FACHBEREICH I – PSYCHOLOGIE

COMBINING EEG AND FMRI IN EMOTION RESEARCH – HOW TO APPROACH ITS RESULTS

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GENERAL ABSTRACT

Magnet Resonance Imaging (MRI) and Electroencephalography (EEG) are tools used to investigate the functioning of the working brain in both humans and animal studies. Both methods are increasingly combined in separate or simultaneous measurements under the assumption to benefit from their individual strength while compensating their particular weaknesses. However, little attention has been paid to how statistical analyses strategies can influence the information that can be retrieved from a combined EEG fMRI study. Two independent studies in healthy student volunteers were conducted in the context of emotion research to demonstrate two approaches of combining MRI and EEG data of the same participants. The first study (N = 20) applied a visual search paradigm and found that in both measurements the assumed effects were absent by not statistically combining their results. The second study (N = 12) applied a novelty P300 paradigm and found that only the statistical combination of MRI and EEG measurements was able to disentangle the functional effects of brain areas involved in emotion processing. In conclusion, the observed results demonstrate that there are added benefits of statistically combining EEG-fMRI data acquisitions by assessing both the inferential statistical structure and the intra-individual correlations of the EEG and fMRI signal.

TABLE OF CONTENTS

INDEX OF FIGURES

INDEX OF TABLES

INDEX OF ABBREVIATIONS

Ag-AgCl	Silver-silver-chloride
ANOVA	Analyses of variance
ASL	Arterial spin labeling
BESA	Brain electric source analyses
BOLD	Blood oxygen level dependence
CBF	Cerebral blood flow
cm	Centimeter
ECoG	Electrocorticography
EEG	Electroencephalogram
efMRI	Event-related functional magnetic resonance imaging
EMO	Emotion
EOG	Electrooculogram
EPI	Echo Planar Imaging
ERP	Event related potential
fMRI	Functional magnetic resonance imaging
GLM	General Linear Model
Hz	Hertz
IAPS	International Affective Picture System
ICA	Independent component analysis
ISI	Inter stimuli interval
kOhm	Kilo Ohm
LORETA	Low resolution brain electromagnetic tomography
LFP	Local field potential
M	Average
mm	Millimeter
MOhm	Milli Ohm
MRI	Magnetic resonance imaging
MUA	Multi-unit activity
NEG	Negative

NEU	Neutral
NIRS	Near infrared spectroscopy
O^2	Oxygen
PET	Positron emission tomography
ROI	Region of interest
s	Seconds
SD	Standard deviation
SNR	Signal to noise ratio
SPM2	Statistical Parametric Mapping 2
T	Tesla
T_1	Longitudinal relaxation time
T_2	Transversal relaxation time
TE	Echo time
TR	Repetition time
µV	Microvolt
µm	Micrometer

INTRODUCTION AND OBJECTIVES OF THE THESIS

CHAPTER I

1.1 INTRODUCTION

Non-invasive methods that allow the in vivo observation of brain activity in humans have greatly expanded the knowledge of our brain. In fact, modern neuroscience and its techniques has brought men far from believes such as held by Aristotle of the 4th century B.C. who thought that the brain was a secondary organ that simply served as a cooling agent for the heart (Lythgoe, Thomas, & Calamante, 2003). Today, the profound importance of the central nervous system for human survival and well-being is very clear, reaching from the domains of visual attention, cognition, emotion, ocular motor control, memory, decision making to reward behavior, to name just a few. These and its other functions are implemented by the brain via dendritic currents, action potentials, and synaptic signaling which can be directly observed via electrophysiological recordings (Snyder & Raichle, 2010).

Electrophysiological recording techniques that are generally applicable for the human brain include recordings directly from the brain's surface (electrocorticography, ECoG), magnetoencephalography (MEG), and electroencephalography (EEG). Whereas the EEG recordings enable essentially unlimited temporal resolution, they only provide limited spatial resolution of the ongoing activity, and cannot record signals from the entire brain at the same time. These apparent limitations have led to efforts to combine electrophysiological recordings with more spatially resolved and increasingly available techniques of functional neuroimaging, such as positron emission tomography (PET), near infrared spectroscopy (NIRS), or functional magnetic resonance imaging (fMRI) (Snyder & Raichle, 2010) - these techniques allow good sampling resolutions in spatial but only rather fair resolution in the temporal domain - see Figure 1.1.1 for details on spatiotemporal resolutions of neuroscience techniques.

While PET, NIRS, and fMRI are far below the temporal abilities of the electrophysiological techniques, they are able to provide a three-dimensional representation of ongoing human brain activity in the resolution of centimeters to sub-centimeter scale. In fact, fMRI based on blood oxygenation level dependent (BOLD) contrasts (Ogawa et al. 1992) are now the technique of choice when visualizing the location of human neural activity of the brain, allowing resolutions of 2 to 4 mm in the

more common 3T scanner types (Kim, Jin, & Fukuda, 2010). Due to its increased availability, BOLD fMRI has become a popular functional imaging technique for neuroscientists, which resulted for fMRI to be the most obvious choice to combine it with electrophysiological techniques. The combination of fMRI and EEG in particular, is the most common combination for wide areas of topics (Mulert & Lemieux, 2010).

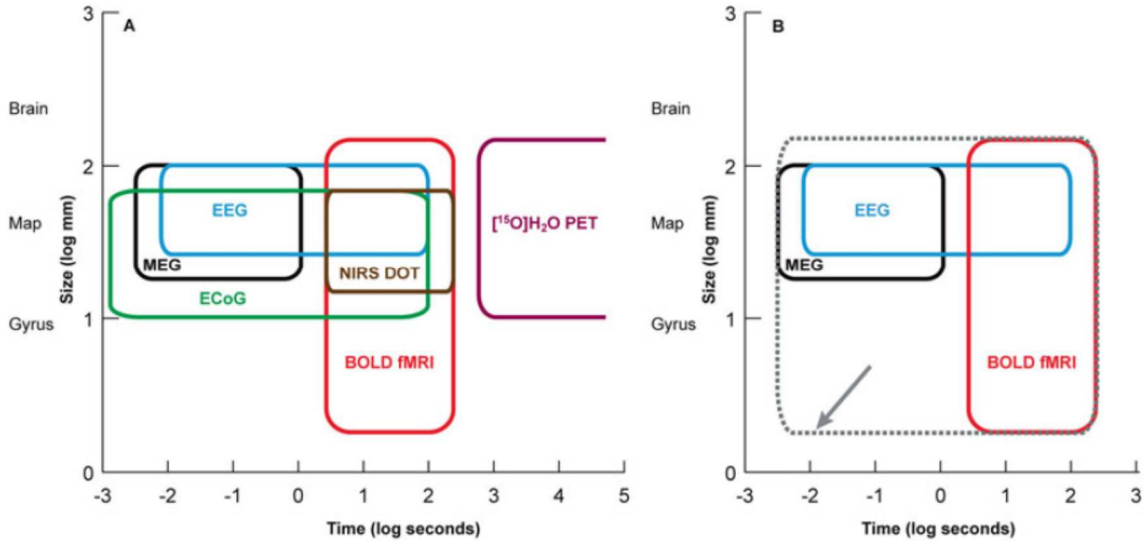


Figure 1.1.1 Sampling Space of electrophysiological and neuroimaging techniques.

A: Spatio-temporal sampling characteristics of neuroscience techniques, represented as closed regions. The left edge of each region represents the reciprocal of the highest physiologically meaningful temporal frequency accessible to each technique whereas the right edge represents the longest practical period of continuous observation. The lower and upper edges indicate the smallest and largest practical distance between independent samples respectively. **B:** Techniques used for combined electrophysiological and functional neuroimaging studies. By combining EEG and BOLD fMRI a superior spatio-temporal resolution can be achieved (dotted line) (illustration and description adapted from, Snyder & Raichle, 2010).

Consequently, the combination of electrophysiological with neuroimaging techniques has become one of the technological focal points of neuroscience (Mulert & Lemieux, 2010). The remaining introduction will focus on why combined EEG and fMRI analyses are applied by addressing each measures strength and weakness. This will set the frame work to discuss the benefits from the combination of these two methods.

1.1.1 Electroencephalogram

The EEG reflects the immediate mass action of neural networks from widespread brain regions that provide the direct and noninvasive opportunity to investigate human brain function. The neuronal brain activity induces electrical fields that extend to the surface of the head, where they can be sampled accurately as specific topographical distributions, provided that sufficient electrodes cover the entire head surface (Brandeis, Michel, & Amzica, 2009). The particularly high temporal resolution of EEG recordings enables neuroimaging to investigate generators of rhythmic oscillations in different frequency ranges which is directly linked to neuronal firing rates (Sanei & Chambers, 2007). Understanding these rhythmic oscillations on the scalp contributes to the understanding of cortical or subcortical networks inside the brain in a way which non-electrically driven neuroimaging techniques, such as BOLD MRI would be unable to achieve. Therefore, regardless of the more than eight decade long history (Berger, 1929; Luck, 2005), EEG measurements still provide the most direct and time accurate non-invasive link to neuronal processing.

With the EEG it is crucial to understand which neural events of what kind of generator are measureable and what kind of EEG signals can be obtained in the time- or frequency domain.

1.1.1.1 Neural activity and EEG generators

When neurons are activated, synaptic currents are produced within the dendrites which generate electrical fields. However, the signal recorded from this activation via EEG would be vastly different if recorded using deep brain electrodes.

Electrical events from individual neurons, also called multi-unit activity (MUA), are focal, large and fast action potentials (> 300 Hz) that depolarize the cell's resting potential by over 80 mV when measuring them intracellular only a few nanometers away from the cell membrane. Extracellular recordings reveal corresponding spikes, which resemble the first temporal derivative of their intracellular counterparts and can reach at least 600 µV. However, these so called spike amplitudes fall off rapidly to a tenth of their original strength (60 µV) outside a 50 µm radius (Henze et al., 2000). This limits the spatial spread of their measurable output to the sub-millimeter scale and prevents individual spikes

from becoming potentially measurable as far fields at the scalp using the EEG. After all, scalp electrodes of the EEG are at a minimum 2 cm away from the neural substrate of the brain (Brandeis et al., 2009). With the exemption of early auditory brain stem potentials (Scherg & von Cramon, 1985a, 1985b) or early somatosensory oscillations (Gobbele, Buchner, Scherg, & Curio, 1999)(which both are very small, fast, heavily averaged, and high frequency oscillations), singular spikes and action potentials as well as neural events in the white matter can be disregarded for main EEG generators (Brandeis et al., 2009).

The major generators of the scalp EEG are slower (< 250 Hz) local field potentials (LFP). Such field potentials originate in extended patches of gray matter that contain thousands of cortical columns, where large pyramidal cells are aligned perpendicular to the cortical surface and where the different layers consists of synaptic connections from different neural structures (Michel & Brandeis, 2010). If considering realistic cell geometries, models actually suggest that not only apical but also basal dendrites of the neurons may contribute to the EEG (Murakami & Okada, 2006). When these cells are activated, extracellular currents flow between the different layer columns. Thus, current opinion sees the EEG scalp potential as the representation of a weighted sum of all active currents within the brain that generate open fields (Megevand, Quairiaux, Lascano, Kiss, & Michel, 2008). The sum of these open field generators form the equivalent to a dipole generator (Scherg, Vajsar, & Picton, 1989), which make the widely used concepts of so called *current dipoles* into simple idealized models that describe "strength, orientation and localization of the sum vectors of volume-conducted open field activity of all layers of the cortical or subcortical brain structures" (Michel & Brandeis, 2010, p. 5).

In consequence, if the geometry of current sources in a given brain area were to be dominated by opposing directions, i.e. opposite current vectors, then this would lead to the full cancellation of these LFP. Therefore, areas of synchronized polarized brain tissue must have one dominant orientation in order to result in a *far field* potential that is detectable at the scalp. This restricts detectable brain activity to flat, extended, and polarized patches of cortical tissue. The orientation of the averaged directions of all source vectors that are active at one time will determine the morphology of a given mixture of sources on the scalp (Michel & Brandeis, 2010). These source characteristics also carry a number of implications:

A) Orientation of sources. The orientation of averaged source vectors determines their scalp topography as much as their actual anatomical location inside the brain. Tangential and radial sources at the same brain area for example may result in completely different scalp EEG potentials as is illustrated in Figure 1.1.2.

B) Strength of sources in relation to other sources. A strong generator signal can be cancelled out by i) another equally strong generator or ii) a collection of multiple other generators whose average vector is equally strong, if they point in the opposite direction.

C) Folded cortex regions. Heavily folded areas of the cortex such as the cerebellum or hippocampus and amygdala (which are in addition very deep inside the

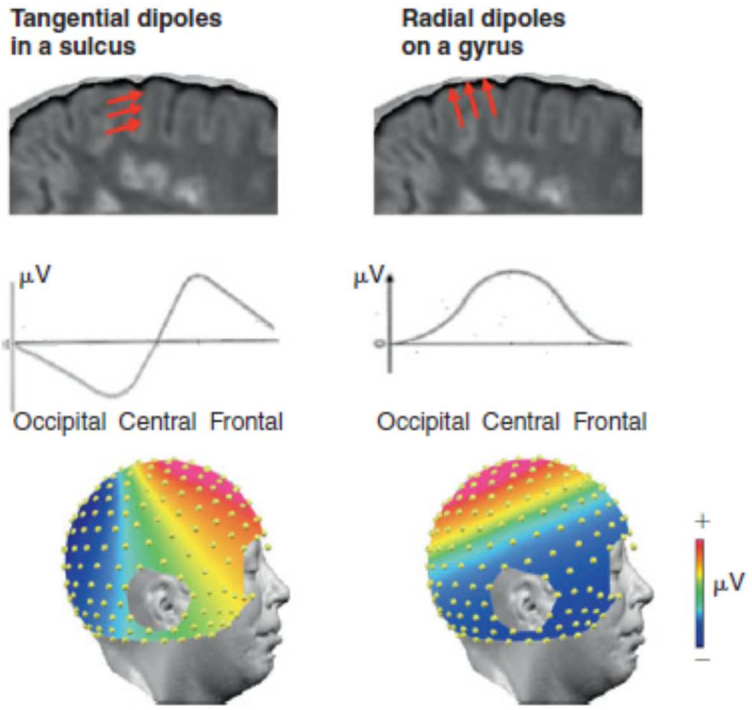


Figure 1.1.2 Sources and their corresponding EEG scalp potential maps.

Volume currents due to mass activity of synchronized, aligned pyramidal neurons can be modeled as point-like polarization dipoles and corresponding EEG maps. Pyramidal neurons located in a sulcus will lead to tangential dipoles, whereas those located on a gyrus lead to radial dipoles. The resulting dipoles induce electric potentials that spread to the surface and generate potential fields with positive and negative polarities. The topographical maxima of the scalp potentials from tangential and radial dipoles differ greatly from each other even though their generators (i.e. sources) are located in the same brain area only with a different orientation (illustration and description adapted from, Michel & Brandeis, 2010).

brain) are less likely to produce detectable EEG scalp potentials. LFPs of these regions are most likely to cancel each other out before reaching the scalp. Recently, however, a number of reports came forth stating that under particular recording conditions these structures may produce detectable scalp potentials (Ioannides & Fenwick, 2005; James, Britz, Vuilleumier, Hauert, & Michel, 2008; Martin et al., 2006; Michel et al., 2004; Timmermann et al., 2002). In any case, activations of deep and heavily folded cortex areas remain difficult to detect.

Taken together, the above mentioned characteristics of neural generators are the theoretical ground work for the problems surrounding the ability to definitely locate neural sources based on EEG recordings alone. This difficulty is fundamental and is related to the *inverse problem.* The inverse problem states that it is (mathematically) impossible to reconstruct a unique intracranial current source for a given EEG signal because by their nature, multiple current potentials can cancel each other out and multiple generator combinations can lead to the same EEG scalp potentials (Niedermeyer & Silvia, 2011). In other words, it is not possible to deduce neural origins based only on EEG scalp topography. In addition, even the non-existence of signal changes during an EEG recording would not necessarily mean that individual or groups of intracranial signal sources (e.g. entire subcortical regions or individual neuronal columns) have not changed.

1.1.1.2 Oscillations of Brain Networks

The most prominent features of the EEG scalp potentials are their oscillation patterns across a wide frequency spectrum in which particular electrical brain oscillations characterize different brain states, such as wakefulness or sleep (Brandeis et al., 2009; Engel, Fries, & Singer, 2001). In EEG, meaningful neural oscillations can range from below 1 Hz, e.g. for cortical delta rhythms (Molle, Marshall, Gais, & Born, 2002), up to 100 Hz for gamma-activities that are believed to play a major role in synchronizing distant brain areas (Fries, Nikolic, & Singer, 2007). Rhythms of different frequencies can also coexist and interact with each other to produce a much wider range of brain states (Steriade, 2001).

Traditionally, the recording of oscillatory brain activity of the frequency-domain is conducted during the absence of rapid repetitive external stimulus presentation in which

the frequency power spectrum of several minutes of EEG is averaged and assessed - external stimuli would evoke event related brain responses (i.e. event-related potentials, see below) that influence resting brain activity (Raichle & Snyder, 2007). Non-rapid stimulus presentations (i.e. very long inter-stimulus intervals), have been successfully applied in the context of analyzing oscillatory brain activity in emotion research (e.g. Hewig, Hagemann, Seifert, Naumann, & Bartussek, 2004), demonstrating that the differentiation between "activation" and "rest" is rather continuous than dichotomous. The brain in resting represents what has recently been termed the brains *default mode* which reflects the realization that the brain is never inactive but simply in an a mode of default activation that does include large aspects of conscious awareness, attention and thinking (Hermes et al., 2009; Raichle et al., 2001; Raichle & Snyder, 2007) (commonly compared to a state of non-active day dreaming – or letting one's mind wander effortlessly). For that reason, an increased amount of attention is being paid to oscillatory changes in relation to changes in the default network during (often repetitive) events, by means of time-locked frequency analyses (i.e. time-frequency analyses) (Makeig, Debener, Onton, & Delorme, 2004).

The general difficulties in detecting the signal generators (as described above), however, remain unchanged in the frequency domain of the EEG.

1.1.1.3 Event-Related Brain Activity

In EEG time-domain approaches, researchers traditionally average a set of data trials (or epochs) time-locked to certain events. Averaging is thought to provide a source of noise reduction that presents the ability to assess the common aspects of the brains response to the given time-locked event, for every electrode, called an even related potential (ERP) waveform (Sanei & Chambers, 2007). Much of past and current neuroscience literature is concerned with specific ERP paradigms that are able to investigate topics such as language (Kiang, Kutas, Light, & Braff, 2008; Kutas & Hillyard, 1980), auditory (Hillyard, Hink, Schwent, & Picton, 1973; Naatanen & Picton, 1987), and face processing (Itier, Latinus, & Taylor, 2006; Taylor, Batty, & Itier, 2004), conflict processing (Roberts & Hall, 2008), or attention (Naumann et al., 1992; Polich, 2007; Sutton, Braren, Zubin, & John, 1965), to mention only a few. In the traditional ERP view,

the signs of neural processing are considered to be the reliable sequence of monophasic 'evoked' potential peaks that are present on top of 'random background' EEG processes whose phase distributions are independent of, and totally unaffected by experimental events (Makeig et al., 2004). However, an increasing amount of neuroscientists have come to the realization that time and frequency domains of the EEG cannot be assessed separately anymore. Novel approaches to EEG data analysis, therefore, apply trial-by-trial visualization and time-frequency analysis to the EEG – i.e. analysis of the event-related changes in spectral power and phase across single trials time locked to experimental events (Makeig et al., 2004; Tallon-Baudry & Bertrand, 1999).

Consequently, for the remainder of this thesis any general statements about 'electrophysiological activity' or its sources will, therefore, refer to both frequency- and time-domain aspects of the EEG signal.

1.1.2 Strategies to obtain electrophysiological signal sources

Signals from electrophysiological recordings (ECoG, MEG, or EEG) are the best indicator for neural processing (see section 1.1.1.1 above) but to date there is no single measurement technique that would allow an appropriate temporal and spatial sampling of neuronal activity. Snyder and Raichle (2010) categorize the current strategies that are therefore perused by researcher to better define the spatial specificity of electrophysiological data. The ultimate goal of such strategies is to better understand human brain functioning and to reduce spatial ambiguity in its interpretation.

I) Analysis in data space without inverse modeling. Electrophysiological signals can be investigated on the basis of specific recording sites (electrodes/sensors) and their interpolated scalp topographies. No generator or conductivity models are applied.

II) Unconstrained inverse current source (generator) localization. Brain electric source analyses (BESA) finds neuronal generators within the brain based on 'best-fitting' models that determines one or more dipoles sources. Low resolution brain electromagnetic tomography (LORETA, Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002) determines neural generators as a continuous current density distribution over the brain volume. In any case, all available inverse source modeling techniques depend on the

definition of a head conductive model. Even good fitting models, however, do not necessarily lead to good model validity.

III) Constrained inverse current source localization. In these approaches, the location, called 'seed', of a current generator (but not its orientation) is restricted by the researcher to certain assumed response foci, in order to result in better fitting models.

IV) Cortical surface constrained inverse generator localization. Segmented structural images an individual's brain are used to better constraint their optimal seed regions for model fitting (Dale, Fischl, & Sereno, 1999). The orientation of the generator region can then be restricted to areas of the cortex that are perpendicular to the cortical surface.

V) Completely a priori generator geometry. The location and orientation of all current generators is determined by a combination of anatomical and functional restraints which equals a combination of approach III and IV. The electrical state of the system is then completely specified by this head conductive model.

VI) Temporal independent component analysis (temporal ICA). The recorded EEG (or MEG for that matter) data is decomposed into temporally independent 'components' by means of using independent component analyses (ICA, Makeig et al., 2004; Onton, Westerfield, Townsend, & Makeig, 2006). Each component is the product of a fixed spatial distribution (channel weights) that can then be used to more clearly detect sources based on methods II to V.

VII) Joint EEG-fMRI analysis. In this approach, EEG signals can be directly related to signals from fMRI because different from strategies I to VI the EEG and MRI data was analyzed concurrently, rather than sequentially. The entire EEG-fMRI dataset can be subjected to joint ICA (Martinez-Montes, Valdes-Sosa, Miwakeichi, Goldman, & Cohen, 2004).

It is important to realize that electrophysiological sources obtained through strategies I to VI are also often used in conjunction with a neuroimaging signal (such as MRI, PET, or NIRS) by relating them with each other. Neuroimaging can occur simultaneously or separately (in another acquisition session) to the electrophysiological recordings and multiple combinations of the above mentioned strategies may be applied to the same datasets. In effect, the combination of neuroimaging and electrophysiological

recordings is to date the most optimal combination in regards to minimizing the impact of the inverse problem on interpreting neural brain activity. Whether or not the statistical approaches that are applied to combine these measurements can impact the resulting interpretations will be a main focus point of this thesis and will be addressed specifically in the General Discussion.

1.1.3 Functional Magnet Resonance Imaging

Most functional neuroimaging studies of the human brain rely on functional MRI (Shmuel, 2010). The BOLD fMRI contrast (Ogawa et al., 1992) is the most commonly used, is based on task invoked metabolic and hemodynamic responses that are coupled to underlying local changes in neuronal activity (Goense & Logothetis, 2010). The fMRI signal may, therefore, only be considered an indirect marker of neuronal activity which is a mere representation of the neurovascular coupling that is induced by neural activity – fMRI does not directly measure electrical neuronal currents (Huettel, Song, & McGarthy, 2009). BOLD fMRI provides a very high spatial resolution and is entirely non-invasive.

However, it becomes important to understand the signal source of BOLD fMRI, and its fundamental limitations for neuroscience interpretations.

BOLD signal origin and characteristics

A local BOLD signal is inversely related to the content of deoxyhaemoglobin (dHb). Following neural activation and the resulting metabolic changes, local (arterial) cerebral blood flow (CBF) increases more than oxygen consumption, resulting in lower dHb content in the local capillaries, venules and draining veins which increases the BOLD signal (Buxton, Uludag, Dubowitz, & Liu, 2004). However, many details about the BOLD signal are still poorly understood. In particular the relative contributions of venous, arterial, and capillary fractions to the BOLD signal and the relative contributions of blood flow increases and oxygen consumption are not yet clear (Buxton et al., 2004). It is generally accepted though to expect different MRI acquisition sequences to lead to relative shifts in the signal location read-outs. Goense and Logothetis (2010) for example state that gradient echo (GE) BOLD sequences, are believed to represent mostly a venous signal which is more strongly weighted towards smaller venules and capillaries as the

scanner field strength increases, whereas spin-echo (SE) BOLD is believed to represent mostly a capillary signal. They continue in stating that cerebral blood volume (CBV) signals are thought to represent smaller vessels (arteries and veins) and capillaries, and the CBF signal is believed to represent mostly arterioles and capillaries.

The origin of the neural event that trigger the BOLD response was determined by means of simultaneous recordings of electrophysiological and fMRI signals in monkeys

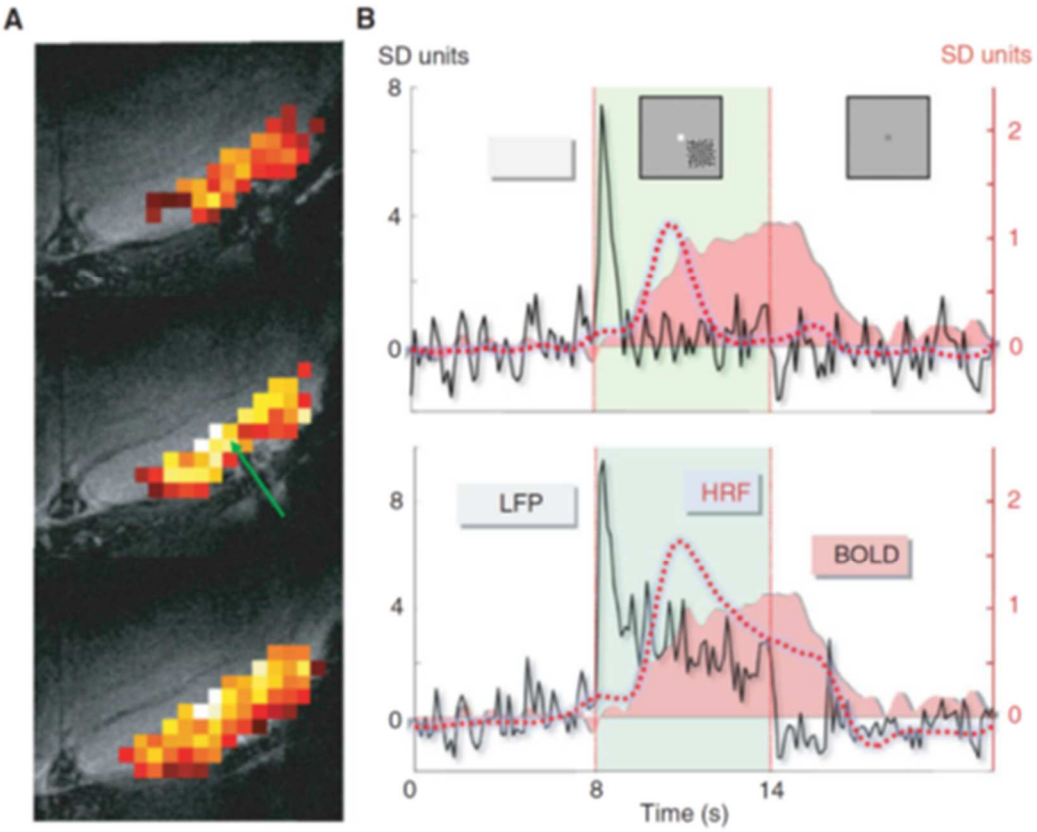


Figure 1.1.3 Dissociation between MUA and BOLD response.

