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Classical conditioning of the BOLD signal for mental state classification: a contribution for the development of a BCI for Alzheimer patients

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Introduction

Brain-computer interfaces (BCIs) provide alternative methods for communicating and acting on the world, by allowing the acquisition and transformation of brain activity to convey messages and commands, therefore not involving the normal paths of peripheral nerves and muscles.

Patients with Alzheimer's disease may benefit from a BCI aimed at conveying basic thoughts (e.g., "yes" and "no") and emotions. There is currently no report of research in this direction, mostly because cognitive deficits in patients with dementia pose serious limitations to the use of traditional BCIs, which normally require users to self-regulate their brain activity, and are based on operant learning.

In the present thesis, we propose a paradigm shift from operant learning to classical conditioning, with the aim of discriminating affirmative and negative thoughts (associated to congruent and incongruent semantic stimuli respectively) within an fMRI-BCI setting. This represents a basic step in the development of a BCI that could be used by Alzheimer patients, lending a new direction not only for communication, but also for rehabilitation and diagnosis. The proposed paradigm is here validated with healthy subjects, in view of a future application with a clinical population.

The thesis is structured in six chapters. *Chapter 1* describes the development of BCIs as technologies for machine control and communication. Several kinds of BCIs based on different methodologies, such as electroencephalography (EEG), magnetoencephalography (MEG), near-infrared spectroscopy (NIRS) and functional magnetic resonance imaging (fMRI) are presented. Particular attention is given to brain state detection and classification with fMRI, stressing the remarkable advances in data acquisition and processing techniques that have lead to consider this methodology as elective for mental state detection and BCI-based neurorehabilitation. Most of the BCIs that have been developed so far require an active participation of the user, who has to learn to self-regulate brain signals, often following demanding and time-consuming trainings. For this reason, most existing BCI cannot be used with patients with cognitive impairment, such as patients with mental retardation or dementia. To this end, *Chapter 2* introduces new possibilities for BCI applications, focusing particularly on the idea of developing a so-called “passive” brain computer interface, based on classical conditioning instead of the more traditionally adopted operant conditioning paradigm. Such a paradigm could be applied for mental state detection and basic yes/no communication with Alzheimer patients. In fact, several researchers have shown how, even in the most advanced stages of this neuropathology, when the communication deficit is pervasive and often leads to mutism, patients still seek for social contact. Three main aspects of Alzheimer’s disease that are particularly important for the development of our paradigm will be tackled, namely communication deficits, recognition of emotions, and the ability to develop a conditioned response within a classical conditioning paradigm. In *Chapter 3*, the challenge of developing a paradigm based on classical conditioning of the BOLD signal within a BCI-setting was taken up. The chapter presents a paradigm validation with healthy subjects, with the aim of discriminating between brain responses related to congruent and incongruent word-pairs (the conditioned stimuli, CS), respectively eliciting “affirmative” and “negative” thinking, after associating them to a positive and a negative emotional sound (the unconditioned stimuli, US). Since the analysis and classification of the BOLD signal was developed with two distinct procedures (univariate and multivariate), such methods are described in two separate chapters, together with the provided results. *Chapter 4* describes univariate analysis of the fMRI data, considering response variations at the level of individual voxels. This analysis was performed with the Statistical Parametric Mapping method, which is based on the General Linear Model and the Gaussian Random Field theory. Results from this method indicate that a classical conditioning paradigm, in which congruent and incongruent semantic stimuli are associated with positive and negative emotional stimuli, allows the discrimination between affirmative and negative thinking. The differential activation was interestingly found in areas that are mostly involved in emotional processing, such as the insula and the anterior cingulate cortex (ACC). Given the encouraging results obtained at voxel-level, multivariate analysis of the fMRI data were also performed, as described in *Chapter 5.* In contrast to conventional univariate analyses, which are strictly location-based, multivariate analyses take into account the global spatial pattern of brain activity. In this study, the multivariate approach was embraced by focusing on machine learning and developing a Support Vector Machine (SVM), a supervised learning method used for the classification and prediction of novel data. Results following this method indicate that, while prior to the classical conditioning procedure the classification accuracy relative to affirmative and negative thinking was around chance-level, percentages of accuracy increased significantly with the acquisition of the conditioned response. *Chapter 6* presents the possible conclusions that can be drawn from this investigation, and the future directions in this research field, which include primarily experimentation with Alzheimer patients, an online implementation of the SVM for real-time basic communication, and the validation of the paradigm with more portable neuroimaging techniques, such as NIRS.

Part of this thesis is drawn from published and submitted articles. The first three chapters are based on the articles: “Toward a Brain-Computer Interface for Alzheimer’s disease patients by combining classical conditioning and brain state classification”, written for the “Journal of Alzheimer’s Disease” (Liberati, Dalboni da Rocha, van der Heiden, Raffone, Birbaumer, Olivetti Belardinelli & Sitaram, 2012); “Classical conditioning of the BOLD signal as a paradigm for basic BCI communication in Alzheimer patients”, published in the journal “Alzheimer’s and Dementia” (Liberati, van der Heiden, Sitaram, Kim, Rana, Raffone, Birbaumer & Olivetti Belardinelli, 2011); “Cognitive reserve and its implications for rehabilitation and Alzheimer’s Disease”, written for the journal “Cognitive Processing” (Liberati, Raffone & Olivetti Belardinelli, 2012). The fourth chapter is based on the submitted article “Semantic classical conditioning of two brain responses using emotional sounds as unconditioned stimuli" (Liberati, van der Heiden, Sitaram, Kim, Jaśkowski, Raffone, Olivetti Belardinelli, Birbaumer & Veit, 2012). The fifth chapter is based on the article in preparation "Double semantic conditioning with emotional stimuli for the development of a SVM-based binary fMRI-BCI" (Liberati, van der Heiden, Dalboni da Rocha, Veit, Rana, Kim, Jaśkowski, Raffone, Olivetti Belardinelli, Braymer & Sitaram, 2012).

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1. Brain Computer Interfaces (BCIs) and mental state detection

1.1 Introduction

The present chapter describes the development of Brain-Computer Interfaces (BCIs) as technologies for machine control and communication, focusing mostly on functional magnetic resonance BCIs (fMRI-BCIs) and mental state detection and classification.

In the first section, BCIs based on electroencephalography (EEG), magnetoencephalography (MEG), near-infrared spectroscopy (NIRS) and fMRI are introduced. Such interfaces have been developed especially to allow communication and environmental control in patients with severe motor disabilities, and have seen a great development in the last decades.

In the second section, particular attention will be given to fMRI signal classification, since the experimental paradigm that we propose in our research, and which will be presented in the next chapters, involves the classification of different mental states in an fMRI-BCI setting. Pattern classification literature is reviewed relatively to methodological studies based on machine learning, mental state discrimination, and BCIs and neurorehabilitation.

1.2. Brain-Computer Interfaces for communication and control

Research on BCIs originates from studies on biofeedback and neurofeedback. Biofeedback can be defined as the process of becoming aware of various physiological functions, such as heart function, breathing, muscle activity, skin temperature and brainwaves, by using instruments that provide information on the activity of those same systems, with the aim of manipulating them at will. According to the Association for Applied Psychophysiology and Biofeedback, it is *"a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance"* ("The Association for Applied Psychophysiology and Biofeedback," 2008). By allowing a person to control physiological functions, biofeedback has been found to be effective in the regulation of pain perception and in the treatment of headaches and migraines (deCharms et al., 2005; Nestoriuc & Martin, 2007; Nestoriuc, Martin, Rief & Andrasik, 2008).

Neurofeedback, sometimes also called EEG-biofeedback, uses real-time visual or auditory displays of EEG brain activity, which is measured by placing sensors on the scalp (Masterpasqual & Healey, 2003). Starting from the 1970s, thanks to the technological achievements in rapid computer analysis of EEG patterns, which allowed online feedback of different kinds of neuroelectric activity, a large number of studies on neurofeedback training were published, showing solid evidence of positive effects in patients with pharmacologically intractable epilepsy and attention disorder deficit (Birbaumer, Ramos Murguialday, Weber & Montoya, 2009). BCIs traditionally exploit neurofeedback principles to train users to self-regulate their brain activity, in order to control computers or machines. It is important to note, however, that not all BCIs developed up to now require an active involvement of users in the regulation of brain signals.

BCIs can be considered as direct communication pathways between the brain and an external device (Fig. 1). They measure brain signals, extract certain features from these signals, and translate such features into output signals, which are fed back to the user and/or serve as commands to control computers or machines (Birbaumer, 2006; Birbaumer et al., 1999; Daly & Wolpaw, 2008; McFarland & Wolpaw, 2011; Pasqualotto, Federici & Olivetti Belardinelli, 2012; Wolpaw, Birbaumer, McFarland, Pfurtscheller & Vaughan, 2002). In the first international meeting of BCI technology in 1999, at the Rensselarville Institute of Albany, New York, Jonathan R. Wolpaw proposed the first formalized definition of BCI system: "*A brain-computer interface is a* *communication or control system in which the user's messages or commands do not depend on the brain's normal output channels. That is, the message is not carried by nerves and muscles, and, furthermore, neuromuscular activity is not needed to produce the activity that does carry the message"* (Wolpaw et al., 2000).

Two major clinical applications of BCIs are movement restoration in patients affected by spinal lesions or stroke (Belda-Lois et al., 2011; Birbaumer & Cohen, 2007; Birbaumer, Ramos Murguialday & Cohen, 2008; Daly & Wolpaw, 2008; Daly et al., 2009; Kaiser, Kreilinger, Müller-Putz & Neuper, 2011), and the development of communication systems for patients with motor disability (Cecotti, 2011; Escolano, Ramos Murguialday, Matuz, Birbaumer & Minguez, 2010; Kübler et al., 2009; Kübler et al., 2005; Nijboer et al., 2008; Ramos Murguialday et al., 2011). Recently, several studies aimed at assessing the possibility to use BCIs for allowing patients with motor impairment to control electronic devices in a home environment (Babiloni et al., 2007; Cincotti et al., 2008).

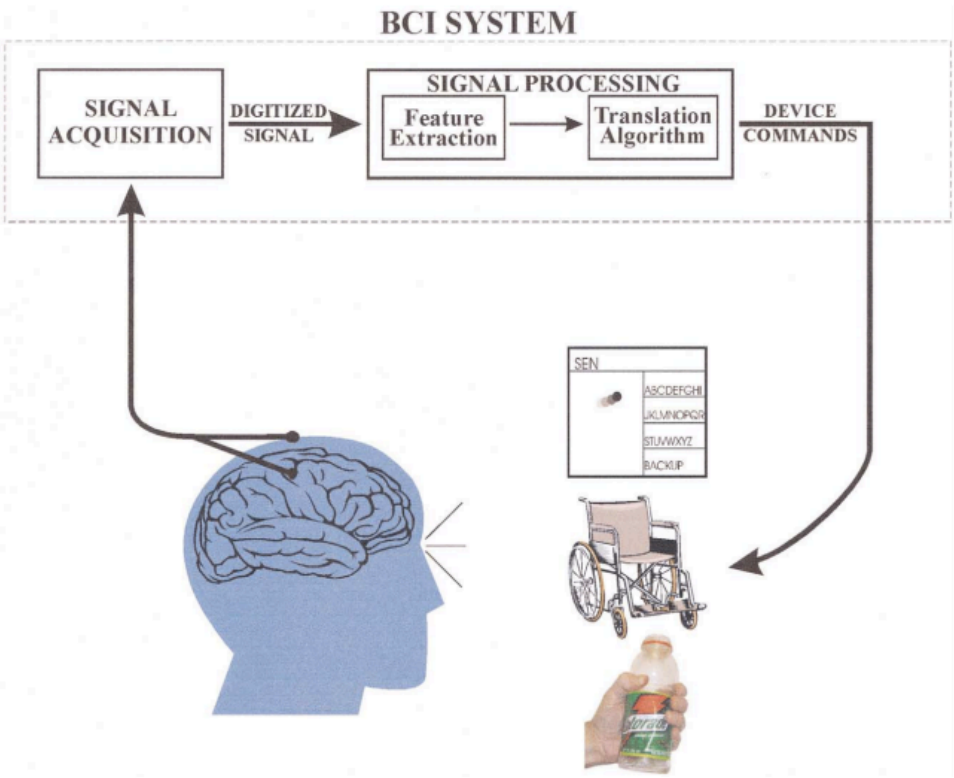


Fig. 1 Basic BCI system. Signals from the brain are acquired and processed to extract specific signal features. These features are translated into commands that operate a device. Reprinted from Clinical Neurophysiology, Wolpaw et al. (2002), "Brain-computer interfaces for communication and control", vol. 113, pp. 767-791, with permission from Elsevier.

It is possible to identify two main BCI approaches, namely invasive and non-invasive (Lebedev & Nicolelis, 2006; Pasqualotto et al., 2012). While invasive BCIs imply the intracranial recording of electrical activity performed directly on single neurons or on neural assemblies by implanting electrodes in the skull, non-invasive BCIs do not expose patients to surgical operations, and usually exploit brain activity recorded using EEG. Although the quality of data transmission may have some limitations, non-invasive BCIs overcome the ethical and technical problems related to the implant of electrodes in patients (Lebedev & Nicolelis, 2006).

In the following sections, we will describe different kinds of BCIs that are based on distinct non-invasive techniques.

1.2.1. Electroencephalography-BCIs

Most non-invasive BCIs developed so far are based on the recording of slow cortical potentials (SCP), sensory-motor rhythms (SMR), and the P300 event-related potential (Pasqualotto et al., 2012).

The first report on EEG, a system able to measure synaptic potential differences from the scalp, was published by Hans Berger in 1929 (Swartz & Goldensohn, 1998), but the intuition that EEG could be used to control machines with the modulation of brain impulses only spread in the early 1970s, with the article published by Jacques J. Vidal, which first introduced the concept of brain-computer communication (Vidal, 1973).

Pasqualotto and collaborators (2012) have proposed a classification of EEG-BCIs based on the dependence of the user on the conscious regulation of the brain activity exploited. More specifically, while some systems require users to intentionally modulate some aspects of their EEG activity and are based on voluntary learning of biofeedback procedures, other systems exploit spontaneous occurrences of brain electrical activity that do not require any intentional learning. Systems depending on voluntary modulation mostly exploit SCPs (Birbaumer, 1999; Kübler et al., 2001; Neumann, Kübler, Kaiser, Hinterberger & Birbaumer, 2003) and SMRs (McFarland, Krusienski & Wolpaw, 2006; Pfurtscheller et al., 2000; Wolpaw, McFarland, Vaughan & Schalk, 2003). Systems depending on non-voluntary modulation exploit visually evoked potentials (VEPs, Sutter, 1992), steady-state visual evoked potentials (SSVEPs) (Allison et al., 2008; Bin, Gao, Yan, Hong & Gao, 2009; Gao, Xu, Cheng & Gao, 2003; Lin, Zhang, Wu & Gao, 2007; Middendorf, McMillan, Calhoun & Jones, 2000; Müller-Putz, Eder, Wriessnegger & Pfurtscheller, 2008; Vialatte, Maurice, Dauwels & Cichocki, 2010; Wang, Wang, Gao, Hong & Gao, 2006; Zhang et al., 2010), and P300 (Bayliss, Inverso & Tentler, 2004; Brunner et al., 2010; Furdea et al., 2009; Guger et al., 2009; Halder et al., 2010; Kleih, Nijboer, Halder & Kübler, 2010; Klobassa et al., 2009; Krusienski, Sellers, McFarland, Vaughan & Wolpaw, 2008; Kübler et al., 2009; Lenhardt, Kaper & Ritter, 2008; Mugler, Ruf, Halder, Bensch & Kubler, 2010; Nijboer, Birbaumer & Kübler, 2010; Piccione et al., 2008; Sellers, Kübler & Donchin, 2006; Zhang, Guan & Wang, 2008).

EEG has several advantages: it is widely available at low cost, has a long history of usage, and its mechanisms are therefore very well known. However, it also has remarkable disadvantages, such as artifacts, low spatial resolution, and difficulty in the application and fixation of electrodes, which can require a long time, especially with patients with motor deficits (Sitaram et al., 2007).

1.2.2. Magnetoencephalography-BCIs

By recording the magnetic fields that are produced by electrical currents in the brain, MEG is closely related to EEG (Hämäläinen, Hari, Ilmoniemi & Lounasmaa, 1993), but has a higher spatiotemporal resolution (Mellinger et al., 2007). Although EEG-BCIs can allow communication in healthy and paralyzed patients in a relative safe and inexpensive way, such communication is usually very slow. To overcome this issue, MEG-BCIs were developed. Mellinger and colleagues (2007) presented a MEG-BCI based on the μ rhythm, showing that participants were able to efficiently control their own brain activity within 32 minutes of feedback training. Buch et al. (2008) used a MEG-BCI to train chronic stroke patients to modulate the μ rhythm amplitude originating in sensorimotor areas of the cortex, which served to move a screen cursor that allowed controlling an orthosis attached to the paralyzed hand. Spüler and collaborators (Spüler, Rosenstiel & Bogdan, 2011) have recently developed a fast feature selection method to increase accuracy and reduce classification time in the analysis of high dimensional MEG-BCI data.

1.2.3. Near-infrared spectroscopy-BCIs

NIRS is a non-invasive optical method that utilizes light in the near-infrared range (700-1000 nm) to determine brain oxygenation, blood flow and metabolic status of specific brain areas (Sitaram et al., 2007). Regional brain activation is accompanied by increases in the cerebral blood flow (rCBF) and in the regional cerebral oxygen metabolic rate ($rCMRO_2$), but since the degree of increases in rCBF exceeds that of increases in $rCMRO_2$, the result is a decrease in deoxygenated hemoglobin in venous blood. As a consequence, an increase in total hemoglobin and oxygenated hemoglobin, accompanied by a decrease in deoxygenated hemoglobin in a specific region, indicates that such region is activated during the measurement (Sitaram et al., 2007).
Although NIRS is still relatively new, it promises flexibility of use, portability, good spatial resolution and affordability (Sitaram et al., 2007; Villringer & Obrig, 2002). Sitaram et al. (2007) observe that NIRS also presents several disadvantages, such as slowness due to the inherent latency of the hemodynamic response and motion artifacts. However, the ability of this technique to record localized brain activity with a relatively high spatial resolution (in the order of a centimeter) provides an opportunity to control several motor and cognitive activities in a BCI. The use of NIRS in several cognitive and motor tasks has been shown to be particularly suitable for BCI development (Coyle, Ward & Markham, 2007; Coyle, Ward, Markham & McDarby, 2004; Power, Kushki & Chau, 2011; Sitaram et al., 2007; Villringer, Planck, Hock, Schleinkofer & Dirnagl, 1993).

1.2.4. Functional Magnetic Resonance Imaging-BCIs

fMRI is a procedure that, similarly to NIRS, measures brain activity by detecting associated changes in blood flow. Typically, fMRI measures the blood oxygenation level-dependent (BOLD) signal, which is correlated with blood flow increases (Uludag, Dubowitz & Buxton, 2006).

