** The sensory context of this simple task was around 32Hz, provided 2 different frequencies of F1 (randomly and equally distributed) and a constant task difficulty with the second stimulation (F2) always higher or lower than 2Hz compared to F1.

Predictive models of neurophysiological data tested with ADO

Today it is difficult to implement online generative models such as dynamical causal modeling (DCM) in real-time at the single trial level due to computational limitations. However, we found that the first stimulation's late transient response (around 200ms) located in frontal regions is related to discrimination performance during the first part of the experiment and decreases over time in the same way that behavioral performance increases (see Transient responses amplitude :). It should be possible to extract this specific marker's amplitude at the single trial level, much like for other evoked responses such as the MMN or P300. As a simple example, let us discuss further a potential application of ADO to comparing alternative generative models of the link between the amplitude of this neurophysiological response and the evolution of a hidden variable representing the state of

implicit learning and their causal relationship to behavioral performance. The experiment could be similar to behavioral study 1: the first frequency (F1) takes different values that define on average a sensory context while the task difficulty remains stable with the second frequency (F2) being always 2Hz higher or lower than F1 (see table in Figure 24). To infer whether this specific response amplitude is related to sensory contextual learning or simply to a global learning process unrelated to the sensory context, we can propose different predictive hypotheses (see Figure 24).



Context	F1	F2
A	Mean(F1) = 26Hz (24 or 28Hz)	F1 ± 2Hz
B	Mean(F1) = 30Hz (28 or 32Hz)	F1 ± 2Hz
C	Mean(F1) = 34Hz (32 or 36Hz)	F1 ± 2Hz
D	Mean(F1) = 38Hz (36 or 40Hz)	F1 ± 2Hz

Figure 24: Schematic representation of four speculative alternative models describing the relationship between the electrophysiological marker (i.e. the late transient evoked response to the first stimulation) and the task set across experimental time. The table represents different perceptual context centered on different frequencies. Red line profiles represent the schematic evolution of the evoked response amplitude depending on the sensory context. We could consider four alternative models for this profile:
-M0: No correlation with the task set (Null hypothesis)
-M1: Correlation with a global learning process uncorrelated to context change (Task learning hypothesis)
-M2: Correlation with context modification (Perceptual learning hypothesis)
-M3: Interaction between the task learning and a contextual learning (Task and perceptual learning hypothesis)

In this situation the relevant stimulation parameter is the context. Thus, given the alternative hypothesis, the ADO procedure computes posterior model evidence after each trial (or group of trials) and might decide when to change the sensory context (i.e. the average of the presented tactile frequencies). Obviously, we could complicate the alternative models, and thus the ADO procedure, by building in some assumptions about the effect produced by the intensity of sensory contextual change on response amplitude (e.g. modifying the sensory context from a 30Hz to a 34Hz frequency average might have a different effect than modifying the context from a 30Hz to a 38Hz frequency average).

Here, I just wanted to give some taste to the interested reader of a potential application of the ADO procedure described in the second study within the experimental context of the first study. Our team in Lyon is currently investigating the neural correlates of such sensory contextual modification using a classical MEG recording experiment (non-adaptive protocol) based on the findings of the first study from this thesis.

6.4. GENERAL LIMITS

The principle of adaptive design optimization (ADO) proposed in this thesis is still in its infancy and obviously needs further investigation. I discuss here some limitations that future studies should explore.

- Formalize hypotheses: ADO presents the same disadvantages as any classical offline study regarding the hypothesis testing. That is, it is crucial to define the hypotheses before thinking about a smart experimental design. It could be difficult to formulate under mathematical terms the alternative hypotheses about brain mechanisms and the generation of electrophysiological responses. Additionally, one might wonder how sensitive is the optimal design to variations of the neuronal and biophysical state equations used in the generative models. In most cases, preliminary studies based on classical offline experiments will be necessary to identify and detail the mechanistically interpretable models underlying the studied brain process. Otherwise, a one-step solution might be to include multiple variants of generative models in the comparison set, and then use family level inference (Penny et al., 2010).