A) Functional activation maps in response to a 6 degree visual stimulus. The arrow indicates the location of the electrode. B) Comparison of the time course of the BOLD signal and the neural signals in the MUA- and LFP bands in an awake monkey during (green shaded area) and after watching the visual stimulus. While the neuromodulary component of the LFP stayed elevated for the duration of the stimulus, the MUA rapidly returned to baseline after an initial onset response. The dotted lines show the regressor of the neural signal convolved with the theoretical hemodynamic response function that indicates that the MUA-derived regressor cannot capture the prolonged BOLD response (graphics and description adapted from Goense & Logothetis, 2010).

(Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). As Figure 1.1.3 illustrates, the BOLD response of a visual task is better correlated with LFP then with MUA, implying that BOLD is better correlated with the input and local processing of the neurons in an area than with the output of large pyramidal cells. The metabolistic demands of neurotransmission and the neuronal spiking determine the blood flow to an area. Neurovascular coupling is, therefore, determined by processes that have the most demand for nutrients, O^2, as well as for the removal of heat and waste products (Goense & Logothetis, 2010). Glycolysis and oxidative cell metabolisms are very different in this respect. Whereas the oxidative (i.e. active oxygen consumption) metabolism will lead to an immediate demand for nutrients and oxygen, short neuronal firing bursts may still be initiated by means of the glycolytic metabolism before oxidative processes are required (Goense & Logothetis, 2010). In addition, phase-shifts and phase-resets (i.e. phase-locking) of neuronal firing (Makeig et al., 2002; Tallon-Baudry & Bertrand, 1999) may not induce detectable metabolic changes. In effect, not all neural activity or changes thereof will change metabolic demands beyond a measurable threshold.

The relative time lag between neural activation and the peak blood flow and BOLD responses can be quite substantial and may not be achieved until 5-6 seconds after the onset of a stimulus. As a result, vascular response to synaptic input at an active region is still developing when neuronal processing may have already moved on to different processes (Shmuel, 2010). Consequently, fMRI BOLD signals are un-doubtfully related to neural processes but there may be cortical processes where this relationship and thus the interpretation of the BOLD signal are not so straightforward. The representation of neural activity by the mean of BOLD depends as much on the imaging sequence as on the duration, extend and nature of the electrophysiological activation.

1.2 OBJECTIVES

There has been an increased effort aimed at elucidating how to non-invasively locate neuronal brain activity that has been recorded by means of electrophysiological and functional neuroimaging techniques such as the EEG and BOLD fMRI. The goal is to arrive at measures for interpreting neural functioning at high temporal and spatial resolution in humans.

Neither the EEG nor the BOLD fMRI signals, however, are true representations of actual neural activity – they are both mere schematic traces of neural-network (i.e. brain-wide) interactions that take place in local isolated multi-layered cortices as well as between far apart regions of the brain. EEG is inherently insensitive to current sources that are deep within the brain, or that are heavily folded, which can lead to signal cancellations and apparent null findings (when in fact neural processing has changed). In addition to possible signal cancellations, the inverse problem is a major contributor to limitations in signal interpretations. BOLD fMRI signals are inherently lagging behind the actual neural activity and overlap with subsequent activations, the signal location (draining veins vs. capillaries) depends on the particular imaging sequence and not all neural activity may actually induce a hemodynamic response. In that sense, combined EEG fMRI measurements are the most optimal (and possibly only) way to deal with the apparent weaknesses of each signal. However, little attention has been paid to how statistical analyses strategies can influence the information that is retrieved from combined EEG fMRI studies.

In general, EEG and fMRI measurements of the same participant that were acquired separately or simultaneous can be analyzed in two fashions: i) each measures outcome undergoes its separate statistical inference statistical analyses and results are put into relation to each other; ii) each measures outcome is joint through combined analyses that investigates the intra- and/or inter-individual variability that both measures share with each other. In some cases, both approaches are combined (Horovitz, Skudlarski, & Gore, 2002).

Two independent studies in healthy student volunteers were conducted to demonstrate both approaches and to determine their benefits.

The first study that is presented in Chapter II was particularly aimed to explore to what extent an event-related visual search paradigm for emotional stimuli would lead to equivalent result interpretations when looking at EEG and fMRI activity separately, without statistically connecting the two measures in any way.

The second study that will be presented in Chapter III was aimed at exploring theoretical implications of combined statistical analyses using another event-related search paradigm that also used emotional stimuli.

Together, these studies demonstrate that it is important to understand the implications that go along with choosing separate or joint EEG-fMRI data analyses – especially in regards to gaining the most information out of their combination. Even though separate and joint analyses both revealed valuable insights in current paradigmatic issues of emotion research, well applied joint analyses can provide valuable additional insight into the functional equivalence of electrophysiological and hemodynamic signals in the human brain.

VISUAL SEARCH FOR FEAR-RELEVANT STIMULI INVESTIGATED BY EEG - FMRI

Chapter II

ABSTRACT

Visual search paradigms for fear-relevant stimuli show that emotions have a crucial impact on human cognition. When participants had to judge if all pictures of a 2 x 2 or 3 x 3 grid were from the same category, fear-relevant deviants were detected faster than neutral deviants. This effect, however, may not be due to the fear-relevance of the stimuli alone. The experimental paradigm was therefore further tested and optimized by: i) intra-individually testing fear-relevant and neutral stimuli from the same category in front of a neutral background, and ii) measuring all participants with three measurements: behavioral, event-related potential, and event-related functional magnet resonance imaging. The results could replicate former findings, which suggest that the optimizations worked as expected. However, fear-relevant stimuli displayed no general search advantage, questioning whether the fear-relevance of the stimuli is processed in the investigated paradigm. In conclusion, separate EEG-fMRI analysis did reach converging results in that both methods did not find evidence that the applied paradigm was able to capture the action of the proposed fear module – both measures complimented each other, suggesting that the emotion effect was absent in both the electrophysiological and hemodynamic domain.

2.1 INTRODUCTION

Humans survive under conditions in which fast and accurate perception of certain visual stimuli are vital for further development, and reproduction. Neuronal mechanisms developed that preferred the processing of certain classes of crucial afferences such as fear relevant visual stimuli. Fear processing has been suggested to incorporate special neuronal networks (LeDoux, 1993) and processing advantages have been reported for fear-relevant stimuli compared to neutral ones, such as a better sub-threshold perception (Öhman & Soares, 1994), easier fear conditioning (Cook, Hodes, & Lang, 1986; Öhman & Soares, 1998), and harder extinction (Hugdahl & Karker, 1981). Therefore, a visual search paradigm with fear relevant aspects seems best for the investigation of complex cognitive, behavioral, and neural interaction in both EEG and fMRI signals.

2.1.1 Visual search paradigm

Öhman and Mineka (2001) proposed the existence of *an evolved fear-module* with the amygdala as a core structure. This module is thought to preattentively process the fear-relevance of a stimulus, in such a way that fear-relevant stimuli are always processed, independently of attention – they are thought to be not under the control of higher order processes (Öhman & Mineka, 2001). As a result, the processing by the fear-module is guided towards the fear relevant stimulus. In other words, the fear-module is thought to lead to a pre-attentive capturing of attention due to the fear-relevance of a stimulus. Hence, this theory predicts a faster detection of fear-relevant stimuli compared to neutral stimuli (Öhman, Flykt, & Esteves, 2001). This hypothesis can be investigated using visual search paradigms.

Öhman et al. (2001) implemented a visual search paradigm using emotional stimuli in search grids of 2 x 2 and 3 x 3 pictures. Threatening targets (snakes and spiders) surrounded by non-threatening distractors (flowers and mushrooms) were detected faster than non-threatening targets surrounded by threatening distractors. Furthermore, response times for threatening targets were almost identical in 2 x 2 grids and 3 x 3 grids. The authors explained these findings in sense of a pop out due to fear relevance.

The paradigm of visual search for fear-relevant stimuli is thought to provide support for the theory of the evolved fear-module. As the theory considers the amygdala a core structure (Öhman & Mineka, 2001), activation differences of this structure may be predicted, since an increase in amygdala activity is found for fear-relevant stimuli compared to neutral ones (LeDoux, 1993, 1996; Stark et al., 2007; Tabbert, Stark, Kirsch, & Vaitl, 2005).

Other brain areas may be involved in the processing of fear-relevant stimuli (visual search task) as well, but the present evidence is less clear-cut than for the amygdala. For example, the primary visual cortex is more activated for fear-relevant stimuli (Stark et al., 2007; Tabbert et al., 2005) but it also differs in activity for other (non-emotional) differences in category (Ishai, Ungerleider, Martin, & Haxby, 2000). Because no event related fMRI (efMRI) study has been conducted with the search task used by Öhman and colleagues (2001) to date, the involvement of other brain structures in the processing of fear-relevant stimuli in search tasks is presently unknown.

Even though the theory of the evolved fear-module receives strong empirical support from several lines of evidence (see Öhman & Mineka, 2001, for a review), there is an ongoing controversy whether or not the findings from visual search paradigms really can be interpreted as support for the theory. The search advantage for fear-relevant animals has been replicated several times (Brosch & Sharma, 2005; Flykt, 2005; Lipp, Derakshan, Waters, & Logies, 2004; Tipples, Young, Quinlan, Broks, & Ellis, 2002). But in a study by Lipp and colleagues (2004), scary as well as neutral animals were detected faster compared to plants. This implies a search advantage for animals in general as opposed to scary animals in particular. Due to these non-specific results of the visual search paradigm, its ability to support the discussed theory may be questioned. Moreover, Wolfe and Horowitz are critical to whether or not fear-relevance has an impact upon such a visual search paradigm. “An ability to find threatening snakes and spiders efficiently seems to have more to do with their visual status as distinctive shapes than their affective status as scary objects” (Wolfe & Horowitz, 2004, p. 500).

Overall, it is not clear whether or not the established paradigm of visual search for fear-relevant stimuli can provide firm support for the theory of the evolved fear-module, which in turn provides a suitable opportunity to test to what extend EEG and efMRI, apart

from more common assessment of reaction time measurements, are useful in finding answers to such paradigmatic questions.

2.1.1.1 Visual ERPs

Early effects of fear-relevance can be observed with ERPs. Fearful faces had an impact on the N2Pc-component even if they were task irrelevant and surrounded by distractors (Eimer & Kiss, 2007). Fear-relevant stimuli like the ones used by Öhman and colleagues (2001) had an impact on the P3 component (Schienle, Schäfer, & Naumann, 2008). Contrary to these findings, Flykt (2005) did not find any fear-specific early differences in the ERP for a search task comparable to the one used by Öhman and colleagues (2001). The authors explain this by the fact that the key structure of the fear-module (the amygdala) is not visible with the ERP. However, as the studies cited above suggest the existence of an observable effect with ERPs, other explanations should be considered as well. As discussed earlier, it is doubtful whether the behavioral effects of the visual search paradigm are due to the fear-relevance of the stimuli, and other categorical differences seem to be important.

In particular, some studies with visual search tasks reported early ERP effects of categorical judgments and category differences. For example, there is evidence of an early visual discrimination after 150 ms of animals from the background even if the pictures were only shown for 20 ms (Thorpe, Fize, & Marlot, 1996). Also, the discrimination of animals from non-animals in natural scenes was observable in the ERP as early as 150 ms after stimulus onset (VanRullen & Thorpe, 2001). This effect was still present in the ERP when the images were presented in the periphery of the visual field (Thorpe, Gegenfurtner, Fabre-Thorpe, & Bulthoff, 2001). Even if four natural scenes were presented at once, there was an effect within the ERP after 200 ms. In trials with a target animal compared to trials without a target animal, there was an increase in occipital negativity and a decrease in frontal positivity (Rousselet, Thorpe, & Fabre-Thorpe, 2004). In sum, even under difficult conditions an early ERP effect of category is found.

2.1.1.2 Criticism to the originally applied paradigm

Two criticisms were brought forth against the originally applied visual search paradigm: First, there are concerns to whether or not the search advantage is due to the

target or due to the background that were used (e.g. Rinck, Reinecke, Ellwart, Heuer, & Becker, 2005). Therefore, it would be best to test a neutral target against a fear-relevant target in front of the same neutral background. Second, levels of stimulus categories (Rosch, Mervis, Gray, Johnson, & Boyes-Braem, 1976) seem to be crucial for visual search. With a comparable task to the one used by Öhman and colleagues (2001), Lipp and colleagues (2004) and Flykt (2005) reported faster detection of snakes among spiders and spiders among snakes compared to flowers among mushrooms and mushrooms among flowers (stimuli of the same category, animals and plants respectively). The finding of a faster detection of fear-relevant animals among plants (stimuli of different categories) were replicated by Tipples and colleagues (2002). But they also found a faster detection of fear-irrelevant animals (like rabbits and cats) among plants (stimuli of different categories). All those findings demonstrate a faster detection of stimuli from one category (animals) compared to stimuli from another (plants). To minimize a possible influence of category, the stimulus categories should ideally only vary in fear-relevance.

2.1.1.3 The optimizations of the visual search paradigm

So far, it was pointed out that it is critical to investigate the paradigm on the three levels of measurement (reaction times, EEG, fMRI). However, optimizing the paradigm in terms of large effects should improve all three levels of measurement. In order to allow the effect of fear-relevance to emerge more clearly four previous behavioral studies of our laboratory (Hagemann, Brosch, Britz, Strelzyk, & Naumann, in preparation) were reanalyzed and stimuli and experimental conditions that would maximize the effect were selected. This process revealed that snakes among flowers compared to flowers among snakes produced a greater effect than other combinations of stimuli (e.g., spiders among flowers). Moreover, this effect was more prominent for the 3 x 3 grids than for the 2 x 2 grids. Therefore a paradigm optimized to study the effect of fear-relevance in the visual search may use 3 x 3 grids, and snakes as fear-relevant stimuli and flowers as neutral stimuli.

As mentioned above, category differences may be important. Therefore, to minimize category differences between the fear-relevant subcategory (snakes) and a neutral subcategory, turtles were used as a third stimulus subcategory. Turtles and snakes are a very similar in category (reptiles), although turtles are rated as neutral in valence (Hagemann et al., in preparation). These optimizations were implemented in the present study (see Figure 2.1.1).

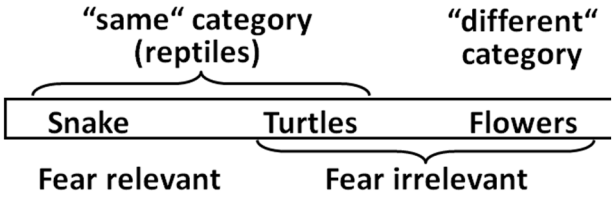


Figure 2.1.1 Overview of stimulus subcategories.

Snake and turtle are the same category but turtle and flower are fear irrelevant. By choosing these stimuli subcategories it is possible to disentangle the complex processes that occur during visual search.

2.1.2 General task

All participants performed an identical visual search task in an EEG- and an efMRI-session. They viewed nine pictures arranged in a 3 x 3 grid. The grids consisted of eight images of one of the subcategories mention above (snake, turtle, and flower) as a background (independent variable BACKGROUND) and a single target (independent variable TARGET) picture which was also from one of the three subcategories. If the background and the target were from the same subcategory (the grid consisted of nine pictures from the same subcategory), this grid was labeled as a homogeneous grid. Otherwise the grid was labeled as a grid with target. Participant had to judge whether all the pictures of the grid belonged to the same subcategory or not.

2.1.3 Visual Search Paradigm Hypothesis

Behavior. Reaction times for fear-relevant targets are expected to be faster than neutral ones. This will be tested with two sets of planed comparisons. The first set consists of two comparisons, each comparing two categories with one being the target and the other being the background and vice versa, i.e. *original comparison* (snake among flowers vs. flower among snakes) and *category optimized comparison* (snake among

turtles vs. turtle among snakes). The *original comparison* is labeled 'original' because it is expected to replicate the findings of Öhman and Mineka (2001) in which snakes among flowers are detected faster than flowers among snakes. The *category optimized comparison* label is chosen because the two stimulus subcategories differ in their fear-relevance but belong to the same category (reptiles). The second set contained three comparisons, each comparing the difference of two subcategories with the third sub category as a background. The first of the three comparisons was a *category and background optimized comparison* (snake among flowers vs. turtle among flowers). This comparison label is chosen because the two target stimuli are optimized with respect to category differences and they are presented among the same neutral background. The second and third of these comparisons were *among turtles comparison* (snake among turtles vs. flower among turtles) and *among snakes comparison* (turtle among snakes vs. flower among snakes). Together, the second set of these comparisons are designed to disentangle the effect of fear-relevance of the target from the effect of the targets category.

EEG. An early emotion-specific variation of the ERPs can be expected if the theory of the evolved fear module can be assessed using the applied paradigm. This effect should be present for the *original comparison* (comparison of snakes among flowers vs. flowers among snakes) and for the *category optimized comparison* (snakes among turtles vs. turtles among snakes). If there is an early ERP effect for the former two comparisons, it becomes important to determine whether or not the effect is due to the fear-relevance of the targets or due to some interaction with the background. An early ERP effect for the *category and background optimized comparison,* which compares targets that differ only in fear but not in category, would clearly reflect not only target processing but differences in target processing due to the fear-relevance of target stimuli. Therefore, this comparison is the most crucial comparison regarding the ERPs for this study. Further evidence may be provided by the *comparison among turtles* which should also reveal an effect of emotion, and by the *comparison among snakes* which should show a null effect as the targets do not differ in emotionality.

efMRI. The amygdala is expected to be activated for trials with fear-relevant stimuli. Activity differences are expected for the *original comparison* (snakes among flowers vs.

flowers among snakes) and for the *category optimized comparison* (snakes among turtles vs. turtles among snakes). As mentioned for the ERP, it is important to determine whether or not the efMRI effect found is due to the features of the target or due to an interaction with the background. Again, this question is addressed by the *category and background optimized comparison.* For this comparison, pronounced differences in amygdala activity are expected. Also, further evidence should be provided by the *comparison among turtles* which is also expected to reveal an effect of emotion and by the *comparison among snakes* where no effect is expected as the targets do not differ in emotionality.

2.2 METHODS

2.2.1 Participants

Twenty healthy volunteers (10 female and 10 male, ages ranging from 20 to 29 years, mean 23) participated in this study. All participants gave written informed consent after procedures had been fully described. All participants were right handed and had normal or corrected to normal vision. The majority of participants were University students, who received 100 Euro for their participation. The study was approved by the local ethics committee.

2.2.2 Experimental procedure

Participants were measure twice, in a repeated measurements design, one week apart and their sequence was balanced across participants. All participants participated in an EEG and an fMRI recording session (independent variable APPARATUS) with exactly the same task (same stimuli, same random sequence, same timing).

2.2.2.1 EEG session

Participants arrived thirty minutes prior to the start of the measurement and were seated in an acoustically and electrically shielded room where they were also prepared for the electrophysiological recording. Each experimental session began with the experiments' instructions and 18 practice trials including feedback to familiarize the participants with the task.

Stimuli. Three types of pictures were chosen to implement three subcategories: fear-relevant and neutral pictures from a similar category and neutral pictures from a different category. As mentioned above, snakes, flowers, and turtle images were used. Twenty-seven colored pictures were used to construct the stimulus grids. Some of the pictures were taken from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1995) and the rest were taken from the internet to fill each category. The pictures retrieved from the internet had a similar visual and emotional appearance to those taken from IAPS. To ensure the intended valence of the stimuli they were rated by 20 participants prior to the experiment. Figure 2.2.1 provides samples of the grid (also see APPENDIX A for samples of all used pictures).

Positions of the pictures were randomized. The target was placed in one of the eight noncentral positions of the 3 x 3 grid. Targets never appeared at the center position and all eight noncentral positions were used equally often for each target subcategory. Each of the nine types of grids was presented randomly, with the restriction that one type of grid could only be repeated three times in a row. All stimuli were presented in a distance of 1m on a 19" CRT screen, had a size of 167 x 167 mm, and had a visual angel of 9.5° x 9.5°.

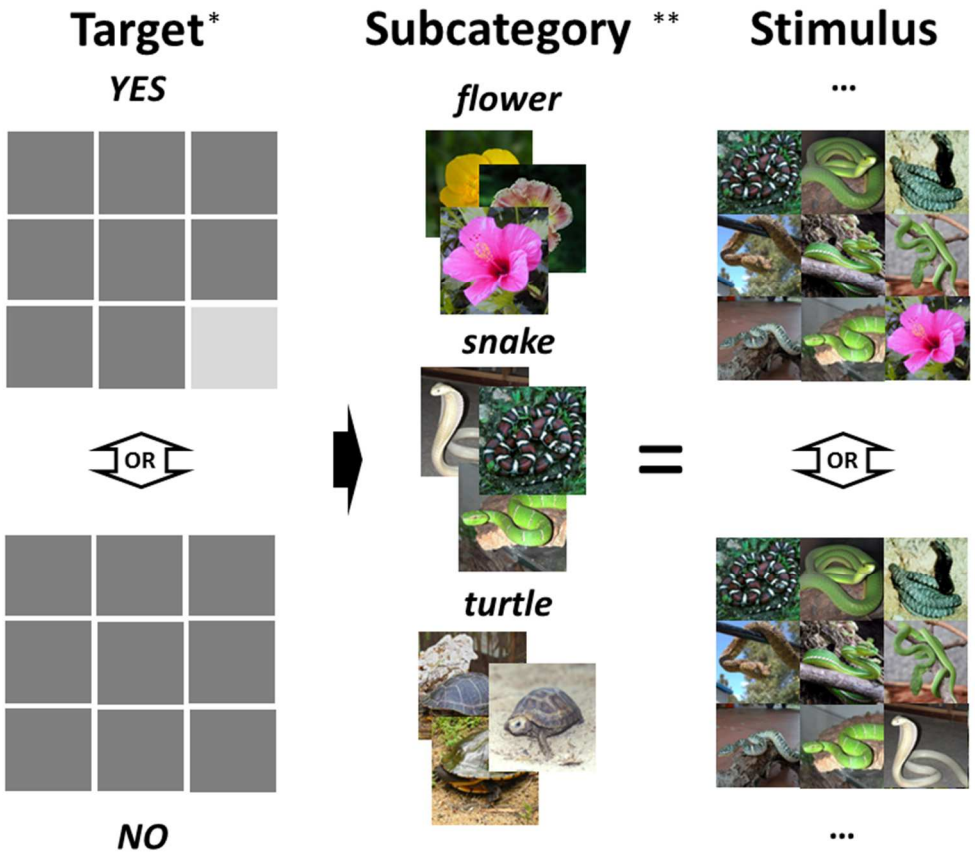


Figure 2.2.1 Make-up of experimental stimuli.

Target: The grid of pictures contained either one picture that had belonged to different category (light grey, target picture) than the rest of the pictures or all pictures belonged to the same category (dark grey). *Subcategory:* Target and background pictures either consisted of flower, snake or turtle images. *Stimulus:* Sample displays one possible configuration of pictures for the stimulus-matrix-combinations that were possible with snakes as a background, flower among snakes (top) and homogenous snake matrix (bottom).

*Target position and slots for the target and background pictures were randomized. **The selection of pictures that were used per category for the target and background were random.

Task. Participants performed a visual search task. During the experiment, participants viewed 288 stimulus grids. A trial consisted of a fixation cross and a stimulus grid. The fixation cross was presented for two seconds and was then replaced by the grid, which was presented for 4 seconds or until the participant responded. A fixation cross followed the stimulus grid and was presented until the remaining time of the 4000 ms epoch and a random interval (varying from 0 to 2.5 seconds) passed. The average trial to trial interval was 7.25 seconds. The participants had to lay their right index finger (on the "arrow down" key) in the middle between the left and the right arrow key. For each trial participants had to decide whether all pictures of the grid were from the same subcategory (pressing the left arrow key) or not (pressing the right arrow key) (independent variable TARGET). They had to react as fast and as accurately as possible. The latency and accuracy of the reaction was recorded.

2.2.2.2 fMRI session

Stimuli and Task. The experimental procedure was kept was the same during the EEG measurements as much as possible and participants performed the same task. Participants were equipped with ear protection (in order to better shield them from the gradient noise of the subsequent BOLD sequence) and placed inside the MRI scanner. A projector (model EPSON EMP-7250) was used to display the experimental stimuli and instructions on a screen at the head-end of the scanner which the participants could see via a mirror that was mounted on the head coil and the visual angel here was also 9.5° x 9.5°. The fMRI session differed from the EEG session in regards to the participants' position in which they performed the task (they had to lie on their back in the scanner), the scanner noise and, the response device used for experimental feedback (they had to give their responses by means of a three key response pad).

2.2.3 Data acquisition and processing

2.2.3.1 EEG and EOG data

EEG was recorded with the Easy-Cap electrode system (Falk Minow Services, Munich) from 32 sites of the 10-10 electrode system (Chatrian, Lettich, & Nelson, 1988) including the mastoids. All sites were referenced to vertex (Cz). A bipolar horizontal

electrooculogram (EOG) was recorded from the epicanthus of each eye, and a bipolar vertical EOG was recorded from supra- and infra-orbital positions of the right eye. The EEG and the EOG were recorded with Ag-AgCl electrodes. Prior to the placement of electrodes, the expected electrode sites on the participant's scalp and face were cleaned with alcohol and gently abraded. All impedances of the EEG electrodes were below 5 kOhm. EEG and EOG were amplified with a 32-channel SynAmps Model 5083 amplifier (input impedance: 10 MOhm; Neuroscan, Inc.) in AC mode. The highpass-filter was set to 0.05 Hz (24 dB/octave rolloff), a lowpass-filter was set to 40 Hz; the signals were digitized at 200 Hz and stored to hard disk for later analysis.

The EEG was re-referenced to mathematically linked mastoids and then refiltered (lowpass: 12 Hz; 24 db). EEG was first segmented into epochs of 6000 ms starting 200 ms before the onset of the stimulus. Artifacts due to eye movements were corrected via the algorithm developed by Gratton and colleagues (Gratton, Coles, & Donchin, 1983). Then the EEG was re-epoched for periods of 2200 ms, starting 200 ms before onset of the stimulus. Epochs with non-physiological artifacts were removed after visual inspection. A baseline correction was performed using the first 200 ms as baseline reference. Artifact free averages were computed separately for each electrode location, type of the nine grids, and participant. Visual inspection of the difference wave of the *original comparison* (flower under snakes minus snake under flower) revealed five spatio-temporal areas (see Figure 2.2.2) which were further analyzed – see following page:

1 - *Early occipital positivity* between 130 -150 ms around at O1, Oz, and O2.
2 - *Later frontocentral positivity* between 190 - 210 ms at F1, F, F2 Fc1, Fc, Fc2 C1, C, and C2.
3 - *Frontocentral negativity* between 390 - 410 ms at F1, F, F2 Fc1, Fc, Fc2 C1, C, and C2.
4 - *Centroparietal positivity* between 600 – 800 ms at C1, C, C2, Cp1, Cpz, Cp2, C1, Cz, and C2.
5 - *Positive late slow wave* between 1200 – 1400 ms C1, C, C2, Cp1, Cpz, Cp2, C1, Cz, and C2.