By using fMRI, it is possible to measure brain activity repeatedly every few seconds in a large number of voxels, each of a few millimeters (Haynes & Rees, 2006). The signal that is measured in each voxel reflects local changes in oxygenated and deoxygenated hemoglobin, elicited by neural activity (Logothetis & Pfeuffer, 2004).
In the last years, fMRI data acquisition and processing techniques have seen remarkable improvement. The increase in image-encoding gradient power and the possibility to use stronger magnetic fields allow encoding images with an adequate signal-to-noise ratio (SNR). Moreover, faster computers and more advanced data processing software allow online image reconstruction and statistical analyses (Weiskopf et al., 2003).
Due to the low spatial resolution of EEG, fMRI-BCIs have been developed in the last years. Such systems allow the recording of neuronal activity from the entire brain with a relatively high spatial resolution, so that brain activity from very specific cortical and subcortical regions can be extracted (Caria, Sitaram & Birbaumer, 2011; deCharms, 2008; Sitaram, Caria & Birbaumer, 2009; Sitaram et al., 2007; Weiskopf, 2011; Weiskopf et al., 2004).
We will discuss fMRI-BCIs more thoroughly in the following section, describing mental state detection with magnetic resonance imaging, and focusing also on the use of these kinds of systems in rehabilitation contexts.

1.3. Mental state detection with functional magnetic resonance imaging

fMRI is an important tool to address what Norman and colleagues (2006) have defined as the three main questions in cognitive neuroscience: 1) What information is represented in which brain structures? 2) How is such information represented? 3) How is that information transformed during different processing stages? Several human neuroimaging studies have provided strong evidence of the possibility to decode mental states from brain activity (Haynes & Rees, 2006). The prediction of mental states from brain activity is a major aim of neuroscience and could be applied to many different fields, such as the assessment of affect in verbally incompetent people with dementia, minimally conscious state (MCS) and locked-in syndrome (LIS), the development of BCIs for the control of artificial limbs or computers, and lie detection (Haynes & Rees, 2006; Sitaram et al., 2011).

In the last years, the development of new acquisition techniques, the increase of computational power, and the development of more advanced algorithms have increased the possibility to perform a mental state classification based on the analysis of the BOLD signal (Norman et al., 2006). These improvements include linear classifiers, such as correlation-based classifiers (Haxby et al., 2001; Spiridon & Kanwisher, 2002), neural networks (Polyn, Natu, Cohen & Norman, 2005), linear discriminant analysis (Carlson, Schrater & He, 2003; Davatzikos et al., 2005; Haynes & Rees, 2005a; Haynes & Rees, 2005b; Kamitani & Tong, 2005; O'Toole, Jiang, Abdi & Haxby, 2005) Gaussian Naive Bayes classifiers (Mitchell et al., 2004), and Support Vector Machines (SVMs, described more in detail in Chapter 5, (Cox & Savoy, 2003; LaConte, Strother, Cherkassky, Anderson & Hu, 2005; Lee, Halder, Kübler, Birbaumer & Sitaram, 2010; Mourão-Miranda, Bokde, Born, Hampel & Stetter, 2005; Mourão-Miranda, Friston & Brammer, 2007; Mourão-Miranda, Reynaud, McGlone, Calvert & Brammer, 2006; Sitaram et al., 2011; Vapnik, Golowich & Smola, 1997).

Although most of the research in the field of mental state detection focused on offline pattern classification, using techniques that allow the classifier to learn, new approaches attempt to obtain online or quasi-online classification of mental states (Carlson et al., 2003; Davatzikos et al., 2005; Hasson, Nir, Levy, Fuhrmann & Malach, 2004; Haxby et al., 2001; Haynes & Rees, 2005a; Haynes & Rees, 2005b; Haynes & Rees, 2006; Lee et al., 2010; Lee, Ruiz, Caria, Birbaumer & Sitaram, 2010; Logothetis & Pfeuffer, 2004; Mitchell et al., 2004; O'Toole et al., 2005; Polyn et al., 2005; Sitaram et al., 2005; Sitaram et al., 2007; Sitaram et al., 2011; Spiridon & Kanwisher, 2002; Tsao, Freiwald, Tootell & Livingstone, 2006). This way, users do not need to be trained to self-regulate their brain activity, since the system learns to recognize the activation patterns that occur spontaneously in the brain.

Sitaram et al. (2011) distinguish between three major themes in the study of pattern classification of brain signals. The first theme includes several methodological studies aiming at incorporating and adapting existing methods in the field of machine learning to fMRI data classification (LaConte et al., 2003; LaConte et al., 2005; Martínez-Ramón, Koltchinskii, Heileman & Posse, 2006; Shaw et al., 2003; Strother et al., 2004). A second research topic focuses on the application of pattern classification to obtain greater knowledge of spatial and temporal patterns of brain activity during cognitive, affective and perceptual states, represented by studies on the neural antecedents of voluntary movement (Soon, Brass, Heinze & Haynes, 2008), visual processing (Kamitani & Tong, 2005), memory recall (Polyn et al., 2005), lie detection (Davatzikos et al., 2005), and emotion perception (Pessoa, Padmala & Morland, 2005). Finally, a third class of studies is related to the field of BCIs and neurorehabilitation (Caria et al., 2006; deCharms et al., 2004; deCharms et al., 2005; Posse et al., 2003; Rota et al., 2006; Ruiz et al., 2008; Sitaram et al., 2005; Veit et al., 2006; Weiskopf et al., 2004; Weiskopf et al., 2003; Yoo & Jolesz, 2002; Yoo et al., 2004). For our aims, it is particularly important to review the main aspects of mental state discrimination with fMRI, together with possible applications in neurorehabilitation.

1.3.1. Mental state discrimination and neurorehabilitation with fMRI

BOLD fMRI signals measure neural responses indirectly (Logothetis & Pfeuffer, 2004), and the relationship between mental state detection and the underlying neural activity can be extremely complex.

In order to decode a mental state (i.e. a cognitive or emotional state), it is necessary that the brain activity corresponding to a particular state can be separated and distinguished from other possible mental states (Haynes & Rees, 2006). In an ideal situation, such distinction is given when different mental states are encoded in spatially separated brain areas. This kind of approach has been most commonly examined concerning the human visual field and in the perception of objects and visual images. It is known that it is possible to distinguish separable cortical modules, which represent specific kinds of visual information. For example, the fusiform face area (FFA) is a region of the human ventral visual stream that responds more strongly to faces than to other kinds of objects, while the parahippocampal place area (PPA) is a region of the parahippocampal gyrus that responds more strongly to visual scenes and views of buildings (Allison et al., 1994; Epstein & Kanwisher, 1999; Kanwisher, McDermott & Chun, 1997; O'Craven & Kanwisher, 2000). Since these cortical representations are separated from a certain distance in the brain, it is possible to determine whether a person is thinking about faces or visual scenes on the basis of the levels of activation in these two brain areas (Haynes & Rees, 2006). Similar separable neural representations are also present in the visual field maps of the early visual cortex (Engel et al., 1994). Distinct modular processing regions in the visual pathway have been proposed for many different other object categories, such as body parts (Downing, Jiang, Shuman & Kanwisher, 2001) and letters (Cohen et al., 2000). Moreover, the activity in separate brain areas can be used to infer behavior. Dehaene and colleagues (1998) demonstrated the possibility to discriminate whether participants were moving their right or their left thumb, according to the difference between left and right primary motor cortex activations.

Haxby and colleagues (2001) showed that not only location-based approaches, but also multi-voxel approaches could be used to distinguish between cognitive states. In this study, participants were presented with different visual stimuli such as faces, buildings, and different kinds of objects. The data were then split in half, and the multi-voxel response pattern to each category was characterized separately for each half. By doing a within-subject correlation of the first-half patterns with the second-half patterns, the Authors showed that each category was associated to a distinct activity pattern, since each first-half pattern matched its relative second-half pattern more than the patterns associated with other categories. Similar findings are reported in other studies (Carlson et al., 2003; Cox & Savoy, 2003; Hanson, Matsuka & Haxby, 2004; O'Toole et al., 2005; Spiridon & Kanwisher, 2002; Tsao, Freiwald, Knutsen, Mandeville & Tootell, 2003). Mitchell and colleagues (2004) report that multivariate pattern analysis methods are effective in discriminating whether a subject is looking at a picture or a sentence, whether the subject is reading an ambiguous or a non-ambiguous sentence, and the semantic category of a read word. Other multivariate pattern analysis studies focused on mental states that cannot be inferred directly from the stimulus, such as lying during a card game (Davatzikos et al., 2005), or which of three categories the subject is thinking about during a memory retrieval task (Polyn et al., 2005).

If the mental states that have to be discriminated are distinct enough from one another, multivariate pattern analysis techniques allow having a reliable discrimination based on single brain scans acquired over a period of circa 2-4 seconds (Carlson et al., 2003; LaConte et al., 2003; LaConte et al., 2005; Mitchell et al., 2004; Mourão-Miranda et al., 2005; O'Toole et al., 2005; Polyn et al., 2005; Strother et al., 2004). Such increase in temporal resolution allows the definition of a temporal trace of a particular mental state over the course of the experimental task, which could subsequently be related to the subject's ongoing behavior (Norman et al., 2006). Despite the intrinsic limitations in the temporal resolution of multivariate pattern analysis, due to the temporal dispersion in the hemodynamic response measured by fMRI, several studies used these methods to trace cognitive variations occurring in the order of seconds, for example in predicting the time course of recall behavior in a memory task (Polyn et al., 2005) or second-by-second changes in perceived stimulus dominance during a binocular rivalry task (Haynes & Rees, 2005b).

Unconscious mental states, such as the perceptual representation of invisible stimuli (Reingold & Merikle, 1988) or unconscious motor preparation, are a specific kind of covert information. Research on decoding unconscious states seems to be promising, also for tracking their temporal dynamics (Haynes & Rees, 2005b), leading to important implications for theoretical models of human consciousness (Haynes & Rees, 2006). These approaches can also be used to decode more complex cognitive states, such as unconscious racial biases (Golby, Gabrieli, Chiao & Eberhardt, 2001; Hart et al., 2000; Phelps et al., 2000), or unconscious motor intentions immediately preceding a voluntary action (Blankertz et al., 2003; Haggard & Eimer, 1999). Since these studies have demonstrated the possibility to access neural information about intentions before they become conscious, they raise the issue of whether they could also reveal unconscious determinants of human behavior (Haynes & Rees, 2006).

Affective neuroscience has seen a huge proliferation in the last years thanks to modern neuroimaging approaches such as positron emission tomography

(PET) and fMRI, aiming at revealing the neural basis of emotion and personality by investigating emotional recognition, experience, memory, regulation, and individual differences in the human brain (Allman, Hakeem, Erwin, Nimchinsky & Hof, 2001; Canli & Amin, 2002; Davidson, Pizzagalli, Nitschke & Putnam, 2002; Davis & Whalen, 2001; Drevets, 2000; LeDoux, 2000). A consequence of these approaches is the growing interest in “social neuroscience” (Cacioppo, Berntson, Sheridan & McClintock, 2000; Ochsner & Lieberman, 2001) and in “forensic neuroimaging” (Abbott, 2001; Aggarwal, 2009; Greene, Sommerville, Nystrom, Darley & Cohen, 2001; Kiehl, 2004; Moll, de Oliveira-Souza, Bramati & Grafman, 2002), with the aim of predicting violent behavior and psychopathy.

The assumption that emotional processing involves the limbic system (LeDoux, 1996; Papez, 1937) has been recently verified with fMRI and PET, which have shown emotion-related increases in cerebral blood flow or BOLD signal in cortical, limbic, and paralimbic regions (Phan, Wager, Taylor & Liberzon, 2002). Several researchers have hypothesized that specific regions are specialized in different emotional processes (Davidson & Irwin, 1999; LeDoux, 2000; Maddock, 1999). However, imaging studies taken individually cannot completely define which brain regions are responsible for emotional processing due to low statistical power, and heterogeneity of experimental design, imaging methods and analyses. For this reason, Phan and colleagues (2002) performed a meta-analysis of 55 activation studies (43 PET and 12 fMRI), with the goal of determining the common or distinct patterns of activation across different emotional tasks. The first result of this research was that no specific brain region was consistently activated across studies, emotions, and induction methods, indicating that no single brain area is commonly activated by all emotional tasks. However, the Authors did find that the medial prefrontal cortex (MPFC) was commonly activated in four out of five specific emotions, in at least 40% of the studies. These results are consistent with the ones reported by Lane and collaborators (Lane, Fink, Chau & Dolan, 1997; Lane, Reiman, Ahern, Schwartz & Davidson, 1997; Lane et al., 1997) and Reiman et al. (1997), which indicate that the MPFC is involved in the processing of emotional films and pictures, and in both negative and positive emotions. This can be explained by the assumption that several processes, such as emotional appraisal, regulation, and decision-making, should be common to different emotional tasks, and the MPFC could be involved in the more cognitive aspects of emotional processing (Drevets & Raichle, 1998), although the literature shows controversial results (Cabeza & Nyberg, 2000; Duncan & Owen, 2000).

Phan and colleagues (2002) also report that fear induction is strongly associated with the amygdala. More specifically, the amygdala appears to be involved in the recognition of fearful facial expressions (Calder, 1996), aversive pictures (Irwin et al., 1996; Simpson et al., 2000; Taylor et al., 1998), fear conditioning (Bechara et al., 1995; LaBar, Gatenby, Gore, LeDoux & Phelps, 1998; LeDoux, 1993; Morris et al., 1998; Morris, Ohman & Dolan, 1998), fearful emotional responses from direct stimulation (Halgren, Walter, Cherlow & Crandall, 1978) and detection of environment threat (Isenberg et al., 1999; Scott et al., 1997). An alternative interpretation for the role of the amygdala is its involvement in vigilance and salience processing (Davis & Whalen, 2001; Whalen et al., 1998).

The meta-analysis performed by Phan et al. (2002) also showed that sadness was significantly associated with the activation of the subcallosal cingulated cortex (SCC), localized to the ventral/subgenual anterior cingulated, more than twice as frequently as any other emotion. Consistently with this finding, SCC hypometabolism and hypoperfusion was found in resting state studies of patients with clinical depression (Drevets et al., 1997; Mayberg, Lewis, Regenold & Wagner, 1994). Phan and colleagues (2002) report that almost 70% of happiness induction studies show activation in the basal ganglia (BG), in agreement with several studies on positive emotions, regarding the use of addictive substances (Stein et al., 1998), pleasant activities like playing videogames (Koepp et al., 1998), reward processing (Rolls, 1999), sexual pleasure and competitive arousal (Rauch et al., 1999). Other interesting findings described by Phan et al. (2002) concern activations associated with the induction method. Emotional induction via visual stimuli activated the amygdala and the occipital cortex; induction by emotional recall or imagery as well as emotional tasks with cognitive demand activated the anterior cingulated cortex (ACC) and the insula.

Given the encouraging results, the emerging field of fMRI-BCIs can be considered as a promising tool for affective neuroscience and neurorehabilitation, with the aim of treating emotional disorders such as anxiety, sociopathy, chronic pain and schizophrenia (Sitaram et al., 2011).
Both healthy individuals and patients can learn to voluntarily self-regulate their brain activation in specific regions. This self-regulation training can be exploited in order to obtain behavioral modifications, which can be useful for neurorehabilitation (Caria et al., 2006; deCharms et al., 2004; deCharms et al., 2005; Posse et al., 2003; Rota et al., 2006; Sitaram et al., 2005; Sitaram et al., 2011; Veit et al., 2006; Weiskopf et al., 2004; Weiskopf et al., 2003; Yoo & Jolesz, 2002; Yoo et al., 2004). When the neurobiological basis of a disorder are known in terms of abnormal activations in specific brain areas, fMRI-BCIs can be developed with the aim of modifying such activations (Sitaram et al., 2011).
Weiskopf and colleagues (2003) presented an fMRI-BCI that allowed a volunteer to control the activation in the rostral-ventral and dorsal portion of the ACC. DeCharms et al. (2005) used real-time fMRI to train subjects to self-regulate activation in the rostral ACC (rACC), which is associated to pain perception and regulation. The authors showed that when participants voluntarily increased or decreased the activation in the rACC, there was a variation in pain perception. Chronic pain patients benefited from this treatment, reporting a decrease in the ongoing level of pain.
Posse and collaborators (2003) reported that real-time fMRI analyses of activations in temporolimbic regions, which play an important role in the regulation of emotions, could be used to detect amygdala activity during self-induced sadness. This kind of fMRI-BCI could be helpful in the treatment of several neuropsychiatric conditions that are related to the regulation of amygdala activations, such as depression.
Ruiz et al. (2011) recently exploited the possibility for subjects to achieve self-regulation of circumscribed brain regions to train schizophrenic patients to voluntarily control the bilateral anterior insula with contingent real-time fMRI neurofeedback, through a two-week training. Following self-regulation, patients improved the ability to discriminate between different facial emotions, which is severely compromised in schizophrenia. These results open the path

for further real-time fMRI studies in psychiatric populations, with consequent rehabilitative applications.

1.4. Conclusions and future directions

The last years have seen a remarkable development in the field of mental state classification and the consequent application on BCIs. Not only EEG-BCIs based on both voluntary and non-voluntary regulation, but also systems based on MEG, NIRS and fMRI have been developed. So far, most BCIs have been tested on patients with communication difficulties due to motor impairment. Often, these BCIs require an active involvement of the user, who needs to learn to voluntarily self-regulate brain signals. For this reason, it is very difficult to utilize existing BCIs with patients with cognitive impairment, such as mental retardation or dementia. The basic principle of BCIs, namely inferring different states of the user from brain activity, could be however exploited to design new BCIs that may be used also in presence of cognitive impairment. Such BCIs could rely on involuntary signals, such as the ones related to emotions.

Particularly interesting for our aims is the differentiation of mental states using fMRI, in order to develop a basic communication system based on differential brain activations, which do not necessarily require the user to learn a new task or to self-regulate brain activity. The possibility to perform a classification of different mental states by using different kinds of algorithms is evident from the literature. So far, most research focused on offline pattern classification, although the need to apply this methodology for instant communication urges to develop more complex algorithms to obtain online classification of mental states.

Although it is possible to decode some aspects of mental states by extracting neuroimaging signals, there are still some technical limitations related to spatial and temporal resolution (Haynes & Rees, 2006), and regarding the complete understanding of the BOLD signal (Logothetis & Pfeuffer, 2004). Another obstacle is given by the high costs and the lack of transportability of the current methodologies that are mostly used in neuroimaging, such as fMRI and MEG. At this time, only EEG and NIRS can be considered transportable and relatively affordable technologies, but these advantages are counterbalanced by a lower resolution. It is obviously misleading to imagine that fMRI-based BCIs could one day be used by a patient with communication problems in everyday life. Nevertheless, fMRI represents an extremely powerful methodology to identify with a good spatial resolution the areas and the brain patterns that could be exploited in BCI communication, constituting a preliminary and fundamental step towards the development of an efficient and more portable system (e.g. based on NIRS).