- Definition of priors: the optimal design could depend on the choice of priors for model's parameters (Daunizeau et al., 2011b). In Bayesian parameter estimation, the choice of the prior has little impact on inference when the data available are sufficiently informative. In contrast, Bayesian model selection is sensitive to the exact choice of prior. Priors are often deemed to bring an unwanted level of arbitrariness to the conclusions. In practice, it has often lead researchers to uniform, flat, or weakly informative priors, in an attempt to limit the information injected into the model selection (Vanpaemel and Lee, 2012). Strictly speaking, we cannot use completely noninformative priors when optimizing the design for model comparison. This is because, in most cases, this would induce flat prior predictive densities for all models, which would prevent any design optimization procedure. This means that we have to choose mildly informative priors for the model's parameters. However, the precise way in which the priors affect the efficiency of the design depends on the comparison set. A generative model is defined by all the probabilistic assumptions that describe how the data are generated, including the prior.

- Simulation results *versus* Real data: to validate the ADO procedure, I used a noisy data generation process based truly on one of the included models for comparison. Obviously, such an assumption is likely to be violated in practice, given that the "true" model does not exist and alternative model comparisons are imperfect representations of the real process under study. Thus, to fully appreciate the results from the second study of this thesis future investigations are needed. Moreover, the ADO procedure using real-time electrophysiology will have to rise to the challenge of online signal acquisition. By definition, real-time (online) acquisition does not allow the experimenter to perform offline analysis of data in order to improve the signal-to-noise ratio and separate relevant

brain activity from muscular or oculomotor artifacts. Thus, adaptive experiments based on electrophysiology must be able to deal with on-line artifact correction techniques. Thankfully, the machine learning community and BCI fields have developed several tools to tackle this issue because artifact management is a critical problem in any application involving online processing of electrophysiological signals. For instance, a recent study showed an automatic and adaptive artifact detection method for online experiments (Barachant et al., 2013). These authors used a multivariate statistical framework that takes into account the spatial properties of the artifact detected by comparison with a reference baseline activity. This algorithm is thus sensitive to many kinds of artifacts. Using such methods in the context of ADO experiments might provide the ability to reject trials containing artifacts. However, this rejection will result in the inability to inform the adaptive process with the data from that specific trial. Thus it will be necessary to repeat the same stimulation on the next trial, while accounting for what this stimulation might have modified in the subject's mind. In order to minimize information loss, another solution would be to apply on-line artifact correction. For instance, regression analysis can be used to provide an automated online correction of oculomotor artifacts (i.e. blinks or eyes movement) (Schlögl et al., 2007). To sum-up, the principled approach proposed in this thesis to optimize hypothesis testing using real-time electrophysiology could become a new BCI application dedicated to basic science which would benefit from advances related to online signal processing.

6.5. General Perspectives

The aim of this thesis was to use BCI technology to provide a principled approach to improve hypothesis testing in general. Although BCI applications are often evaluated with respect to their clinical utility, I would like to emphasize that ADO (when combined with real-time electrophysiology) has a wide range of practical applications in basic neuroscience research. This work is in line with a growing literature in cognitive neuroscience aiming at developing practical methods for adaptive online stimulus generation (DiMattina and Zhang, 2013; Myung et al., 2013). The adaptive design optimization procedure applied to electrophysiological model-based hypothesis testing is an exciting and promising new tool. By combining dynamical causal modeling and the power of the Bayesian inference, it provides efficient and optimal experiments given a multiple models hypothesis testing problem. Such a procedure reveals several advantages making this new tool attractive to the research situation. The optimization process focuses on a stimulation space (i.e. design) that is maximally informative, based on error selection rate minimization criteria It thus leads to the choice of an hypothesis in fewer trials than classical methods. Such a gain in time could be invaluable when the experimental period is limited as in single neuron recordings (Lewi et al., 2009). Moreover, fast experiments can reduce the cost of equipment and are well suited for participants in non-natural or constrained postures as in some MEG or fMRI recordings. By combining real-time data analysis and model-based hypothesis testing optimization, this approach ensures maximally conclusive results at the single subject level. Moreover, the procedure allows complex non-linear hypothesis testing where specific model parameters can be estimated online taking into account inter-individual variability. This combination of efficiency and flexibility could results in faster scientific discovery in cognitive science and beyond. I hope that such a generic tool using real-time electrophysiology will benefit to basic research and will greatly enhance knowledge about brain mechanisms. In return, the BCI field is likely to benefit from the identification of new markers based on tested generative models of brain processes.