Amplitudes of the ERP components were extracted via average amplitudes for the described time windows and electrode locations.

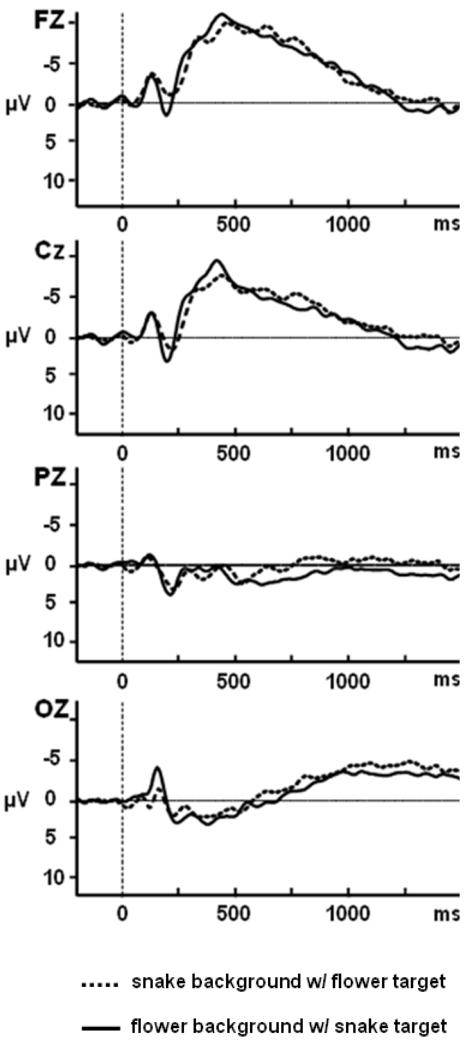


Figure 2.2.2 Stimulus locked event related potentials of the original comparison on midline electrodes.

The solid line depicts the ERP of a snake among flowers and the dotted line the ERP of a flower among snakes. From these two ERPs a difference wave was calculated to identify the spatial temporal areas, which were then used for the further analysis.

2.2.3.2 BOLD fMRI data

Brain images were acquired at the Bender Institute of Neuroimaging using a 1.5-T whole-body tomograph (Siemens symphony with a quantum gradient system) with a standard head coil. First, T1-weighted anatomical images were collected. For functional imaging a total of 844 volumes were registered using a T2*-weighted gradient echo-planar imaging sequence (EPI) with 30 slices covering the whole brain (slice-thickness = 5mm, no gap, interleaved, TA=100 ms, TE=60 ms, TR=3 s, flip angle=30°, field of view=192 mm ×

192 mm, grid size=64 × 64). The orientation of the axial slice was parallel to the AC-PC line. The statistical parametric mapping software (SPM02, Welcome Department of Cognitive Neurology, London) implemented in Matlab (Mathworks, Inc., Natick, MA, USA, release R2007a) was used for preprocessing and statistical analysis. Slice time correction, realignment (since interpolation) and normalization to the standard brain of the Montreal Neurological Institute (MNI) were performed. Smoothing was executed with an isotropic three-dimensional Gaussian filter with a full width at half the maximum of 9 mm. The experimental conditions were modeled by a stick function convolved with a hemodynamic response function in the GLM. The six movement parameters of the rigid body transformation, applied by the realignment procedure, were introduced as covariates in the model. The voxel-based time-series were filtered with a high pass filter (time constant=128 s).

2.2.4 Statistical analyses

The experiment was set up as a three by three factorial ANOVA with repeated measures on both factors. The first factor was the subcategory of the eight background pictures with the levels snakes, turtles, and flowers. The second factor was the subcategory of the single target picture with the same levels as the background (snake, turtle, and flower). If the background and the target were from the same subcategory, then all pictures of the stimulus matrix were from the same subcategory. The case in which target and background pictures belonged to the same subcategory will be labeled "homogeneous grids" from here on. If the background and the target were not from the same subcategory the condition will be labeled “with target”. This resulted in three kinds of homogeneous grids (only snakes, only turtles, only flowers) and in six grids with a target: two grids with neutral background and a neutral target (flower among turtles, turtle among flowers), two grids with neutral background and an emotional target (snake among turtles, snake among flowers) and two grids with emotional background and a neutral target (flower among snakes, turtle among snakes). Every combination of the two factors (equals nine types of grids) was used with the same frequency.

Each of the three levels of measurement – behavior, EEG, and efMRI – were subject to the same inferential statistical analyses, yet none of these level were joined by means any covariance analysis.

2.2.4.1 Behavioral data

Reaction time outliers were excluded after they were identified via an intra-individual stem and leaf procedure (Tukey, 1977; Wilkinson, 1999). A 2 (SEQUENCE) x 2 (APPARATUS) x 3 (BACKGROUND) x 3 (TARGET) factorial ANOVA was used to assess the interactions and main effects. The factors were the following: a between-subjects factor encoding the SEQUENCE of the recording sessions (EEG - fMRI, fMRI - EEG), and three repeated measurement factors with - the first for the APPARATUS (EEG, fMRI), the second for the BACKGROUND condition (snake, turtle, flower), and the third for the TARGET condition (snake, turtle, flower).

The ANOVA yielded significant results for the main effects of the background, the target, and the interaction between background and target, which will be described below. In addition, there was a main effect of apparatus, $F(1, 18) = 6.42$, $p = 0.021$. The participants reacted faster in the EEG session than in the fMRI session, but there were no interactions with the experimental conditions. Moreover, there were no significant effects involving the sequence of the recording sessions. Therefore, the reaction times were averaged across both recording sessions for planned comparisons.

Two sets of planed comparisons as described in the hypotheses section were computed and the significance level was corrected with a Bonferroni-Holm procedure for each of these sets (Holm, 1979). Only results that withstood this correction will be reported.

2.2.4.2 Electrophysiological data

ERP amplitudes (see 2.2.3.1.) were analyzed by the above described five planned comparisons (see 2.1.3). The significance level was corrected for each hypothesis with the Bonferoni-Holm procedure. Only results that withstood this correction will be reported.

2.2.4.3 efMRI data

Student-t contrasts were computed for each participant according to the logic of the five planned comparisons described above (see 2.1.3). For a random effect analysis the individual contrast images (first level) were used in a second level analysis.

For the statistical analysis of the whole brain, results will be reported on a threshold of $\alpha = 0.05$ on voxel-level, corrected for multiple testing, according to the false discovery rate (FDR-cor) implemented in SPM2. An extended threshold of a minimum clusters size of 40 connected voxels was used. Significant clusters will be reported with their maximum t-value, the coordinates of the t-value and with the cluster size by number of voxels.

For the statistical analysis of the regions of interest (ROIs) the left and right amygdala was selected. The ROIs were defined by the anatomical parcellation of the normalized brain (single-subject high-resolution T1 volume of the Montreal Neurological Institute) as described by Tzourio-Mazoyer and colleagues (2002). The Software MARINA (Walter et al., 2003) was used for creating the appropriate masks. The threshold for the ROI analysis was set to $\alpha = 0.01$ on voxel-level, corrected for multiple testing, according to the false discovery rate (FDR-cor) for the searched volume as implemented in SPM2. Regions were regarded significant if the analyses revealed 20 connected voxel.

2.3 RESULTS

2.3.1 Behavioral data

The planned comparisons revealed that participants in the *original comparison* reacted, on average, 38 ms faster to the snake among flowers (M = 1140 ms) than to the flowers among snakes (M = 1178 ms), t(19) = 1.97, p= 0.031. Similarly, in the *category optimized comparison* participants reacted, on average, 145 ms faster to the snake among turtles (M = 1322 ms) than to the turtle among snakes (M = 1468 ms), t(19) = 7.61, p= 0.000. These findings are in line with the hypothesis concerning fear-relevant targets. In line with these expectations, the reaction time advantage for a snake target was greater in the category optimized comparison than in the original comparison. At this point the results replicate earlier findings by Öhman and colleagues (2001) and provide evidence for a successful category optimization.

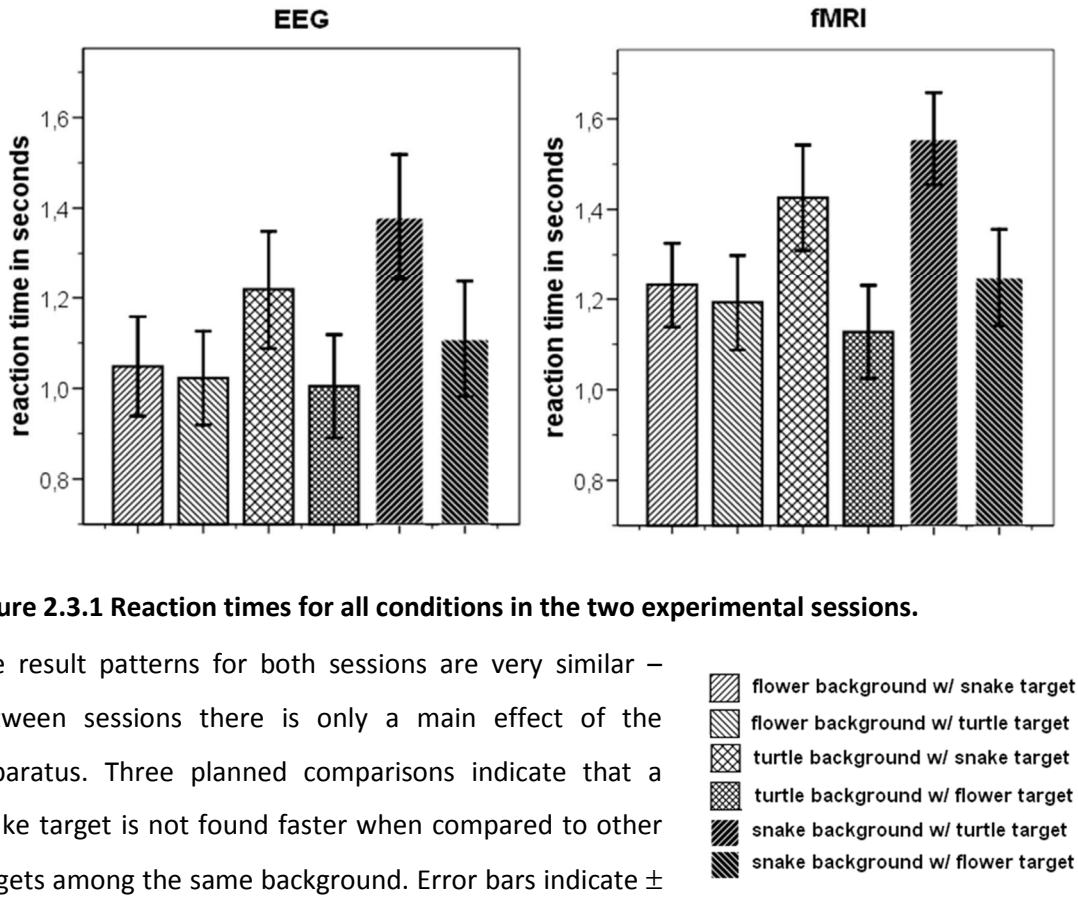


Figure 2.3.1 Reaction times for all conditions in the two experimental sessions.

The result patterns for both sessions are very similar – between sessions there is only a main effect of the apparatus. Three planned comparisons indicate that a snake target is not found faster when compared to other targets among the same background. Error bars indicate ± 2 SD.

However, the category and background *optimized comparison* of snake and turtle targets among a neutral flower background revealed that participants reacted, on average, 33 ms faster to a turtle (M = 1107 ms) than to a snake (M = 1140 ms), t(19) = 3.09, p= 0.003. The result for this critical test concerning the fear-relevance of the target was unexpected, but a further comparison supports this finding. In the *among turtles comparison*, participants reacted, on average, 256 ms slower to a snake (M = 1322 ms) than to a flower (M = 1066 ms) as a target, t(19) = 18.50, p= 0.000 (Figure 2.3.1). Participants never reacted faster to the snake targets compared to the neutral ones presented on the same background.

The greatest reaction time difference in the second set of comparisons was found in the *among snakes comparison*. Here, the participants reacted, on average, 289 ms slower to a turtle (M = 1468 ms) than to a flower (M = 1179 ms) as a target, t(19) = 14.76, p= 0.000 (Figure 2.3.1).

To summarize, behavioral results confirm earlier findings and indicate that the applied category optimization worked. However, the results do not confirm the expectations that fear-relevant targets always lead to faster reactions than neutral ones.

2.3.2 Electrophysiological data

The planned comparisons revealed significant differences for the three early spatio-temporal areas. No differences were found for the two late spatio-temporal areas. Figure 2.3.2 shows the ERP average amplitudes separately for all six with target conditions, three homogenous grid conditions and for the five analyzed time intervals.

Occipital negativity around 140 ms. The *original comparison* of the occipital negativity between 130 and 150 ms revealed that amplitudes were, on average, 2.32 µV smaller in magnitude for snake targets (*M* = -0.37 µV) than for the flower targets (*M* = 1.95 µV), *t*(19) = -3.42, *p*= 0.004. There was no effect for the comparison of targets in front of a constant background. However, given the result of the *original comparison* in terms of the backgrounds, a decrease of amplitudes for a flower background compared to a snake background is found. Therefore, the results of the occipital negativity around 140

ms may be interpreted as more negative amplitudes for flower backgrounds compared to snake and turtle backgrounds.[1]

Frontocentral positivity around 200 ms. The *original comparison* of the frontocentral positivity between 190 and 210 ms revealed that amplitudes were, on average, 2.29 µV greater for snake targets (*M* = 1.94 µV) than for the flower targets (*M* = -0.36 µV), *t*(19) = 2.63, *p*= 0.017. In the *comparison among turtles*, snake targets (*M* = -1.21 µV) evoked, on average, 1.19 µV greater negative amplitudes than flower targets (*M* = -0.02 µV), *t*(19) = -2.63, *p*= 0.017. Further findings for the frontocentral positivity around 200 ms were that amplitudes were more positive for flower backgrounds compared to the other two categories. This is found for all comparisons with a flower background.[2]

Frontocentral negativity around 400 ms. The analysis of the frontocentral negativity between 390 and 410 ms revealed that amplitudes were, on average, 1.97 µV smaller for snake targets (*M* = -8.83 µV) than for flower targets (*M* = -6.86 µV), *t*(19) = -

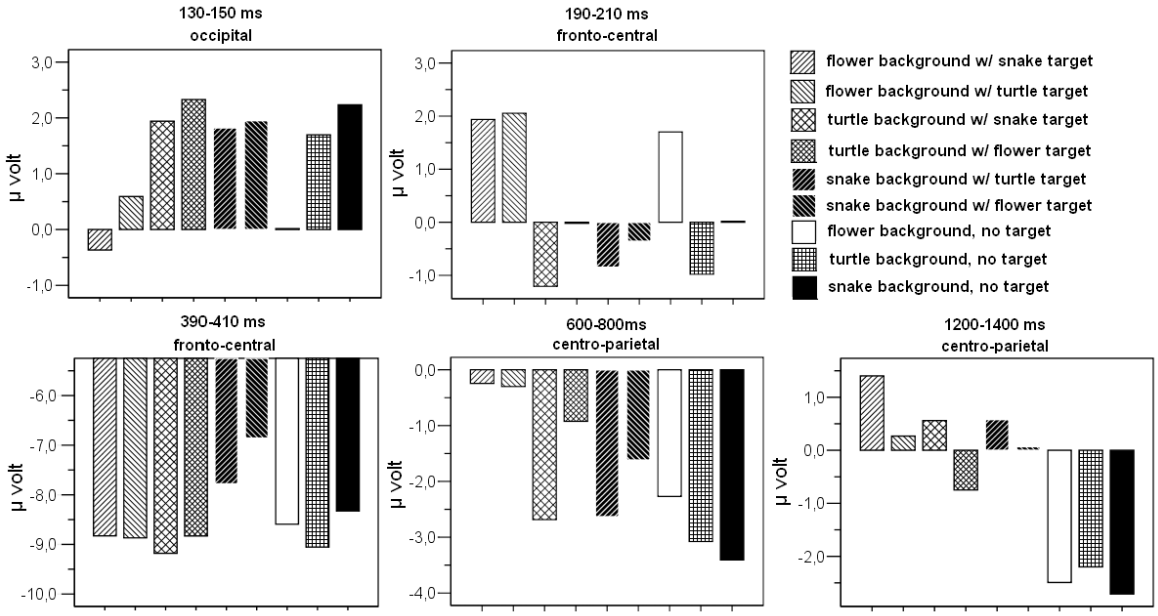


Figure 2.3.2 Mean ERP amplitudes of all experimental conditions and all spatial temporal areas.

[1] For the homogeneous grids the spatio-temporal area was more negative for flowers than for snakes (2.22 µV) or for turtles (1.68 µV). Homogeneous snake and turtle grids differed not from each other.

[2] For the homogeneous grids there was more positivity for flowers than for snakes (1.68 µV) or for turtles (2.68 µV). Homogeneous snake and turtle grids differed by 1.00 µV.

2.96, *p*= 0.008. This spatio-temporal area revealed no other effects for the planned comparisons. [3]

In summary, even though there were three significant spatio-temporal regions for the *original comparison,* there was no effect of fear-relevance for the *category optimized comparison* and for the *category and background optimized comparison*. This indicates that there is no effect that would be specific for fear-relevance. However, the frontocentral positivity differed significantly at 200 ms for all comparisons involving category differences except for the comparison among snakes. This could indicate an early effect of category.

2.3.3 Functional imaging data

No amygdala activity differences were found for any of the planned comparisons. This finding is confirmed by the ROI analysis, which could not find any significant activation differences within the amygdala despite the liberal criterions.

All comparisons which aimed to find an effect of fear-relevance did not reveal any significant differences. Neither the *original comparison*, the *category optimized comparison*, nor the *category* and *background optimized comparison* which compared snake targets against turtle targets in front of flowers, showed any significant differences.

The other two comparisons of targets in front of a constant background which both compared targets from different categories (*among turtles* - snakes vs. flowers and *among snakes* - turtles vs. flowers) revealed homogenous results (see Table 2.3.1 and Figure 2.3.3). The strongest activation for both comparisons was a widespread occipital network that was more active for the condition where the target and the background were from the same category compared to the condition where the target was from another category (Figure 2.3.3). For both comparisons, the occipital cluster was similar in size (*among turtles*: 3798 voxel and *among snakes*: 3894 voxel in the standard brain), both had very similar maximum t-values (*among turtles*: 8.70 and *among snakes*: 8.88) and for both, the t-value maxima were located in the right middle occipital gyrus (Table

[3] The comparison of homogenous grids *snakes vs. flowers* and of *snakes vs turtles* also revealed no differences in amygdala activity.

2.3.1). The second strongest activation of the comparison of snake targets to flower targets among turtles was also found for the comparison of turtle targets to flower targets *among snakes*, with a comparable maximum t-value (*among turtles*: 6.69 and *among snakes*: 5.63). Additionally, both maxima were at exactly the same location (x = 48, y = 12, z = 33). Also, out of the other twelve significant clusters, the maxima of six clusters were located in identical brain regions for both comparisons (Table 2.3.1). Furthermore, the insula was activated near the voxel threshold for both comparisons, but differed in hemisphere (Table 2.3.1). Both comparisons revealed no significantly deactivated brain region.

Table 2.3.1 Event-related fMRI results for the planned comparisons

		Planned comparison *(t-test one-tailed)*			
		Same background			
		among turtles		***among snakes***	
Brain area	**Region**	***x y z***	***voxels (t_{max})***	***x y z***	***voxels (t_{max})***
Frontal lobe	inf. frontal gyr. right	48 12 33	212 (6.69)	48 12 33	117 (5.63)
	inf. frontal gyr. left			-33 21 -15	211 (5.92)
	middle fr. gyr. left	-27 -3 51	52 (5.48)		
	supp. motor a. left	-6 18 48	170 (5.92)	-9 9 57	67 (5.30)
Central region	precentral gyr. left	-54 9 33	81 (5.38)	-33 -9 57	95 (4.69)
Occipital		33 -90 12	3789 (8.70)	42 -81 15	3894 (8.88)
Parietal lobe	inf. pariet. gyr. left			-42 -30 36	150 (5.19)
Subcortical	thalamus left			-3 -15 6	215 (7.49)
Insula	left	-30 24 3	52 (5.46)		
	right			36 15 -9	53 (4.43)

Note. Significant clusters are displayed by their Tailarach coordinates of their maximum t-value, their maximum t-value, the name of the brain area in which their maximum is located, and the number of connected voxels.

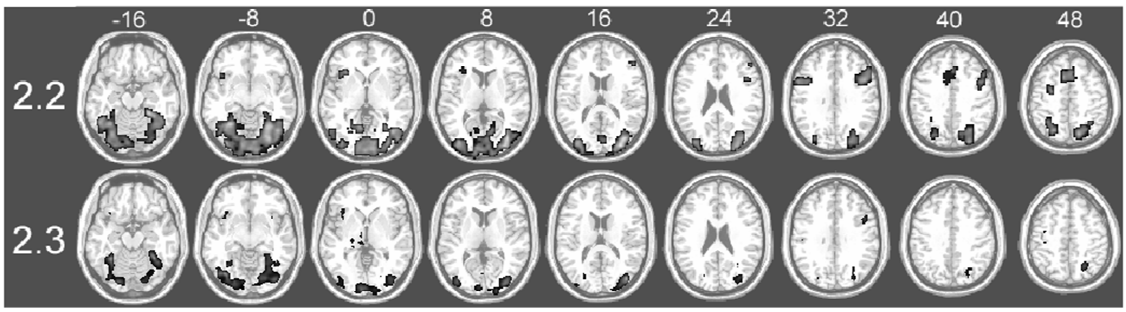
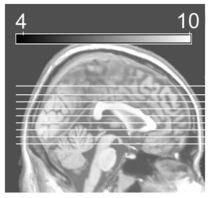


Figure 2.3.3 MRI Results for among turtles and among snakes comparisons



Activated areas (t = 3,84; extended threshold as implemented in SPM2 of 40 connected voxels) of all planned comparisons with significant results in the efMRI, superimposed on a mean brain scan, for nine horizontal slices (Tailarach coordinates z = -16 to z = 48, step 8) each. Only the planned comparisons *among turtles* (2.2) and *among snakes* (2.3) showed significant fMRI activation differences.

To conclude, there was no difference for the *original comparison*, for the *category optimized comparison* or for the *category* and *background optimized comparison*. The amygdala did not show differences in activity for any of the investigated comparisons even at a liberal criterion. Comparisons of targets which differed in category in front of identical backgrounds revealed activation differences in the occipital cortex and some other regions. In summary, no specific effect of fear-relevance was found with the efMRI.

2.4 DISCUSSION

2.4.1 Visual search paradigm

Even though this study was set up to investigate the evolved fear-module with an optimized visual search task, findings indicate that the fear-relevance of the stimuli was most likely not processed in the investigated task. Neither an ERP effect nor an efMRI effect was found that is attributable to the fear-relevance of the stimuli. This is in line with the behavioral results from this study indicating that there is no general search advantage for fear-relevant stimuli. These findings are supported by the fact that this study replicated former findings, successfully optimized the paradigm, and revealed very similar behavioral results for the two sessions.

In the following, findings of the three levels of measurement concerning the impact of fear-relevant stimuli will be discussed. Since the results indicate that the fear-module was not active in this task, reasons for this are discussed. However, the results are consistent with other studies which indicated that fear-relevance is not processed when a task is very demanding. Therefore, the implications of this argument for the theory of the evolved fear-module will be discussed. It may be hypothesized that the evolved fear-module is under control of higher-order processes. If this assumption is correct, then the theory of the evolved fear-module might be extended by including the situational context. In addition, as the original findings were replicated, explanations for the results of the *original comparison* and the impact of category level differences are shortly discussed below.

2.4.1.1 Behavioral findings

Regarding the comparison of snakes among flowers with flowers among snakes (*original comparison*) there is a search advantages for snakes. This replicates former findings (Brosch & Sharma, 2005; Flykt, 2005; Lipp et al., 2004; Tipples et al., 2002). Moreover, reducing the category differences, that is, using turtles instead of flowers as neutral stimuli (*category optimized comparison*), enhanced the search advantage for fear-relevant stimuli further, and increasing the advantage from 38 ms for the *original comparison* to 146 ms for the *category optimized comparison*.

Here it seems noteworthy that the studies cited in the paragraph above used comparisons in which two categories were always compared to each other as pairs of target and background (for example snake as background with a flower target were compared to flower as background with a snake and vice versa). For the *category and background optimized comparison* the targets differ in fear-relevance but they were from the same category and they were both presented among the same neutral background. Therefore, this comparison allowed the investigation of the specific effect of fear-relevance best. However, no search advantage was found in this comparison for the snake targets. This implies that fear-relevant stimuli (here snakes) were not always detected faster than neutral stimuli.

Regarding the comparison among turtles, the snake was found slower than the flower. This suggests that the participants benefited from the category differences, which were bigger between flowers and turtles (plants and animals) than between snakes and turtles (both animals). The search advantage was diminished by reducing the target-distractor difference in the dimension of category. Among flowers, the targets were from a similar category but different from the category of the background. They were found fast and their detection times differed only slightly (32 ms). For the other two comparisons (among turtles, among snakes) the targets belonged to different categories, which was associated with a detection advantage for the target which differed from the background in category. The search advantage for flowers among snakes was 289 ms and for flowers among turtles it was 256 ms (Figure 2.3.1). These findings suggest that the dimension of category (Rosch, et al., 1976) is a central construct in this kind of visual search. This is in line with the criticism of Wolfe and Horowitz (2004) that was cited in the introduction (see 2.4.1.1). It seems that not fear-relevance but other visual attributes distinguishing between the categories account for much of the search time differences.

Regarding the *original comparison* and the *category optimized comparison* there is still a search advantage for snakes. However, taking the comparison of turtles among flowers vs. snakes among flowers into account, there is no general search advantage for fear-relevant stimuli. One alternative explanation for the findings of the *original comparison* is that target and background effects are entirely confounded, since neutral targets are always presented with a fear-relevant background and vice versa. Thus the

search time differences could be due to an effect of the background, which is possibly due to a greater difficulty in disengagement from an emotional background (e.g. Rinck et al., 2005). The findings suggest that visual attributes that separate the categories have a profound impact on visual search. The answer to the question, which visual attribute causes these effects is beyond the scope of this thesis. Possible visual attributes, which separate the investigated subcategories may be the aposematic coloration of dangerous animals, or as Wolfe and Horowitz (2004) suggest, their distinct shapes.