Besides the hindrances given by the high costs and the low portability of the techniques that are actually used in mental state decoding, there are several issues that need to be considered. Most prominently, there is the issue of generalization of the findings. In most of the decoding studies, an algorithm was trained individually for each subject for a given set of mental states, based on data recorded in a single session. It is still questionable whether this extremely simplified situation may be generalized to more practical applications, over time, across subjects, and in different situations (Haynes & Rees, 2006).

Another complex issue concerns the generalization across the same instances of the same mental state, given the impossibility to train the classifier on an infinite series of exemplars (e.g., different stimuli that aim at eliciting “happiness”). Consequently, the classification algorithm should be flexible enough to ignore the differences that are not relevant for the mental state classification. It has been shown that pattern classifiers can generalize to new features (Kamitani & Tong, 2005), new stimulation conditions (Haynes & Rees, 2005b), and new exemplars (Cox & Savoy, 2003). Notwithstanding, the identification of a unique brain pattern associated with an invariant feature of different exemplars is strongly dependent on the grouping of different mental states as belonging to one class. If a class of mental states is very heterogeneous, it might not be possible to map them to a univocal neural pattern. For this reason, it is very important to categorize mental states carefully, also considering that generalization can often be obtained with the compromise of having a reduced discrimination of individual exemplars (Haynes & Rees, 2006).

Ideally, it should be possible to generalize the classification of mental states across different individuals, requiring little or no calibration at all for new subjects. Several algorithms for data pre-processing, such as spatial alignment and warping of individual structural brain images to stereotactic templates (as in the Statistical Parametric Mapping software, SPM) are well established (Friston et al., 1995), but the spatial correspondence between analogous functional locations in different brains is not always perfect, especially when considering old individuals, or patients affected by neuropathology.

Another issue that arises in the decoding of mental states is the measurement of concurrent mental states, since the spatial patterns corresponding to the different states might overlap. Some degree of separation can be achieved by assuming (as a simplification) that the patterns are linearly superimposed (Mitchell et al., 2004), but difficulties stand out when different mental states are encoded in the same neuronal populations.

As observed by Haynes & Rees (2006), the main challenge to mental state detection is that the number of possible mental states is infinite, while the number of training exemplars or categories is obviously limited. For this reason, mental state decoding is restricted to simple situations, with a fixed number of alternatives with available training data. The generalization from a sampled set of categories to new categories requires an extrapolation, which is only possible if an underlying representational space is determined, in which different mental states are encoded. This seems to be obtainable for at least some kinds of mental content.

Overall, classification of fMRI data, and more specifically, of the BOLD signal, is a promising methodology that could be used in the field of BCIs. As we will see more in detail in the following chapters, our aim is to combine mental state classification with classical conditioning, in order to obtain a paradigm in which different mental states can be detected without requiring subjects to learn to actively self-regulate their brain signals. Such paradigm could be used more feasibly with patients with cognitive impairment, such as patients with Alzheimer's disease (AD).

In the following chapter, we will describe how BCIs could be adapted to be used with AD patients, by exploiting a so-called "passive" BCI paradigm, in order to allow basic yes/no communication.

2. Can we apply brain-computer interfaces with Alzheimer patients?

2.1. Introduction

In the present chapter we will introduce the possibility to apply BCIs for basic communication with individuals with Alzheimer's disease (AD, Liberati et al., 2012; Liberati et al., 2011a; Liberati et al., 2011b). Most BCIs realized for communication that have been developed in the last years are based on operant conditioning and intentionally learned responses, thus requiring users to actively learn to self-regulate their own brain activity. These kinds of BCIs, however, are not suitable for patients with an impaired cognitive system. We decided to realize a paradigm based on classical conditioning instead of operant conditioning, focusing particularly on the idea of developing a "passive" brain computer interface for mental state detection and basic yes/no communication with Alzheimer patients in the most advanced stages of the disease.

Our aim was to introduce a system able to convey information related to the patients' mental states, such as their emotions (e.g. happiness or sadness) and cognitive states (e.g. "yes" or "no" thinking), since the ability to have such mental states is preserved in the course of the neuropathology (Woods, 2001).

The main characteristics of AD, and particularly communication deficits and emotional recognition within this neuropathology, will be reviewed in the following sections.

2.2. Alzheimer's Disease

AD, first described by Emil Kraeplin and Alois Alzheimer in 1906 (Berchtold & Cotman, 1998; Weber, 1997), is the most common kind of dementia. It can be defined as a fatal, progressive and neurodegenerative disorder, clinically manifested by cognitive deterioration, impairment of activities of daily living, and a variety of neuropsychiatric symptoms and behavioral disturbances (Cummings, 2004). Although AD mostly affects memory, other symptoms, such as the occurrence of confusional states, time and space disorientation, mood and personality changes, apathy, and language disorders, can influence patients' functioning pervasively (Alzheimer's Association, 2011).
According to the "World Alzheimer Report", commissioned by Alzheimer's Disease International (ADI) and based on research data available in 2009, the number of people living with dementia worldwide in 2010 was estimated to be 35.6 millions (Alzheimer's Disease International, 2009). Moreover, this number is estimated to nearly double every 20 years, reaching 65.7 millions in 2030, and 115.4 millions in 2050. It is clear that demographic aging, which on one side reflects the successes of improved health care over the last century, is on the other side inevitably leading to an alarming growth of AD and related dementias. AD has been identified in all countries and cultures in which systematic research has been carried out (Alzheimer's Disease International, 2011). Especially in low and middle income countries, the disturbed behavior that characterizes people with dementia is poorly understood, and can lead to stigma, blame, and distress for caregivers (Ferri, Ames & Prince, 2004). Several studies have reported high levels of psychological morbidity among caregivers of people with dementia, especially concerning major depression (Cuijpers, 2005; Murray, Schneider, Banerjee & Mann, 1999; Prince & 10/66 Dementia Research Group, 2004; Thompson et al., 2007).
The main cause of AD is mostly unknown, but there are several competing hypotheses that involve a reduced synthesis of acetylcholine (*cholinergic hypothesis*, Francis, Palmer, Snape & Wilcock, 1999; Shen, 2004; Wenk, 2003), amyloid beta (Aβ) deposits (*amyloid hypothesis*, Games, 1995; Hardy & Allsop, 1991; Hsiao et al., 1996; Lott & Head, 2005; Masliah et al., 1996; Polvikoski, 1995), abnormalities in the tau protein (*tau hypothesis*, Chun &

Johnson, 2007; Goedert, Spillantini & Crowther, 1991; Iqbal, 2005; Mudher & Lovestone, 2002), herpes simplex virus type 1 (Itzhaki & Wozniak, 2008), age-related myelin breakdown (Bartzokis, 2011), and oxidative stress (Butterfield & Sultana, 2011; Lee et al., 2012; Su et al., 2008).

AD is characterized by a substantial loss of neurons and of the synapses that connect them throughout the neocortex. Plaques and tangles first develop in the enthorinal cortex, spread over time, and finally reach the neocortex. The degeneration in the basal forebrain reduces the supply of some brain chemicals, including neurotransmitter acethylcohline, which has a very important role in memory (Whitehouse et al., 1982). Over time, neuronal death and tissue loss lead the brain to shrink dramatically, affecting many of its functions (Double et al., 1996).

AD is often diagnosed in people over 65 years of age. The onset can be earlier, however, in 5-10% of the cases (Brookmeyer, Gray & Kawas, 1998). Early symptoms are often misconceived and considered as normal age-related concerns. The difficulty in remembering recent events and the inability to acquire new information are often the first indicators of AD (Hort et al., 2010; Salmon, 2011). Not all memory abilities are equally compromised. Episodic, semantic and implicit memory are normally not affected as much as the acquisition of new information (Carlesimo & Oscar-Berman, 1992; Jelicic, Bonebakker & Bonke, 1995).

The progression of the illness from a subclinical to a severe stage is relatively slow, and it is possible to distinguish between four main stages: pre-dementia, mild dementia, moderate dementia, and severe dementia (Förtsl & Kurz, 1999). The main aspects of these stages will be described in the following paragraphs.

Pre-dementia

Neuropsychological investigation can reveal very mild cognitive impairment, regarding mostly difficulties in acquiring new information, around five years before the clinical diagnosis of dementia (Förtsl & Kurz, 1999; Linn et al., 1995).

The ability to plan or to access the semantic memory store may also be mildly affected, but with no deterioration in the Activities of Daily Living (ADL), since at this stage individuals are able to use memory aids and different supportive strategies to compensate their impairment (Förtsl & Kurz, 1999). Non-cognitive alterations of behavior, such as social withdrawal and depressive dysphoria, may also emerge during this first stage (Jost & Grossberg, 1995).

Mild dementia

In mild dementia, declarative recent memory starts to be evidently affected, while short-term memory, old declarative memory and implicit/procedural memory are usually relatively preserved. ADL can be affected due to the reduced ability to plan, judge, and organize (Förtsl & Kurz, 1999). Spatial disorientation, together with a decreased ability in estimating distances and speed, lead to an increased risk of having accidents, especially when driving (Trobe, Waller, Cook-Flannagan, Teshima & Bieliauskas, 1996). Patients can, however, still live independently for most of the time (Förtsl & Kurz, 1999), and complex motor tasks do not show significant impairment on standard neurological examination (Kluger et al., 1997). Symptoms of depression and apathy may also be evident at this stage of the neuropathology (Burns, Lewis, Jacoby & Levy, 1991; Craig et al., 1996; Zubenko et al., 1989).

Moderate dementia

Beatty and colleagues (Beatty, Salmon, Butters, Heindel & Granholm, 1988) observed how, due to their severe retrograde amnesia, patients in the moderate state of dementia could appear to be “living in the past”, therefore not understanding part of their present. Patients become also more distractible and lose insight in their condition, so that the use of supportive memory strategies is highly compromised. Spatial disorientation increases, together with cortical visual agnosia and prosopagnosia (Förtsl & Kurz, 1999). Patients can suffer from mood disorders, which may be accompanied by aggressive and assaultive behavior (Devanand et al., 1997; Eastley & Wilcock, 1997). Aimless activities, such as wandering and hoarding, are also common (Devanand et al., 1997), and the burden for partners and caregivers is often very high due to the patients’ loss of independence (Cuijpers, 2005; Murray et al., 1999; Prince & 10/66 Dementia Research Group, 2004; Thompson et al., 2007; Varela, Varona, Anderson & Sansoni, 2011).

Severe dementia

In the latest stages of dementia, almost all cognitive functions are severely impaired, and even early biographical memories can be lost. Patients may fail to recognize not only close relatives, but also their own reflection in the mirror (Grewal, 1994). They can manifest several behavioral disturbances, such as restlessness, aggression, a disturbed circadian rhythm, apathy, and exhaustion (Förtsl & Kurz, 1999). Motor abilities can also be compromised, leading to difficulties in chewing and swallowing (Förtsl & Kurz, 1999), incontinence (Franssen, Kluger, Torossian & Reisberg, 1993), rigidity and primitive reflexes (Förstl et al., 1992; Förtsl & Kurz, 1999).

The most common instrument used to screen dementia and to evaluate the severity of cognitive impairment is the Mini Mental State Examination (MMSE, (Folstein, Folstein & McHugh, 1975), a 30-point test that can be administered in circa 10 minutes. The MMSE can also be used longitudinally, to assess the course of individual cognitive changes over time. The main categories that are evaluated are place and time orientation, name registration (repeating name prompts), attention and calculation, name recall, language (naming some objects), repetition of a phrase, and the ability to follow complex commands. Scores equal or higher than 25 indicate intact cognitive function; scores between 21 and 24 indicate mild cognitive impairment; scores between 10 and 20 and indicate moderate cognitive impairment; scores lower than 9 indicate severe cognitive impairment.

In the following paragraphs, we will describe in more detail two aspects of AD that give grounds for the development of our experimental paradigm (described in Chapter 3), namely communication and recognition of emotions.

2.2.1. Communication deficits in Alzheimer's disease

Communication impairment can be pervasive in AD, and is believed to occur in 88-95% of the individuals with the disease (Förtsl & Kurz, 1999; Frank, 1994; Thompson, 1987). The presence of a language disorder is one of the accepted criteria for its diagnosis (Alzheimer's Association, 2011). Such impairment begins early in the course of AD and may precipitate the transfer of patients from their homes to long-term care facilities, further enhancing interaction difficulties (Kaakinen, 1995).

Language disorders can be an early indicator of AD (Taler, Baum, Chertkow & Saumier, 2008), and according to some researchers, may be prior to memory problems (Bayles & Tomoeda, 1991). Difficulties in starting or following an extended conversation, together with anomia, circumlocutions, repetitions and digressions, are among the first discernable symptoms at the beginning of the disease (Kemper, Marquis & Thompson, 2001). In this first phase, discourse can be characterized by so-called “empty speech”, with high fluency but low propositional content (Kemper, LaBarge, Ferraro, Cheung & Storandt, 1993; Nicholas, Obler, Albert & Helm-Estabrooks, 1985).

In mild dementia, communication can be characterized by shrinking vocabulary and decreased word fluency (Förtsl & Kurz, 1999). Neuropsychological tests can show an impairment of object naming and word generation (Chobor & Brown, 1990; Locascio, Growdon & Corkin, 1995).

The ability to understand complex or abstract speech gradually diminishes with the progressing of the dementia (Goldfein, 2007), showing a reduction in grammatical complexity (Bates, Harris, Marchman & Wulfeck, 1995), an exacerbation of anomia (Kemper, 1991), and the deterioration in the ability to self-monitor linguistic errors (McNamara, Obler, Au, Durso & Albert, 1992). In the moderate stage of the disease, the abilities to read and write also deteriorate (Cummings, Houlihan & Hill, 1986; Harnish & Neils-Strunjas, 2008; Neils, Boller, Gerdeman & Cole, 1989).

In the most advanced stages of AD, short and repetitive high-frequency fragments mostly characterize patients’ speech. As the disease progresses, patients may be left with the ability to utter only a word or two (Förtsl & Kurz, 1999; Miller, 1989) or regress to mutism (Au, Albert & Obler, 1988). Despite these symptoms, even in the latest stages of the disease patients may seek for social contact and attempt to respond to conversational stimuli (Kim & Bayles, 2007; Mayhew, Acton, Yauk & Hopkins, 2001). By video-recording AD patients at different times of the day, Mayhew and colleagues (2001) showed that even when they were in the most advanced stage of the disease (MMSE score < 4), they sought for social contact through gestures, body language and eye gaze. Such behaviors indicate that, despite the cognitive decline and the remarkable difficulties in articulating words and sentences, the will to communicate persists in the most severe stages of AD. Förstl and Kurz (1999) observed that even when patients are unable to articulate their simplest needs, they can receive and return emotional signals. This receptiveness should be taken into consideration, and should exploited for an emotional-based kind of communication.

2.2.2. Recognition of emotions in Alzheimer's disease

Affectivity, as well as the ability to recognize and identify affective non-verbal stimuli (e.g. images and sounds), can be preserved in the course of AD, (Zaitchik, Koff, Brownell, Winner & Albert, 2006). Roudier and colleagues (Roudier et al., 1998) observed that although a deficit in facial identity discrimination is present in AD, patients are still able to discriminate between emotional expressions, showing that there is a dissociation between processing identity and processing emotions. Moreover, in their study, the ability to discriminate between emotions did not correlate with measures of cognitive impairment, such as the MMSE or the Raven Progressive Matrices scores. Similar results regarding facial emotion recognition were obtained in further studies (Fernandez-Duque & Black, 2005; Lavenu, Pasquier, Lebert, Petit & Van der Linden, 1999; Luzzi, Piccirilli & Provinciali, 2007; Shimokawa et al., 2000).

Koff et al. (Koff, Zaitchik, Montepare & Albert, 1999) studied the ability to process emotional information both in AD and healthy controls, by using auditory stimuli, pictures of emotional situations, and videos representing facial expressions, gestures, and body movements. Results indicated that there were no significant differences between patients and controls relatively to the ability to process emotions presented through the auditory domain, such as non-verbal sounds like crying or screams. The control group, however, was better compared to the AD group in identifying emotions depicted in the drawings or presented in the videos, suggesting that the difficulties of patients in perceiving emotions could be secondary to the visuo-spatial deficits associated with the neuropathology, and not depending on a

general processing deficit. This perspective was also supported by Bowers and colleagues (Bowers, Bauer & Heilman, 1993). Moreover, studies focusing on the perception of auditory emotional stimuli, prosody, and music, confirmed the ability of AD patients to discriminate between different emotions (Drapeau, Gosselin, Gagnon, Peretz & Lorrain, 2009; Gagnon, Peretz & Fülöp, 2009).
We believe that the preserved ability to process and discriminate between emotional stimuli could allow the use of an emotion-based communication system. Moreover, exploiting emotion processing in AD patients may have a relevant effect on the quality of life of both sufferers and families (Bucks & Radford, 2004).

2.3. Adapting BCI-systems to allow basic communication in Alzheimer patients

BCI systems could be implemented to allow basic communication with AD patients in the advanced stages of the disease. So far, no research exists in this direction, due to the fact that, traditionally, BCIs were considered to require an intact cognitive system in order to function as a communication method. Moreover, most of the BCIs developed so far require active participation of the users, and long trainings to allow them to learn to self-regulate their brain activity. Since BCIs based on operant training are obviously problematic for patients with cognitive deficits, we propose to adopt a paradigm shift from instrumental-operant learning to classical conditioning (Birbaumer, 2006).
It has been recently suggested that not only voluntary auto-regulated brain signals that have been commonly used for BCI control, but also involuntary signals, independent from the user’s effort, may provide important information related to the user’s cognitive or emotional state (Nijboer et al., 2009). In the last years, so-called “affective” BCIs based on emotion-related brain signals have been introduced. The advantages of these interfaces is that, being emotion-based, they do not necessarily require users to actively perform a cognitive task, and can therefore be considered as “passive” BCIs (Fig. 2). These kinds of interfaces can be particularly useful with users that are not

able to accurately perform active tasks, such as persons with mental retardation or patients of dementia. As stated by Nijboer and colleagues (2009), affective BCIs could enable simultaneous expression of affect and content, hence providing a greater quality of life, not only for the patient, but also for the caregiver. For instance, the Authors point out that an emotion detection system could even serve as an alarm to inform the caregiver to check on the patient, e.g. in situations of psychological distress.

One of the benefits of using a BCI for AD patients is that, besides allowing basic communication, its usage could promote neuroplasticity, opening up new opportunities for cognitive rehabilitation (Liberati, Raffone & Olivetti Belardinelli, 2012). In addition, patients' capability to use the BCI, a faculty that may potentially be related to different stages or severity of the disease, may also serve in the future as useful diagnostic information.

