



Dissertation

Processing of prior probability: combined evidence from EEG and fMRI data

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Abstract

To prepare actions in advance, prior information about the probability of decision alternatives is integrated into the decision-making process. In the present dissertation, I investigated preparatory processes elicited by prior probability (PP) and the neural basis of PP processing. In three studies, I collected behavioral data and, furthermore, recorded electroencephalographic (EEG) data separately as well as simultaneously with functional magnetic resonance imaging (fMRI). While applying these methods, participants had to perform a number comparison task with a precue delivering PP about a subsequent response-demanding stimulus.

The probability precue elicited the preparation of the response, as shown by the parametrical modulation of response time (RT) depending on PP (Study 1). The EEG study (Study 2) revealed a parametrical effect of PP on the contingent negative variation (CNV) during the foreperiod, which is an indicator for premotor response preparation. Furthermore, a dipole was located in the anterior cingulate cortex (ACC) with its activity parametrically modulated by PP. These EEG results suggest that PP influences premotor response preparation in a parametrical fashion. An analysis of fMRI data showed that neural activity in the posterior medial frontal cortex (pmMFC) increased with increasing PP (Study 3a), which is attributed to a monitoring function of this region with respect to behavioral adjustment and initiation of response preparation depending on the PP. By applying an EEG-informed fMRI analysis (Study 3b), I focused on trial-to-trial fluctuations in PP processing and general response preparation as represented by the single-trial CNV amplitude. I found that the CNV amplitude was correlated with neural activity in a network consisting of frontal, parietal, and striatal regions reflecting general preparatory processes independently of PP. Parts of the network, namely, the dorsolateral prefrontal cortex (DLPFC), the inferior frontal gyrus (IFG), and the inferior parietal lobule (IPL), showed activations, which exclusively represented the contributions of PP to the CNV amplitude fluctuations.

These results suggest that PP elicits premotor response preparation and activates the pmMFC parametrically signaling the need for behavioral adjustment. In contrast, DLPFC, IFG, and IPL are involved in dynamically fluctuating PP processing mechanisms.

Keywords: Prior probability, Response preparation, CNV, simultaneous EEG/fMRI

Zusammenfassung

Um eine Entscheidung zu treffen, muss Information interpretiert und in eine Handlung übersetzt werden. Dafür wird die a priori Wahrscheinlichkeit bezüglich der Entscheidungsalternativen in den Prozess der Entscheidungsfindung integriert und löst Mechanismen der Handlungsvorbereitung aus. In der vorliegenden Dissertation habe ich untersucht, welche Vorbereitungsprozesse aufgrund von wahrscheinlichkeitsbasierter Vorinformation stattfinden und welche Gehirnareale mit der Integration dieser Information assoziiert sind. Um diese Fragen zu beantworten, habe ich eine Verhaltensstudie, eine Studie mit Ableitung des Elektroenzephalogramms (EEG) und eine Studie mittels der funktionellen Magnetresonanztomographie (fMRT) mit simultaner Ableitung des EEGs durchgeführt. Die Versuchspersonen bearbeiteten währenddessen eine Zahlenvergleichsaufgabe mit einem Hinweisreiz, der Wahrscheinlichkeitsinformation bezüglich der erforderlichen Antwort enthielt. Die Reaktionszeit wurde durch die wahrscheinlichkeitsbasierte Vorinformation des Hinweisreizes parametrisch moduliert (Studie 1). Daraus lässt sich schlussfolgern, dass Vorbereitungsprozesse in Abhängigkeit der Wahrscheinlichkeitsinformation stattfinden. Die EEG Studie (Studie 2) ergab einen parametrischen Effekt von Wahrscheinlichkeitsinformation auf die Amplitude der Contingent Negative Variation (CNV), einer EEG-Komponente, die Vorbereitungsprozesse auf prämotorischer Ebene reflektiert. Darüber hinaus fand sich mittels einer Dipolquellenanalyse ein Dipol im anterioren Cingulum (ACC), dessen Aktivität ebenfalls durch die Wahrscheinlichkeitsinformation parametrisch moduliert war. Diese Ergebnisse lassen auf prämotorische Vorbereitungsprozesse aufgrund von Wahrscheinlichkeitsinformation schließen. In den fMRT-Ergebnissen zeigte sich eine parametrisch modulierte neuronale Aktivierung im posterioren Teil des medial-frontalen Kortex (pmFC), die auf eine Kontrollfunktion zur Handlungsanpassung dieses Areals zurückgeführt werden kann (Studie 3a). Um dynamische Fluktuationen der Wahrscheinlichkeitsverarbeitung zu untersuchen, wurde die CNV Amplitude der Einzeltrials in das Modell der fMRT-Analyse integriert (Studie 3b). Die CNV Amplitude korrelierte mit der neuronalen Aktivität in einem Netzwerk, bestehend aus frontalen, parietalen und striatalen Arealen, das mit allgemeiner wahrscheinlichkeitsunabhängiger Handlungsvorbereitung im Zusammenhang steht. Dagegen zeigten sich im dorsolateralen Präfrontalkortex (DLPFC), im inferioren frontalen Gyrus (IPG) und im inferioren Parietallappen (IPL) Aktivierungen, die sich auf die dynamische Integration von Wahrscheinlichkeitsinformation zurückführen lassen.