To summarize the behavioral results, two critical points were made. First, there is no general search advantage for fear-relevant stimuli in this paradigm and second, other category differences besides fear-relevance seem to have a crucial impact upon the search in the investigated task.

2.4.1.2 Electrophysiological findings

For the *original comparison*, ERP differences were found for three early spatio-temporal areas, which could be interpreted as early effects of fear-relevance for a start. However, very similar to the behavioral findings for this comparison, this interpretation is not consistent with the findings of the other comparisons. As there were no significant results for the *category optimized comparison* and for the *category and background optimized comparison* this suggests that none of the effects found for the *original comparison* are specific for fear-relevance. The findings of the current study are partly consistent with those of Flykt (2005), who also found no early ERP effect of fear-relevance in a very similar task. However, finding no ERP effect for fear-relevance seems to be in contrast to other studies which found early effects of fear-relevance or emotion with different paradigms (Pizzagalli, Koenig, Regard, & Lehmann, 1998; Schienle et al., 2008). This conflict may be resolved when task demands are taken into account. The latter two studies used picture viewing without any further demands and can, therefore, be considered much easier as the here implemented visual search task. This is in line with other recent studies which found ERP effects related to fear (or emotion) only for their easy, but not for their demanding task condition. Recent evidence suggests that under some conditions the fear-relevance of stimuli is not processed or is processed to a lesser extent (Eimer & Holmes, 2007; Eimer, Holmes, & McGlone, 2003; Eimer & Kiss, 2007;

Schupp et al., 2007). For example, Eimer and colleagues (2003) found an early ERP effect of fear-relevance only when participants attended the fear-relevant stimuli but not if participants performed a demanding perceptual discrimination task. Schupp and colleagues (2007) investigated whether or not the early capture of attention by emotional stimuli is an automatic process or if it is participant to interference by competing processing demands. For their low demanding task condition, they found an early ERP effect of emotion which was absent for the demanding task condition. Because fear is an emotion, it may be concluded from these findings that the processing of the fear-relevance of stimuli is attenuated or even nullified by increasing task demands. Therefore, the lack of an early ERP effect of fear-relevance in the presented study could be due to the type of task or, more specifically, due to high task demands in the present study.

In contrast to the negative findings concerning an ERP effect for fear-relevance, the fronto-central positivity differed significantly at 200 ms for all comparisons involving category differences except for the comparison among snakes. This parallels the behavioral results, which also suggest that participants performed the task by some other visual category information than fear-relevance. This result is in line with other ERP findings (Rousselet et al., 2004; Thorpe et al., 1996; Thorpe et al., 2001). Even though the effect is not as prominent as the one found by Rousselet and colleagues (2004) it is encouraging to compare the data of this study with their findings, which showed that the effect of category decreased with the number of presented stimuli. However, the latency of the effect was constant indicating a parallel process. Even though the current study presented nine pictures at once, the effect of category could still be replicated.

In summary, finding an early category effect but no fear-relevance effect adds to evidence that within this paradigm of visual search the fear-relevance of the stimuli might not be processed.

2.4.1.3 efMRI findings

Although a very liberal criterion was applied, no activity differences were found within the amygdala for the *original comparison*, *the background optimized comparison,* and the *category and background optimized comparison.* Even the exploratory comparison between homogenous grids of fear-relevant stimuli to homogenous grids of

neutral stimuli did not reveal differences in amygdala activation. These findings coherently indicate that the fear-relevance of the stimuli was processed to a lesser extend or not processed at all in this task. As the behavioral results show that the task is very demanding this is in line with other studies which suggest that there is no fMRI observable processing of the fear-relevance of the stimuli if a task is very demanding (Pessoa, Kastner, & Ungerleider, 2002; Pessoa, Padmala, & Morland, 2005). Pessoa and colleagues (2005) found that there was amygdala activity for fear-relevant faces only in an easy task, but not in a hard one. If all resources are already needed by processes under the control of the frontal cortex, it is most adaptive to draw resources away from the limbic structures (for a discussion see Pessoa et al., 2005). This effect of task demands is in accordance with the ERP studies mentioned earlier.

Regarding other brain areas besides the amygdala, no activity differences were found for the *original comparison*, *the background optimized comparison,* and the *category and background optimized comparison.* The null findings of these comparisons seem to be partly inconsistent to the behavioral and ERP findings, which revealed effects for some of these comparisons although these effects were probably category effects and not effects of fear-relevance. One possible explanation for this result might be that the efMRI analysis for the whole brain is less sensitive than the other analyses. This reasoning is in line with the observation that the reaction time differences for the three comparisons that showed no efMRI effects were small (see behavioral results). However, this thesis already addressed this limitation with the more sensitive ROI analyses, which also provided null findings.

The other two comparisons that used an identical background revealed very similar efMRI effects. Both compared targets from different categories but one compared two neutral targets and one compared a fear-relevant target to a neutral one. As their results are comparable, this indicates that the difference of category and not the fear-relevance is reflected in the efMRI activation differences of these two comparisons. This line of reasoning is consistent with the null findings for the *category and background optimized comparison,* which compared targets that differ in fear-relevance but not in category. The activation difference within the occipital lobe is in line with other studies finding that the activity in the occipital lobe co-varies with the demands of the visual task

(Gerlach, Law, Gade, & Paulson, 1999, 2000) or, as stated in the introduction (see 2.1.1) with non-emotional differences in category (Ishai et al., 2000).

These two comparisons yielded further efMRI effects in the right inferior frontal gyrus (see results section and Table 2.3.1). These effects are very similar for both comparisons, which is also in line with the suggestion that participants performed the task by category differences. The activity of the right inferior frontal gyrus is found to differ for categorical judgments that vary in difficulty (Devlin et al., 2002; Gerlach et al., 2002; Gerlach et al., 2000).

In an additional exploratory comparison of homogeneous grids (snakes vs. flowers, snakes vs. turtles) there was no effect of fear-relevance, either. This is an interesting finding insofar as a comparison of homogeneous grids would disprove the criticism of Wolfe and Horowitz (2004) by demonstrating that fear-relevance would have an impact on the visual processes during this kind of task. Contrary to these expectations, this study did not find a significant effect of fear-relevance. However, these findings are in accordance with the findings from the other levels of measurement from this study and indicate that visual features of the categories other than fear-relevance were central for this task.

In summary, the amygdala did not show differences in activity for any of the investigated comparisons even at a very liberal criterion. There is no effect of fear-relevance for the *category and background optimized comparison*. Comparisons of targets in front of identical backgrounds revealed no activation differences when the target stimuli were from the same category and differed in fear-relevance. Contrary to this, there were effects for comparisons of targets in front of identical backgrounds when the target stimuli differed in category. The efMRI results of this study indicate that the fear-relevance of the stimuli was not processed.

2.4.2 Conclusion

The behavioral results of this study suggest that there is no general search advantage for fear-relevant stimuli in this paradigm and that it is more likely that participants performed the task by category information. This does not answer the question to what extend the fear-relevance of the stimuli is processed in this task. Two

explanations seem to be possible: reaction times towards targets did not benefit from their fear-relevance because this information was not processed or because the information was processed but did not influence task performance. However, ERP and efMRI findings clearly support the former explanation.

The ERP findings corroborate the findings of (recent) previous work in this field, which also found the processing of fear-relevance or emotion to be reduced when a task was very demanding (Eimer & Kiss, 2007; Schupp et al., 2007). These findings are interpreted as a inhibitory influence of higher order processes over the fear-module (Schupp et al., 2007).

The efMRI results also point towards the possibility that the fear-module is not active when a task is very demanding, and are consistent with those of Pessoa and colleagues (2005) who found that the emotional content of stimuli is not processed if a task is very demanding. These findings further support the idea that the evolved fear-module is under control of higher order processes.

The conclusions drawn so far are not weakening the hypothesis, that a long co-evolution of animals with other potential threatening animals has led to neuronal mechanisms capable to perform a highly efficient visual search in terms of survival. However, as the fear-module is thought to alert an inattentive participant, it can be questioned whether or not this process should have an impact during a highly demanding task. Thus, the theory of the evolved fear-module might be extended by including the situational context. This is in line with other recent suggestions like: “These findings implicate to assess the presumed automatic nature of emotion processing at the level of specific aspects rather than considering automaticity as an all-or-none phenomenon“ (Schupp et al., 2007, p. 16).

In conclusion, humans survived under conditions where meeting snakes were rare events which became most dangerous when the person was not alert. For a better understanding of the function of the evolved fear-module, an experimental paradigm has been suggested that uses a visual search task with fear-relevant stimuli. In the present study, this paradigm was optimized and provided converging results from behavioral, ERP and efMRI measurements, which indicate that the fear-relevance of the stimuli was not processed. This finding seems to be attributable to the high cognitive demands of the

paradigm, which suggests that one may have to present the fear-relevant stimuli in a very low demanding task and at a low frequency of fear-relevant stimuli in order to study the attention guiding effect of these stimuli. Moreover, this finding adds to a growing body of evidence which suggests that the theory of the evolved fear-module has to be extended (Eimer & Kiss, 2007; Pessoa et al., 2005; Schupp et al., 2007) by incorporating the condition-specific cognitive control or influence on the fear-module.

2.4.3 Methodological implications

EEG and BOLD fMRI did reach converging results in that both methods did not find evidence that the applied paradigm was able to capture the action of the proposed evolved fear module. At the same time, the results of both methods provided evidence that the theory of the evolved fear module has to be further extended. Combining EEG and fMRI in the same participants was, therefore, effective by using separate statistical analyses. The inherent weakness of each measure, i.e. signal cancellations in EEG and temporal insensitivity for fMRI, was limited by assessing both measures together.

The resulting null findings regarding the critical target contrast (among flowers comparison among snakes, among turtles), require additional replications regarding a more general scientific note. The absence of experimental effects, as well as the presence of such for that matter, does require additional confirmation from independent data acquisitions. However, even if the absents of effects can be confirmed through additional replications other functional relationships that are not based on group average can exist. In other words, the approach of Study 1 was solely based on group averages that were not statistically joined and which disregarded intra-individual signal differences which may still have existed and that can be detected via correlational (i.e. combined) analyses. An approach of statistically joining EEG and fMRI signals on the basis of individual participants will be further explored in Chapter III.

INTEGRATING FMRI AND EEG ON THE EMOTIONAL P300

CHAPTER III

ABSTRACT

The processing of emotion related information is a constant aspect of human brain activity and a wide range of measuring techniques and statistical analyses have been applied to quantify neuronal emotion processing. The aim of this study was to identify brain areas which are functionally equivalent to the P300-amplitude in terms of their reactivity to emotion while statistically joining EEG and fMRI through correlation analyses. These analyses revealed that the amplitude of the P300 was only influenced by valence and not by the decoding conditions. There was functional equivalent activity to the reactivity of the P300 towards emotion and decoding conditions within the amygdala and the temporal pole. Divergent statistical findings lead to the conclusion that the left superior frontal gyrus plays of key role in explaining the inter-individual differences in reactivity of the P300 towards emotional stimuli. In conclusion, this could only be determined via combined EEG-fMRI analysis that focusses on intra-individual correlations between EEG and fMRI signals.

3.1 INTRODUCTION

The visual paradigm described in Chapter II provided support to the notion that the theory of the evolved fear module has to be further extended. This conclusion was reached based on a null-finding of neural target effects in separate measurements of both EEG and BOLD fMRI. However, a number of possible intra- and inter-individual neuronal processes may have occurred that cannot be assessed via independent average based statistical analyses. The following study investigated the opportunities that lay within combined analyses of combined EEG and BOLD fMRI acquisitions of the same participants. Once again, an emotion relevant ERP paradigm was applied that seemed well suited for obtaining for assessing combined data acquisitions.

3.1.1 Emotion

The processing of emotion related information is a constant aspect of human brain activity. Consequently, the number of studies examining emotion has increased considerably over the last years (Phan, Wager, Taylor, & Liberzon, 2004). Within those studies, a wide range of measuring techniques and statistical analyses has been applied in order to quantify emotion. However, the time course of emotion specific processes can best be studied by means of ERP, which provide information within a time resolution of milliseconds. The location of specific emotional activation can be studied by using fMRI, which provides information within a spatial resolution of millimetres. The following study combines these two methodologies and is guided by results from ERP research on emotion, concentrating on the P300 component. The P300 component reacts automatically to the emotional content of stimuli independent of task demands (see 3.1.1.2). Similar results are obtained for several brain regions in fMRI experiments (see 3.1.1.3). Whether or not these EEG and fMRI effects are functionally related remains the object of on-going investigations. The aim of the present study is, therefore, to identify brain areas which are in terms of reactivity to emotion (functionally) equivalent to the P300-amplitude.

3.1.1.1 Automatic processing of emotion

The difference between an automatic processing and a more conscious based processing of emotion can be investigated by different means. One way is to compare subliminal presentation of the stimuli to conscious presentation. A second way is to compare an easy task to a task that is so hard that attention is diverted away from the emotion or that the processing of emotion is suppressed. A third way of doing so is to create a task which can either be solved just by perception or just by decoding the emotional content. In this study, the last two methods will be considered since they are expected to involve the same underlying process. Stimuli conditions were designed that differ in regard to their easiness to detect (repetition of identical stimuli vs. new stimuli) and their emotional encoding characteristics (emotional stimuli, i.e. valance decoding vs. structural stimuli)

3.1.1.2 Emotion and P300

The late positive complex of this ERP consists of a parietal maximal P300-component (Donchin & Coles, 1988, 1991; Verleger, 1988) and a slow wave whose polarity and topography is task dependent (Rösler, Heil, & Röder, 1997; Rösler, Heil, M., 1991; Sutton & Ruchkin, 1984). The P300 component is enhanced, mainly at parietal locations, for emotional positive and negative verbal and pictorial stimuli when compared to neutral ones (Bartussek, Becker, Diedrich, Naumann, & et al., 1996; Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Diedrich, Naumann, Maier, & Becker, 1997; Naumann, Bartussek, Diedrich, & Laufer, 1992b; Naumann et al., 1992; Naumann, Maier, Diedrich, Becker, & Bartussek, 1997; Palomba, Angrilli, & Mini, 1997; Schupp et al., 2000; Schupp, Junghöfer, Weike, & Hamm, 2003). This effect seems to be independent of task demands. Naumann, Bartussek et al. (1992a) asked their participants either to categorize negative, neutral or positive adjectives by their length (structural decoding: is the word shorter, equal or longer than 5 letters?) or by the subjective emotional value (emotional decoding: is the word more likely emotional negative, neutral or positive?). They reported more positive P300 amplitudes for emotional stimuli in both tasks. The same results were observed when a structural or emotional decoding task was performed with negative, neutral, and positive pictures (Diedrich et al., 1997). The latter result could also be

explained by task difficulty, as the structural task was easier than the emotional categorization task. However, in a follow up-study (Naumann et al., 1997), a more demanding structural task confirmed the previous result: P300 amplitudes at parietal locations were enhanced for emotional positive and negative stimuli in both tasks.

A widely accepted model of P300 states that the P300 amplitude increases when the information a particular stimulus contains is important with respect to future behaviour (Donchin, 1981; Donchin & Coles, 1988; Donchin, Ritter, & McCallum, 1978). The more important the information is for strategic information processing, the larger the P300 amplitude is going to be. From this point of view the emotional quality of a stimulus adds important information to a stimulus, quite likely as a result of a more pre-attentive affective evaluation process (LeDoux, 1989; Öhmann & Mineka, 2001), which takes place in limbic structures. The outcome of the pre-attentive evaluation process adds to the salience of the stimulus as indicated in the P300 amplitude. The electrophysiological data suggest that this process is independent of task demands, as it is also observable when the focus of attention is directed away from the emotional content of the stimuli. Thus, the emotional relevant information is always available for further processing.

3.1.1.3 Emotion and fMRI

It is far beyond the scope of this chapter to provide a review over the reactivity of fMRI to emotional stimuli or emotional situations (see Murphy, Nimmo-Smith, & Lawrence, 2003 and Phan, Wager, Taylor, & Liberzon, 2002 for reviews). This chapter will concentrate on studies showing pre-attentive, more automatic reactivity to emotional stimuli with the aim to identify those areas which show pre-attentive reactivity.

From several fMRI studies it is known that there are emotion specific structures in the brain which react to the emotional content of stimuli, even when those stimuli are not perceived consciously or when the attention is drawn away from the emotional relevant information. A core candidate for this pre-attentive part is the amygdala (see Zald, 2003 for a review). The amygdala displays a reaction pattern to emotional stimuli, which is very similar to the P300 component of the ERP. However, the reactivity of the amygdala and the reactivity of the P300 generating network reflecting the same processes remain unclear. Emotional stimuli show increased amygdala activity

independent of a specific task and even independent of conscious awareness. One line of evidence is provided by studies where the conscious awareness of emotional stimuli is disabled by the masked representation of emotional and neutral stimuli (Rauch et al., 2000; Whalen et al., 1998). These studies demonstrate enhanced amygdala activity to masked emotional (fearful) faces, although participants were not able to perceive the masked faces consciously. Similar effects were obtained during conditioning of masked faces (Critchley, Mathias, & Rolan, 2002; Morris, Buchel, & Rolan, 2001; Morris, Oehman, & Rolan, 1998).

Other results show enhanced amygdala activation for emotional stimuli (mainly faces) even when participants were distracted from the emotional content of the stimuli (Chritchley et al., 2000; Gorno-Tempini et al., 2001; Rotshtein, Malach, Hadar, Graif, & Hendler, 2001; Vuilleumier, Armony, Driver, & Dolan, 2001, 2003; Winston, Strange, O'Doherty, & Dolan, 2002). Results from other studies are contradictory (Pessoa et al., 2005), showing effects of emotion only when the participants attended to the emotional content of the stimuli. However, the relative high type II error (falsely accepting the null hypothesis) in these studies makes an unambiguous interpretation of the results problematic. To determine whether or not the pattern of results is specific for a brain area or common for a widespread network it would be necessary to explore other brain areas which are also considered relevant for the process of interest. In at least two studies from the literature cited above, other brain areas besides the amygdala are reported to show reactivity to emotional stimuli, independent of conscious recognition of emotional stimuli and/or task demands – these areas are: orbitofrontal cortex, insula, anterior cingulate cortex, middle temporal gyrus, inferior temporal gyrus, inferior gyrus of the temporal pole and middle gyrus of the temporal pole (see APPENDIX F for ROI overview).

3.1.2 The P300 network

The P300 component is usually elicited using the "oddball" paradigm, wherein two stimuli are presented in a random order, with one occurring more frequently than the other (see for example Picton, 1992). The participant is instructed to discriminate an infrequent target stimulus from the frequent standard stimulus by responding covertly or

overtly to the target - typically a relatively easy discrimination (for an example see, Picton, 1992). The target elicits the P300, which is not apparent in the ERP from the standard stimulus. This basic paradigm has been used in several fMRI experiments (Bledowski et al., 2004; Horovitz, Rossion, Skudlarski, & Gore, 2004; Horovitz et al., 2002; Kiehl et al., 2005). The most convincing data on the brain structures activated by the rare, task relevant stimulus comes from a large scale study (n=100) of Kiehl and colleagues (2005). Regions most strongly activated by the rare, task relevant stimulus include left precentral gyrus, left postcentral, left inferior parietal/supramarginal gyrus, right inferior parietal/supramarginal gyrus and left inferior frontal gyrus. The network identified for target processing by these authors also include regions pre-attentively reacting to emotional stimuli as anterior cingulum, insula, superior, middle and inferior temporal areas and amygdala (see APPENDIX F for ROI overview).

In summary, it can be argued that the P300 is sensible to the emotional content of stimuli, irrespective of DECODING CONDITION or task demands and that there are areas sensitive to emotion which seems to have the same characteristics as the P300. Furthermore, some of these areas are part of the network activated for the classical P300 target effect. This leads to the inference that the target processing network and the network which pre-attentively detects the emotionally relevant aspects of stimuli have something in common. The present study was used to explore if the overlap of these two networks is also functional. If indeed a functional overlap exists, then it is possible that changes in P300 reactivity may at least in part influence the network that processes emotional relevance. Such a functional overlap of the networks is expected to be found in some of the above mentioned areas. Especially for the amygdala a lot of literature is pointing in this direction.

3.1.3 Methodological considerations

In experimental science in general and physiology in particular, processes are typically studied through varying an independent variable (experimental conditions) and determining the *inferential statistical structure* of the dependent variable (i.e. EEG or fMRI signal). The *inferential statistical structure* is describing the particular distribution of

experimental effects (main effects, interactions, or more general contrasts) that are constituted by the combination of the individual conditions (i.e. levels) of the independent variables (e.g. valence of stimuli). Identical inferential statistical structures in two independent recording sessions for example, would indicate identical experimental outcomes in both measurements (even though the absolute values, i.e. group means may be different, the resulting effect structure is the same).

By combining EEG and fMRI, the goal of the present study is to identify brain regions that are functionally equivalent to the P300 component and show reactivity to emotional stimuli in the same way. Ideally, EEG and fMRI will produce identical inferential statistical structures which would indicate that a given experimental effect in one measure (e.g. fMRI) can be related to the effect in the other measure (e.g. EEG). Different to Study 1 that is described in Chapter II, the EEG and fMRI results will also be related by use of correlation analysis. Whereas the analyses based on the inferential statistical structure is solely based on group or condition averages, correlation analyses relates each participant's individual results with each other in order to reach its outcome. The following paragraphs will provide additional information on the outcome of previous P300 research in regards to correlational methods used to combine ERP and fMRI, the inferential statistical structure of ERP and fMRI results, and will point out how correlations and inferential statistical structures may relate to each other.

3.1.3.1 Inter-individual correlation

An inter-individual correlation assesses the participants' individual experimental outcome of two measures (such as EEG and fMRI) across all participants in a particular experimental condition – e.g. across all participants, high responses in one experimental condition of one measure correspond to high responses in the same experimental condition in the second measure. Expressed as a Person correlation coefficient (r) (Cohen, Cohen, West, & Aiken, 2002) this would equate to:

$$r = \frac{1}{n-1}\sum_{i=1}^{n}\left(\frac{X_i - \bar{X}}{s_x}\right)\left(\frac{Y_i - \bar{Y}}{s_y}\right)$$

With n as the total number of participants, i as each individual's signal score in a given experimental condition, Y and X as EEG and fMRI signal, $\bar{Y}$ and $\bar{X}$ as the signal

average across all individuals for EEG and fMRI respectively, and s_y and s_x as the group variance of EEG and fMRI signals.

Ford and colleagues (2004) investigated a Go-NoGo paradigm and conducted an inter-individual correlation of NoGo fMRI Values and NoGo P300 amplitudes. This approach identified brain areas in which participants who show larger ERP´s also displayed a greater hemodynamic response. However, it can be easily shown that even a perfect inter-individual correlation does not imply that the two measures react similar to the experimental manipulation on the level of the individual participant (APPENDIX B illustrates the relation between intra-individual and inter-individual correlation). Moreover, it does not provide any information about the inferential statistical structure over all participants (APPENDIX C illustrates the relation between effect structure and inter-individual correlation). Hence, inter-individual correlation cannot determine shared functionality. In other words, an inter-individual correlation between EEG and fMRI results does not equate to functional similarity.

3.1.3.2 Intra-individual correlation

An intra-individual correlation assesses the participants' individual experimental outcome of two measures (such as EEG and fMRI) across all or a selection of experimental conditions disregarding the outcomes of any other participant – e.g. within each participant, high responses in one experimental condition of one measure correspond to high responses in the same experimental condition in the second measure. Expressed as a Person correlation coefficient (r) for one participant this would equate to:

$$r = \frac{1}{k-1}\sum_{j=1}^{k}\left(\frac{X_j - \bar{X}}{s_x}\right)\left(\frac{Y_j - \bar{Y}}{s_y}\right)$$

With k as the total number observed experimental conditions, j as each signal score of an experimental condition of one given individual, Y and X as EEG and fMRI signal, $\bar{Y}$ and $\bar{X}$ as the signal average across all involved conditions for EEG and fMRI respectively, and s_y and s_x as the condition variance of EEG and fMRI signals.

When combining ERP´s and fMRI, this method of analysis is also referred to as *parametric modulation*. The BOLD signal can be predicted either by ERP´s that were averaged across conditions or by single-trial amplitudes. Liebenthal and colleagues (2003)

for example, used the former approach to investigate brain areas coupled with the mismatch negativity. Nagai and colleagues (2004) used the latter approach to investigate brain areas correlated with the contingent negative variation (for a review of the combination of EEG and fMRI see Debener and colleagues (Debener, Ullsperger, Siegel, & Engel, 2006b) or Herrmann and Debener (2008)). However, even if there is a high intra-individual correlation, the reactivity of the two measures can look different for each participant. Moreover, because the intra-individual correlation ignores differences in value deviations within both measures and across participants, it is possible to find a high intra-individual correlation over all participants in spite of a different inferential statistical structure in the two measures (APPENDIX D illustrates the relation between effect structure and intra-individual correlation). In other words, a strong correlation between EEG and fMRI reactivity may exist on the level of the individual participant only, in effect this link may not show up across all participants, since the individual participants' reactions may be very different from another and may not add up to a generalizable group correlation.

3.1.3.3 Inferential statistical structure

As already mentioned above, physiological processes are typically studied through varying an independent variable and determining the inferential statistical structure of the dependent variable. The easiest way to do this is to survey the same processes with two physiological measures separately, such as EEG and fMRI, and to analyze the gathered information collectively (as demonstrated in Chapter II). This was done for example by Brazdil and colleagues (2005) and Kiehl and colleagues (2005). Brazdil and colleagues (2005) investigated the oddball paradigm (a paradigm that has been extensively researched with the EEG) with efMRI and intra-cerebral ERP recordings. They found that there was a P300 like electric activation for all areas which had been described earlier as sources of the P300. However, they also found P300 like activity within areas which did not show any significant results for the efMRI. Kiehl and colleagues (2005) also studied the oddball paradigm and found a widespread network of activations, consisting of areas crucial for the execution of the task as well as, according to the authors, areas not relevant for the task. Even though both studies conceive good explanations about how these findings could be further disentangled, it seems desirable to apply a method

that is able to determine the functional relationship between the perfusion changes of brain areas and an ERP that is caused by the particular process that is to be investigated by a given paradigm.

3.1.3.4 Possible outcomes of the fMRI analysis

The same inferential statistical structure within two measures (i.e. the same experimental effect in EEG and fMRI) does not imply that those measures are correlated (see Appendix C – "effect in both measures" / correlation "none"). In addition, even if there is a perfect intra-individual correlation for all participants, the inferential statistical structure could differ across participants (see Appendix B – inter-individual correlation "none"). Because neither the inferential statistical structure nor correlations can answer the question of functional equivalence on its own, the combination of two methods has to be taken into consideration. A combination of the inferential statistical structure and a correlational approach was considered earlier by Horovitz and colleagues (2004). They first identify areas by their inferential statistical structure. Subsequently, the correlation between bold activity and ERP amplitude is calculated for these areas. This is done for all experimental conditions and all participants at once. A clear disadvantage of this approach is that intra-individual and inter-individual contributions to the correlation cannot be clearly disentangled. Consequently, areas are only functionally equivalent to an EEG parameter if they have the same inferential statistical structure (meaning similar results in an analysis of ERP and fMRI data) and if the BOLD signal shows a high intra-individual correlation with the EEG parameter across all participants.