Finally, the adaptive design optimization procedure presented in this thesis reveals several advantages for many clinical issues: it leads to individual conclusions and can infer the subject's mental state from electrophysiological markers only (no behavioral response is needed). Essentially, a promising application of ADO is differential diagnosis, whereby one seeks to discriminate between alternative pathological mechanisms. One such example is the inference of patients' mental states from electrophysiological makers in coma and related disorders (Fischer et al., 2010; Morlet and Fischer, 2013). Today, electrophysiological markers that differentiate the state of consciousness of non-communicating patients are now better understood and investigated using computational and neuronal models (Boly et al., 2011; King et al., 2013; Dehaene et al., 2014). In the near future, one could be able to define and formalize generative models as alternative hypotheses about the state of

consciousness of non-communicating patients and let ADO find the optimal and individually adapted experimental design.

Beyond such diagnostic objectives, ADO could prove useful in model-based predictions of individual treatment responses or in choosing the most appropriate timing for treatment administration. Currently, the most common use of any mathematical or statistical model in therapy evaluation or pathophysiology consists in organizing and characterizing the system's behavior (i.e. pharmacology, physiology, bioengineering) into a rigorously testable framework (Vicini et al., 2002). In other words, clinical studies involve the precise evaluation of some physiological dynamics in relation to some varying internal state (e.g. the kinetics of drugs in the organism). In such situations, one must establish a quantitative framework for the studied system in order to evaluate alternative models and estimate unknown parameters (e.g. the drug's absorption rate by targeted organs). For instance, such modeling approaches can be used to understand the multiple factors of disease progression and response to therapeutic interventions, the most likely causes of variability in population and individual responses to therapy. However clinical trials involving such predictive models must be evaluated with appropriate designs that could be difficult to infer before data acquisition. This is why such studies may benefit from the use of Bayesian adaptive methods for optimizing sequential clinical trials (Wathen and Thall, 2008). The generic approach proposed in this thesis fall into such a framework and could also be used to improve design and efficiency of model-based clinical trials.

CONCLUSION

As observers and actors of our life, we can transform our environment while being continuously influenced by it. This complex and adaptive interaction finds a particular resonance in brain function studies. Today neuroscientists have new tools to uncover and infer the dynamics of brain processes. Throughout the thesis, I wanted to show how some hypotheses about perceptual learning processes based on generative models can be optimally tested using an adaptive real-time brain-computer interface (BCI) paradigm. In this thesis, we provided new insights on perceptual learning and decision-making processes in humans. In the empirical part, our findings improve our understanding of implicit contextual dependent learning in a typical tactile frequency discrimination task. In the methodological part, we validated a principled approach to optimize generative model testing by adapting the experimental design online. Further investigations are clearly necessary to overcome the technical challenge of such new BCI applications for basic research. However, I hope that the contribution of the present thesis toward the extension of adaptive design optimization (ADO) to cover realistic models of brain functions will prove useful to real-time electrophysiology and basic research in the short term. If so, I envisage that the present work could pave the way for future BCI applications in both basic and clinical research.

CONCLUSION

En tant qu'observateurs et acteurs de notre vie, nous modifions notre environnement tout en étant constamment influencés par lui. Cette interaction complexe trouve une résonance particulière lorsque l'on étudie les fonctions cérébrales. Aujourd'hui les neuroscientifiques possèdent de nouveaux outils pour élucider la dynamique des processus cérébraux. Au cours de ce travail de thèse, j'ai pu montré comment l'étude des processus d'apprentissage perceptif sur la base de modèles génératifs pourrait être optimale en utilisant le paradigme temps-réel des interfaces cerveau-machine (ICM). Ainsi j'ai pu approfondir la compréhension et l'étude de l'apprentissage perceptif et de la prise de décision chez l'homme. La partie expérimentale de ce travail m'a permis d'améliorer la compréhension de l'apprentissage implicite dépendant du contexte dans une tâche typique de discrimination de fréquence tactile. La partie méthodologique, quant à elle, m'a permis de valider une approche basée sur l'optimisation du dessin expérimental au cours de l'acquisition des données pour tester efficacement et comparer des hypothèses portant sur des modèles génératifs. Evidemment d'autres études seront nécessaire pour franchir le défi technique de l'application de cette nouvelle ICM à la recherche fondamentale. Cependant, j'espère que la contribution de cette thèse, grâce à l'extension de l'optimisation adaptative du dessin expérimental (ADO) pour tester des modèles réalistes de fonctions cérébrales s'appuyant sur un apprentissage perceptif, sera utile à l'emploi de l'électrophysiologie temps-réel en recherche fondamentale dans un futur proche. A plus long terme et grâce à la compréhension croissante de la dynamique des activités cérébrales, j'envisage que ce travail pourrait ouvrir la voie à des applications futures des ICM pour la recherche fondamentale mais aussi clinique.