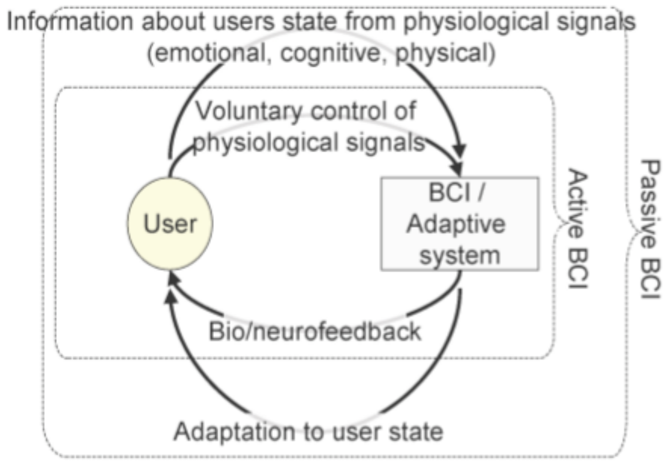


Fig. 2 Schematic overview of active and passive BCIs.
© 2009, IEEE. Reprinted, with permission, from Nijboer et al. (2009), "Affective Brain-Computer Interfaces: Psychophysiological Markers of Emotion in Healthy Persons and in Persons with Amyotrophic Lateral Sclerosis", International Workshop on Social Signal Processing.

2.3.1. *Classical conditioning in Alzheimer's disease*

One possible way to develop a passive BCI that could be used for basic communication with AD patients is to modulate brain responses through a semantic classical conditioning paradigm (Furdea et al., 2012; Montoya, Larbig, Pulvermüller, Flor & Birbaumer, 1996), thus moving away from the operant conditioning paradigm, which requires subjects to voluntarily modify a behavior (Domjan, 2009). Classical conditioning, which was first described by the Russian physiologist Ivan Pavlov in 1927 on the basis of his observations of salivation in dogs (Pavlov, 1927), is a simple kind of learning, which does not imply an active effort from the subjects. To obtain a conditioning effect, it is necessary to associate a specific so-called "neutral" stimulus (that is, a stimulus that does not elicit an evident response) to a "significant" stimulus, defined as unconditioned stimulus (US), which elicits a response (sometimes as a reflex). If the neutral stimulus is repeatedly presented with the US, it can become a conditioned stimulus (CS), producing a conditioned response (CR). From a neurobiological perspective, conditioning leads to the reinforcement of neural connections between neuronal pools and to the creation of cell assemblies (Hebb, 1949), distributed on different cortical areas, which are observable through fMRI.

A classical conditioning paradigm could allow, for instance, associating an affirmative response ("yes") to a positive emotion, and a negative response ("no") to a negative emotion. A similar classical conditioning paradigm has been already used for the development of an EEG-BCI for the communication of paralyzed patients, indicating the possibility to discriminate between affirmative and negative thinking (Furdea et al., 2012).

Classical conditioning may be partially compromised in AD, as shown in some studies on eye-blinking conditioning (Moore, Bondi, Salmon & Murphy, 2005; Solomon, Levine, Bein & Pendlebury, 1991; Woodruff-Pak & Papka, 1996; Woodruff-Pak, Logan & Thompson, 1990; Woodruff-Pak, Papka, Romano & Li, 1996). Moore et al. (Moore et al., 2005) showed that AD patients are able to acquire a conditioned response, although more slowly than healthy subjects. The study, however, does not clarify how early in the course of the neuropathology is the possibility to obtain classical conditioning compromised. For our aims, it is important to consider that classical conditioning has been conceptualized as a form of implicit or procedural memory (Squire, 1987). The neural substrates of implicit memory are the circuits that connect the nucleus profundus of the cerebellum to the pons and to the red nucleus (Thompson & Krupa, 1994), which are regions that are usually not primarily affected by Alzheimer neurodegeneration. Therefore, it is reasonable to expect the acquisition of a conditioned response also in AD patients. Several studies have demonstrated that the acquisition of the cognitive response is possible in AD patients, if they have a prolonged exposition to the stimuli (Solomon et al., 1995; Woodruff-Pak & Papka, 1996; Woodruff-Pak et al., 1996).

2.4. Conclusions

In the present chapter, the idea of developing a BCI that could be used with AD patients is presented.

BCIs provide alternative methods for communicating and acting on the world, since messages or commands are conveyed from the brain to an external device without using the normal output pathways of peripheral nerves and muscles. AD patients in the most advanced stages, who have lost the ability to communicate verbally, could benefit from a BCI that may allow them to convey basic thoughts (e.g. “yes” and “no”) and emotions. There is currently no research in this direction, mostly because the cognitive impairment that characterizes AD poses serious limitations to the use of traditional BCIs, which are normally based on instrumental learning and require users to self-regulate their brain activation. However, it would be useful to develop a BCI for basic communication with AD patients, since their will to communicate appears to be preserved even in the most advanced stages of the disease, and understanding patients’ basic mental states could relieve caregivers at least partially from their burden.

We propose a paradigm shift from instrumental learning to classical conditioning, with the aim of discriminating “yes” and “no” thoughts after associating them to positive and negative emotional stimuli respectively. This would represent a first step in the development of a BCI that could be used by AD patients, lending a new direction not only for communication, but also for rehabilitation and diagnosis.

As for rehabilitation, it could be interesting to link the possibility to establish some kind of communication with AD patients with new cognitive training strategies. AD has been widely studied in relation to the cognitive reserve model (Liberati et al., 2012), according to which, patients with the same degree of neural degeneration may have different individual abilities in using cognitive strategies, due to life experiences such as a high educational attainment and a mentally engaging occupation (Stern, 2009). A challenge that has been raised in the last years is the possibility to exploit cognitive reserve in the rehabilitation of AD patients (Liberati et al., 2012; Vance & Crowe, 2006; Vance, Roberson, McGuinness & Fazeli, 2010). Such perspective emphasizes how cognitive reserve should not be considered as a fixed factor, but rather as the result of a combination of experiences and environmental expositions that can take place during the entire life course. From a detailed examination of the literature, what emerges is that most efforts directed to AD rehabilitation were performed in the earliest stages of the disease (Liberati et al., 2012). One of the main problems in the more advanced stages of AD is represented by the huge communication difficulties with the patient, which render the interaction burdensome and unsuccessful.

Restoring basic communication could represent a valid strategy to trigger neuroplasticity phenomena, following the “use it or lose it” perspective supported by Hultsch et al. (Hultsch, Hertzog, Small & Dixon, 1999), according to which, cognitive processes can be modified by exercise and experience, since the traffic of impulses strengthens synaptic connections.

It is extremely important to point out that, since cognitive deterioration in AD strongly affects memory and reasoning abilities, it is necessary to exploit communication paths that are different from the ones that are normally used with subjects that have an intact cognitive system (e.g. answering complex questions). Such a system would also be useful in other situations of cognitive impairment, such as other types of dementia or mental retardation.

A BCI based on classical conditioning could also serve for diagnostic purposes, for instance allowing the observation of the variations and the delays in the acquisition of the CR during the course of the neuropathology.

The importance of developing a BCI system that could also be used by patients with cognitive impairment, such as in the case of Alzheimer’s disease, explains the need of testing such a system on healthy subjects and therefore validating our new paradigm, which will be described hereafter in Chapter 3.

3. Classical Conditioning of the BOLD signal as a paradigm for basic yes/no discrimination

3.1. Introduction

The present chapter introduces a paradigm validation study on healthy subjects, based on classical conditioning of the BOLD signal within a BCI-setting, with the aim of discriminating affirmative and negative thinking, after associating the relative responses to positive and negative emotional stimuli respectively.

As explained in the previous chapters, the reason why we decided to develop a paradigm that diverges from the more traditional operant conditioning paradigm, which is commonly used in the BCI field, is the need to acquire a system that could be also used with individuals with cognitive impairment, who are not able to learn a new task or to actively self-regulate their own brain signals. In particular, the final aim of this new BCI system would be the application with AD patients in the more advanced stages of the disease, who have lost their ability to communicate, but still manifest some kind of communicative intention.

Differential conditioning has been well studied over the last century. The basic principle of this learning mechanism is that one conditioned stimulus (CS+) is paired with an unconditioned stimulus (US), while another CS remains unpaired (CS-). The pairing of CS with US results in a conditioned response (CR) (Pavlov, 1927). Traditionally, three main phases can be identified in a classical conditioning paradigm, namely habituation, acquisition and extinction. Habituation consists in presenting a series of unpaired CS and US, mostly to verify that the CS does not originate an evident CR before being paired with the US. Acquisition refers to the process of CR development, and has become a synonym for the term conditioning itself. Extinction is the gradual diminution of a CR that takes place when the US no longer occurs with the CS (Moore, 2002). Many variations on this model have been tested, such as different CS modalities, using pleasant/reward or aversive/punishment US and conditioning behavior or brain responses.

In the present fMRI study, we introduce a semantic double conditioning paradigm with emotional sounds, in which incongruent and congruent word-pairs are associated with a negative and a positive emotional sound respectively. Differently from previous conditioning studies, we try to condition two different responses, since once validated, this paradigm should be applied for communication, namely conditioning an affirmative ("yes") and a negative ("no") response.

Classical semantic conditioning refers to the conditioning of responses to meaningful words or sentences, irrespective of the specific letters or sounds that constitute the words (Razran, 1939; Razran, 1961). The repeated association of words or sentences with a significant stimulus (the US) results in conditioning and produces a CR, measured at the level of cortical evoked responses (Montoya et al., 1996).

Biconditional discrimination is a design in which multiple CSs are paired with one US (Saavedra, 1975). This design was first tested with humans in 2002 (Lober & Lachnit, 2002) by pairing visual stimuli (different types of letter combinations) with one type of US (electrical shock), while other visual stimuli remained unpaired. With the term "double conditioning" we describe here a form of conditioning in which different CSs are paired with different USs (Lachnit, 1991). Lachnit (1991) showed that combining two USs in one experiment changes the properties of each US. In 1997, Watt and Honey performed conditioning experiments with rats using two auditory and two visual CS, which were cross-paired with 2 US (food or sucrose) (Watt & Honey, 1997). They concluded that rats do not simply encode the general affective properties of appetitive reinforcers during a Pavlovian conditioning procedure, but rather have a more elaborate encoding, which influences performance.

fMRI represents a privileged technique for studying classical conditioning of brain responses (Büchel & Dolan, 2000). Most reported studies concern conditioning with aversive stimuli (Büchel, Morris, Dolan & Friston, 1998; Klucken et al., 2012; LaBar et al., 1998; Ploghaus et al., 1999; Schneider et al., 1999). LaBar and colleagues (1998) performed a single-trial fMRI study of differential fear conditioning, using different geometric shapes as CS and an electric shock as US, showing that amygdala was activated during acquisition and extinction. Additional activation was also found in the ACC. The elicited responses were stronger during the early phase of each trial (early acquisition and early extinction), suggesting an interaction between time and condition. In another fear conditioning paradigm performed with fMRI, Büchel et al. (1998) found a greater response to the CS+ compared to the CS- not only in the ACC and in the amygdala, but also in motor-related areas such as the premotor cortex, which could be an expression of the readiness to escape an aversive situation. Also in this study, the evoked responses decreased over time. An fMRI study involving pain conditioning (Ploghaus et al., 1999), where a thermal pain (US) was associated to a color (CS) indicated the involvement of the ACC and the insula.

Regions that are involved in classical conditioning, language and emotion processing are often located deep in the brain. For this reason, fMRI, with its relatively high spatial resolution that allows recording brain activity from very specific cortical and subcortical regions, represents a reasonable choice for studying a classical conditioning process involving semantic and emotional stimuli.

The aim, the methods and the procedure adopted in our study will be described in detail in the following sections.

3.2. Aim and hypothesis

The present study investigated the possibility to develop an auditory classical conditioning paradigm in a fMRI-BCI setting. Such paradigm was conceived to condition subjects to associate unconditioned emotional stimuli (US1 and US2, respectively an emotionally negative and an emotionally positive stimulus,) to incongruent (CS1) and congruent (CS2) word-pairs, eliciting a negative ("no") and affirmative ("yes") response respectively, in view of an application for communication with AD patients. More specifically, we investigated the possibility to discriminate a negative response from an affirmative response by means of a classification of the BOLD signal, following classical conditioning with emotional stimuli (Fig. 3). The advantage of this procedure is that it should be easier to classify emotional states (e.g. with a SVM, as in the study performed by Sitaram et al. (2011), than to discriminate the mental states related to "yes" and "no" thinking.

In agreement with Sitaram and collaborators (2011) and with Anders and collaborators (Anders, Eippert, Weiskopf & Veit, 2008), we hypothesized obtaining, following the conditioning, a greater differentiation between negative and affirmative responses in areas that are mostly involved in emotional processing, such as the insula and some portions of the superior temporal gyrus (STG) and superior frontal gyrus (SFG). We also hypothesized the activation of areas directly involved in classical conditioning, such as the hippocampus (Berger & Thompson, 1978; Berger, Alger & Thompson, 1976; Clark, Manns & Squire, 2002; Holland & Bouton, 1999; Phillips & LeDoux, 1992; Schneider et al., 1999; Solomon, Solomon, Schaaf & Perry, 1983; Thompson, 1990) and the amygdala (Büchel et al., 1998; LaBar et al., 1998).

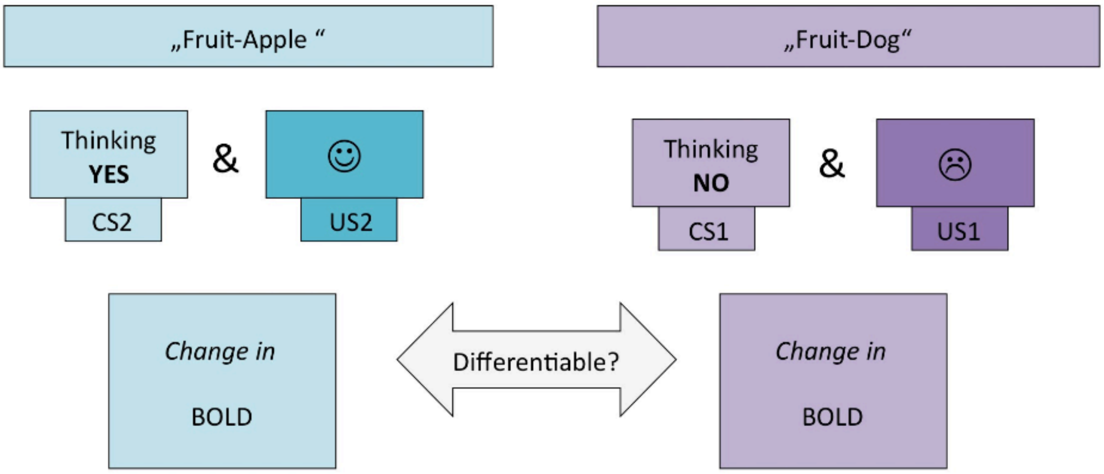


Fig. 3 The aim of the present study is to condition subjects to associate unconditioned emotional stimuli (US1 and US2, an emotionally negative and an emotionally positive sound, respectively) to incongruent (CS1) and congruent (CS2) word-pairs, eliciting a negative ("no") and an affirmative ("yes") response, respectively.

3.3. Methods

3.3.1. Subjects

Ten subjects (five women, five men), aged between 21 and 28 (mean = 25.3, SD = 1.77), recruited at the University of Tübingen, participated to the study, receiving reimburse of 12€. All participants were right-handed native German speakers.

All subjects received an informative document regarding the properties and risks of fMRI, and signed the informed consent for data handling. Before entering the scanner, subjects filled in a form to ascertain their suitability for participation in the study (e.g. absence of metal in the body, no epilepsy, no pregnancy, no claustrophobia). The study was approved by the Ethics Committee of the Medical Faculty of the University of Tübingen.

3.3.2. Stimuli

We decided to use auditory stimuli, considering that the final aim of the development of this BCI would be to allow basic communication with AD patients. It has been demonstrated that although AD patients differ significantly from healthy controls in emotional processing of visual stimuli, there are no consistent differences in processing emotions *via* the auditory domain (Koff et al., 1999). Moreover, an interview with Alzheimer's and dementia specialists shed light on the difficulty of patients in focusing on visual images, since their gaze often directs elsewhere. In addition, the volume of the stimuli may be adjusted according to the patients' hearing acuity. We decided to use word-pairs, which can include very simple terms belonging to common categories (such as animals or countries), so that the recognition of their congruence or incongruence may be detectable, at least implicitly, even by AD patients. In fact, several authors have claimed that semantic information that may not be explicitly accessible to AD patients could be relatively intact at an implicit level (Hartman, 1991; Laisney et al., 2011; Nebes, 1994; Nebes, Brady & Huff, 1989; Ober & Shenaut, 1988). For this reason, one of the methods that are frequently used in the assessment of dementia is the word semantic priming paradigm, which allows semantic memory to be evaluated implicitly, minimizing the influence of non-semantic cognitive processes. In a typical word semantic priming paradigm, the priming effect is demonstrated by a shorter reaction time and/or greater accuracy when the target word is associated to a semantically related prime rather than an unrelated one (Laisney et al., 2011). In a study by Rogers and Friedman (2008), AD patients exhibited normal priming for category superordinates (e.g. “Bomb-Weapon”), indicating that their semantic network was at least partially intact.

The stimuli in our paradigm consisted of:

- 300 German word-pairs, half congruent (e.g. “Obst-Apfel”, “fruit-apple”) and half incongruent (e.g. “Obst-Hund”, ”fruit-dog”), read aloud by a native speaker, recorded using a SpeedLink USB microphone and QuickTime Player 7 program for Macintosh. The duration of each word-pair was 1.5 s. The word-pairs constituted the CS.
- Two standardized emotional sounds drawn from the International Affective Digitized Sounds (IADS, (Bradley & Lang, 1999) , which represented the US: a positive emotional stimulus (a baby-laugh) and a negative emotional stimulus (a scream). Information on the characterization of the IADS sounds

by discrete emotional categories can be found in Stevenson & James (Stevenson & James, 2008). The duration of each sound was 1.5 s.

The volume of the stimuli was standardized using an *ad hoc* Matlab script. To ascertain that all the stimuli (word-pairs and emotional sounds) had the exact length, their duration was adjusted using Audacity software.

Stimuli presentation in the fMRI scanner was performed with interfaces developed using Matlab v. 6.5 (Mathworks, Inc., Sherbon, MA). Participants heard all auditory stimuli through MRI-compatible headphones with efficient gradient noise suppression (up to 45 dB) and a filter system with more than 90 dB RF-suppression (MR confon System, Leibniz Institute for Neurobiology at Magdeburg, Germany).

3.3.3. Procedure

Behavioral measures

The Self-Assessment Manikin (SAM, (Bradley & Lang, 1994) was used to ask the participants to rate the pleasantness/unpleasantness and the arousal related to the two emotional US (scream and laugh) at the end of the first block and at the end of the fifth block. The SAM comprises two 9–point scales ranging from ‘pleasant’ to ‘unpleasant’ and from ‘not arousing at all’ to ‘very arousing’, respectively (Fig. 4).