Four different outcomes can result when conducting an intra-individual correlation for ERP and fMRI data and when comparing the inferential statistical structure of ERP and fMRI:

i) A correlation and an identical inferential statistical structure, indicating a functional equivalence (***convergent finding***);

ii) No correlation but an identical inferential statistical structure, indicating brain areas that reflect the same process as the ERP´s without a significant functional relation (***divergent finding***);

iii) A correlation but different inferential statistical structures, indicating correlated areas that do not reflect the same process (***divergent finding***);

iv) No correlation and a different inferential statistical structure ***("true" null-finding)***.

Out of the four possible results, only convergent findings of the first case are meaningful when investigating true functional equivalence of EEG and fMRI signals. Functional implications, however, may still exist for divergent findings if an intra-individual correlation can be found (case iii).

The present study explores the covariation of P300 and fMRI reactivity in specified brain areas with respect to their covariation with the emotional content of visual stimuli under a less demanding structural decoding task and more demanding emotion decoding task. The goal is to find brain areas which have the same inferential statistical structure as the P300 amplitude and which also show a high intra-individual correlation with the P300 amplitude. Such a functional overlap is expected to exist in the areas mentioned above (also, see APPENDIX F) but especially in the amygdala.

3.2 METHODS

3.2.1 Participants

Twelve healthy right handed female volunteers (age ranging from 20 to 30 years, mean 23) participated in this study and none of them reported vision problems to would require them to wear corrective lenses or glasses. All participants gave written informed consent after the experimental procedures had been fully described. The majority of participants were University students, who received 50 Euro for their participation and all of them took part in both, an EEG and fMRI recording session that were a week apart. The order of the recording sessions was balanced across participants. The study was approved by the ethics committeeof Rhineland-Palatinate and was in accordance with the ethical guidelines of the Declaration of Helsinki.

3.2.2 Stimuli

Negative, neutral, and positive picture stimuli (independent variable VALENCE) were selected from the International Affective Picture System (IAPS; Lang et al., 1995). Four sets of stimuli were constructed in which two sets were used for the EEG and two the fMRI sessions. For EEG and fMRI, one of the two sets consisted of a single picture per valence condition whereas the second set consisted of 30 pictures per valence condition (independent variable DECODING CONDITION). The order in which the stimuli sets were used during the EEG or MRI session was balanced. Table 3.2.1 provides an overview of the valence and arousal scores for the different pictures sets. The valence and arousal of the two sets with only one picture per valence correspond to the averages of the sets with 30 pictures per valence. In the EEG-session the pictures were presented in a distance of 1m on a 17” (40cm width) screen visual angel horizontal (22.6°) vertical (17.3°). For the stimulation during the fMRI acquisition, a projector (model EPSON EMP-7250) projected the pictures on a screen at the head-end of the scanner (visual field=18°). Pictures were viewed by means of a mirror mounted on the head coil.

Table 3.2.1 Overview of the valence and arousal scores for the different stimulus pictures sets

		Valence		Arousal	
		Mean	**Std. Error**	**Mean**	**Std. Error**
Set 1	Negative	1.724	.048	6.537	.147
	Neutral	5.007	.048	3.144	.147
	Positive	8.034	.048	4.961	.147
Set 2	Negative	1.749	.048	6.502	.147
	Neutral	4.998	.048	3.221	.147
	Positive	8.092	.048	4.954	.147

Set 1 – different pictures per valence (valence decoding); Set 2 – same pictures per valence (structural decoding).

3.2.3 Experimental Procedure

Participants viewed two blocks of 90 slides in each experimental session. During one block, participants watched 30 different slides of each of the three VALENCE condition (DECODING CONDITION: valence-decoding; more demanding), whereas in the other block, participants watched one and the same slide of the three VALENCE conditions for 30 times (DECODING CONDITION: structural-decoding; less demanding) – see Figure 3.2.1 top. The order of the pictures within the two blocks was randomized with the restriction that no more than three slides of the same valence were presented successively. Also order of the of stimulus sets was intra- and inter-individually balanced between the EEG-fMRI sessions. There was a 5 minute break between the two blocks. Before starting the presentation of the 90 slides, participants were asked to perform 6 training trials to get familiarized with the task – see Figure 3.2.1 middle.

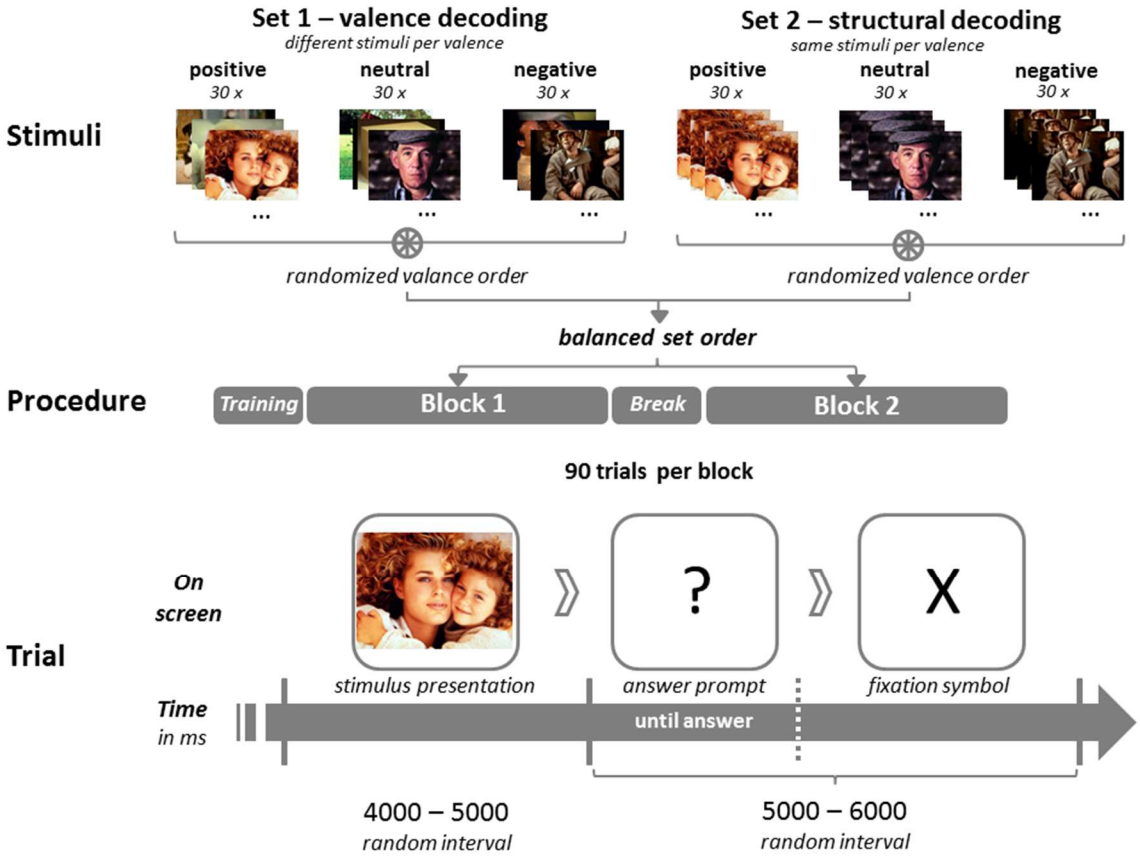


Figure 3.2.1 Depiction of stimuli set creation, experimental procedure, and trial timing.

Two sets of 90 stimuli were constructed for each participant in whom Set 1 (valence decoding) used 30 different stimuli per valence condition and Set 2 (structural decoding) used 30 identical stimuli per valence conditions. The order of stimuli/valence order was randomized and the order of stimuli sets was balanced between and within participants. Each trial lasted between 9000 and 1100 ms and contained Stimulus, answer prompt and a fixation symbol.

Each slide was presented for a random interval of 4 to 5s. The participants were instructed to concentrate on the content of the picture. Immediately after each slide, a question mark was presented signalling the participant to categorize the emotional valence of the picture (negative, neutral, positive) by pressing the appropriate response keys on a three-button response pad (index finger of the right hand was assigned to negative, middle finger to neutral, ring finger to positive pictures). After the response, a fixation symbol was presented. Between two slides there was a total random interval of 5 to 6s – see Figure 3.2.1 bottom.

3.2.4 Data acquisition and processing

3.2.4.1 EEG and EOG Data

EEG was recorded with the EasyCap electrode system (EasyCap GmbH, Munich) from 60 sites of an equidistant electrode system (for details see APPENDIX E) with Cz as the recording reference. The sites CP5 and PO1 were excluded due to inferior data quality and the remaining sites were re-referenced to an average reference. A horizontal EOG was recorded from the epicanthus of each eye, and a bipolar vertical EOG was recorded from supra- and infra-orbital positions of the right eye. The EEG and the EOG were recorded with Ag-AgCl electrodes. Prior to the placement of electrodes, the expected electrode sites on the participant's scalp and face were cleaned with alcohol and gently abraded. All impedances of the EEG electrodes were below 5 kOhm.

EEG and EOG were amplified with two 32-channel SynAmps Model 5083 amplifiers (input impedance: 10 MOhm; Neuroscan, Inc.) in AC mode. The pass-band was set to 0.01-30 Hz (-12 dB/octave rolloff); the signals were digitized at 200 Hz.

The EEG was analysed offline with the Brain Vision Analyzer2 software (Brain Products GmbH, 82205 Gilching Germany). The EEG was re-referenced to an average reference, artifacts due to eye movements were corrected via the algorithm developed by Gratton and colleagues (Gratton & Coles, 1989; Gratton et al., 1983) Epochs with non-physiological artifacts were removed. The EEG was epoched for periods of 4000 ms, starting 200 ms before picture presentation and artefact free averages were computed at each electrode location for each combination of DECODING CONDITION (valence-decoding, structural-decoding) and VALANCE (positive, neutral, negative). After inspecting the grand mean ERP, P300 components were quantified as a baseline corrected average amplitude in the time range from 400 to 700 milliseconds post stimulus.

Preliminary analysis indicated that the results for P300 did not differ as a function of hemisphere. For this reason and for the sake of simplicities the statistical analysis was restricted to the nine midline electrodes (Fpz, Afz, Fz, Fcz, Cz, Cpz, Pz, Oz, Iz – independent variable LOCATION).

In order to keep the statistical analysis for P300 and hemodynamic data as parallel as possible, the P300 data at each of the nine midline locations were analysed by the

same 5 orthogonal contrasts which form the predictor set for the design matrix in the fMRI analysis. These contrasts depicted in Table 3.2.2. The significance level for each contrast was Bonferroni corrected for the nine electrode positions ($\propto_{corrected} = \frac{0.05}{9} = 0.0056$). Because the five contrasts at each location are orthogonal, further Bonferroni correction of significance level is not necessary.

The most important effect of VALENCE which is emotional (EMO) vs. neutral pictures (NEU) pictures, was defined as the contrast *Valence-I* between all negative and positive pictures against all neutral pictures, regardless to whether or not these pictures were repeatedly presented or not (EMO > NEU). In addition, the contrast *Valence-II* between negative (NEG) vs. positive (POS) evaluated differences between negative and positive pictures. The main effect of DECODING CONDITION was defined as contrast between all pictures presented in structural-decoding (same picture per valence

Table 3.2.2 Contrast coefficients for the DECODING CONDITION x VALENCE ANOVA

	Decoding Condition					
	structural-decoding			valence-decoding		
	negative	neutral	positive	negative	neutral	positive
DECODING CONDITION	-1	-1	-1	1	1	1
Valence-I (EMO > NEU)	1	-2	1	1	-2	1
Valence-II (NEG > POS)	1	0	-1	1	0	-1
DECODING CONDITION x Valence-I	-1	2	-1	1	-2	1
DECODING CONDITION x Valence-II	-1	0	1	1	0	-1

The contrast DECODING CONDITION compares structural-decoding vs. valence-decoding. Valence-I tests whether or not negative (NEG) and positive (POS) conditions together are larger than neutral (NEU). Valence-II tests negative against positive pictures regardless of DECODING CONDITION. The two interaction contrasts were obtained by the multiplication of DECODING CONDITION with Valence-I and Valence-II.

presentation) condition vs. all pictures presented in the valence-decoding (different pictures per valence presentation) condition: valence-decoding > structural-decoding. The

remaining two interaction effects were defined by multiplying the contrast weights of the main effects: The first interaction effect investigates whether or not the effect between emotional and neutral pictures differs between structural-decoding and valence-decoding conditions. The second interaction effect describes whether or not the effect between negative and positive pictures differs between structural-decoding and valence-decoding conditions.

3.2.4.2 BOLD fMRI data

Brain images were acquired at the Bender Institute of Neuroimaging (BION) using a 1.5-T whole-body tomograph (Siemens symphony with a quantum gradient system) with a standard head coil. First, T1-weighted anatomical images were collected. For functional imaging, a total of 656 volumes were registered using a T2-weighted gradient echo-planar imaging sequence (EPI) with 30 slices covering the entire brain (slice-thickness= 5mm, no gap, interleaved, TA=100 ms, TE=60 ms, TR=3 s, flip angle=30°, field of view=192 mm × 192 mm, matrix size=64 ×64). The orientation of the axial slice was parallel to the AC-PC line. A five minute break was inserted after 328 scans that equals the presentation time of each block. The statistical parametric mapping software (SPM02, Welcome Department of Cognitive Neurology, London) implemented in Matlab (Mathworks, Inc., Natick, MA, USA, release 13) was used for pre-processing and statistical analysis. Slice time correction, realignment and normalisation to the standard brain of the Montreal Neurological Institute (MNI) were performed separately for each of the two blocks. Smoothing was executed with an isotropic three-dimensional Gaussian filter with a full width at half maximum of 9 mm. The experimental conditions were modelled by a boxcar function incorporating the variable durations of the picture presentation and convolved with a hemodynamic response function in the GLM. Button presses were modelled by a boxcar function with a constant duration of 1000 ms. The six movement parameters of the rigid body transformation, applied by the realignment procedure, were introduced as covariates in the model. The voxel-based time-series were filtered with a high-pass filter (time constant = 128 s). T-contrasts were calculated for each participant according to the same logic as for the EEG contrasts described above (Table 3.2.2). For a

random effect analysis, the individual contrast images of the first level analysis were used in a second level analysis.

3.2.5 Statistical analyses

For the statistical analysis, regions of interest (ROIs) - as described in the chapter introduction (chapter 3.1.1.3 or APPENDIX F) - were used. The ROIs were defined by the anatomical parcellation of the normalized brain (single-subject high-resolution T1 volume of the Montreal Neurological Institute) as described by Tzourio-Mazoyer and colleagues (2002). The Software MARINA (Walter et al., 2003) was used for creating the appropriate ROI-masks. The threshold for the analysis was set to $\alpha = 0.05$ on voxel-level, corrected for multiple testing, according to the false discovery rate (FDR-cor) implemented in SPM2.

Correlational analyses

A regressor which was modelled with the timing of the experimental events and the z-transformed amplitudes of the P300 at Pz (from each experimental condition) was applied. This regressor was entered in the parametric modulation option of SPM2 for both fMRI blocks. A correlation of 0.5 (r^2=0.25) or higher was regarded as relevant for the relationship between fMRI and EEG. The effect size of this correlation is identical to a t-value of 1.83 and which is equal to $p < 0.05$ uncorrected (in the applied paradigm).

Convergence and divergence of EEG and fMRI

Only significant contrasts of the EEG analyses were selected for subsequent fMRI analyses in order to determine the functional overlap of both measures by using the above mentioned correlational analyses. In addition, only voxel clusters larger than 40 voxels were considered for interpretation. Anatomical areas which are not part of the target ROIs (see APPENDIX F) but still show divergent results will be reported if at least 25% of their voxels show the effect. For the convergent activity, areas with more than 12.5% of the voxels active will be reported. The halved percentage level is due to the fact that a voxel has to accomplish the threshold of p= 0.05 twice, to be regarded as active within this analyses.

3.3 RESULTS

3.3.1 Event related potentials

Figure 3.3.1 displays the ERPs elicited by negative, neutral and positive pictures under the valence-decoding and structural-decoding conditions for the electrode locations FPz and Pz.

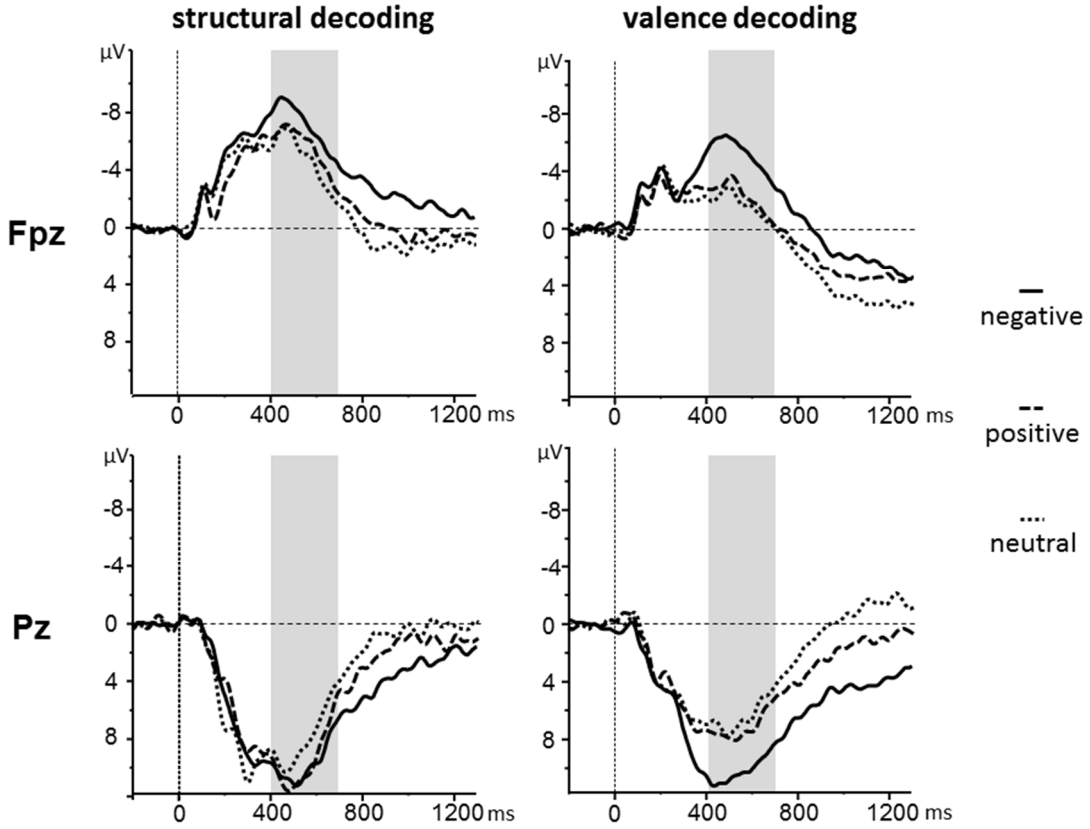


Figure 3.3.1 Event related potentials under valence and structure DECODING CONDITIONs for the electrode locations FPz and Pz.

Areas in grey indicate the duration of the average amplitude (400-700 ms) that were used for statistical analyses. Valence-I contrast (EMO > NEU) was significant at Fpz and Pz and CONDITION and Valence-II contrast (NEG > POS) was also significant at Fpz.

The P300 component, measured as the average amplitude between 400 and 700 milliseconds after picture onset, showed the typical topography, with a parietal maximum (see Figure 3.3.1 right). Figure 3.3.2 displays the group averages used for the five orthogonal contrasts at the nine midline electrodes – complete results for all contrasts are displayed in APPENDIX G.

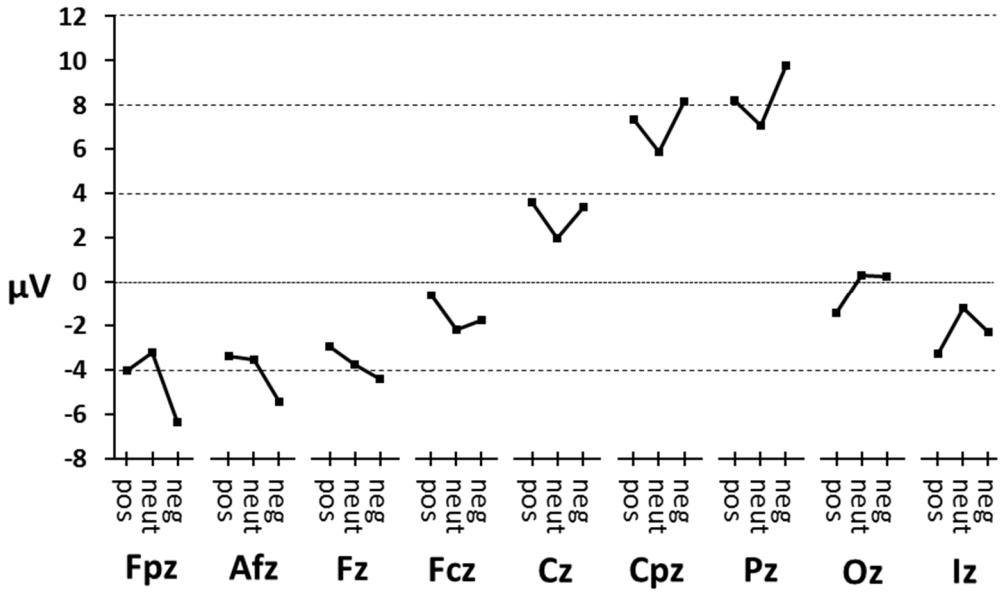


Figure 3.3.2 Condition averages used for five orthogonal contrasts at the nine midline electrodes.

Largest descriptive effects of emotional versus neutral stimuli occurred at Fpz, Cz, Cpz, Pz and Iz. Inferential analyses revealed significant effects at Fpz, CPz Pz, and Iz.

Effects of the Valence-I contrast (EMO > NEU) indicate larger amplitudes for emotional as compared to neutral pictures most prominent at Pz and Cpz. At Cz this contrast (p= 0.01) just fell short of the corrected significance level of 0.0056. The Valence-II contrast (NEG > POS) was not significant at these electrode locations. It is important to note, that these effects were not moderated by the DECODING CONDITION, as the interaction DECODING x VALENCE was not significant. It seems worth mentioning that the second interaction contrast approached significance at Cz (p= 0.031) Cpz (p= 0.014) and Pz (p= 0.024). At these three locations negative pictures elicited larger P300 amplitudes than positive pictures but only in the valence-decoding condition (see Figure 3.3.2, location Cz, Cpz and Pz).

At location Iz, positive and negative pictures elicit more negative amplitudes than neutral pictures which were independent of DECODING CONDITION. At locations Fpz and Afz, negative pictures elicit more negative amplitudes than neutral and positive pictures because both valence contrasts were significant. Again this effect was not modified by the DECODING CONDITIONs. Fpz and Afz were the only locations at the main effect of the DECODING CONDITION were observed: the structural-decoding elicited more negative amplitudes than the valence-decoding condition.

3.3.2 fMRI data

Statistical analysis of the ROIs (see 3.2.5) revealed the following results. Compared with the structural-decoding condition, the valence-decoding condition was associated with an enhanced BOLD response in the right superior temporal gyrus (p= 0.018), right middle temporal gyrus (p= 0.007) and right inferior temporal gyrus (p= 0.018) and with a decrease in BOLD response for the right and left anterior cingulated gyrus (left: p= 0.010, right: p= 0.049) and the limbic middle temporal gyrus (p= 0.043) – see Table 3.3.1.

Table 3.3.1 Task demands (valance-decoding > structural-decoding)

Brain area	Region	L/R	X Y Z	Voxel (t_{max})
Temporal lobes	superior temporal gyrus	R	57 -39 12	251 (5.97)
	middle temporal gyrus	R	60 0 -21	354 (7.52)
	inferior temporal gyrus	R	54 -75 -6	199 (6.63)
Limbic lobes	middle temporal gyrus	L	-45 15 -30	64 (-4.61)
	anterior cingulated gyrus	L	0 27 -3	180 (-5.17)
		R	3 30 0	70 (-6.39)

Statistically significant (t > 1.80, p < 0.05) results for the contrasts of interest. Coordinates x, y, and z are provided according to the *Montreal Neurological space.*

When comparing all emotional pictures with all neutral pictures, they were associated with an enhanced BOLD response bilaterally in the precentral gyrus (left: p= 0.008, right: p= 0.037) and in the postcentral gyrus (left: p=0.006, right: p= 0.021), the left inferior parietal gyrus (p= 0.048), bilaterally in the middle temporal gyrus (left: p= 0.032, right: p< 0.001) and the inferior temporal gyrus (left: p= 0.043, right: p= 0.001), in the amygdala (left: p= 0.037, right: p= 0.026) and the middle temporal gyrus of the temporal pole (left: p= 0.016, right: p= 0.034) – see Table 3.3.2.

Table 3.3.2 Valence-I (EMO > NEU)

Brain area	Region	L/R	X Y Z	Voxel (t_{max})
Central region	precentral gyrus	L	-39 -24 66	627 (6.09)
		R	39 -24 69	327 (5.78)
	postcentral gyrus	L	-63 -15 33	810 (7.00)
		R	39 -30 63	634 (5.63)
Parietal lobes	Inferior parietal gyrus	L	-54 -33 45	173 (5.32)
Temporal lobes	middle temporal gyrus	L	-51 -66 3	302 (5.27)
		R	57 -63 12	700 (10.28)
	inferior temporal gyrus	L	-42 -42 -27	184 (5.73)
		R	45 -48 -27	491 (7.95)
Limbic lobes	amygdala	L	-30 -3 -27	45 (3.70)
		R	21 0 -21	38 (4.15)
	temporal pole: middle temporal gyrus	L	-21 6 -39	129 (5.41)
		R	51 18 -36	212 (4.84)

Statistically significant (t > 1.80, p < 0.05) results for the contrasts of interest. Coordinates x, y, and z are provided according to the Montreal Neurological space.

For the Valence-II contrast (NEG > POS), there were enhanced BOLD responses in the right inferior frontal gyrus (p= 0.017), the right middle temporal gyrus (p= 0.002) and the left inferior temporal gyrus (p= 0.022) – see Table 3.3.3

Table 3.3.3 Valence-II (NEG > POS)

Brain area	Region	L/R	X Y Z	Voxel (t_{max})
Frontal lobes	inferior frontal gyrus	R	48 12 21	957 (5.62)
	inferior frontal gyrus: orbital part	R	48 39 -15	170 (4.51)
Temporal lobes	middle temporal gyrus	R	54 -72 15	588 (8.77)
	inferior temporal gyrus	L	-51 -66 -6	243 (5.51)

Statistically significant (t > 1.80, p < 0.05) results for the contrasts of interest. Coordinates x, y, and z are provided according to the Montreal Neurological space.