PUBLICATIONS OF THE AUTHOR

ARTICLES INCLUDED IN THE THESIS

Two chapters and part of the discussion in this thesis have been accepted in or submitted to international peer reviewed journals. They were slightly adapted here in order to increase consistency and facilitate readability.

Chapter IV. **Sanchez G.**, Partouche J., Daligault S., Maby E., Bouet R., Bertrand O., and Mattout J. (2014) Build-up of an internal reference during tactile frequency discrimination: a behavioral and MEG study. *(in preparation)*

Chapter V. **Sanchez G.**, Daunizeau J., Maby E., Bertrand O., Bompas A., Mattout J. (2014) Toward a New Application of Real-Time Electrophysiology: Online Optimization of Cognitive Neurosciences Hypothesis Testing. Brain Sciences, vol. 4, pp. 49-72.

Discussion **Sanchez G.** & Mattout J. (2014) A principled approach for cross-fertilization between BCI, basic and clinical neurosciences. *(submitted)*

OTHER PUBLICATIONS

Albouy P., Mattout J., Bouet R., Maby E., **Sanchez G.**, Aguera P-E., Daligault S., Delpuech C., Bertrand O., Caclin A., Tillmann B. (2013) Impaired pitch perception and memory in congenital amusia: the deficit starts in the auditory cortex. Brain vol. 136 pp.1639–1661.

Maby E., Perrin M., Bertrand O., **Sanchez G.,** and Mattout J. (2012) BCI Could Make Old Two-player Games Even More Fun: A Proof of Concept with 'Connect Four'. Advances in Human-Computer Interaction. vol. 2012 pp.1

CONFERENCE COMMUNICATIONS

Poster: Sanchez G, Daligault S, Maby E, Bouet R, Bertrand O, Mattout J, Neural correlates of tactile frequency discrimination: a MEG study, 17th international conference organization for human brain mapping **HBM 2011**

Poster: Sanchez G, Daligault S, Maby E, Bouet R, Bertrand O, Mattout J, Buildup of a perceptual internal reference during tactile frequency discrimination: a MEG study, 18th international conference on biomagnetism - **BIOMAG 2012**

Poster: Sanchez G, Partouche J, Daligault S, Maby E, Bouet R, Bertrand O, Mattout J, Slow and fast adaptive processes in tactile perceptual decision making: behavioral and MEG evidence, 19th international conference organization for human brain mapping **HBM 2013**.

Poster: Sanchez G, Partouche J, Daligault S, Maby E, Bouet R, Bertrand O, Mattout J, Slow and fast adaptive processes in tactile perceptual decision making: behavioral and MEG evidence, **Donders Discussions 2013** (at Nijmegen) - **Best Poster Award**

Poster: Sanchez G, Daunizeau J, Maby E, Bertrand O, Bompas A, Mattout J, Online optimization of neurocognitive hypothesis testing thanks to real-time electrophysiology, 20th international conference organization for human brain mapping - **HBM 2014**

Oral presentation: Slow and fast adaptive processes in tactile perceptual decision making: behavioral and MEG evidence. Société de Psychophysiologie et de Neurosciences Cognitives 2012

Oral presentation: MEG/EEG Source reconstruction. Lyon SPM EEG/MEG Course 2012

Oral presentation: Studying and modeling human perceptual learning: some methodological and empirical work. Invited talk in Trento (Italy) at Center for Mind/Brain Sciences (CIMeC) 2013

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