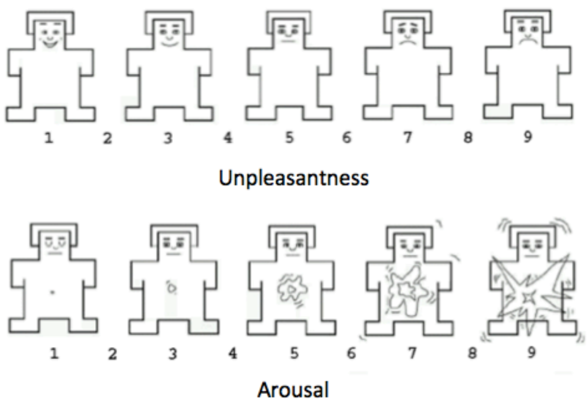


Fig. 4 The Self Assessment Manikin scales (Bradley et al., 1994), administered after the first and after the fifth block.

Experimental paradigm

To test our hypothesis, we used a paradigm comprising all three stages of conditioning (habituation, acquisition and extinction). The habituation phase, as in standard conditioning protocols, was included to detect the activations for all types of stimuli (congruent and incongruent word-pairs, laugh, and scream), independently from their association. The early acquisition phase was necessary to condition the negative and the affirmative responses (associated to the incongruent and congruent word-pairs respectively) with the emotional stimuli (the scream and the laugh respectively). The late acquisition phase included both paired and unpaired word-pairs, in order to reinforce the conditioning, while observing the first conditioned responses. The extinction phase, as in the standard conditioning protocols, was included to assess the classical conditioning effect.

The acquisition of fMRI data took place in one single session, divided into six blocks, using an image acquisition system based on an Echo-Planar Imaging (EPI) sequence, developed on a Siemens Tim Magnetic Trio 3.0 tesla scanner (Erdingen, Germany). A standard EPI was used (TR = 1.5 s., matrix size = 64 x 64, TE = 30 ms., flip angle α = 70°). Sixteen oblique slices (voxel size = 3.3 x 3.3 x 5.0 mm^3, slice gap = 1 mm), AC/PC aligned in axial orientation were acquired. For superposition of functional maps upon brain anatomy a high-resolution T1-weighted structural scan of the whole brain was collected from each participant (MPRAGE, matrix size = 256 x 256, 160 partitions, 1 mm^3 isotropic voxels, TR = 2300 ms., TE = 3.93 ms., TI = 1100 ms, α = 8°).

Block 1 – Habituation

In the first block, 25 incongruent word-pairs (CS1) and 25 congruent word-pairs (CS2), 25 negative emotional stimuli (scream, US1) and 25 positive emotional stimuli (laugh, US2) were presented to the subject in a random order (Fig. 5). The inter-stimulus interval (ISI) was also randomized to optimize statistical efficiency, and could last either 4.5, 6, or 7.5 s. The total block duration was 15 min. The total number of acquired slices was 600.

This block was useful to detect the activations for each of the four types of stimuli independently from their association, and to verify that there was no differentiation between affirmative response (associated to congruent word-pairs) and negative response (associated to incongruent word-pairs).

At the end of this block, participants were asked to rate the unpleasantness and the arousal related to the two emotional stimuli (scream and laughter) that constituted the US through the SAM.

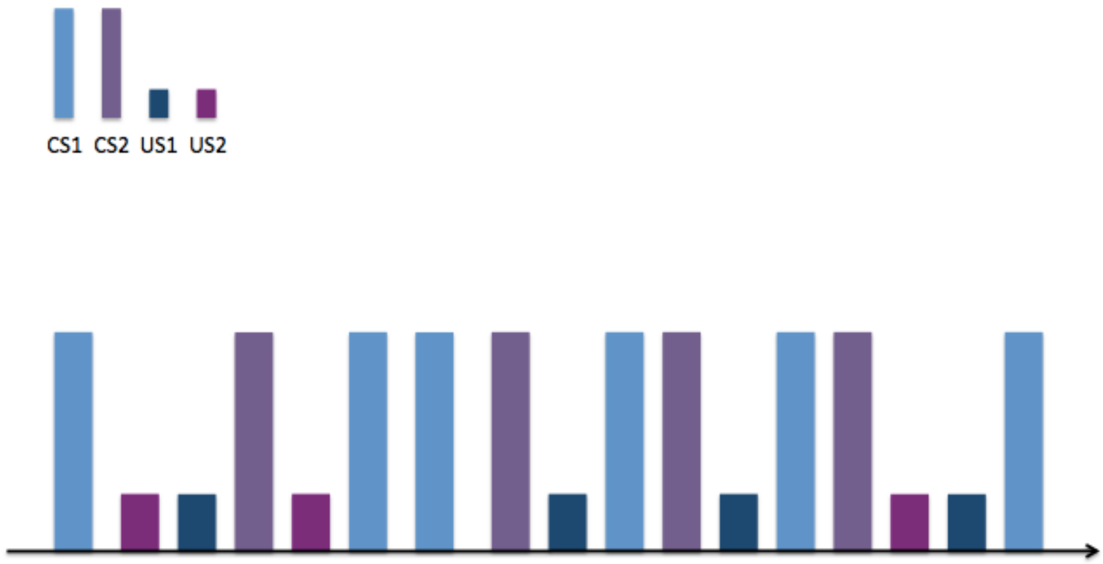


Fig. 5 Block 1 – Habituation phase. 25 incongruent word-pairs (CS1) and 25 congruent word-pairs (CS2), 25 negative emotional stimuli (scream, US1) and 25 positive emotional stimuli (laugh, US2) were presented to the subject in a random order.

Blocks 2 and 3 – Early acquisition

In the second and third blocks (which were structured identically), 25 incongruent word-pairs (CS1) and 25 congruent word-pairs (CS2) were presented in a random order (Fig. 6). Each word-pair was immediately followed by an emotional sound (100% pairing): negative (scream, US1) after incongruent word-pairs, and positive (laugh, US2) after congruent word-pairs. As in block 1, the ISI was randomized (4.5, 6, or 7.5 s.). The total duration of each block was 7.5 min. The total number of acquired slices was 350.

The aim of this block was to condition the negative and the affirmative response (associated to the incongruent and congruent word-pairs respectively) with the emotional stimuli (the scream and the laugh respectively), in order to discriminate between the two responses.

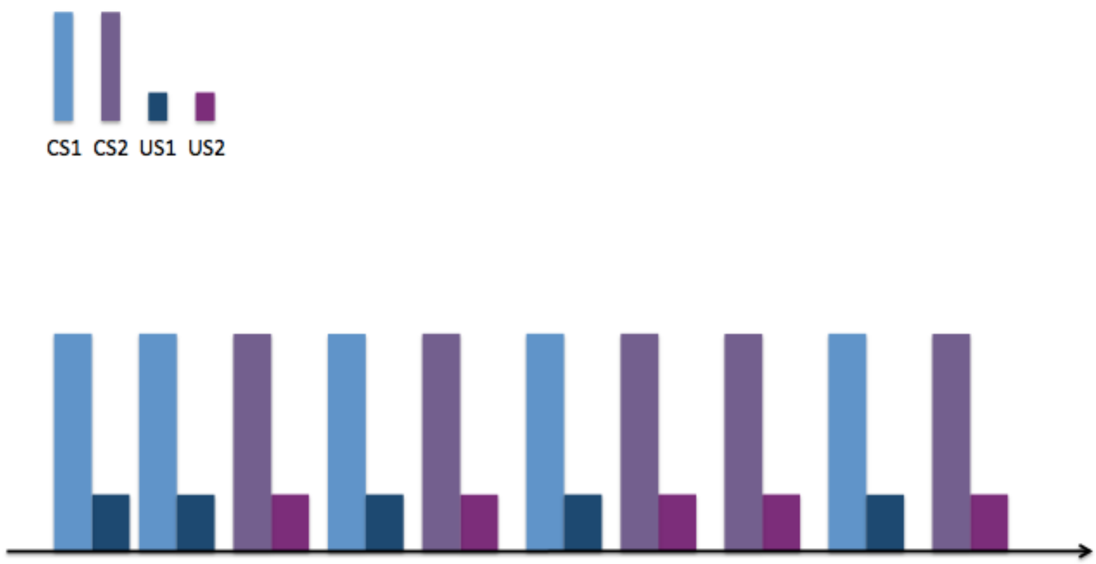
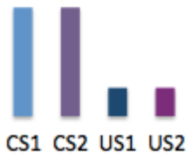


Fig. 6 Blocks 2 and 3 – Early acquisition phase. 25 incongruent word-pairs (CS1) and 25 congruent word-pairs (CS2) were presented in a random order. Each word-pair was immediately followed by an emotional sound: negative (scream, US1) after incongruent word-pairs, and positive (laugh, US2) after congruent word-pairs.

Block 4 – Late acquisition

In the fourth block, 25 incongruent word-pairs and 25 congruent word-pairs were presented in a random order (Fig. 7). In this block, only 10 incongruent word-pairs were followed by the negative emotional stimulus, and only 10 congruent word-pairs were followed by the positive emotional stimulus (40% pairing). As in the former blocks, the ISI was randomized (4.5, 6, or 7.5 s.). The total duration of the block was 7.5 min. The total number of acquired slices was 330.

The aim of this block was to verify whether classical conditioning had taken place, looking at the differentiation between incongruent and congruent word-pairs that were not followed by stimulation.



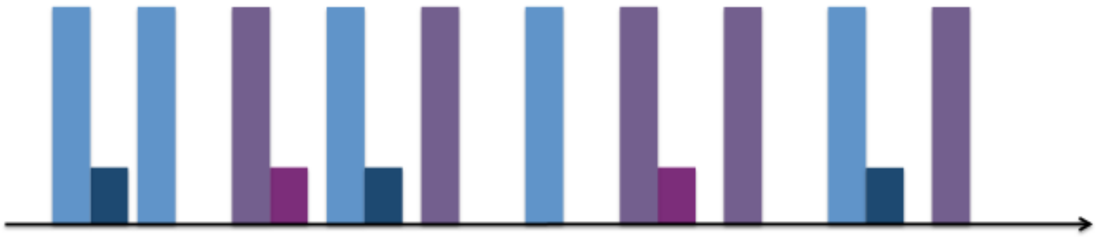


Fig. 7 Block 4 – Late acquisition phase. 25 incongruent word-pairs and 25 congruent word-pairs were presented in a random order. Only 10 incongruent word-pairs were followed by the negative emotional stimulus, and only 10 congruent word-pairs were followed by the positive emotional stimulus (40% pairing).

Block 5 – Late acquisition

In the fifth block, 25 incongruent and 25 congruent word-pairs were presented in a random order (Fig. 8). This time, only 5 of the incongruent word-pairs and 5 of the congruent word-pairs were followed by the emotional stimulation (20% pairing). As in the other blocks, the ISI was randomized (4.5, 6, or 7.5 s). The total duration of the block was 7.5 min. The total number of acquired slices was 320.

The aim of this block, as in block 4, was to verify the classical conditioning effect in the word-pairs that were not associated to emotional stimuli.

At the end of this block, subjects were asked once more to rate the unpleasantness and the arousal associated to the emotional stimuli using the SAM.

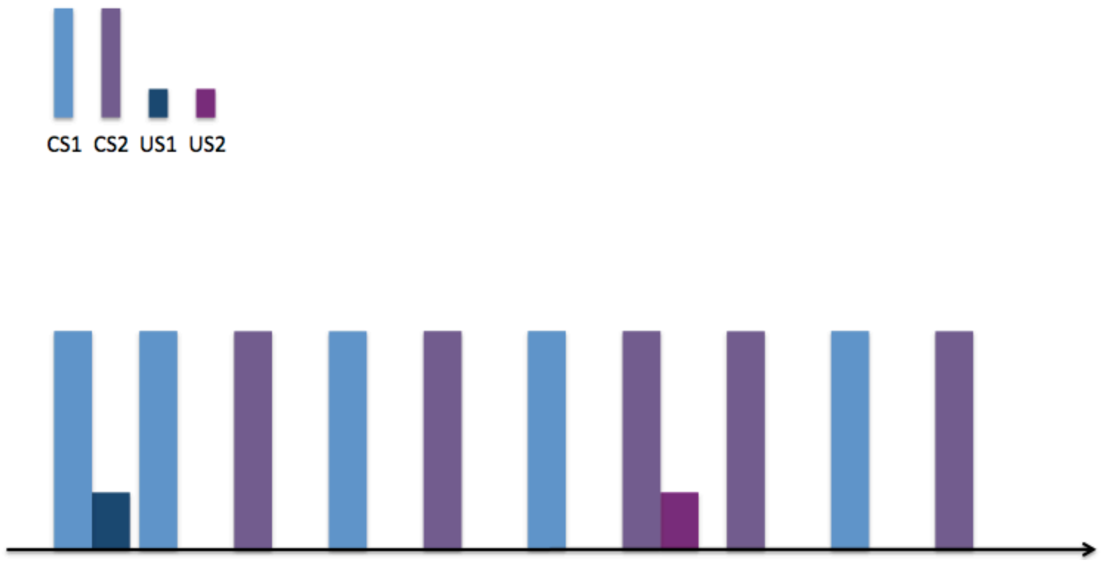


Fig. 8 Block 5 – Late acquisition phase. 25 incongruent word-pairs and 25 congruent word-pairs were presented in a random order. Only 5 incongruent word-pairs were followed by the negative emotional stimulus, and only 5 congruent word-pairs were followed by the positive emotional stimulus (20% pairing).

Block 6 – Extinction

In the sixth block, 25 incongruent and 25 congruent word-pairs were presented in a random order (Fig. 9). This time, none of the word-pairs were followed by emotional stimuli (0% pairing). The ISI varied randomly (4.5, 6, or 7.5 s). The total duration of the block was 7.5 min. The total number of acquired slices was 310.

The aim of this block was to assess the classical conditioning effect, this time removing completely the US.

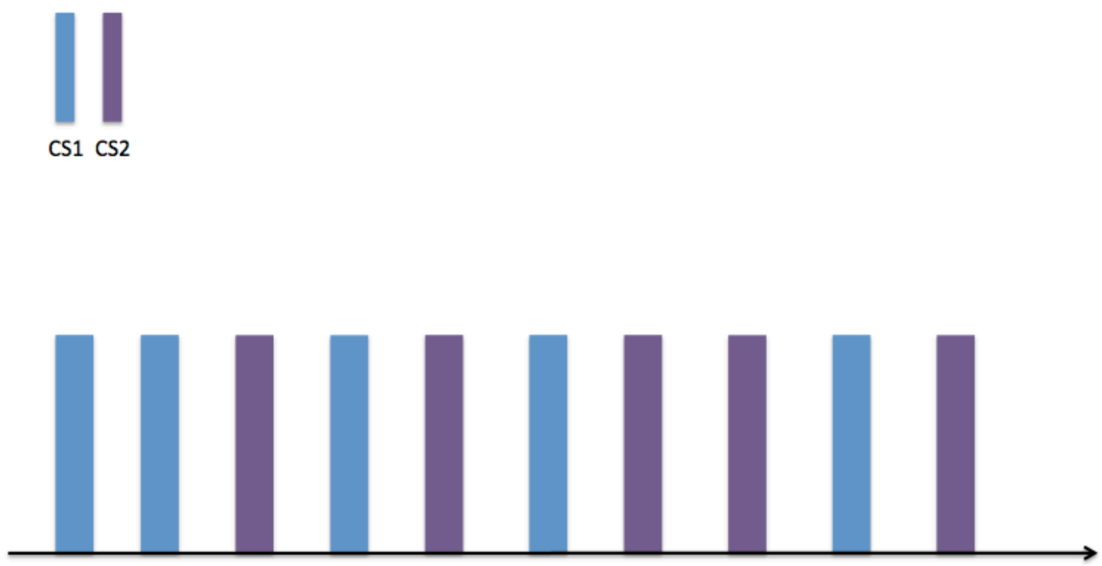


Fig. 9 Block 6 – Extinction phase. 25 incongruent word-pairs and 25 congruent word-pairs were presented in a random order. None of the word-pairs were followed by emoitonal stimuli (0% pairing).

The complete experimental session lasted around one hour. A global overview of the procedure can be seen in Fig. 10 and Fig. 11.

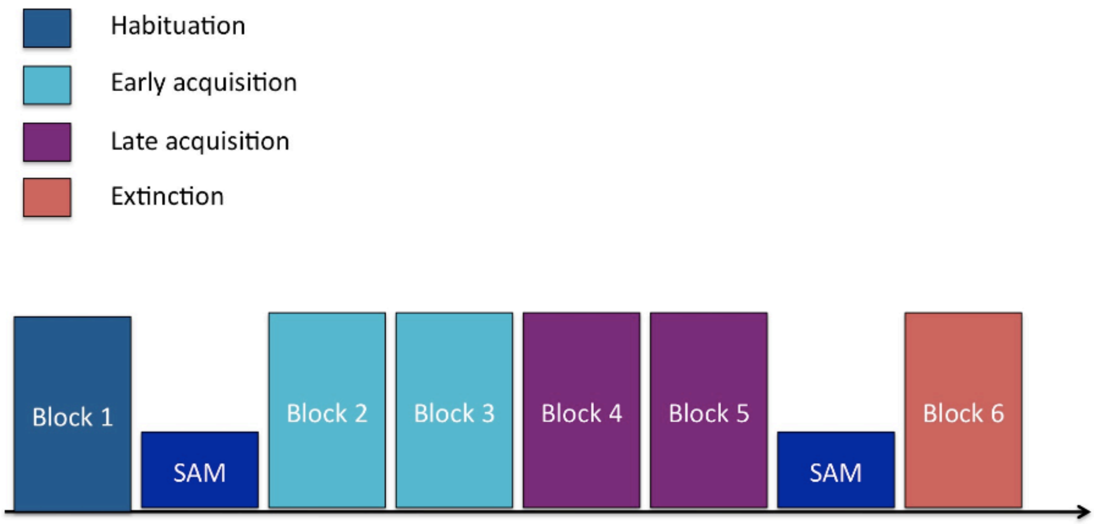


Fig. 10 General overview of the experimental paradigm. Block 1 was the habituation block, in which CS and US were presented randomly, without any association; blocks 2 and 3 were early acquisition blocks, in which all CS were paired with US; blocks 4 and 5 were late acquisition blocks, in which the number of CS paired with US diminished gradually; block 6 was the extinction block, in which CS were presented alone. After block 1 and after block 5 the SAM was administered, in order to evaluate how pleasant /unpleasant and how arousing were the US at the beginning and at the end of the measurement.