Significant interaction effects between Valence-I contrast (EMO > NEU) and DECODING CONDITION (VALENCE > STRUCTURE) were only observed in the left anterior cingulum (p= 0.016) and in the orbitofrontal cortex (left p= 0.005, right p= 0.003). Within the orbitofrontal cortex activations were found bilateral in the medial part of the superior frontal gyrus (left: p= 0.002, right: p= 0.001) and the gyrus rectus (left: p= 0.001, right: p<0.001) – see Table 3.3.4.

Table 3.3.4 DECODING CONDITION x Valence-I

Brain area	Region	L/R	X Y Z	Voxel (t_{max})
Frontal lobes	orbitofrontal cortex	L	0 24 -21	393 (7.54)
		R	3 24 -21	303 (8.51)
	gyrus rectus	L	0 24 -21	167 (7.54)
		R	3 24 -21	110 (8.51)
	superior frontal gyrus medial part	L	0 60 -6	168 (7.05)
		R	3 57 -9	136 (7.58)
Limbic lobes	anterior cingulated gyrus	L	-6 26 -6	80 (5.14)

Statistically significant (t > 1.80, p<0.05) results for the contrasts of interest. Coordinates x, y, and z are provided according to the Montreal Neurological space.

Negative interaction effects between the Valence-II contrast (NEG > POS) and DECODING CONDITION (VALENCE > STRUCTURE) were observed bilaterally in the inferior temporal gyrus (left: p= 0.045, right: p= 0.028) and in the superior temporal gyrus of the left temporal pole (p= 0.027) – see Table 3.3.5.

Table 3.3.5 DECODING CONDITION x Valence-II

Brain area	Region	L/R	X Y Z	Voxel (t_{max})
Limbic lobes	temporal pole: superior temporal gyrus	R	-57 9 -6	45 (-5.29)
Temporal lobes	inferior temporal gyrus	L	-45 -42 -27	90 (5.67)
		R	54 -63 -18	245 (5.72)

Statistically significant (t > 1.80, p<0.05) results for the contrasts of interest. Coordinates x, y, and z are provided according to the Montreal Neurological space.

3.3.3 Convergence / Correlation of ERP and BOLD

Statistical convergence and correlation analysis between the ROIs and ERPs (see 3.2.5) revealed the following results.

Activations associated with the Valence-I contrast (EMO > NEU) but not with the variability of the P300 were found in the right gyrus rectus (37% - of the voxels of the gyrus were regarded as active), all investigated central regions: precentral gyrus (left: 55%, right: 29%), postcentral gyrus (left: 68%, right: 48%), all investigated temporal regions except the right superior temporal gyrus: the left superior temporal gyrus (29%), middle temporal gyrus (left: 29%, right: 29%), inferior temporal gyrus (left: 28%, right: 42%), the supramarginal gyrus (49%), bilaterally in the amygdala (left: 50%, right: 31%), and the middle temporal gyrus of the temporal pole (left: 43%, right: 56%) and in the right superior temporal gyrus of the temporal pole (28%).

Activations positively associated with the variability of the P300 and with the Valence-I contrast (EMO > NEU) were found in the middle temporal gyrus (20%), the left supramarginal gyrus (18%), bilaterally in the amygdala (left: 19%, right: 14%), and in the middle temporal gyrus of the temporal pole (left: 13%, right: 13%). No area was found to be active when investigating for activity negatively associated with the variability of the P300, and with the negative Valence-I contrast.

Activations associated with the variability of the P300 but not associated with the Valence-I contrast was only found in right inferior frontal gyrus (26%). In addition, a negative association was found in the orbital part of the left superior frontal gyrus (27%).

3.4 DISCUSSION

The aim of this study was to identify brain areas which are functionally equivalent to the P300-amplitude in terms of their reactivity to emotion by using joint statistical analyses of the EEG and fMRI signals. For both hemispheres it was found that the BOLD response in parts of the amygdala and the middle temporal gyrus of the temporal pole were functionally equivalent to the emotional variability of the P300. This finding is in accordance with the view that the P300 and the amygdala activity reflect a task independent evaluation of stimuli valence. Other areas such as middle temporal gyrus and pre-central gyrus seem to be activated during the processing of emotional stimuli but they are not functionally associated with the P300. Thus, by combining EEG and fMRI it was possible to disentangle anatomical regions that were activated during the processing of emotional stimuli regarding their specific functionality.

3.4.1 ERP Results

The observed increase in the P300 amplitude with a maximum at Pz for emotional pictures compared to neutral ones is a common finding in the literature (Cuthbert et al., 2000; Diedrich, 1996; Diedrich et al., 1997; Naumann, Bartussek et al., 1992b; Naumann et al., 1997; Palomba et al., 1997; Schupp et al., 2000; Schupp et al., 2003). For the P300, there was no significant effect of DECODING CONDITION and no significant interaction of DECODING CONDITION and the valence (i.e. emotion) of the stimuli, which could have also been expected (Naumann et al., 1997). Within the ERPs, therefore, the paradigm outcomes reflected the intended processes.

3.4.2 fMRI Results

The present findings are in large parts consistent with previous studies that have implicated a widespread network that reacts towards the emotional content of a stimulus (Murphy et al., 2003; Phan et al., 2002). As discussed above, the amygdala seems to play a central role for the processing of emotions (e.g. LeDoux, 1993). Amygdala was activated bilaterally and also in its temporal pole where the amygdala receives strong protections from (Amaral & Insausti, 1992). The temporal pole is regarded as the end of the so called ventral stream in the temporal cortex, which is thought to evaluate the meaning of

objects (Van Essen, 1995). Therefore the activation found bilaterally in the middle temporal gyri and inferior temporal gyri also fit in to the former view. However, the sensitivity for emotion of all investigated central regions does not match the literature reviewed above (see Murphy et al., 2003; Phan et al., 2002). As those regions are involved in the formation of the motor output, a speculative explanation for the finding might also be that these regions are activated by a stronger tendency to react towards emotional stimuli.

The findings of the current study concerning the attention related stimulus decoding are in general consistent with those of Kiehl and colleagues (2005) who also found the following areas to be influenced by attention and not only emotion: The bilateral anterior cingulum and the left middle temporal gyrus which were deactivated for the valence-decoding (more demanding) task. Superior, middle, und inferior gyrus of the right temporal lobe were more active for the valence-decoding condition. In contrast to previous findings (Pessoa et al., 2002; Pessoa et al., 2005; Vuilleumier et al., 2001), an influence of the attention demands in the amygdala could not be found. Pessoa and colleagues (2002) found an interaction for the amygdala only in the low demanding condition of their paradigm, whereas Vuilleumier and colleagues (2002) found the same interaction in a more demanding condition, but not in the low demanding condition. However, the conditions in which the interactions were found were similar with respect to the error rates. Thus, it can be concluded that an interaction can possibly only be observed within a certain range of task difficulty. As our paradigm was relatively easy even compared to the low demanding condition (structural-decoding) from Vuilleumier and colleagues (2002), it is entirely conceivable effect of the attention demand in the amygdala could not be found in the current study.

3.4.3 Convergence between ERP and BOLD

Only the amygdala and the temporal pole of the parietal lob revealed areas with bilateral functional equivalence to the P300. This finding is in accordance with the work of Brazdil and colleagues (2005). In an oddball paradigm, Brazdil and colleagues (2005) found the activity in the amygdala to display a similar effect with a similar timing as it is known for the P300 acquired from the scalp. However, all four brain areas mentioned

above also revealed activity differences associated with emotion which was not functionally connected to the P300. These findings further support the idea of functionally different substructures within those brain areas. For the amygdala, there is a large amount of work demonstrating such differences (Kim, Somerville, Johnstone, Alexander, & Whalen, 2003; Pessoa et al., 2005; Whalen et al., 1998). Two other brain areas were found functional equivalent to the P300, namely the left supermarginal gyri, and the right middle temporal gyri. The former may contribute directly to the P300 as a source (Bledowski et al., 2004). The activation in the latter brain area is located at its very rostral end in close proximity to the temporal pole.

Amygdala, temporal pole and the meaning of stimuli. The amygdala receives input from the higher stages of sensory processing and also projects back to those areas as the middle temporal gyrus and temporal pole (Amaral & Insausti, 1992). The amygdala receives information which is processed up to the object level and is involve in the analyses of the meaning of stimuli. Together, the amygdala and the temporal pool are regarded as the final stages of the processing of the meaning of a stimulus (Amaral & Insausti, 1992). The P300 reflects the temporal end of the evaluation of the meaning of a stimulus (Picton, 1992). For the parts of the amygdala and temporal pole which were found functional equivalent to the P300 in this study it can be concluded that they reflect the same part of the emotion evaluating process, namely the evaluation of the meaning of the stimuli.

Amygdala and DECODING CONDITION. As discussed for the fMRI results it is still under debate if the processing of the valence of stimuli depends on the attention resources. In this current study the P300 reacted towards the valence of the stimuli independent of the DECODING CONDITIONs. Therefore, the brain areas which were functional equivalent to the P300 also reacted independent of DECODING CONDITIONs to the valence. To conclude the amygdala is processing the valence of stimuli independent of the DECODING CONDITIONs or task demands. However, this conclusion could be limited to the range of DECODING CONDITIONs and task demands as they were manipulated in this study.

Amygdala and targeted detection. Target detection can still be performed even if there are sever neuronal damages (Kiehl et al., 2005) like damages to the temporal pool

or the loss of the amygdala (Hirayasu, Ohta, Fukao, Ogura, & Mukawa, 1995; Scott et al., 1997). Although the amygdala seems to be not necessary for the detection of targets it is activated by rear targets. This is regarded as an advantage for survival because a possible emotional content of the new stimulus could be processed faster (Kiehl et al., 2005). Discrimination of emotional content of stimuli depends on the amygdala. The central structure found functional equivalent to the reactivity of the P300 towards emotion are not necessary for target detection. Despite their similarities the variability of the P300 due to valence and due to the frequency of a stimulus seems to be two functional different processes. A target can be discriminated as a target without evaluating its meaning or valence.

3.4.4 Divergence between ERP and BOLD

It would go beyond the scope of this paper to discuss all divergent findings, however, the possible functional contribution of brain areas which show only a correlation with the P300 but no results for valence contrast one seems to be worth speculating. In other words, the inferential statistical structure between EEG and fMRI are different, but an intra-individual correlation could be found.

Valence-I (EMO > NEU) contrast. Brain areas showing only a valence-I contrast are involved in other functional parts of the processing of emotion. Those areas could be functional related to other ERP components such as the positive slow wave or to other processes not observable with the ERP.

Correlation with P300 without Valence-I contrast. The left superior frontal gyrus showed no effect for Valence-I contrast, but an effect for the correlational analysis. As mentioned in the methodological considerations of the introduction, such an area might influences the P300 generating network and it may contribute to the variability of the P300 as it is specific for each participant.

Evidence from clinical studies indicates that the left superior frontal gyrus influences the P300 generating network. Patients with frontal lobe damage exhibited markedly reduced amplitude of the novelty P300 response compared to matched participants (Schankin, Hagemann, Danner, & Hager, 2011). Daffner and colleagues (2000) conclude that damage to the frontal lobes may prevent the generation of a signal which

indicates that a novel event in the environment requires additional attention. As mentioned before, the emotional quality of a stimulus adds important information to a stimulus. Thus, it is reasonable to argue that the frontal lobe is generally involved in modulating the brain processes according to salience of stimuli, regardless of the reason of the salience. Furthermore several lines of evidence indicate that this brain area is involved in the interaction of emotion and attention (Northoff et al., 2000; Phan et al., 2004). More specifically, it is likely concerned with the shifting of attention (Nagahama et al., 1999) or with a process of hyper monitoring of the evaluation process (Badre, 2008).

In summary, this divergent finding leads to the conclusion that the left superior frontal gyrus plays of key role in explaining the inter-individual differences in reactivity of the P300 towards emotional stimuli. Unfortunately, since this finding was unforeseen, no suitable experimental measures (e.g. questionnaires, interviews) were acquired that were able to further quantify the inter-individual differences between the participants that could be related to the modulated attributes of the left superior frontal gyrus. If indeed and to which extend the left superior frontal gyrus modulates the P300 in healthy participants will have to be clarified in future experimental investigations.

It is noteworthy to point out again that the findings of inferential statistical structure of the EEG and fMRI found no effect in this region of the brain and would not have suggested that the left superior frontal gyrus is related to P300 paradigm in any way. Only the joint investigation of the inferential statistical structure and correlational measures made these inferences feasible.

3.4.5 Conclusion

With this study it has been demonstrated that the combination of EEG and fMRI can disentangle the brain areas involved in emotion processing concerning their functionality. The amplitude of the P300 was only influenced by valence and not by the decoding conditions. There was functional equivalent activity to the reactivity of the P300 towards emotion and decoding conditions within the amygdala and the temporal pole. Divergent statistical findings lead to the conclusion that the left superior frontal gyrus plays of key role in explaining the inter-individual differences in reactivity of the P300 towards emotional stimuli.

GENERAL DISCUSSION

CHAPTER IV

Non-invasive methods that allow the in vivo observation of brain activity have greatly expanded our knowledge of the human brain and the combination of electrophysiological with neuroimaging techniques such as EEG and BOLD fMRI has become one of the technological focal points of neuroscience. Two independent studies in healthy student volunteers were used to demonstrate separate and joint statistical analyses of EEG – fMRI data and both studies provide valuable information on the two investigated emotional paradigms.

In Study 1, EEG and fMRI measurements both provided converging results that complimented the behavioral findings and which indicate that the fear-relevance of the presented stimuli was not processed by the use of the applied paradigm. The finding further suggests that fear-relevant stimuli need to be presented in a very low demanding task and at a low frequency of fear-relevant stimuli in order to observe the attention guiding effect of emotional stimuli. This finding also adds to a growing body of evidence which suggests that the theory of the evolved fear-module has to be extended (Eimer & Kiss, 2007; Pessoa et al., 2005; Schupp et al., 2007) by incorporating the condition-specific cognitive control or influence on the fear-module. By incorporating both EEG and fMRI results it becomes unlikely that null-effects are related to either neural signal cancellation of the EEG or insufficient temporal resolution of the fMRI.

In Study 2, combined analyses joined EEG and BOLD fMRI measures to draw inferences that would otherwise not have been possible without measuring both EEG and fMRI in the same participants. Thus, by combining EEG and fMRI it was possible to disentangle anatomical regions that were activated during the processing of emotional stimuli regarding their specific functionality. The convergent findings between the ERP and BOLD signals (in context of the amygdala) confirm the expected results in the context of P300 and emotion research. However, a divergence between the inferential statistical structure and correlation analysis leads to the conclusion that the left superior frontal gyrus plays of key role in explaining the inter-individual differences in reactivity of the P300 towards emotional stimuli.

Whereas Study 1 did not statistically join EEG and fMRI, the results of Study 2 were able to point out the importance of such joint statistical analyses. As could be demonstrated in Chapter III, the inferential statistical structure of EEG and fMRI do not

exclusively determine the functional connection between both measures. For that matter, the theoretical examples provided in the Appendix D already suggested that cases exist in which none of the measures (EEG or fMRI) show any effect in their inferential statistical structure and yet meaningful intra-individual correlations do exist. In that sense, meaningful functional interpretations do not require significant effects in the inferential statistical structure.

The added benefit from looking at results of combined EEG and fMRI studies in a joint statistical approach perspective is quite significant for a number of reasons. In the case of Study 2 for example, the left superior frontal gyrus plays of key role in explaining the inter-individual differences in reactivity of the P300 towards emotional stimuli. In other words, even though EEG and fMRI showed no inferential statistical effects in that region of the brain, a person's individual tendency to respond to an emotional stimulus will be determined by the activity of the left superior frontal gyrus. For psychologists, such statements may make all the difference when trying to assess why, for example, certain clinical populations react differently from healthy groups. Assessing neural activity with a clear understanding of the relationship between inferential statistical structures and intra- versus inter-individual correlation can be a powerful tool to try and explain any measurable inter-individual difference – may it be personality, cognition, or behaviour.

Expressed in statistical terms, the left superior frontal gyrus was the source of parts of the unexplained variance in Study 2. In theory, the variability of the left superior frontal gyrus could have been assessable (through questionnaires, interviews, or any other kind of quantification) and, therefore, been transformed into a covariate. Furthermore, by introducing this covariate, the results of the inferential statistical structure may have turned out quite differently. Unfortunately, the need for such quantification was unforeseeable and was therefore not undertaken in Study 2. Future investigations, however, may utilize the results of Study 2 to quantify the variability of the left superior frontal gyrus before or while repeating the same experimental paradigm. The resulting variability measure will consequently allow the prediction of parts of the EEG variability from fMRI signals and vice versa.

Utilizing divergent EEG and fMRI results in such a way is not yet part of currently applied, let alone main stream research strategies. However, it is important to be aware

of different functional meanings of intra- and inter-individual correlations in regards to the inferential statistical structure. Especially since it is crucial to not mix intra- and inter-individual correlations, such as mentioned earlier (see section 3.1.3.4) in the case of Horovitz and colleagues (2004).

The value of the analytical approach of Study 2 seems to be not known yet since there are not any methodological publications which propagate this way of investigating EEG and fMRI measurements. Instead, many resources are contributed for developing solutions to better measure, interpret, and analyse simultaneous EEG-fMRI acquisitions (Vincem & Eichele, 2010). Thus, the potential to how EEG-fMRI signals are statistically perceived and interpreted has not yet been fully utilized.

The statistical approach of Study 2 seems promising to further explore the functionality of the human brain and it is not limited to the kind of data acquisition. The applied methodological concept can also be applied to other possible method combinations of: MEG, EEG, NIRS, fMRI; including for various measures/signals derived from those methods such as for EEG: ERPs, frequency responses, time-frequency measures and connectivity. Both, separate and simultaneous acquisition strategies will benefit from optimizing their statistical approaches as suggested in Chapter III. As a matter of fact, the true need for simultaneous measurements is limited to clearly definable circumstances which represent only a part of psychologies multitude of relevant topics. However, for these select topics it remains mandatory to obtain EEG and fMRI data at exactly the same time.

Consequently, for any combined EEG and fMRI experiment it becomes crucial to decide whether to record the data in separate sessions (as it was done in Chapter II and III) or in a single joint recording. Even though there are some experimental restrictions that favor the one or the other approach, the new combined statistical analysis strategy proposed in Chapter III also contains implications in regards to separate or simultaneous recordings, which will be addressed in the following paragraphs.

The case for simultaneous acquisitions

The main advantage of measuring EEG and fMRI data in the scanner is that the two resulting signals reflect the same neural processes. For example, experimental

settings of a simultaneous acquisition ensure that participants use the same strategy to solve the experimental task measured with both signals because they are in the same emotional or physical state (e.g. same thoughts, same tiredness, same hunger feelings, etc.). Simultaneous recordings are mandatory for experiments that intend to quantify complex cognitive processing or very rare neural events - especially in clinical settings such as for epileptic seizure localization during investigations of interictal discharges (Lemieux et al., 2008; Salek-Haddadi et al., 2006; Salek-Haddadi, Friston, Lemieux, & Fish, 2003). Also, in non-clinical settings, simultaneous EEG-fMRI recordings are mandatory when generators of ongoing, stimulus independent EEG activity, such as alpha activity in awake resting state, are to be investigated (de Munck et al., 2007; Goldman, Stern, Engel, & Cohen, 2002; Goncalves et al., 2006; Laufs, Kleinschmidt et al., 2003; Laufs, Krakow et al., 2003; Laufs, Lengler, Hamandi, Kleinschmidt, & Krakow, 2006; Moosmann et al., 2003). Simultaneous recordings are also undeniably important in experimental paradigms that investigate rapid learning processes or drug effects (e.g. Balsters et al., 2011) that occur within a limited amount of time or trials. Studies of single-trial EEG and fMRI in which researchers seek to better understand neuronal processing that is not necessarily time locked to external events (Debener, Ullsperger, Siegel, & Engel, 2006a; Eichele et al., 2005) also depend on simultaneous recordings. Finally, for studies where continuous EEG tracks various stages of sleep (e.g., rapid eye movement/non-rapid eye movement), simultaneous acquisition of EEG and fMRI data is imperative (e.g. Czisch et al., 2004).

In contrast, there are a considerable amount of applications for which separate EEG and fMRI acquisitions are perfectly suitable and even preferable for a number of reasons.

The case for separate EEG fMRI acquisitions

A number of studies have combined fMRI and EEG using data recorded in separate sessions (e.g. Ball et al., 1999; George et al., 1995; Heinze et al., 1994; Opitz, Mecklinger, Von Cramon, & Kruggel, 1999; Snyder, Abdullaev, Posner, & Raichle, 1995) which at that time was mainly due to the lack of readily available equipment to measure EEG and fMRI simultaneously, safely and with well enough data quality. Today, the advantages of recording electrophysiological and neuroimaging data separately are mainly due to

improved signal-to-noise-ratio (SNR) (Wibral, Bledowski, & Tun, 2010), more degrees of freedom in designing the experimental paradigms, and practical reasons.

Separate recordings are more likely to meet the requirements of various analysis routines that rely on ICA. The reason is that even excellently recorded and analyzed EEG data from simultaneous EEG-fMRI acquisitions still contain added signal residual components from scanner related artifacts (gradient artifact, heart-beat related artifact), hence, likely increasing the number of signals components above the number of measured channels (for more insight into ICA, see Debener, Thorne, Schneider, & Viola, 2010). In addition, the usable band-width in which the EEG data can produce meaningful results is usually limited as compared to outside recordings. Especially in older scanner models, MR scanner related artifact sources such as the helium pump of the scanners cooling head or scanner bore fans can introduce non-physiological noise into the EEG data which can spread anywhere from 30 to 60 Hz. Even though newer MR scanners models are less likely to face cooling noise artifacts (cooling can be temporarily turned off during recording), EEG bandwidth still reaches its upper limits at around 50 Hz (personal communication with technical support of Brain Products, GmbH, Gilching, Germany). As a result, EEG measurements inside the MRI tend to have a more unfavorable SNR, which can make it much harder to find small or rare ERP components.

Introducing, the EEG equipment (leads, electrodes, amplifiers) into the MR-scanner environment (even if non-ferromagnetic) will limit the range of safe MR-sequences that do not cause rapid heating of the components and the accompanied risk of injuring the participants or damaging the equipment[4]. The range of allowed safe sequences can be a limiting factor in the MR signal quality that could be achieved in simultaneous EEG-fMRI acquisitions.

[4] For structural scans, only sequences with an inherently low Specific Absorption Rate (SAR) are allowed. These include: Magnetization Prepared Gradient and Spoiled Gradient Echo, including gradient echo sequences based on Localizer and Scout with a flip angle <90°. Structural sequences with a high SAR, such as diffusion tensor imaging (DTI), arterial spin labeling (ASL), Spin Echo, Fast Spin Echo, Fluid Attenuated Inversion Recovery (FLAIR), and sequences with inverting pulses (e.g. Fast Spin Echo (FSE) or Turbo Spin Echo (TSE)) are not allowed with current MR-compatible EEG equipment. Use of these sequences can result in rapid heating of equipment and cause the subject painful burns and permanent injury (Brain Products GmbH, Gilching, Germany).

During separate recordings, experimental paradigms can be more easily tuned and optimized to suit the particular needs for EEG and MRI recordings without compromising data quality in any of the two measures. In fact, SNR is likely to be superior, with fewer trials needed for the same signal strength, wider usable band-width, and better spatial resolutions (for MR-scans).

Simultaneous versus separate data acquisitions for joint statistical analyses

During joint statistical analyses, the difference between simultaneous and separate data acquisitions manifests in the *state* in which a participant is in. While during the simultaneous recording the participant is in the same state (or temporary condition) for both modes of signal acquisitions (EEG or fMRI), the participant will be in different states during separate recording sessions. Therefore, if an investigated dependent variable is influenced by the participant's state, then the underlying neuronal processes that the EEG and fMRI signals detect will be the same when measured in simultaneous but will not be the same in separate recording sessions.

Consequently, if a state affected dependent variable is investigated using separate measurements then the additional state-bound variability will reduce the intra-individual correlation between EEG and fMRI signals. For simultaneous measurements, things are different. Due to the shared state bound variability the intra-individual correlation between EEG and fMRI will be higher. This is true even though the inferential statistical effects (i.e. effect sizes) should not be affected by the state variability, since the variations within the population are considered to happen randomly (independent of each other and result in an average change of zero).

Thus, the simultaneous measurements will be able to find convergent effects even if they are not stable over time, whereas separate measurements are more sensitive towards dependent variables that do not change over time. For psychologists, the ladder is often of larger importance when investigating general or trait specific behavior, instead of identifying a large number of state dependent convergent findings that can become misleading. The degree to which an investigated concept varies within participants over time should, therefore, be considered even during the early research planning stage.

For future work it would be interesting to investigate the effect variability over time in order to determine the best use of simultaneous measurements. This would require making an assumption about the stability of the investigated effects which can best be achieved via at least two simultaneous measurements and to then calculate Latent-State-Trait models similar to approaches demonstrated by Hagemann and colleagues for basic resting state measures (e.g. Hagemann, Hewig, Seifert, Naumann, & Bartussek, 2005).

The above mentioned implications of simultaneous or separate EEG/fMRI data acquisitions also affect the interpretation of the studies presented in Chapter II and III. Since these studies were performed in the context of separate data acquisitions, their results would indicate that the reported effects are stable over time and are less influenced by a person's individual state or temporary condition. Separate and simultaneous data acquisitions both benefit from better informed intra-individual correlation analyses regardless of their inherent acquisition differences. The principle approach introduced in Chapter III therefore, provides an advanced strategy of how to more effectively analyse combined EEG-fMRI data analyses – regardless if the investigation relates to emotion research or any other effort that intends to further our understanding of human adaptation and well-being.

In conclusion, the present results demonstrate that combined EEG-fMRI data acquisitions would benefit from assessing joint statistical analyses. In particular, joint interpretation of the inferential statistical structure with intra-individual correlations between the EEG and fMRI signal provide valuable additional insight into the functioning of the human brain.