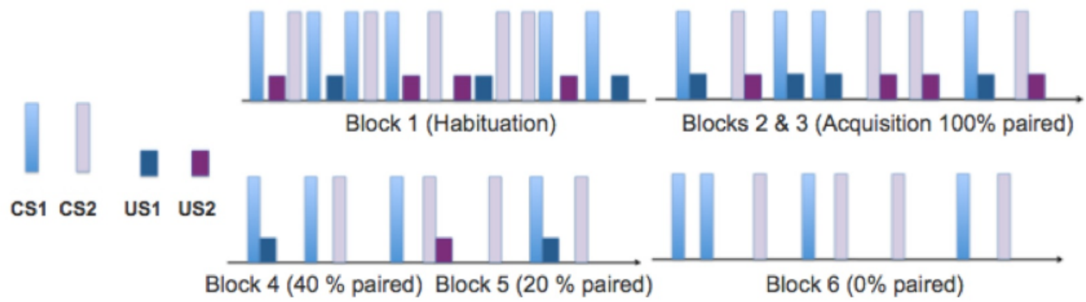


Fig. 11 General overview of the different blocks. In block 1, word-pairs (CS) and emotional sounds (U2) were presented randomly. In blocks 2 and 3, 100% of the word-pairs were followed by a sound; in blocks 4 and 5, the association percentage decreased gradually, first to 40% and then to 20%; in block 6, none of the word-pairs were followed by sounds.

3.4. Behavioral results and discussion

A two-tailed t-test indicated that participants rated the scream as significantly more unpleasant (block 1: $t(20) = 10.62$, block 5: $t(20) = 3.09$, $p<0.01$) and more arousing (block 1: $t(20) = 5.87$, block 5: $t(20) = 2.66$, $p<0.02$) than the laugh, both at the beginning and at the end of the measurement. The arousal associated to the scream was significantly less at the end of block 5 compared to the end of block 1 ($t(20) = 2.96$, $p<0.01$), although no significant difference was found for the laugh. The valence associated to the scream and laugh did not change significantly during the experiment.

These results confirm that the scream can be considered as a negative sound and that the baby-laugh can be considered as a positive sound, justifying their association respectively with the negative response related to incongruent word-pairs ("no thinking") and with the affirmative response related to the congruent word-pairs ("yes thinking"). The fact that the arousal associated to the scream decreased may indicate a habituation of the subjects to the sound, which however, was not reflected in the pleasantness/unpleasantness rating, since the scream was always rated as very unpleasant.

In the following chapters we will describe two different types of fMRI data analyses performed on the data obtained in the present experiment: univariate with Statistical Parametric Mapping (Chapter 4) and multivariate with a Support Vector Machine (Chapter 5).

4. Univariate data analysis using Statistical Parametric Mapping (SPM)

4.1. Introduction

Traditional neuroimaging approaches aim to determine how a specific perceptual, cognitive or emotional state is encoded in brain activity, by considering which brain areas are involved in a particular task. This is achieved by repeatedly measuring the activity from different locations in the brain, but analyzing each location in isolation (Norman et al., 2006). Therefore, the measure of any difference in the activity is gained by comparing two or more mental states at each individual sampled location. Theoretically, if the responses at any brain location differ between two mental states, it should be possible to determine which of the mental states reflects what the subject is thinking. Brain imaging statistical analyses that consider how responses vary at many single voxels, but considering each individual voxel separately, are defined as univariate analyses. Differently from multivariate approaches, univariate analyses support inferences about regionally specific effects and are more sensitive to focal effects (Friston, 2003).

Statistical parametric mapping (SPM) is a kind of univariate analysis, which considers only single-decision variables at any time (Haynes & Rees, 2006). This procedure is based on the General Linear Model (GLM) and on the Gaussian Random Field (GRF) theory (Friston, 2003). In the present chapter, after describing the main aspects of SPM analyses, we will show the results obtained by analyzing the data from our semantic classical conditioning study.

4.1.1. Statistical Parametric Mapping

SPM is commonly used for the identification of functionally specialized brain responses. It is a voxel-based approach, which utilizes classical inference to relate regionally specific responses to experimental factors. Friston (2003) described two main principles of brain functional organization, namely functional integration and functional specification, where the integration within and among specialized areas is mediated by effective connectivity. While functional localization implies that a function can be localized in a specific brain region, specialization suggests that a particular area is specialized for some aspects of a function, and this specialization is anatomically segregated within the cortex. The neural basis of a single function, therefore, may involve several specialized and functionally integrated areas (Friston, 2003; Zeki, 1990).

SPM implies the design of spatially extended statistical processes to test hypotheses about regionally specific effects (Friston, Frith, Liddle & Frackowiak, 1991). Statistical parametric maps are image processes, with voxel values that are, under the null hypothesis, distributed on the basis of a known probability density function, usually Student's T or F distributions (T-maps or F-maps). More precisely, SPM consists in analyzing each and every voxel by using a standard univariate statistical test. Statistical parametric maps refer to the probabilistic behavior of Gaussian fields (Friston, Worsley, Frackowiak, Mazziotta & Evans, 1994; Friston, 2003). Unexpected excursions of the statistical parametric map are interpreted as regionally specific effects, due to the process that has been experimentally manipulated (Friston, 2003).

SPM implies the joint use of the GLM and the GRF theory. The GLM is used to estimate some parameters that could explain the spatially continuous data, identically as in conventional analyses of discrete data. With few exceptions, every analysis of fMRI time-series is a variant of the GLM and can be implemented with the same equations and algorithms, including t-tests on scans assigned to different conditions, correlation coefficients between observed responses and stimulus functions, inferences using multiple linear regression, evoked responses estimated with linear time invariant models, and selective averaging to estimate event-related responses. What distinguishes the different types of analysis is the design matrix encoding the experimental design (Friston, 2003).

In the next paragraph, data analyses performed with SPM on the data from our semantic double classical conditioning study will be described.

4.2. Methods

4.2.1. Pre-processing

Before starting the data analysis, a series of spatial transformations were performed, in order to reduce unsought variances induced by movement or shape differences among scans. Since voxel-based analyses are based on the assumption that the data obtained from a specific voxel all derive from the same part of the brain, violations of such assumption will obviously introduce artifacts in the voxel values that can obscure the effects of interest (Friston, 2003). Image pre-processing was carried out using SPM-8 software package (Wellcome Department of Cognitive Neurology, London, England, UK) running under a Matlab 7.7 environment (Mathworks Inc., Sherborn, Massachusetts, USA). The images from each subject were realigned and unwarped to correct for head movement, and were normalized to a standard EPI (echo-planar image) template in MNI (Montreal Neurological Institute) space. Functional images were spatially smoothed using a 9 mm full-width half maximum isotropic Gaussian kernel.

4.2.2. SPM data analysis

Statistical analysis was carried out using the general linear model (GLM) with the canonical hemodynamic response function (HRF) as a basis set. In a first level analysis, regressors were defined to allow the investigation of the experimental conditions, especially to discriminate between paired (CS+) and unpaired (CS) word-pairs. The defined regressors were CS1+ (paired incongruent word-pairs), CS2+ (paired congruent word-pairs), CS1 (unpaired incongruent word-pairs), CS2 (unpaired congruent word-pairs), US1 (scream) and US2 (laughter), separately for each condition phase. The six movement regressors for each block were included as confounds in the design matrix to capture residual movement-related variance. The following contrasts were tested: US1, US2, and US1 vs. US2 for block 1 (habituation); CS1+, CS2+, CS1+ vs. CS2+ for blocks 2-5 (acquisition); CS1, CS2, CS1 vs. CS2 for blocks 4-6 (extinction). In a second level analysis, contrast images of all subjects were used to assess the main effects of the conditioning. A two-sample t-test including the individual contrast images for US1 and US2 from block 1 was computed in order to detect significant activated brain regions related to these emotional unconditioned stimuli during habituation. One-sample t-tests were performed to detect differences in brain regions involved in the US1 vs. US2, and CS1(+) vs. CS2(+) contrasts, in the habituation and extinction phases. To investigate the different brain regions activated by congruent and incongruent word-pairs, a full 2 x 2 factorial model with the factors Congruence (congruence/incongruence) and Block (2 and 3) was performed for the early acquisition phase, and a full 2 x 2 x 2 factorial model with the factors Congruence (congruence/incongruence), Block (4 and 5) and Paired/unpaired for the late acquisition phase. For all group statistics a voxel-level threshold of $p<0.001$ and an extent threshold of 10 contiguous voxels were used to identify clusters of activation within regions of interest, giving a reasonable balance between sensitivity and specificity.

4.3. Results

4.3.1. Habituation phase

The complete list of activations obtained during the habituation phase is presented in Table 1. Activations for US1 and US2 mostly differed in the cingulate gyrus, the superior frontal gyrus (STG) and the inferior frontal triangularis (IFT). The latter, together with the inferior parietal lobule (IPL), was also more active after listening to incongruent compared to congruent word-pairs.

Table 1 Habituation.

Contrast	Region	Lat	t-value	MNI coordinate		
				x	y	z
US1>US2	Cingulate gyrus, BA 24	L	6.03	-18	-19	43
	Inferior frontal triangularis (IFT)	R	5.56	54	20	4
	Superior frontal gyrus (SFG)	R	5.25	24	47	19
	Superior frontal gyrus (SFG), BA 9	R	5.25	15	53	40
US1	Ineferior frontal operculum	L	8.5	-45	5	-11
	Inferior frontal orbitalis	R	6.63	51	17	-8
	Rolandic operculum	R	6.1	57	-19	16
	Supplementary motor area (SMA), BA 6,	R	6.06	6	-1	70
	Superior temporal gyrus (STG)	R	6.01	51	-46	10
	Precuneus	L	4.94	0	-76	43
	Precuneus, BA 5	L	4.81	-3	-43	73
	Middle frontal gyrus (MFG)	R	4.78	27	56	25
	Middle frontal gyrus (MFG)	L	4.55	-36	5	61
	Superior frontal gyrus (SFG)	L	4.49	-12	50	40
	Caudate	L	4.12	-15	-16	25
US2	Superior temporal gyrus (STG)	L	6.58	-63	-10	1
	Rolandic operculum	R	6.3	60	-16	13
	Supplementary motor area (SMA), BA 6	R	5.82	6	-1	76
	Superior temporal gyrus (STG)	L	4.73	-45	2	-11
CS1>CS2	Inferior frontal triangularis (IFT), BA 3	L	3.45	-51	20	28
	Inferior parietal lobule (IPL)	L	3.35	-45	-55	46

$p<0.001$ uncorrected [$k>10$]; R=Right, L=Left

4.3.2. Early acquisition phase

The complete list of activations found during the early acquisition phase (blocks 2 and 3) can be seen in Table 2. Particularly, comparing CS1 and CS2, a higher activation was found in the insula, in the inferior frontal operculum, and in the ACC (Fig. 12 and Fig 13).

Table 2 Early acquisition.

Contrast	Region	Lat	t-value	MNI coordinate		
				x	y	z
CS1+>CS2+	Insula, BA 47	R	4.57	33	26	1
	Insula	L	4.55	-36	20	-8
	Corpus callosum	R	4.12	12	-31	25
	Inferior frontal operculum	R	4.11	48	14	25
	Supplementary motor area (SMA)	L	3.99	-3	14	58
	Anterior cingulate cortex (ACC)	R	3.85	9	14	25

p 0.001 uncorrected [k>10]; R=Right, L=Left

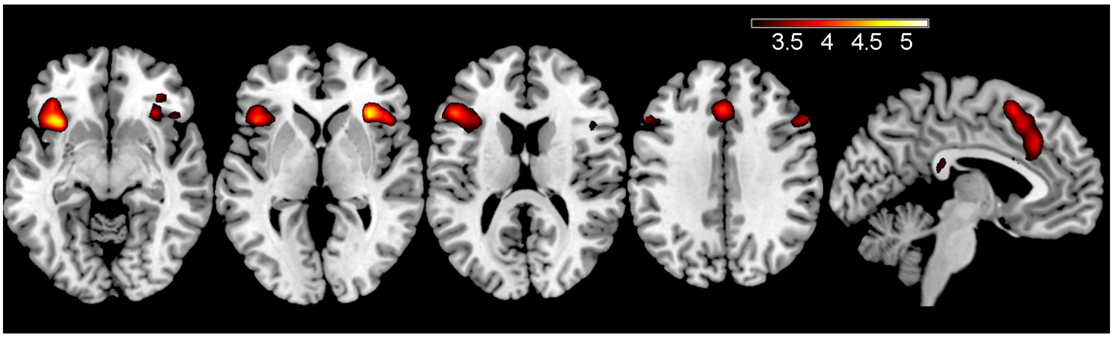


Fig. 12 Early acquisition phase: CS1+ > CS2+ contrast. Activation of bilateral insula, inferior frontal operculum and ACC.

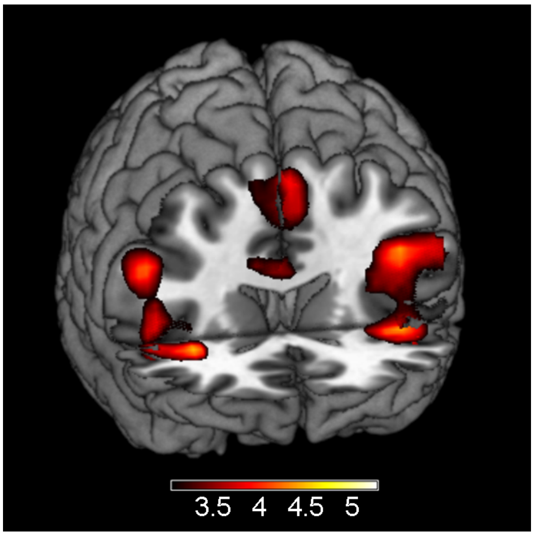


Fig. 13 Early acquisition phase: CS1+ > CS2+ contrast. Activation of bilateral insula, inferior frontal operculum and ACC.

4.3.3. Late acquisition phase

The activations for the late acquisition phase (blocks 4 and 5) are summarized in Table 3. In the late acquisition phase, the STG and the left insula were significantly more activated when comparing CS1+ and CS2+. For the unpaired trials, activation was also found in the right STG for CS1 vs. CS2, and in the inferior frontal orbitalis for CS2 vs. CS1 (Fig. 14).

Table 3 Late acquisition.

Contrast	Region	Lat	t-value	MNI coordinate		
				x	y	z
CS1+ > CS2+	Middle temporal gyrus (MTG)	L	5.13	-60	-7	-5
	Precentral gyrus	L	5.07	-45	-4	58
	Superior temporal gyrus (STG)	R	4.78	48	-40	4
	Putamen	R	4.7	24	-1	13
	Supplementary motor area (SMA), BA 6	R	4.65	3	-1	64
	Insula	L	4.25	-36	23	10
	Middle frontal gyrus (MFG)	L	3.78	-30	38	25
	STG, BA22	R	3.52	54	11	-5
	Middle frontal gyrus (MFG)	R	3.44	48	-1	58
CS2+ > CS1+	Middle frontal gyrus (MFG)	L	4.25	-39	56	-2
	SFG, BA10	L	3.9	-15	65	13
CS1 > CS2	Middle temporal gyrus (MTG)	L	7.28	-60	-7	-5
	Supplementary motor area (SMA)	L	5.47	-6	11	52
	Precentral gyrus, BA6	L	5.33	-54	-1	46
	Precentral gyrus, BA6	R	4.64	57	-7	49
	Superior temporal gyrus (STG)	R	4.56	48	-40	4
	Insula*	L	3.21	-51	-40	19
CS2 > CS1	Inferior frontal orbitalis	R	3.61	48	44	-5

*p< 0.001 uncorrected [k>10]; *=[k>4]; R=Right, L=Left*

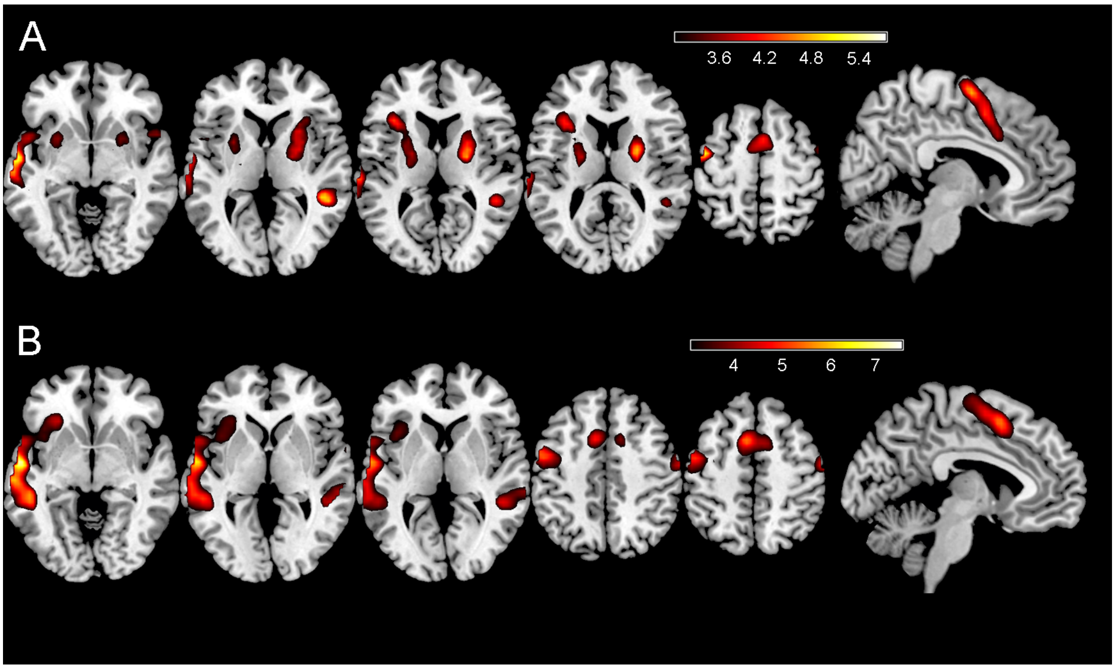


Fig. 14 Late acquisition phase: activations for the CS1+ > CS2+ contrast (A) and for the CS1 > CS2 contrast (B).

4.3.4. Extinction phase

Comparing CS1 and CS2 in the extinction phase (block 6), activations in the right insula, bilateral temporal and frontal lobe were found (listed in Table 4). These activations can be seen in Fig. 15.

Table 4 Extinction.

Contrast	Region	Lat	t-value	MNI coordinate		
				x	y	z
CS1 > CS2	Insula	R	8.47	30	26	7
CS2 > CS1	Middle frontal gyrus (MFG)	R	7.32	9	59	4

p< 0.001 uncorrected [k>10]; R=Right, L=Left

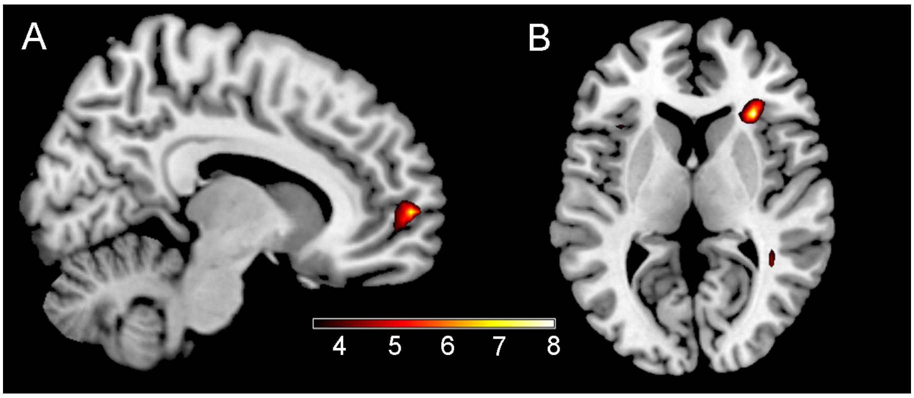


Fig. 15 Extinction phase: activation in the right MFG for the CS2 > CS1 contrast (A) and activation of the right insula for the CS1 > CS2 contrast (B).