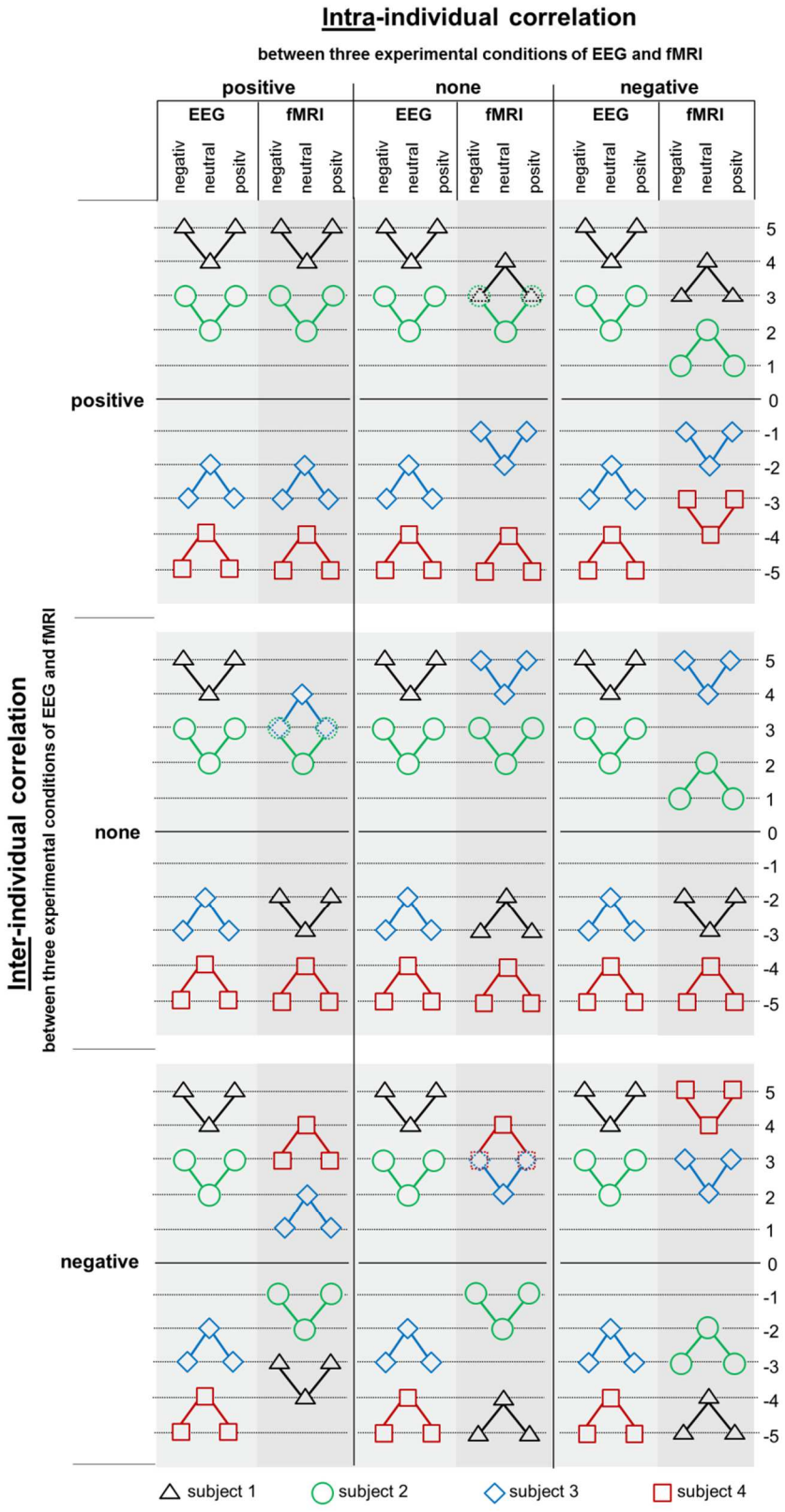
APPENDIX A

Snake pictures

Flower pictures

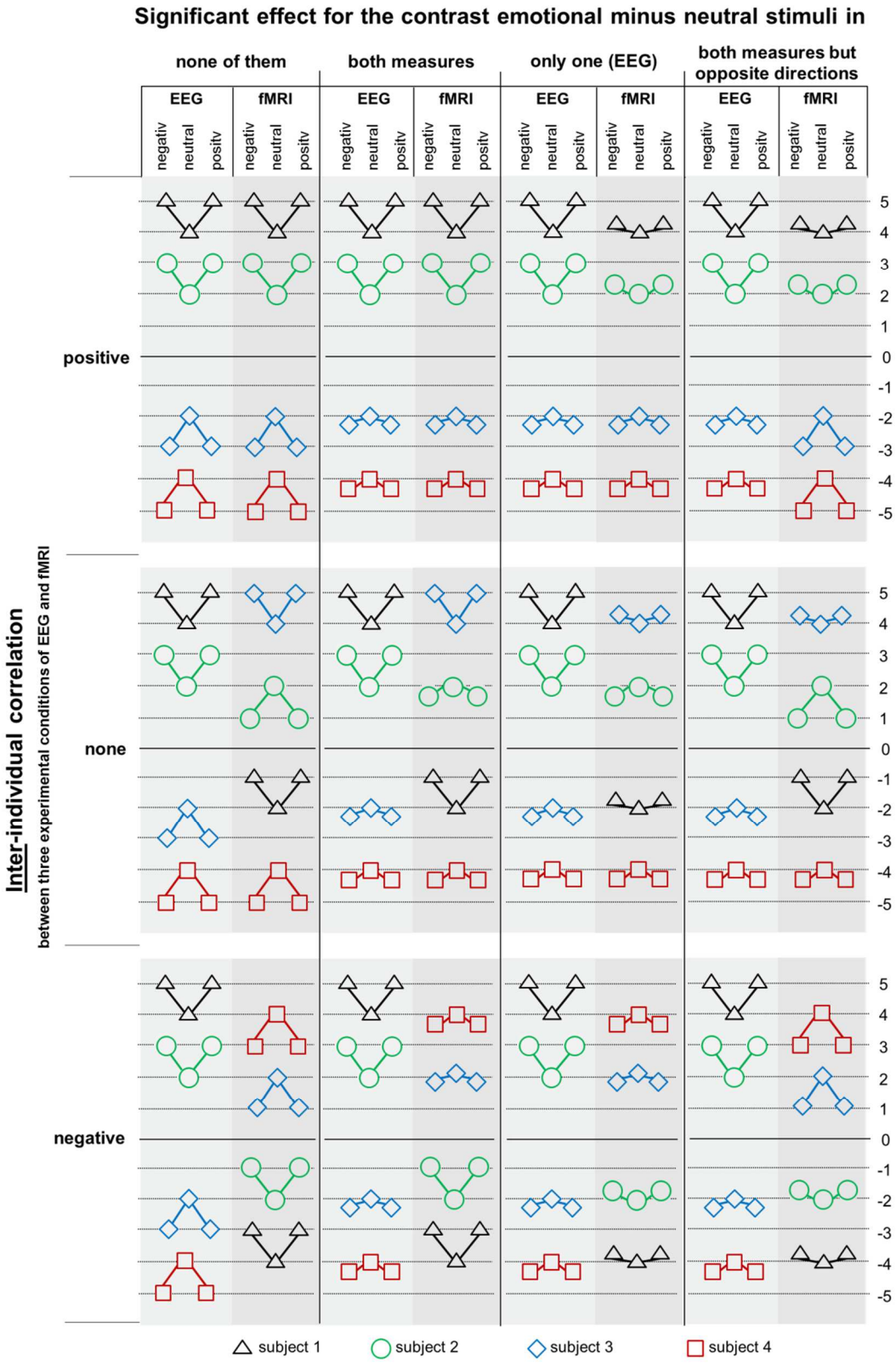
Turtle pictures

APPENDIX B

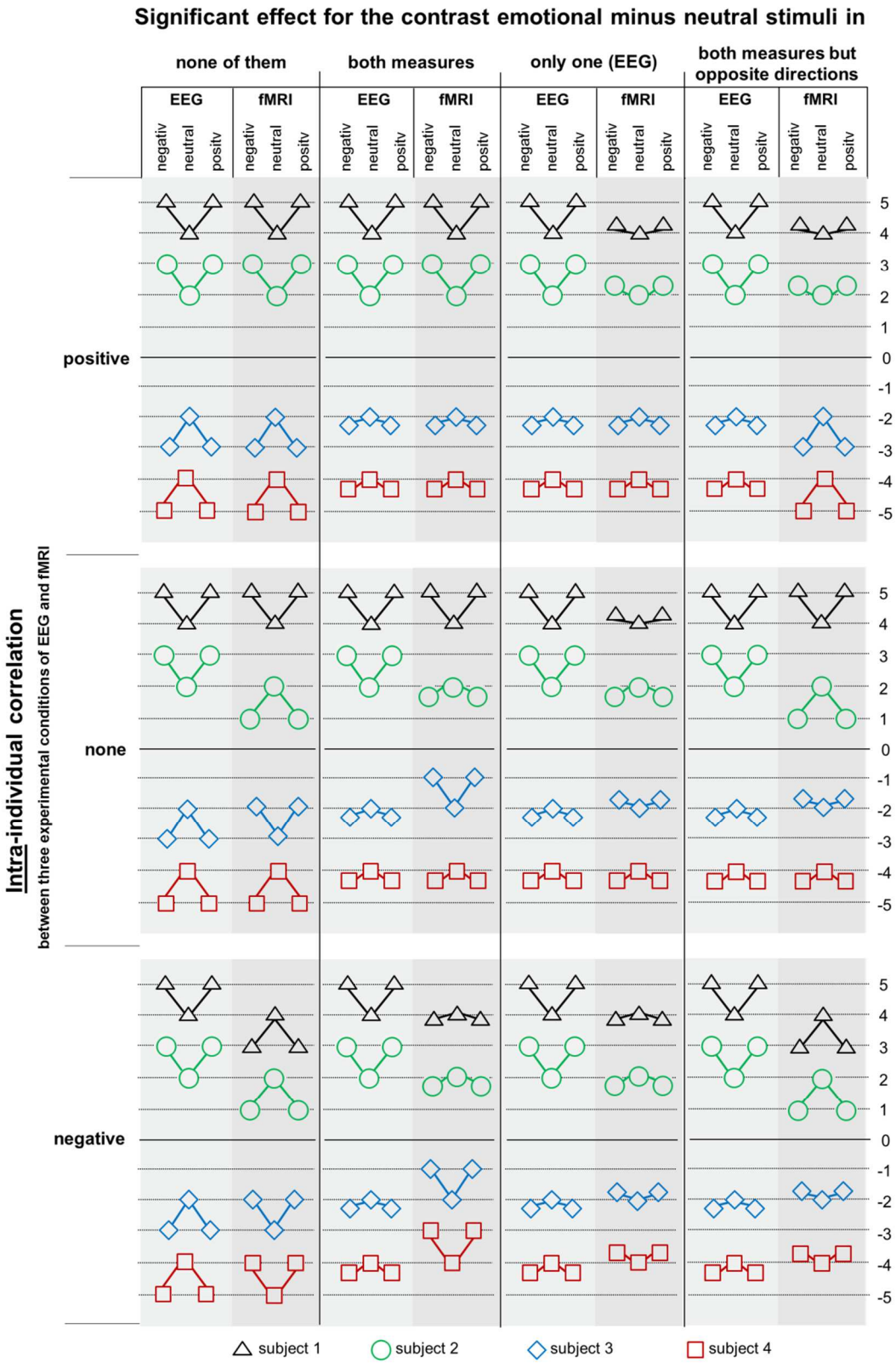


Assumes no effect between emotional minus neutral pictures

APPENDIX C

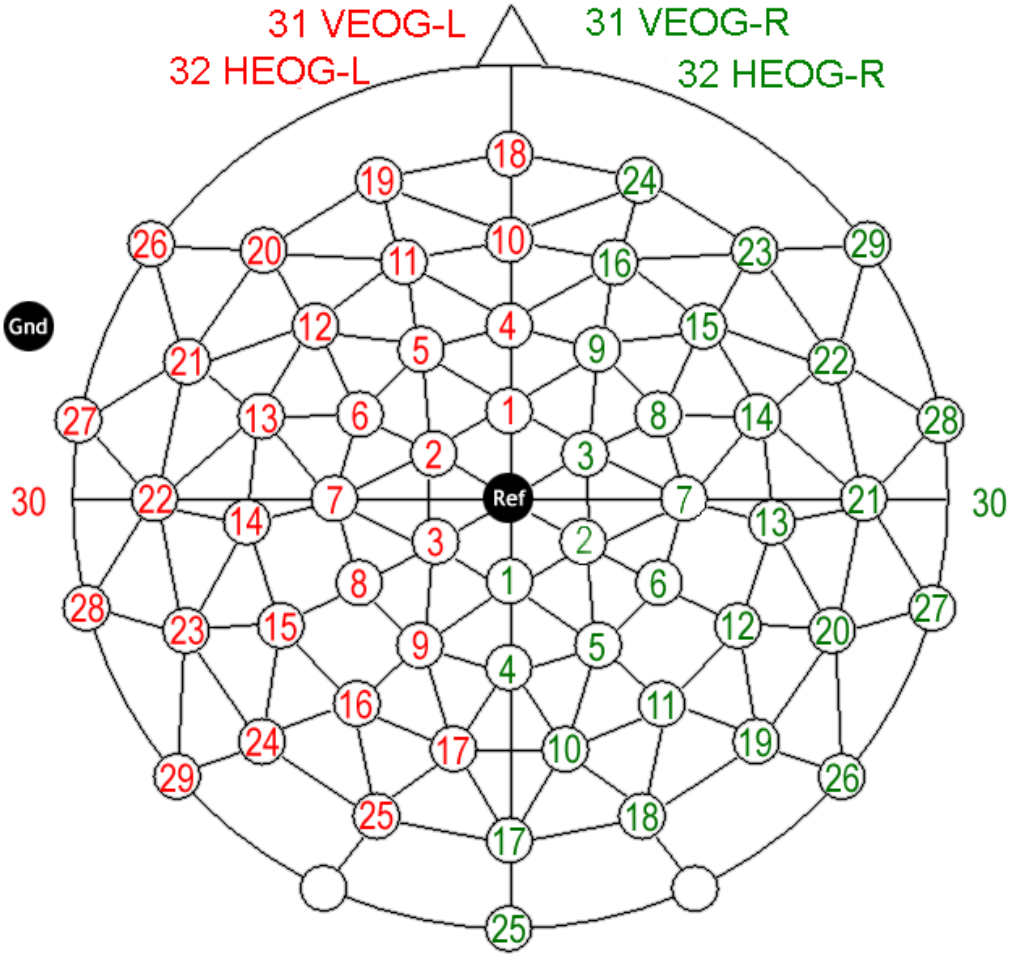

Significant effect for the contrast emotional minus neutral stimuli in
none of them
both measures
only one (EEG)
both measures but opposite directions
EEG
fMRI
negativ
neutral
positv
Inter-individual correlation
between three experimental conditions of EEG and fMRI
positive
none
negative
5
4
3
2
1
0
-1
-2
-3
-4
-5
subject 1
subject 2
subject 3
subject 4

APPENDIX D


Significant effect for the contrast emotional minus neutral stimuli in
none of them
both measures
only one (EEG)
both measures but opposite directions
EEG
fMRI
negativ
neutral
positv
positive
none
negative
Intra-individual correlation
between three experimental conditions of EEG and fMRI
5
4
3
2
1
0
-1
-2
-3
-4
-5
subject 1
subject 2
subject 3
subject 4

APPENDIX E

Electrode positions for EEG acquisition of Study 2



Position labels

Red:

18 - FPZ

10 - AFZ

4 - FZ

1 - FCZ

Ref - CZ

Green:

1 - CPZ

4 - PZ

17 - OZ

25 - IZ

APPENDIX F

Regions of interest for Emotion and P300/target networks

	regions of interest (ROI)
ROIs for Emotion network	
subcortical gray	amygdala
	insula
frontal lobe	orbitofrontal cortex:
	orbital surface, superior frontal gyrus, orbital part
	orbital surface, superior frontal gyrus, medial part
	orbital surface, middle frontal gyrus, orbital part
	orbital surface, inferior frontal gyrus, orbital part
	orbital surface, gyrus rectus
	orbital surface, olfactory cortex
limbic lobe	anterior cingulate and paracingulate gyri
	temporal pole: middle temporal gyrus
temporal lobe	lateral surface, inferior temporal gyrus
	lateral surface, middle temporal gyrus
	inferior gyrus of the temporal pole
	middle gyrus of the temporal pole
ROIs for P300 / target network	
subcortical gray	amygdala
	insula
frontal lobe	L - lateral surface, inferior frontal gyrus, opercular part
	L - lateral surface, inferior frontal gyrus, triangular part
limbic lobe	anterior cingulate and paracingulate gyri
temporal lobe	lateral surface, superior temporal gyrus
	lateral surface, inferior temporal gyrus
	lateral surface, middle temporal gyrus
parietal lobe	L & R - lateral surface, inferior parietal, but supramarginal & angular gyri
central region	L- Precentral gyrus
	L - Postcentral gyrus

L – left; R – right; grey shaded areas indicate overlapping ROIs that are involved both in emotion and P300/target networks

APPENDIX G

LOCATION			F	p
FPZ	DECODING CONDITION		12.779	.004*
	VALENCE	I (EMO > NEU)	22.281	.001*
		II (NEG > POS)	22.110	.001*
	DECODING CONDITION x VALENCE	Valence-I	1.502	.246
		Valence-II	.720	.414
AFZ	DECODING CONDITION		14.540	.003*
	VALENCE	I (EMO > NEU)	12.542	.005*
		II (NEG > POS)	13.745	.003*
	DECODING CONDITION x VALENCE	Valence-I	.057	.816
		Valence-II	.145	.711
FZ	DECODING CONDITION		3.216	.100
	VALENCE	I (EMO > NEU)	.028	.869
		II (NEG > POS)	5.167	.044
	DECODING CONDITION x VALENCE	Valence-I	.432	.524
		Valence-II	.232	.639
FCZ	DECODING CONDITION		.040	.845
	VALENCE	I (EMO > NEU)	3.710	.080
		II (NEG > POS)	2.888	.117
	DECODING CONDITION x VALENCE	Valence-I	.706	.419
		Valence-II	2.281	.159
CZ	DECODING CONDITION		2.041	.181
	VALENCE	I (EMO > NEU)	9.608	.010
		II (NEG > POS)	.091	.768
	DECODING CONDITION x VALENCE	Valence-I	4.166	.066
		Valence-II	6.068	.031
CPZ	DECODING CONDITION		.511	.490
	VALENCE	I (EMO > NEU)	14.243	.003*
		II (NEG > POS)	2.444	.146
	DECODING CONDITION x VALENCE	Valence-I	2.799	.122
		Valence-II	8.459	.014
PZ	DECODING CONDITION		3.071	.108
	VALENCE	I (EMO > NEU)	23.583	.001*
		II (NEG > POS)	7.647	.018
	DECODING CONDITION x VALENCE	Valence-I	.674	.429
		Valence-II	6.896	.024
OZ	DECODING CONDITION		5.610	.037
	VALENCE	I (EMO > NEU)	2.467	.145
		II (NEG > POS)	9.549	.010
	DECODING CONDITION x VALENCE	Valence-I	1.190	.299
		Valence-II	.037	.850
IZ	DECODING CONDITION		1.936	.192
	VALENCE	I (EMO > NEU)	23.735	.000*
		II (NEG > POS)	2.922	.115
	DECODING CONDITION x VALENCE	Valence-I	5.091	.045
		Valence-II	.581	.462

Grey shaped areas indicate significant effect after Bonferroni correction: $\propto_{corrected} = \frac{0.05}{9} = 0.0056$

REFERENCES

Amaral, D. G., & Insausti, R. (1992). Retrograde transport of D-[3H]-aspartate injected into the monkey amygdaloid complex. *Experimental Brain Research, 88*(2), 375-388.

Badre, D. (2008). Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends in Cognitive Sciences, 12*(5), 193-200.

Ball, T., Schreiber, A., Feige, B., Wagner, M., Lucking, C. H., & Kristeva-Feige, R. (1999). The role of higher-order motor areas in voluntary movement as revealed by high-resolution EEG and fMRI. *Neuroimage, 10*(6), 682-694.

Balsters, J. H., O'Connell, R. G., Martin, M. P., Galli, A., Cassidy, S. M., Kilcullen, S. M., Robertson, I. H. (2011). Donepezil impairs memory in healthy older subjects: behavioural, EEG and simultaneous EEG/fMRI biomarkers. *PloS one, 6*(9), e24126.

Bartussek, D., Becker, G., Diedrich, O., Naumann, E., & et al. (1996). Extraversion, neuroticism, and event-related brain potentials in response to emotional stimuli. *Personality and Individual Differences, 20*(3), 301-312.

Berger, H. (1929). Über das Elektroenkephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten*(87), 527-570.

Bledowski, C., Prvulovic, D., Hoechstetter, K., Scherg, M., Wibral, M., Goebel, R., & Linden, D. E. (2004). Localizing P300 generators in visual target and distractor processing: a combined event-related potential and functional magnetic resonance imaging study. *Journal of Neuroscience, 24*(42), 9353-9360.

Brandeis, D., Michel, C. M., & Amzica, F. (2009). From neuronal activity to scalp fields. In C. M. Michel, T. Koenig, D. Brandeis, L. R. R. Gianotti & J. Wackermann (Eds.), *Electrical Neuroimaging* (pp. 1-24). Cambridge: Cambridge University Press.

Brazdil, M., Dobsik, M., Mikl, M., Hlustik, P., Daniel, P., Pazourkova, M., Rektor, I. (2005). Combined event-related fMRI and intracerebral ERP study of an auditory oddball task. *Neuroimage, 26*(1), 285-293.

Brosch, T., & Sharma, D. (2005). The role of fear-relevant stimuli in visual search: a comparison of phylogenetic and ontogenetic stimuli. *Emotion, 5*(3), 360-364.

Buxton, R. B., Uludag, K., Dubowitz, D. J., & Liu, T. T. (2004). Modeling the hemodynamic response to brain activation. *Neuroimage, 23 Suppl 1*, S220-233.

Chatrian, G. E., Lettich, E., & Nelson, P. L. (1988). Modified Nomenclature for the" 10%" Electrode System1. *Journal of Clinical Neurophysiology*, 5(2), 183-186.

Chritchley, H. D., Daly, E., Phillips, M., Brammer, M., Bullmore, E., Williams, S., Murphy, D. (2000). Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional megnetic reonance imaging study. *Human Brain Mapping, 9*, 93-105.

Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (2002). *Applied multiple regression/correlation analysis for the behavioral sciences* (3rd ed.): Psychology Press.

Cook, E. W., 3rd, Hodes, R. L., & Lang, P. J. (1986). Preparedness and phobia: effects of stimulus content on human visceral conditioning. *Journal of Abnormal Psychology, 95*(3), 195-207.

Critchley, H. D., Mathias, C. J., & Rolan, R. J. (2002). Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy. *Neuron, 33*, 653-656.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: covariation with autonomic arousal and affective report. *Biological Psychology, 52*(2), 95-111.

Czisch, M., Wehrle, R., Kaufmann, C., Wetter, T. C., Holsboer, F., Pollmacher, T., & Auer, D. P. (2004). Functional MRI during sleep: BOLD signal decreases and their electrophysiological correlates. *The European journal of neuroscience, 20*(2), 566-574.

Daffner, K. R., Mesulam, M. M., Scinto, L. F. M., Acar, D., Calvo, V., Faust, R., ... & Holcomb, P. (2000). The central role of the prefrontal cortex in directing attention to novel events. *Brain*, 123(5), 927-939.

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage, 9*(2), 179-194.

de Munck, J. C., Goncalves, S. I., Huijboom, L., Kuijer, J. P., Pouwels, P. J., Heethaar, R. M., & Lopes da Silva, F. H. (2007). The hemodynamic response of the alpha rhythm: an EEG/fMRI study. *Neuroimage, 35*(3), 1142-1151.

Debener, S., Thorne, J., Schneider, T. R., & Viola, F. C. (2010). Using ICA for Analyses of Multi-Channel EEG Data. In M. Ullsperger & S. Debener (Eds.), *Simultaneous EEG and FMRI* (pp. 138-150). Oxford: Oxford University Press.

Debener, S., Ullsperger, M., Siegel, M., & Engel, A. K. (2006a). Single-trial EEG-fMRI reveals the dynamics of cognitive function. *Trends in Cognitive Sciences, 10*(12), 558-563.

Debener, S., Ullsperger, M., Siegel, M., & Engel, A. K. (2006b). Single-trial EEG-fMRI reveals the dynamics of cognitive function. *Trends in Cognitive Sciences, 10*(12), 558-563.

Devlin, J. T., Russell, R. P., Davis, M. H., Price, C. J., Moss, H. E., Fadili, M. J., & Tyler, L. K. (2002). Is there an anatomical basis for category-specificity? Semantic memory studies in PET and fMRI. *Neuropsychologia, 40*(1), 54-75.

Diedrich, O. (1996). *Die kortikale Kontrolle emotionaler Reaktionen*. Lengerich: Pabst Science Publishers.

Diedrich, O., Naumann, E., Maier, S., & Becker, G. (1997). A frontal positive slow wave in the ERP associated with emotional slides. *Journal of Psychophysiology, 11*, 71-84.

Donchin, E. (1981). Surprise! ... Surprise? *Psychophysiology, 18*(3), 49-513.

Donchin, E., & Coles, M. G. H. (1988). Is the P300 component a manifestation of context updating? *Behavioral and Brain Sciences, 11*(3), 357-427.

Donchin, E., & Coles, M. G. H. (1991). Behavior, cognition and event-related brain potentials. *Behavioral and Brain Sciences, 14*(4), 735-739.

Donchin, E., Ritter, W., & McCallum, W. C. (1978). Cognitive psychophysiology: the endogenous components of the ERP. In E. Callaway, P. Tueting & S. H. Koslow (Eds.), *Event-related brain potentials in man*. New York: Academic Press.

Eichele, T., Specht, K., Moosmann, M., Jongsma, M. L., Quiroga, R. Q., Nordby, H., & Hugdahl, K. (2005). Assessing the spatiotemporal evolution of neuronal activation with single-trial event-related potentials and functional MRI. *Proceedings of the National Academy of Sciences of the United States of America, 102*(49), 17798-17803.

Eimer, M., & Holmes, A. (2007). Event-related brain potential correlates of emotional face processing. *Neuropsychologia, 45*(1), 15-31.

Eimer, M., Holmes, A., & McGlone, F. P. (2003). The role of spatial attention in the processing of facial expression: an ERP study of rapid brain responses to six basic emotions. *Cognitive Affective & Behavioral Neuroscience, 3*(2), 97-110.

Eimer, M., & Kiss, M. (2007). Attentional capture by task-irrelevant fearful faces is revealed by the N2pc component. *Biological Psychology, 74*(1), 108-112.

Engel, A. K., Fries, P., & Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top-down processing. *Nature reviews. Neuroscience, 2*(10), 704-716.

Flykt, A. (2005). Visual search with biological threat stimuli: accuracy, reaction times, and heart rate changes. *Emotion, 5*(3), 349-353.

Ford, J. M., Gray, M., Whitfield, S. L., Turken, A. U., Glover, G., Faustman, W. O., & Mathalon, D. H. (2004). Acquiring and inhibiting prepotent responses in

schizophrenia: event-related brain potentials and functional magnetic resonance imaging. *Archives of general psychiatry, 61*(2), 119-129.

Fries, P., Nikolic, D., & Singer, W. (2007). The gamma cycle. *Trends in Neurosciences, 30*(7), 309-316.

George, J. S., Aine, C. J., Mosher, J. C., Schmidt, D. M., Ranken, D. M., Schlitt, H. A., Belliveau, J. W. (1995). Mapping function in the human brain with magnetoencephalography, anatomical magnetic resonance imaging, and functional magnetic resonance imaging. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society, 12*(5), 406-431.

Gerlach, C., Aaside, C. T., Humphreys, G. W., Gade, A., Paulson, O. B., & Law, I. (2002). Brain activity related to integrative processes in visual object recognition: bottom-up integration and the modulatory influence of stored knowledge. *Neuropsychologia, 40*(8), 1254-1267.