4.4. Discussion

4.4.1. Brain activations during classical conditioning

The activation of the ACC during the acquisition phase may indicate that the association process was taking place, in agreement with studies showing that this structure is crucial for conditioning (Sehlmeyer et al., 2009). Consistently with this finding, the putamen, which is a region related to implicit learning (Packard & Knowlton, 2002), was activated in the late acquisition phase. Lesion studies suggest a critical role for medial temporal lobe structures, especially the amygdala, in the acquisition of conditioned emotional responses (Büchel et al., 1998; LaBar et al., 1998; LeDoux, 1996). It is relevant to point out that although the amygdala is often activated in studies focusing on fear conditioning (LaBar et al., 1998; Phillips & LeDoux, 1992; Rogan, Stäubli & LeDoux, 1997), we did not detect activation in this area. In fact, although the scream was a remarkably aversive sound, and was rated as both arousing and unpleasant by the subjects, they presumably did not perceive it as a fearful stimulus. Moreover, it has been shown that amygdala activation is subject to habituation during conditioning (Büchel et al., 1998).

The activation of emotion-related regions such as the STG and the insula (Phan et al., 2002; Phillips et al., 1998a; Phillips et al., 1998b; Radua et al., 2010; Sitaram et al., 2011) during the late acquisition and extinction phases, when the emotional US were no more presented, but not during the habituation phase, indicates that classical conditioning has taken place, and that the conditioned response to incongruent and congruent word-pairs was affected by the association with the scream and the laugh.

4.4.2. Language and semantic related brain activations

Several areas related to language processing were activated. In the habituation phase, when the word-pairs were presented separately, the left IFT, known to be involved in the decoding of word meaning (Demb et al., 1995; Mainy et al., 2008), and the left IPL, which has been correlated with language ability (Simon, Mangin, Cohen, Le Bihan & Dehaene, 2002), were more active after listening to incongruent compared to congruent word-pairs. These results are similar to the ones found in studies that used semantically correct and incorrect sentences (Baumgaertner, Weiller & Büchel, 2002; Friederici, Rüschemeyer, Hahne & Fiebach, 2003; Yu, Lang, Birbaumer & Kotchoubey, 2011), which showed higher activation for the latter. Such findings could be explained with a quantitative difference in the processing of congruent and incongruent semantic material (Yu et al., 2011), leading to an increase of metabolic activity in core language areas, due to a higher complexity in the information of incongruent sentences or word-pairs (Baumgaertner et al., 2002).

The early acquisition phase revealed the involvement of the right inferior frontal operculum, part of Broca's area, which was found to be involved in language comprehension (Grewe et al., 2005). Further, late acquisition revealed the involvement of the middle temporal gyrus (MTG), known to be activated when listening to auditory stimuli, particularly during language and comprehension tasks (Binder, Desai, Graves & Conant, 2009), for the paired and unpaired trials comparing the incongruent with the congruent word-pairs. For the same contrast, activation in the STG was found during the late acquisition for paired and unpaired word-pairs, and during extinction. The STG was shown to be involved in both speech processing {SenteCitation (Buchsbaum, Hickok & Humphries, 2001; Zatorre, Evans, Meyer & Gjedde, 1992) and production (Hickok et al., 2000), and in auditory processing (Boly et al., 2004; Galuske, Schlote, Bratzke & Singer, 2000; Howard et al., 2000). For the paired word-pairs, the activation was more specific in the BA 22 of the STG, which also comprises Wernicke's area, involved in language comprehension (Dronkers, Wilkins, Van Valin, Redfern & Jaeger, 2004; Just, Carpenter, Keller, Eddy & Thulborn, 1996; Lesser et al., 1986). The STG is also known to be important for the perception of emotional stimuli (Phillips et al., 1998a; Radua et al., 2010; Sitaram et al., 2011). The angular gyrus was activated more for the unpaired congruent word-pairs compared to the incongruent word-pairs in the late acquisition phase. This area was shown to be activated during language comprehension tasks at a linguistic-semantic level (Binder et al., 1997; Ramachandran, 2004).

4.4.3. Brain activations related to the emotional US

Both US stimuli, considered independently, elicited activations in the left STG, the rolandic operculum and the supplementary motor area (SMA, BA 6). An explanation for the SMA activity could come from the theory proposed by Büchel and coworkers (1998). Bodily movement, such as withdrawal of a body part or lid closure, could be a defensive mechanism to avoid the impact of a US (e.g. pain or air puff). Although subjects were instructed not to move, it is likely that generating a preparatory motor response was plausible in our setting, where they had to listen to segments of screaming and laughter. The activation of the left STG relative to the US is more intuitive (Fig. 12), as this area is not only involved in auditory processing (Boly et al., 2004; Galuske et al., 2000; Howard et al., 2000) but is also important for the perception of emotional stimuli (Phillips et al., 1998a; Phillips et al., 1998b; Radua et al., 2010; Sitaram et al., 2011). The posterior portion of the ACC (BA 24), the right IFT and the right SFG (BA 9) were more activated after listening to the scream compared to the laughter, and could be considered as a consequence of their relation to unpleasant stimuli. ACC (BA 24) is associated to the perception of unpleasant stimuli (Hsieh et al., 1994) and to pain (Jones, Brown, Friston, Qi & Frackowiak, 1991; Talbot et al., 1991) and SFG (BA 9) is involved in the processing of pleasant and unpleasant emotions (Lane et al., 1997). The right IFT was found to be activated for negative but not positive arousing stimuli (Anders et al., 2008), in accordance with our study. A higher activation for the scream compared to the laughter was found, consistently with the SAM ratings, which revealed that the scream was subjectively more arousing then the laughter.

In the early and late acquisition phases, the following areas related to emotion processing were activated: the ACC, the insula and the STG. These activations were greater for the paired incongruent word-pairs compared to the congruent ones. The ACC activation is probably related to the US, while it is known to be associated to the perception of unpleasant stimuli (Hsieh et al., 1994). The insula has been shown to be involved in emotional processing (Phan et al., 2002; Sitaram et al., 2011) and was associated to empathy (Singer et al., 2004). More importantly, in the unpaired word-pairs of the late acquisition and extinction phases, when the emotional US were not presented anymore, the STG and the insula were still activated, showing an effect of classical conditioning.

4.4.4. Potential applications

The results obtained with the univariate (SPM) analysis indicate that emotional stimuli are a valid means for classical conditioning, allowing a differentiation between incongruent and congruent word-pairs, and therefore between negative and affirmative thinking. Interestingly, the differential activations take place in brain areas such as the insula, the STG and the ACC, which are recognized to be involved in emotional processing. The advantage of using this kind of paradigm is that, being emotion-based, it does not require subjects to actively engage in a task, and could therefore be used for basic communication with patients affected by dementia.

Given the encouraging results obtained with the univariate analysis, the data from the present classical conditioning study was also analyzed with a Support Vector Machine-based multivariate approach (presented in Chapter 5).

5. Multivariate data analysis using a Support Vector Machine

5.1. Introduction

In contrast to the conventional univariate neuroimaging approach, which is strictly location-based, recent studies have shown that the efficiency of statistical analyses may be significantly increased by taking into account the whole spatial pattern of brain activity, which can be measured simultaneously at different locations (Haynes & Rees, 2005a). In fact, it is possible that two brain regions do not carry information about a cognitive state individually, but may nevertheless do so when analyzed jointly (Sidtis, Strother & Rottenberg, 2003). An analytical method that considers multiple decision variables, taking into account patterns of information that might be present across multiple voxels, is defined as a multivariate analysis, and is based on the intuition that multiple and spatially distributed regions act in consort during a task (Lee et al., 2010). In this way, information available at each voxel can be efficiently accumulated across many spatial locations (Haynes & Rees, 2005a).

Numerous research groups have used multivariate analyses to study functional relationships between brain areas (Calhoun, Adali, Pearlson & Pekar, 2001; Friston, Harrison & Penny, 2003; McIntosh & Lobaugh, 2004; McIntosh, Bookstein, Haxby & Grady, 1996). The last few years have seen the development of the concept that fMRI analyses can be performed as a pattern-classification problem, therefore recognizing patterns of brain activity as associated with specific mental states (Norman et al., 2006). Multivariate analyses have also been applied to EEG data (Müller-Putz, Scherer, Pfurtscheller & Rupp, 2005; Parra et al., 2002; Peters, Pfurtscheller & Flyvbjerg, 1998; Vallabhaneni & He, 2004; Wang, Deng & He, 2004).

Traditional fMRI analyses aim at finding voxels that show a significant response to experimental stimuli. In order to increase sensitivity to a given stimulus or condition, these methods require a spatial averaging across the voxels that respond significantly to the condition. While reducing noise, this approach also reduces signal, firstly because even voxels with weaker responses may provide some information about the presence or absence of the condition, and secondly because spatial averaging blurs out fine-grained spatial patterns that may discriminate between conditions (Kriegeskorte, Goebel & Bandettini, 2006). Multi-voxel pattern analysis, on the contrary, does not involve spatial averaging of voxel responses, but uses pattern classification techniques to extract the signal present in the response pattern across multiple voxels, even when the individual voxels are not significantly responsive to any of the conditions. Hence, the multi-voxel response pattern can be considered as a high-capacity combinatorial code for the representation of distinction between mental states (Haynes & Rees, 2006; Norman et al., 2006; Polyn et al., 2005).

In the standard multi-voxel pattern analysis method, the patterns that have to be classified are vectors of voxel activity values. Norman et al. (2006) explicated the basic phases of multivariate pattern analysis defining four main steps. The first step, defined as *feature selection*, involves deciding which voxels will be included in the classification analysis, allowing the rejection of noisy and uninformative voxels before classification. One possibility to perform feature selection is to limit the analysis to specific brain areas (Haxby et al., 2001). Another way is to perform univariate voxel-wise statistics to select the voxels that individually work better for discriminating between the considered conditions (Haxby et al., 2001; Mitchell et al., 2004; Polyn et al., 2005). The second step, defined as *pattern assembly*, involves separating the data into discrete brain patterns corresponding to the pattern of activity across the selected voxels at a given point of time during the experiment. Each brain pattern is then labeled according to the corresponding experimental condition. The patterns are then divided into a training set and a testing set. The third step is the *classifier training*, which consists of feeding a subset of labeled patterns into a multivariate pattern classification algorithm. Patterns from the training set are used to train a function that maps between voxel activity patterns and experimental conditions. The fourth step is the *generalization testing*, where the classifier is used to predict a category membership for patterns from the test set (not presented to the classifier previously).

The joint activity of a set of voxels forms a spatial pattern, which can be expressed as a pattern vector. Therefore, different pattern vectors should correspond to different mental states. Each pattern vector can be considered as a point in an N-dimensional space, and each measurement of activity corresponds to a single point. To be successful, a classifier should learn to discriminate between pattern vectors elicited by distinct mental states.

When the response distributions are separable within individual voxels, it is possible for the classifier to work on single voxels. When two distributions are widely overlapping, and the corresponding categories cannot be separable in individual voxels, it is possible to separate the response distributions by taking into account the combination of responses and using a linear decision boundary. In some circumstances, however, a linear decision boundary is not sufficient to separate the response distributions, so a curved decision boundary (which corresponds to a non-linear classifier) is required (Haynes & Rees, 2006). A schematic description of how pattern recognition is performed by a classifier is presented in Fig. 16.

In order to test the predictive power of a classifier, the data is divided into two datasets, one for the training and the other for the test. The proportion of the test data that is correctly classified gives a measure of the classification performance.

Linear classifiers work by computing a weighted sum of voxel activity values, which is subsequently passed through a decision function that creates a threshold for deciding whether a category is present or not (Norman et al., 2006). Other multi-voxel pattern analyses use nonlinear classifiers, such as nonlinear SVMs (Cox & Savoy, 2003; Davatzikos et al., 2005) and neural networks (Hanson et al., 2004). Differently from linear classifiers, nonlinear classifiers can respond to high-level feature conjunction, for instance learning that the coactivity of two voxels indicates a specific mental state, although neither voxel considered individually conveys information about that state (Norman et al., 2006). Cox & Savoy (2003) report that although nonlinear classifiers are more powerful than linear classifiers for what concerns the kinds of maps they can learn, there is no clear performance advantage for using nonlinear classifiers. Kamitani & Tong (2005) also observed that a good performance is more difficult to interpret in a nonlinear classifier compared to a linear one.

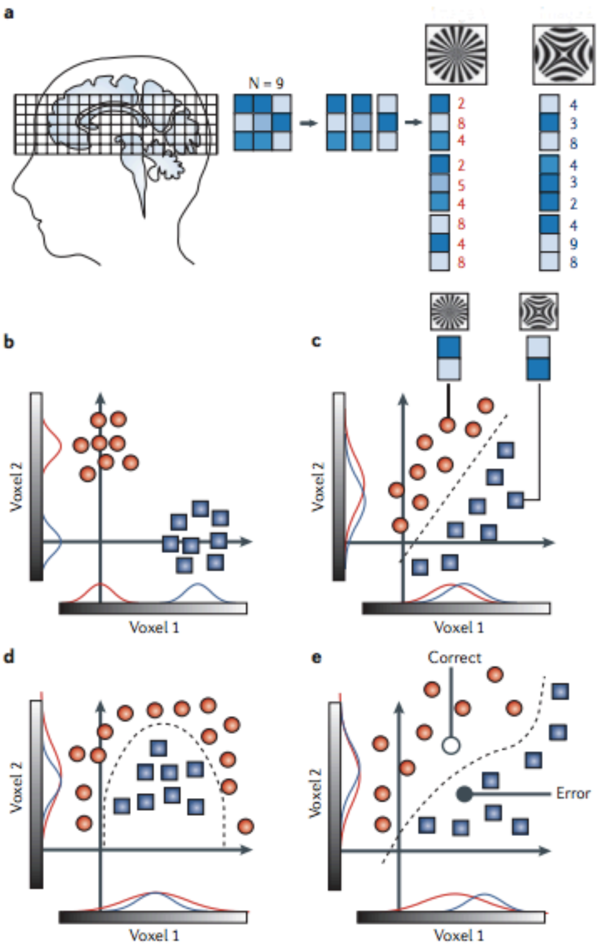


Fig. 16 Statistical pattern recognition. The signal measured in each voxel reflects haemodynamic changes as a consequence of neural activity. The joint activity in a subset (N) of these voxels (here shown as a 3X3 grid) constitutes a spatial pattern, which can be expressed as a pattern vector, corresponding to a specific mental state (a). Each pattern vector can be interpreted as a point in an N-dimensional space, here represented in only two dimensions (b-e). The two different conditions are depicted in blue and red. Each measurement of brain activity corresponds to a single point. A successful classifier will learn to discriminate between pattern vectors measured under different mental states. In (b), the response distributions are separable within individual voxels. In (c), the distributions are largely overlapping, but separable taking into account the combination of responses in both voxels. A linear decision boundary can be used to separate these distributions. In (d) a linear decision boundary is not sufficient, and a curved decision boundary (non-linear classifier) is required. In (e), to test the predictive power of a classifier, data are separated into training and test datasets. Training data (red and blue symbols) are used to train the classifier, which is then applied to new and independent test dataset. The proportion of these independent data that are classified either correctly (open circle) or incorrectly (filled circle) gives a measure of classification performance.
Adapted by permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience (Haynes & Rees, "Decoding mental states from brain activity in humans", 2006), copyright 2006.

Several methods have been developed to determine which voxels are contributing the most to the performance of a classifier (Norman et al., 2006). When using linear classifiers, it is possible to discriminate the contribution of voxel *i* to the detection of category *j* by looking at the weight between voxel *i* and category *j* (Kamitani & Tong, 2005; LaConte et al., 2005; Polyn et al., 2005). For nonlinear classifiers this operation in more complex, since each voxel's contribution to the recognition of a category is a function of multiple learned weights (Davatzikos et al., 2005).

Given the encouraging results obtained from our fMRI classical conditioning study using a Statistical Parametric Mapping univariate analysis (presented in Chapter 4), we performed a multivariate procedure, taking into account the whole spatial pattern of brain activity. This multivariate analysis was performed developing a linear Support Vector Machine (SVM). In the present chapter, after describing the functioning of a SVM, we will show the results obtained by applying SVM classification to the data from our fMRI classical conditioning study.

5.2. Support Vector Machines (SVMs)

SVMs can be defined as a set of supervised learning methods used for classification and regression (Lee et al., 2010). A SVM is an abstract learning machine, which learns from a training dataset and attempts to generalize and make correct classifications and predictions on novel data (Campbell & Ying, 2011).

It is interesting to point out that the first publications about SVMs went largely unnoticed till the beginning of the Nineties, due to the widespread belief in the statistical and machine learning community that SVMs were neither suitable nor relevant for practical applications. SVM classifiers started to be taken seriously into consideration only when remarkable outcomes on practical learning benchmarks were achieved (Wang, 2005). Up to now, SVMs have been used to classify spatial, temporal and spectral patterns, and have been applied successfully in character recognition, speech recognition, and image recognition applications (Hamel, 2009; Jain, Duin & Jianchang, 2002; Lee et al., 2010).

Data mining and statistical techniques have seen a remarkable progress in the last years, together with the increase of computing power, allowing the manipulation of huge amounts of neuroimaging data for multivariate pattern analysis (Haynes & Rees, 2006; LaConte et al., 2005; Mourão-Miranda et al., 2005; Mourão-Miranda et al., 2007; Mourão-Miranda et al., 2006; Norman et al., 2006). The advantage of using SVMs is that they have strong classification accuracy with small sample sizes and high dimensional inputs (Abe, 2005; Lee et al., 2010). Today, SVMs show better results compared to neural networks and other statistical models concerning several classification problems (Cherkassky & Mulier, 1998; Meyer, Leisch & Hornik, 2003; Wang, 2005).

SVMs are recognized as being universal approximators of any multivariate function to any desired degree of accuracy, and are therefore particularly interesting for modeling the unknown, highly nonlinear, complex systems or processes (Wang, 2005). SVMs, just like neural networks and fuzzy systems, are typical non-parametric classifiers, which means that no *a priori* knowledge of data distribution is assumed (Abe, 2005; Cristianini & Shawe-Taylor, 2000). “Non-parametric” does not mean that SVMs have no parameters at all, but on the contrary, the crucial issue is their “learning”. The parameters are not predefined, and their number is dependent on the training data used (Wang, 2005). This means that the parameters that define the capacity of the model are data-driven, so that they match the model capacity to data complexity.

After training with input-output pairs, classifiers acquire decision functions, which classify the input data into one of the given classes. In a SVM, we determine the optimal decision function that separates a class *i* from the remaining classes. Assuming that the training data of different classes are not overlapping, the decision function is determined so that the distance from the training data is maximized. This is defined as an “optimal decision function”. If one of the *n* decision functions classifies unknown datum into a definite class, the datum is classified into that class. In case more than one decision functions classify a datum into definite classes, or if no decision functions classify the datum into a definite class, the datum is considered as unclassifiable (Abe, 2005).

In training SVMs, the decision boundaries are determined directly from the training data, so that the separating margins of decision boundaries are maximized in the high-dimensional space defined as feature space (Abe, 2005). Such learning strategy, which minimizes the classification errors of the training data and the unknown data, is based on statistical learning theory (Abe, 2005; Vapnik, 1995; Vapnik, 1998). To determine a decision function, the original input space is mapped into a high-dimensional space defined as feature space, where the optimal decision function (or “hyperplane”) is determined (Abe, 2005).

By considering input data as two sets of vectors in an M-dimensional space, a linear SVM will build a separating hyperplane in that space (Lee et al., 2010). A good space separation is obtained by maximizing the margin, whose boundary is the distance from the closest input vectors to the separating hyperplane (Schölkopf & Smola, 2002; Schölkopf, Burges & Smola, 1999; Vapnik et al., 1997). This represents a quadratic optimization problem, and the best solution can be found by applying optimization theory (Strang, 1986).

In some circumstances (e.g. when the training set is too small), the classifier may adapt only to very specific characteristics of the training set and not generalize to the rest of the data. This phenomenon is defined as overfitting. A tradeoff between fitting to the training data and the generalization ability is therefore required (Abe, 2005).

The classifier that realizes the best generalization ability for the given input-output training pairs is defined as *optimal classifier.* The process of determining the optimal classifier is called *model selection*, and is performed by selecting the classifier that gains the highest generalization ability (Abe, 2005). The most reliable - although time-consuming - method of estimating the generalization ability is cross-validation, based on the repetitive training of SVMs (Abe, 2005; Kohavi, 1995). In cross-validation, the *M* data are divided into two datasets: the training set, which includes *l* training data, and the test set, which includes *M-l* test data. For the training dataset, the classifier is trained and tested for the test dataset. This is iterated for all the combinations of the partitioned training and test datasets. The total classification rate for all the test datasets is an estimation of the classifier's performance (Abe, 2005). Since this task can be extremely time-consuming, a *k*-fold cross-validation is often adopted. In this kind of cross-validation, training data are randomly split into approximately equal-sized *k* subsets, and the classifier is trained using *k* – 1 subsets and tested using the remaining subset. The training is repeated for *k* times and the total recognition rate for all the *k* subsets that are not included in the training data is estimated (Abe, 2005).

5.2.1. SVM classification of fMRI data

In a typical analysis of fMRI signals with SVMs, as described by Lee and colleagues (2010), BOLD values from all brain voxels of each repetition time (TR) are contained in an M-dimensional input vector x^i, where M is the number of all the brain voxels. The SVM determines a scalar class label L^i from x^i, as follows:

$$L^i = \mathrm{sgn}\left(y^i = w^T x^i + b\right),$$

$$i = 1,\ldots,N \qquad (1)$$

where the weight vector w and the constant value *b*, estimated by a SVM training algorithm from the training dataset, define a linear decision boundary, *T* is transpose of a vector, sgn(.) is a sign function, sgn(*x*) = +1, 0, -1 if *x* > 0, *x* = 0, *x* < 0, respectively, *N* is the number of input vectors.

When the input vectors x^i and the design labels L^i_D are drawn from the training dataset, the linear SVM algorithm attempts to find a separating hyperplane $y = w^T x^i + b = 0$ in the feature space. If the input vector comes from a condition of interest, then $L^i_D = 1$, while if the input vector comes from a rest condition or a control condition, $L^i_D = -1$.

The weight vector w of a linear SVM is computed by minimizing the function of equation (2) with constraints equations (3) and (4), introducing a slack variable ζ to describe a non-separable case, that is, data that cannot be separated without classification error. C, which is defined as “regularization parameter", indicates the weighting on the slack variable, reflecting the extent to which misclassification is allowed.

$$\frac{1}{2}w^T w + C\sum_{i=1}^{N}\zeta^i \tag{2}$$

with

$$L_D^i\left(w^T x^i + b\right) \geq 1 - \zeta^i \tag{3}$$

and

$$\zeta^i \geq 0 \tag{4}$$

The minimization of equation (2) derives from the concept of margin maximization (margin length = 2 || w ||^2), whose boundaries are defined as y = $w^T x^i$ + b = +-1 built from support vectors in each class.
Equation (2) and constraint terms (3) and (4) can be combined into a non-constraint form by introducing a Lagrange multiplier:

$$w = \sum_{i=1}^{N}\alpha^1 L_D^i x^i \tag{5}$$

where α^i is the Lagrange multiplier, and its value determines whether the input vector x^i is a support vector or not. When the Lagrange multiplier is different from zero, the corresponding input vector is the support vector.

Some SVM analyses of fMRI signals generate functional maps by displaying the weight value at each voxel, assuming that this can identify the most discriminating voxels by multivariate analysis, given that the weight vector is the direction along which the input vectors from two conditions differ most

(Mourão-Miranda et al., 2005; Mourão-Miranda et al., 2007; Mourão-Miranda et al., 2006). Lee and collaborators (2010) observed that these analyses consider only the weight vector, but not the input vector, which is the second factor determining the SVM output. SVMs are normally trained on the input samples to minimize classification error rates by computing the weight vector only from support vectors that are close to the border of the hyperplane. As a consequence, the weight vector is not completely influenced by the statistical distribution of input vectors, which means that only part of the information is presented. To solve this issue, Lee et al. (2010) proposed a new functional-mapping method to overcome the limitations of previous SVM analysis. This new functional mapping method, defined as Effect Mapping (EM), allows the identification of the voxels that are more important for the classification by utilizing information from both the weight vector and the input vector, which represent, as described above, the SVM output. The Authors derived a new quantity defined as Effect Value (EV). The EV for a single voxel is defined as the statistical relation, or mutual information (MI), between the voxel and the SVM output, multiplied by the corresponding weight value of the SVM.

5.3. Methods

Following the same pre-processing procedures described in Chapter 4, we implemented a linear SVM in Matlab 7.7, in order to classify the signals corresponding to the different conditions of our paradigm, namely congruent and incongruent word-pairs. A fixed regularization parameter C=1 was used to control the trade-offs between the classifier complexity and the number of non-separable points (Reeves & Jacyna, 2011).

Since the haemodynamic response to a neural stimulus has a considerable delay (Huettel, Song & McCarthy, 2004), the raw features were extracted from voxels of the third, fourth and fifth image after each word-pair (without combining them). The temporal-spatial voxel selection was based on the Fisher Criterion Score due to its general good performance in feature selection (Gu, Li & Han, 2012; He, Cai & Niyogi, 2005).

A “searchlight” approach (Kriegeskorte et al., 2006) was used, meaning that the imaged volume was scanned, and contents were analyzed multivariately at each location in the brain. More specifically, a spherical multivariate “searchlight” moved through the volume, centered on each voxel in turn, comprising the surrounding voxels. To combine the signals from all voxels falling into the searchlight, multivariate effect statistics were computed at each location. The EM approach developed by Lee and collaborators (2010) was applied to measure the effect of each voxel by considering both the input vector and the weight vector to determine the SVM output. For each voxel, the resulting map showed how well the multivariate signal in the local spherical neighborhood differentiated between the different conditions.
Classification performance obtained with the data from each subject within each block was evaluated through 25-fold cross-validations, meaning that the total dataset was divided into 25 subsets, and at each step one subset represented the validation dataset, while the remainder constituted the training dataset. The process was repeated for all the 25 folds. Training the SVM for each of the 25 subsets served to avoid overfitting issues and biases due to unbalanced sampling.

5.4. Results

We assessed whether our SVM was consistently able to classify, for each subject and in each block, the fMRI data for congruent and incongruent word-pairs (and therefore “affirmative” and “negative” thinking). The percentages of classification accuracy for each subject and the average classification accuracies for each of the blocks can be seen in Table 5.

Table 5 Classification accuracy percentage for each subject in each block

	Block 1	Block 2	Block 3	Block 4	Block 5	Block 6
Subject 1	48%	68%	67%	58%	63%	82%
Subject 2	56%	48%	52%	62%	55%	68%
Subject 3	44%	64%	58%	52%	65%	68%
Subject 4	60%	76%	75%	66%	65%	86%
Subject 5	50%	54%	67%	62%	58%	70%
Subject 6	66%	64%	54%	78%	68%	76%
Subject 7	50%	58%	48%	48%	60%	72%
Subject 8	60%	66%	65%	82%	60%	78%
Subject 9	46%	58%	58%	76%	85%	70%
Subject 10	55%	62%	62%	65%	64%	76%
Average accuracy	**53.50%**	**61.80%**	**60.60%**	**64.90%**	**64.30%**	**74.60%**

The mean classification accuracy for the habituation phase (block 1), when the word-pairs (incongruent and congruent), scream and laughter were presented randomly with no association was 53%. In the early acquisition blocks (2 and 3), when all incongruent word-pairs were associated with the scream and all congruent word-pairs were associated with the laughter, the mean classification accuracies were 61.8% and 60.6%, respectively. In the late acquisition blocks (4 and 5), when the number of word-pairs followed by the emotional stimuli gradually decreased, the mean classification accuracies were 64.9% and 64.3% respectively, with peaks of 82% and 85% of accuracy. Finally, in the extinction phase (block 6), the mean classification accuracy was 74.6%, with a peak of 86% of accuracy.

A repeated-measures ANOVA showed that the difference in mean classification accuracy was significant between the blocks, $F(5,45)=9.79$, $p<0.001$.

One-tail paired samples t-tests were performed between block 1 (habituation) and all the other blocks (acquisition and extinction blocks), in order to verify the changes in classification accuracies following the classical conditioning procedure (Table 6). The difference between classification accuracy in block 1 and in all the other blocks was always significant.

Table 6 t tests between the classification accuracies in block 1 and in the following blocks

	t	Sig. (1-tailed)	Effect size
Pair I: Block 1, Block 2	-2.887	0.009	0.693
Pair II: Block 1, Block 3	-2.187	0.0285	0.59
Pair III: Block 1, Block 4	-4.052	0.0015	0.8
Pair IV: Block 1, Block 5	-2.846	0.0095	0.688
Pair V: Block 1, Block 6	-9.711	< 0.001	0.955

5.5. Discussion

In the present chapter, data from our classical conditioning study was analyzed through a SVM-based multivariate procedure, in order to verify the possibility to discriminate between brain states related to incongruent and congruent word-pairs, and therefore between “negative” and “affirmative” thinking, respectively.

The classification results obtained with our SVM show that although before the conditioning, during the habituation phase, the discrimination between “yes” and “no” responses was around chance-level (53.5%), after the conditioning the classification accuracy was above chance-level, reaching a mean classification accuracy of 74.6% in block 6, with a peak of 86% of accuracy in one of the subjects. The t-tests between block 1 and each of the following blocks confirmed significant differences in classification accuracy in acquisition (blocks 2-5) and extinction (block 6). The fact that the average classification accuracy increased through the blocks may indicate a consolidation of the conditioning process, even when the percentage of word-pairs followed by emotional stimuli was reduced. Quite unexpectedly, the highest classification accuracy scores were obtained during the extinction phase, when none of the word-pairs were followed by emotional stimuli. This could possibly indicate that the consolidation of the conditioned response mostly took place after the very late acquisition phase (at the end of block 5). This should lead to consider using a more extended acquisition phase, with a slower reduction of the US, in order to obtain a faster and stronger acquisition of the conditioned response.

Although the classification results obtained after only one session of classical conditioning are encouraging, several improvements could be applied to the classification method. First of all, specific brain masks could be used to enhance the classification accuracy, allowing focusing only on those brain regions where the distinction between responses is more evident (e.g. based on the results of the univariate analysis). This could also be useful to avoid that areas that are not relevant for the procedure, such as the eye area or

white matter, are selected for classification. Adopting brain masks could therefore increase the classification accuracy by avoiding taking into consideration irrelevant regions.
Another considerable issue is the high variability in the classification between subjects. Unfortunately, high classification accuracy was not obtained with all of the subjects, posing a limitation to the possibility to use this paradigm for communication on individual-basis. It is possible that some subjects acquire the conditioned response more slowly than others, and therefore require more extended classical conditioning sessions. If this method will be used for basic communication of mental states, it is advisable to optimize the existing procedure individually for each subject. Personalized emotional stimuli that are more familiar for the participant could also be adopted, as a replacement of the already existing standardized IADS stimuli.

Future directions in the research with SVM classification comprehend an online implementation of the SVM, in order to allow basic communication of mental states in real-time. Therefore, signal pre-processing should be performed on each volume of brain images as soon as they arrive from the scanner, and feature selection, training and testing of the SVM should be performed right away. The disadvantage of existing online SVMs is that they need to be adapted to each subject, since the training is performed on individual-specific data. Therefore, it is necessary to collect preliminary data for the SVM training, possibly leading to a very time-consuming procedure. As suggested by Sitaram and colleagues (2011), a so-called adaptive classifier could be developed, similarly to the ones that exist in the pattern-recognition field, applicable to new subject data without prior classifier training. Moreover, this classifier could be adapted to the idiosyncrasies of each person's brain size, shape and activation patterns. The main technical improvement in order to achieve this goal would be to obtain real-time co-registration and normalization of functional images. A SVM able to discriminate online between mental states would represent an incredibly valuable tool for basic communication not only for patients with Alzheimer and related dementias, but also for severely paralyzed patients (such as ALS patients).

6. General conclusion and future directions

From a detailed analysis of BCI literature, it is evident that one of the most relevant issues regarding the use of BCI systems is the difficulty in learning to self-regulate brain activity, a process that may require very long and burdensome trainings. These systems can provide alternative methods for communicating and acting on the environment, but may not be easily used with patients with cognitive impairment, such as Alzheimer patients (AD), who have more difficulty in learning and actively engaging in a new task.

We suggested that AD patients could benefit from a BCI able to convey their emotions and basic mental states (e.g. “yes” and “no”). So far, no research existed in this direction, presumably due to the remarkable difficulties in using operant conditioning with patients with cognitive deficits.

We proposed that so-called “affective” or “passive” BCIs, designed to extract information from signals that are not voluntarily modified by the brain (e.g. signals related to emotional states), could be used for basic yes/no communication. In addition, we presented a new paradigm characterized by a shift from operant learning to classical conditioning in a fMRI setting, with the aim of discriminating affirmative and negative thinking. fMRI represents a privileged method to investigate the changes in mental states, since it allows measuring brain activity repeatedly every few seconds at a large number of voxels, both in cortical and subcortical regions. The increase in image-encoding gradient power and the development of more advanced acquisition and processing techniques in the last year indicate that fMRI is particularly promising in the BCI field. Although fMRI is not a portable system that could be practically used for communication with patients in everyday life, studies involving this technique provide the basis for the development of more portable systems, e.g. NIRS-BCIs.

In order to develop a paradigm that could be optimal for AD patients, several aspects of the neuropathology, such as language abilities, emotion recognition and the ability to acquire a conditioned response were taken into consideration. AD patients usually have a remarkable decline in their language abilities, which worsens with the progression of the neuropathology. However, their ability to process and discriminate emotional stimuli, especially from the auditory domain, is comparable to the one of healthy controls. For this reason, auditory emotional stimuli were selected for the paradigm. Studies on classical conditioning of AD patients show that it is possible for them to acquire a conditioned response, even though more slowly than healthy subjects. Moreover, the brain regions that are typically involved in classical conditioning and implicit learning are not primarily affected by the neurodegeneration related to the pathology. As a consequence, developing a classical conditioning paradigm using emotional sounds as unconditioned stimuli represented a reasonable choice. As conditioned stimuli, congruent and incongruent word-pairs constituted by a general category term (e.g. “animal”) and a specific member of a category (e.g. “elephant”) were chosen. The words were extremely simple and of easy comprehension. Several studies indicate that even if semantic memory may not be explicitly accessible to AD patients, it can be nevertheless relatively intact at an implicit level.

Two poles apart techniques were used to analyze the fMRI data: univariate analysis with Statistical Parametric mapping (SPM), and multivariate analysis with a linear Support Vector Machine (SVM), which was developed specifically for this study. Both methods indicated that a classical conditioning effect took place. The SPM analysis showed that it was possible to discriminate between incongruent and congruent word-pairs, and therefore between “affirmative” and “negative” thinking, in the acquisition and extinction phases. Interestingly, differential activation was found in regions that are specifically related to emotional processing, such as the insula and the ACC, which were not active during the habituation phase, confirming that the conditioning process had taken place.

The analysis performed with the SVM showed that classification accuracy, which was around chance-level before classical conditioning, significantly increased in the course of the blocks. Differently from SPM analysis, SVM analysis allowed to individuate brain patterns for the classification of affirmative and negative thinking, but not of specific brain regions for their discrimination. The advantage of using a SVM is that it can be more easily implemented in an online BCI, with the aim of achieving real-time classification. A combination of univariate and multivariate methods could represent an optimal choice for this purpose. The classification ability of the SVM could be improved through a greater focus on regions of interest (e.g. the insula and the ACC), suggested by the results obtained with the univariate analyses. The application of specific 3D masks would improve the feature selection process and increase the classification accuracy. A further step towards the realization of a BCI for basic communication is also the development of more precise online classification algorithms.

Overall, the present study shows that a classical conditioning paradigm allows the discrimination of “yes” and “no” thinking, which would not be possible *a priori*. Moreover, such discrimination may be obtained using a “passive” procedure, which does not require the subjects to be actively involved in a task. The only effort required is to listen to the stimuli, without having to provide an overt response. Differently from operant conditioning, classical conditioning could be used to develop a BCI for patients with dementia.

This novel paradigm was tested for the first time on healthy subjects, in view of a future application with AD patients. It is true that many differences can be found between the brain activation of healthy individuals and patients affected by dementia. There are several remarkable challenges in the implementation of a classical conditioning paradigm for a communication application in AD. First of all, the duration of the acquisition phase may not be enough to elicit a conditioning effect in AD patients. In this case, either prolonging the acquisition phase or performing a more gradual extinction should be considered. Secondly, the conditioning effect may extinguish very quickly, so that more acquisition sessions could be required to maintain it. Furthermore, different patients at different stages of the disease may have different timings related to the acquisition and extinction of the conditioned response. We suggest that, in the future, such differences may be exploited also for diagnostic aims, e.g. by measuring the conditioned response in patients in the first stages of AD, or subjects with mild cognitive impairment who have not yet developed dementia.

Being able to successfully condition brain responses could be exploited in several clinical fields, such as the treatment of psychopathy, drugs and alcohol addiction, eating disorders, anxiety and phobias. Further research should be conducted with different clinical populations and varying the US and CS.

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