Gerlach, C., Law, I., Gade, A., & Paulson, O. B. (1999). Perceptual differentiation and category effects in normal object recognition: a PET study. *Brain, 122 (Pt 11)*, 2159-2170.

Gerlach, C., Law, I., Gade, A., & Paulson, O. B. (2000). Categorization and category effects in normal object recognition: a PET study. *Neuropsychologia, 38*(13), 1693-1703.

Gobbele, R., Buchner, H., Scherg, M., & Curio, G. (1999). Stability of high-frequency (600 Hz) components in human somatosensory evoked potentials under variation of stimulus rate--evidence for a thalamic origin. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 110*(9), 1659-1663.

Goense, J., & Logothetis, N. K. (2010). Physiological Basis of the BOLD Signal. In M. Ullsperger & S. Debener (Eds.), *Simultanous EEG and fMRI* (1st ed., pp. 21-45). Oxford, New York: Oxford University Press.

Goldman, R. I., Stern, J. M., Engel, J., Jr., & Cohen, M. S. (2002). Simultaneous EEG and fMRI of the alpha rhythm. *Neuroreport, 13*(18), 2487-2492.

Goncalves, S. I., de Munck, J. C., Pouwels, P. J., Schoonhoven, R., Kuijer, J. P., Maurits, N. M., . . . Lopes da Silva, F. H. (2006). Correlating the alpha rhythm to BOLD using simultaneous EEG/fMRI: inter-subject variability. *NeuroImage, 30*(1), 203-213.

Gorno-Tempini, M. L., Pradelli, S., Serafini, M., Pagnoni, G., Baraldi, P., Porro, C., Nichelli, P. (2001). Explicit and incidental facial expression processing: an fMRI study. *NeuroImage, 14*, 465-473.

Gratton, G., & Coles, M. G. H. (1989). Generalization and evaluation of eye-movement correction procedures. *Journal of Psychophysiology, 3*, 14-16.

Gratton, G., Coles, M. G. H., & (1983), E. D. (1983). A new method for off-line removal of ocular artefacts. *Electroencephalography and Clinical Neurophysiology, 55*, 468-484.

Hagemann, D., Brosch, T., Britz, P., Strelzyk, F., & Naumann, E. (in preparation). Visual search for fear-relevant stimuli: Two ERP studies.

Hagemann, D., Hewig, J., Seifert, J., Naumann, E., & Bartussek, D. (2005). The latent state-trait structure of resting EEG asymmetry: replication and extension. *Psychophysiology, 42*(6), 740-752.

Heinze, H. J., Mangun, G. R., Burchert, W., Hinrichs, H., Scholz, M., Munte, T. F., et al. (1994). Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature, 372*(6506), 543-546.

Henze, D. A., Borhegyi, Z., Csicsvari, J., Mamiya, A., Harris, K. D., & Buzsaki, G. (2000). Intracellular features predicted by extracellular recordings in the hippocampus in vivo. *Journal of neurophysiology, 84*(1), 390-400.

Hermes, M., Hagemann, D., Britz, P., Lieser, S., Bertsch, K., Naumann, E., & Walter, C. (2009). Latent state-trait structure of cerebral blood flow in a resting state. *Biological Psychology, 80*(2), 196-202.

Herrmann, C. S., & Debener, S. (2008). Simultaneous recording of EEG and BOLD responses: a historical perspective. *International Journal of Psychophysiology, 67*(3), 161-168.

Hewig, J., Hagemann, D., Seifert, J., Naumann, E., & Bartussek, D. (2004). On the selective relation of frontal cortical asymmetry and anger-out versus anger-control. *Journal of Personality and Social Psychology, 87*(6), 926-939.

Hillyard, S. A., Hink, R. F., Schwent, V. L., & Picton, T. W. (1973). Electrical signs of selective attention in the human brain. *Science, 182*(4108), 177-180.

Hirayasu, Y., Ohta, H., Fukao, K., Ogura, C., & Mukawa, J. (1995). Transient P300 abnormality of event-related potentials following unilateral temporal lobectomy. *Psychiatry and Clinical Neurosciences, 49*(4), 223-226.

Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics, 6*, 65-70.

Horovitz, S. G., Rossion, B., Skudlarski, P., & Gore, J. C. (2004). Parametric design and correlational analyses help integrating fMRI and electrophysiological data during face processing. *Neuroimage, 22*(4), 1587-1595.

Horovitz, S. G., Skudlarski, P., & Gore, J. C. (2002). Correlations and dissociations between BOLD signal and P300 amplitude in an auditory oddball task: a parametric approach to combining fMRI and ERP. *Magnetic Resonance Imaging, 20*(4), 319-325.

Huettel, S. A., Song, A. W., & McGarthy, G. (2009). *Functional Magnetic Imaging* (2nd ed.). New York: Sinauer Associates.

Hugdahl, K., & Karker, A. C. (1981). Biological vs experiential factors in phobic conditioning. *Behaviour Research and Therapy, 19*(2), 109-115.

Ioannides, A. A., & Fenwick, P. B. (2005). Imaging cerebellum activity in real time with magnetoencephalographic data. *Progress in brain research, 148*, 139-150.

Ishai, A., Ungerleider, L. G., Martin, A., & Haxby, J. V. (2000). The representation of objects in the human occipital and temporal cortex. *Journal of Cognitive Neuroscience, 12 Suppl 2*, 35-51.

Itier, R. J., Latinus, M., & Taylor, M. J. (2006). Face, eye and object early processing: what is the face specificity? *Neuroimage, 29*(2), 667-676.

James, C. E., Britz, J., Vuilleumier, P., Hauert, C. A., & Michel, C. M. (2008). Early neuronal responses in right limbic structures mediate harmony incongruity processing in musical experts. *Neuroimage, 42*(4), 1597-1608.

Kiang, M., Kutas, M., Light, G. A., & Braff, D. L. (2008). An event-related brain potential study of direct and indirect semantic priming in schizophrenia. *The American journal of psychiatry, 165*(1), 74-81.

Kiehl, K. A., Stevens, M. C., Laurens, K. R., Pearlson, G., Calhoun, V. D., & Liddle, P. F. (2005). An adaptive reflexive processing model of neurocognitive function: supporting evidence from a large scale (n = 100) fMRI study of an auditory oddball task. *Neuroimage, 25*(3), 899-915.

Kim, H., Somerville, L. H., Johnstone, T., Alexander, A. L., & Whalen, P. J. (2003). Inverse amygdala and medial prefrontal cortex responses to surprised faces. *Neuroreport, 14*(18), 2317-2322.

Kim, S. G., Jin, T., & Fukuda, M. (2010). Spatial Resolution of fMRI Techniques. In S. Ulmer & O. Jansen (Eds.), *fMRI - Basics and Clinical Applications* (pp. 15-22). Heidelberg: Springer.

Kutas, M., & Hillyard, S. A. (1980). Event-related brain potentials to semantically inappropriate and surprisingly large words. *Biological psychology, 11*(2), 99-116.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1995). *International affective picture system (IAPS): Technical manual and affective ratings*. Gainsville, FL: NIMH Center for the Study of Emotion and Attention.

Laufs, H., Kleinschmidt, A., Beyerle, A., Eger, E., Salek-Haddadi, A., Preibisch, C., & Krakow, K. (2003). EEG-correlated fMRI of human alpha activity. *Neuroimage, 19*(4), 1463-1476.

Laufs, H., Krakow, K., Sterzer, P., Eger, E., Beyerle, A., Salek-Haddadi, A., & Kleinschmidt, A. (2003). Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proceedings of the National Academy of Sciences U S A, 100*(19), 11053-11058.

Laufs, H., Lengler, U., Hamandi, K., Kleinschmidt, A., & Krakow, K. (2006). Linking generalized spike-and-wave discharges and resting state brain activity by using EEG/fMRI in a patient with absence seizures. *Epilepsia, 47*(2), 444-448.

LeDoux, J. E. (1993). Emotional networks in the brain *(1993). Haviland, Jeannette M (Ed), Lewis, Michael (Ed), Handbook of emotions. (pp.109 118). New York, NY, US: Guilford Press. xiii, 653 pp.*

LeDoux, J. E. (1996). Emotional networks and motor control: a fearful view. *Progress in Brain Research, 107*, 437-446.

LeDoux, J. E. (1989). Cognitive-emotional interactions in the brain. *Cognition and Emotion, 3*, 267-289.

Lemieux, L., Laufs, H., Carmichael, D., Paul, J. S., Walker, M. C., & Duncan, J. S. (2008). Noncanonical spike-related BOLD responses in focal epilepsy. *Human brain mapping, 29*(3), 329-345.

Liebenthal, E., Ellingson, M. L., Spanaki, M. V., Prieto, T. E., Ropella, K. M., & Binder, J. R. (2003). Simultaneous ERP and fMRI of the auditory cortex in a passive oddball paradigm. *Neuroimage, 19*(4), 1395-1404.

Lipp, O. V., Derakshan, N., Waters, A. M., & Logies, S. (2004). Snakes and cats in the flower bed: fast detection is not specific to pictures of fear-relevant animals. *Emotion, 4*(3), 233-250.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412*(6843), 150-157.

Luck, S. J. (2005). *An introduction to the event-related potential technique*. Cambridge, MA: MIT Press.

Lythgoe, M. F., Thomas, D. L., & Calamante, F. (2003). MRI Measurement of Cerebral Perfusion and Application to Experimental Neuroscience In N. Bruggen & T. Roberts (Eds.), *Biomedical Imaging in Experimental Neuroscience* (pp. 21-54). Boca Raton: CRC Press LLC.

Makeig, S., Debener, S., Onton, J., & Delorme, A. (2004). Mining event-related brain dynamics. *Trends in Cognitive Sciences, 8*(5), 204-210.

Makeig, S., Westerfield, M., Jung, T. P., Enghoff, S., Townsend, J., Courchesne, E., & Sejnowski, T. J. (2002). Dynamic brain sources of visual evoked responses. *Science, 295*(5555), 690-694.

Martin, T., Houck, J. M., Bish, J. P., Kicic, D., Woodruff, C. C., Moses, S. N., Tesche, C. D. (2006). MEG reveals different contributions of somatomotor cortex and cerebellum to simple reaction time after temporally structured cues. *Human brain mapping, 27*(7), 552-561.

Martinez-Montes, E., Valdes-Sosa, P. A., Miwakeichi, F., Goldman, R. I., & Cohen, M. S. (2004). Concurrent EEG/fMRI analysis by multiway Partial Least Squares. *Neuroimage, 22*(3), 1023-1034.

Megevand, P., Quairiaux, C., Lascano, A. M., Kiss, J. Z., & Michel, C. M. (2008). A mouse model for studying large-scale neuronal networks using EEG mapping techniques. *Neuroimage, 42*(2), 591-602.

Michel, C. M., & Brandeis, D. (2010). The Sources and Temporal Dynamics of Scalp Electric Fields. In M. Ullsperger & S. Debener (Eds.), *Simultaneous EEG and fMRI* (Vol. 1st, pp. 1-20). Oxford: Oxford University Press.

Michel, C. M., Lantz, G., Spinelli, L., De Peralta, R. G., Landis, T., & Seeck, M. (2004). 128-channel EEG source imaging in epilepsy: clinical yield and localization precision. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society, 21*(2), 71-83.

Molle, M., Marshall, L., Gais, S., & Born, J. (2002). Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 22*(24), 10941-10947.

Moosmann, M., Ritter, P., Krastel, I., Brink, A., Thees, S., Blankenburg, F., Villringer, A. (2003). Correlates of alpha rhythm in functional magnetic resonance imaging and near infrared spectroscopy. *Neuroimage, 20*(1), 145-158.

Morris, J. S., Buchel, C., & Rolan, R. J. (2001). Parallel neural responses in amygdala subregions and sensory cortex during implicit fear conditioning. *NeuroImage, 13*, 1044-1052.

Morris, J. S., Oehman, A., & Rolan, R. J. (1998). Concious and unconcious emotional learning in the human amygdala. *Nature, 393*, 467-470.

Mulert, C., & Lemieux, L. (2010). *EEG - fMRI. Physiological Basis, Technique, and Applications*. Heidelberg: Springer-Verlag.

Murakami, S., & Okada, Y. (2006). Contributions of principal neocortical neurons to magnetoencephalography and electroencephalography signals. *The Journal of physiology, 575*(Pt 3), 925-936.

Murphy, F. C., Nimmo-Smith, I., & Lawrence, A. D. (2003). Functional neuroanatomy of emotions: a meta-analysis. *Cognitive, Affective, & Behavioral Neuroscience, 3*(3), 207-233.

Naatanen, R., & Picton, T. (1987). The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology, 24*(4), 375-425.

Nagahama, Y., Okada, T., Katsumi, Y., Hayashi, T., Yamauchi, H., Sawamoto, N., Shibasaki, H. (1999). Transient neural activity in the medial superior frontal gyrus and precuneus time locked with attention shift between object features. *Neuroimage, 10*(2), 193-199.

Nagai, Y., Critchley, H. D., Featherstone, E., Fenwick, P. B. C., Trimble, M. R., & Dolan, R. J. (2004). Brain activity relating to the contingent negative variation: an fMRI investigation. Neuroimage, 21(4), 1232-1241.Naumann, E., Bartussek, D., Diedrich, O., & Laufer, M. E. (1992a). Assessing cognitive and affective information processing functions of the brain by means of the late positive complex of event-related potential. *Journal of Psychophysiology, 6*, 285-298.

Naumann, E., Bartussek, D., Diedrich, O., & Laufer, M. E. (1992b). Assessing cognitive and affective information processing functions of the brain by means of the late positive complex of the event-related potential. *Journal of Psychophysiology, 6*, 285-298.

Naumann, E., Huber, C., Maier, S., Plihal, W., Wustmans, A., Diedrich, O., & Bartussek, D. (1992). The scalp topography of P300 in the visual and auditory modalities: a comparison of three normalization methods and the control of statistical type II error. *Electroencephalography and Clinical Neurophysiology, 83*(4), 254-264.

Naumann, E., Maier, S., Diedrich, O., Becker, G., & Bartussek, D. (1997). Structural, semantic, and emotion-focused processing of neutral and negative nouns: Event-related potential correlates. *Journal of Psychophysiology, 11*, 158-172.

Niedermeyer, E., & Silvia, F. L. (2011). *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields* (6th ed.). Philadelphia: Lippincot Williams & Wilkins.

Northoff, G., Richter, A., Gessner, M., Schlagenhauf, F., Fell, J., Baumgart, F., Heinze, H.-J. (2000). Functional dissociation between medial and lateral prefrontal cortical Spatiotemporal activation in negative and positive emotions: A combined fMRI/MEG study. *Cerebral Cortex, 10, No. 1*, 93-107.

Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., & Ugurbil, K. (1992). Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the United States of America, 89*(13), 5951-5955.

Öhman, A., Flykt, A., & Esteves, F. (2001). Emotion drives attention: detecting the snake in the grass. *Journal of Experimental Psychology: General, 130*(3), 466-478.

Öhman, A., & Mineka, S. (2001). Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. *Psychological Review, 108*(3), 483-522.

Öhman, A., & Soares, J. J. (1994). "Unconscious anxiety": phobic responses to masked stimuli. *Journal of Abnormal Psychology, 103*(2), 231-240.

Öhman, A., & Soares, J. J. (1998). Emotional conditioning to masked stimuli: expectancies for aversive outcomes following nonrecognized fear-relevant stimuli. *Journal of Experimental Psychology: General, 127*(1), 69-82.

Onton, J., Westerfield, M., Townsend, J., & Makeig, S. (2006). Imaging human EEG dynamics using independent component analysis. *Neuroscience & Biobehavioral Reviews, 30*(6), 808-822.

Opitz, B., Mecklinger, A., Von Cramon, D. Y., & Kruggel, F. (1999). Combining electrophysiological and hemodynamic measures of the auditory oddball. *Psychophysiology, 36*(1), 142-147.

Palomba, D., Angrilli, A., & Mini, A. (1997). Visual evoked potentials, heart rate responses and memory to emotional pictorial stimuli. *International Journal of Psychophysiology, 27*, 55-67.

Pascual-Marqui, R. D., Esslen, M., Kochi, K., & Lehmann, D. (2002). Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. *Methods and findings in experimental and clinical pharmacology, 24 Suppl C*, 91-95.

Pessoa, L., Kastner, S., & Ungerleider, L. G. (2002). Attentional control of the processing of neural and emotional stimuli. *Cognitive Brain Research, 15*(1), 31-45.

Pessoa, L., Padmala, S., & Morland, T. (2005). Fate of unattended fearful faces in the amygdala is determined by both attentional resources and cognitive modulation. *Neuroimage, 28*(1), 249-255.

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage, 16*(2), 331-348.

Phan, K. L., Wager, T. D., Taylor, S. F., & Liberzon, I. (2004). Functional neuroimaging studies of human emotions. *CNS Spectrums, 9*(4), 258-266.

Picton, T. W. (1992). The P300 wave of the human event-related potential. *Journal of Clinical Neurophysiology, 9*(4), 456-479.

Pizzagalli, D., Koenig, T., Regard, M., & Lehmann, D. (1998). Faces and emotions: brain electric field sources during covert emotional processing. *Neuropsychologia, 36*(4), 323-332.

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology, 118*(10), 2128-2148.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences U S A, 98*(2), 676-682.

Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *Neuroimage, 37*(4), 1083-1090; discussion 1097-1089.

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., Pitman, R. K. (2000). Exaggerated amygdala response to masked facial stimuliin posttraumatic stress disorder: a functional MRI study. *Biological Psychiatry, 47*, 769-776.

Rinck, M., Reinecke, A., Ellwart, T., Heuer, K., & Becker, E. S. (2005). Speeded detection and increased distraction in fear of spiders: evidence from eye movements. *Journal of Abnormal Psychology, 114*(2), 235-248.

Roberts, K. L., & Hall, D. A. (2008). Examining a supramodal network for conflict processing: a systematic review and novel functional magnetic resonance imaging data for related visual and auditory stroop tasks. *Journal of cognitive neuroscience, 20*(6), 1063-1078.

Rosch, E., Mervis, C., Gray, W. D., Johnson, D. M., & Boyes-Braem, P. (1976). Basic objects in natural categories. *Cognitive Psychology, 8*, 382-439.

Rösler, F., Heil, M., & Röder, B. (1997). Slow negative brain potentials as reflections of specific modular resources of cognition. *Biological Psychology, 45*, 109-141.

Rösler, F., Heil, M. (1991). Towards a functional categorization of slow waves: taking into account past and future events. *Psychophysiology, 28*, 344-359.

Rotshtein, P., Malach, R., Hadar, U., Graif, M., & Hendler, T. (2001). Feeling or features: different sensivity to emotion in high-order visual cortex and amygdala. *Neuron, 32*, 747-757.

Rousselet, G. A., Thorpe, S. J., & Fabre-Thorpe, M. (2004). Processing of one, two or four natural scenes in humans: the limits of parallelism. *Vision Research, 44*(9), 877-894.

Salek-Haddadi, A., Diehl, B., Hamandi, K., Merschhemke, M., Liston, A., Friston, K., Lemieux, L. (2006). Hemodynamic correlates of epileptiform discharges: an EEG-fMRI study of 63 patients with focal epilepsy. *Brain Research, 1088*(1), 148-166.

Salek-Haddadi, A., Friston, K. J., Lemieux, L., & Fish, D. R. (2003). Studying spontaneous EEG activity with fMRI. *Brain research. Brain research reviews, 43*(1), 110-133.

Sanei, S., & Chambers, J. A. (2007). *EEG Signal Processing*. Cichester: Wiley.

Schankin, A., Hagemann, D., Danner, D., & Hager, M. (2011). Violations of implicit rules elicit an early negativity in the event-related potential. *Neuroreport, 22*(13), 642-645.

Scherg, M., Vajsar, J., & Picton, T. W. (1989). A Source Analysis of the late human auditory evoked potential. *Journal of cognitive neuroscience,* (1), 336-355.

Scherg, M., & von Cramon, D. (1985a). A new interpretation of the generators of BAEP waves I-V: results of a spatio-temporal dipole model. *Electroencephalography and clinical neurophysiology, 62*(4), 290-299.

Scherg, M., & Von Cramon, D. (1985b). Two bilateral sources of the late AEP as identified by a spatio-temporal dipole model. *Electroencephalography and clinical neurophysiology, 62*(1), 32-44.

Schienle, A., Schäfer, A., & Naumann, E. (2008). Event-related brain potentials of spider phobics to disorder-relevant, generally disgust- and fear-inducing pictures. *Journal of Psychophysiology, 22*(1), 5-13.

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T., & Lang, P. J. (2000). Affective picture processing: The late positive potential is modulated by motivational relevance. *Psychophysiology, 37*, 257-261.

Schupp, H. T., Junghöfer, M., Weike, A. I., & Hamm, A. O. (2003). Emotional fasllitation of sensory processing in the visual cortex. *Psychological Science, 14*, 7-13.

Schupp, H. T., Stockburger, J., Bublatzky, F., Junghofer, M., Weike, A. I., & Hamm, A. O. (2007). Explicit attention interferes with selective emotion processing in human extrastriate cortex. *BMC Neuroscience, 8*, 16.

Scott, S. K., Young, A. W., Calder, A. J., Hellawell, D. J., Aggleton, J. P., & Johnson, M. (1997). Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature, 385*(6613), 254-257.

Shmuel, A. (2010). Locally Measured Neuronal Correlates of Functional MRI Signals. In C. Mulert & L. Lemieux (Eds.), *EEG-fMRI* (pp. 63-82). Berlin: Springer Verlag.

Snyder, A. Z., Abdullaev, Y. G., Posner, M. I., & Raichle, M. E. (1995). Scalp electrical potentials reflect regional cerebral blood flow responses during processing of written words. *Proceedings of the National Academy of Sciences of the United States of America, 92*(5), 1689-1693.

Snyder, A. Z., & Raichle, M. E. (2010). Studies of the Human Brain Combining Functional Neuroimaging and Electrophysiological Methods. In M. Ullsperger & S. Debener (Eds.), *Simultaneous EEG and fMRI* (pp. 47-65). Oxford: Oxford University Press.

Stark, R., Zimmermann, M., Kagerer, S., Schienle, A., Walter, B., Weygandt, M., & Vaitl, D. (2007). Hemodynamic brain correlates of disgust and fear ratings. *Neuroimage, 37*(2), 663-673.

Steriade, M. (2001). Impact of network activities on neuronal properties in corticothalamic systems. *Journal of neurophysiology, 86*(1), 1-39.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science, 150*(3700), 1187-1188.

Sutton, S., & Ruchkin, D. S. (1984). The late positive components: Advances and new problems. *Annals of the New York Academy of Science, 425*, 1-23.

Tabbert, K., Stark, R., Kirsch, P., & Vaitl, D. (2005). Hemodynamic responses of the amygdala, the orbitofrontal cortex and the visual cortex during a fear conditioning paradigm. *International Journal of Psychophysiology, 57*(1), 15-23.

Tallon-Baudry, C., & Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in cognitive sciences, 3*(4), 151-162.

Taylor, M. J., Batty, M., & Itier, R. J. (2004). The faces of development: a review of early face processing over childhood. *Journal of cognitive neuroscience, 16*(8), 1426-1442.

Thorpe, S. J., Fize, D., & Marlot, C. (1996). Speed of processing in the human visual system. *Nature, 381*(6582), 520-522.

Thorpe, S. J., Gegenfurtner, K. R., Fabre-Thorpe, M., & Bulthoff, H. H. (2001). Detection of animals in natural images using far peripheral vision. *European Journal of Neuroscience, 14*(5), 869-876.

Timmermann, L., Gross, J., Dirks, M., Volkmann, J., Freund, H.-J., & Schnitzler, A. (2002). The cerebral oscillatory network of parkinsonian resting tremor. *Brain*(126), 199-212.

Tipples, J., Young, A. W., Quinlan, P., Broks, P., & Ellis, A. W. (2002). Searching for threat. *Quarterly Journal of Experimental Psychology A, 55*(3), 1007-1026.

Tukey, J. W. (1977). Some thoughts on clinical trials, especially problems of multiplicity. *Science, 198*(4318), 679-684.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289.

Van Essen, D. C. (1995). Behind the optic nerve: an inside view of the primate visual system. *Transactions of the American Ophthalmological Society, 93*, 123-133.

VanRullen, R., & Thorpe, S. J. (2001). The time course of visual processing: from early perception to decision-making. *Journal of Cognitive Neuroscience, 13*(4), 454-461.

Verleger, R. (1988). A critique of the context updating hypothesis and an alternative interpretation of P3. *Behavioral and Brain Sciences, 11*, 343-356.

Vincem, D. C., & Eichele, T. (2010). Fusion of EEG and fMRI by Parallel Group ICA. In M. Ullsperger & S. Debener (Eds.), *Simultaneous EEG and fMRI: Recording, Analysis, and Application*. Oxford: Oxford University Press.

Vuilleumier, P., Armony, J. L., Clarke, K., Husain, M., Driver, J., & Dolan, R. J. (2002). Neural response to emotional faces with and without awareness: event-related fMRI in a parietal patient with visual extinction and spatial neglect. *Neuropsychologia, 40*(12), 2156-2166.

Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2001). Effects of attention and emotion on face processing in the human brain: An event-related fMRI study. *Neuron, 30*, 829-841.

Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2003). Distict spatial frequncy sensivities for processing faces and emotional expressions. *Nature neuroscience, 6*, 624-631.

Walter, B., Blecker, C., Kirsch, P., Sammer, G., Schienle, A., Stark, R., & Vaitl, D. (2003). MARINA: An easy to use tool for the creation of MAsks for Region of INterest Analyses. Presented at the 9th International Conference on Functional Mapping of the Human Brain, June 19-22, 2003, New York, NY. Available on CD-Rom in NeuroImage, Vol. 19, No. 2.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience, 18*(1), 411-418.

Wibral, M., Bledowski, C., & Tun, G. (2010). Integration of Separately Recorded EEG/MEG and fMRI Data. In M. Ullsperger & S. Debener (Eds.), *Simultaneous EEG and fMRI:*

Recording, Analysis, and Application (pp. 209-234). Oxford: Oxford University Press.

Wilkinson, L. (1999). Statistical Methods in Psychology Journals Guidelines and Explanations. *American Psychologist, 54*(8), 594-604.

Winston, J. S., Strange, B. A., O'Doherty, J., & Dolan, R. J. (2002). Automatic and intentional brain responses dirung evaluation of thrustworthiness of faces. *Nature neuroscience, 5*, 277-283.

Wolfe, J. M., & Horowitz, T. S. (2004). What attributes guide the deployment of visual attention and how do they do it? *Nature Reviews Neuroscience, 5*(6), 495-501.

Zald, D. H. (2003). The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews, 41*(1), 88-123.

EIDESSTATTLICHE ERKLÄRUNG

Hiermit erkläre ich, dass ich diese vorliegende Dissertation selbstständig verfasst und keine anderen als die angegebenen Quellen als Hilfsmittel verwendet habe. Zudem wurde die Arbeit an keiner anderen Universität zur Erlangung eines akademischen Grades eingereicht.

Trier, Dezember 2012

Patrick Britz