Schlagerworte: A priori Wahrscheinlichkeit, Antwortvorbereitung, CNV, EEG/fMRT simultan

List of original publications

The dissertation is based on the following original research articles:

Scheibe C., Schubert R., Sommer, W., Heekeren H.R. (2009). Electrophysiological evidence for the effect of prior probability on response preparation. *Psychophysiology* 4(46): 758-770

Scheibe C., Ullsperger M., Sommer W., Heekeren H.R. (under review). Effects of parametrical and trial-to-trial variation in prior probability processing as revealed by simultaneous EEG/fMRI.

Related conference contributions:

Scheibe C., Ullsperger M., Sommer W., Heekeren H.R. (2008) Neural Correlates of Prior Probability Processing in Decision-making. 14th World Congress of Psychophysiology, St. Petersburg, Russia

Scheibe C., Ullsperger M., Sommer W., Heekeren H.R. (2007) FMRI and EEG data: Combined Evidence for the Influence of Prior Probability on Decision-making. Conference of Human Brain Mapping 2007, Chicago, USA

Scheibe C., Ullsperger M., Sommer W., Heekeren H.R. (2007) Spatiotemporal Dynamics underlying the Integration of Prior Probability Information in Decision-making. Conference of Cognitive Neuroscience 2007, New York, USA

Scheibe C., Schubert R., Sommer W., Heekeren H.R. (2006) Integration of Prior Probability in the Process of Decision-making. Symposium of Independent Component Analysis, Bergen, Norway

Scheibe C., Schubert R., Jatzev S., Sommer W., Heekeren H.R. (2006) Influence of Prior Probability on Decision-making. Conference of Human Brain Mapping 2006, Florenz, Italy

Scheibe C., Schubert R., Jatzev S., Sommer W., Heekeren H.R. (2006) Prior Probability: Effects on Decision-making. 6th Symposium Neuroscience Research Center, Berlin

Invited talks:

Simultaneous EEG/fMRI as a Tool for Cognitive Neuroscience: The Influence of Prior Probability on Decision Processes, Conference of Human Brain Mapping 2007, Chicago

Further publications:

Scheibe C., Wartenburger I., Wüstenberg T., Kathmann N., Villringer A., Heekeren H.R. (2006) Neural Correlates of the Interaction between Transient and Sustained Processes – a Mixed Blocked/Event-related fMRI Study. *Human Brain Mapping* 7, 27:545-551

Prehn K., Wartenburger I., Mériaux K., **Scheibe C.**, Goodenough O.R., Villringer A., van der Meer E. & Heekeren H.R. (2008). Individual differences in moral judgment competence influence neural correlates of socio-normative judgments. *Soc Cogn Affect Neurosci*, 3(1): 33-46.

List of abbreviations

ACC	Anterior cingulate cortex
BOLD	Blood-oxygen-level-dependent
CMA	Cingulate motor area
CNV	Contingent negative variation
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalogram
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
HRF	Hemodynamic response function
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
LRP	Lateralized readiness potential
pMFC	Posterior medial frontal cortex
PP	Prior probability
RCZ	Rostral cingulate zone
RT	Response time
S1	First number (precue)
S2	Second number (imperative stimulus)

1 Theoretical background

1.1 Introduction

The ability to prepare actions in advance and to use information available in advance contributes to the successful completion of many of our everyday activities and decisions. Prior information is mostly allocated with a certain probability that declares how reliable the information content is. This prior probability (PP) is integrated into the decision-making process and influences the preparation concerning the decision. For example, prior information about the rain probability through the weather forecast influences our decision to take an umbrella along. Thus, the ability to prepare depends on the consideration of the PP that is assigned to an event prior to any empirical evidence.

In the present dissertation, I investigated the influence of PP on preparatory processes and the neural basis of PP processing.

1.2 Prior probability and response preparation

Behavioral studies have provided evidence that the PP of the occurrence of an event modulates response time (RT). In situations in which participants have to choose an appropriate response to a particular stimulus from a set of response alternatives, RT decreases with increasing likelihood of this stimulus-response pair (Hick, 1952; Hyman, 1953; Teichner and Krebs, 1974; Carpenter and Williams, 1995; Reddi and Carpenter, 2000; Sharma et al., 2003; Carpenter, 2004). The probability information is apparently integrated into information processing and the decision-making process, and results in faster performance.

To investigate the locus of probability effects in the chain of information processing, two main strategies have been established. Traditionally, measures of overt behavior such as RTs and response accuracy are used to analyze the effects of experimental manipulations. In the context of mental chronometry, independent experimental variables are manipulated that are thought to affect a particular subprocess of information processing. Interaction effects of this manipulation and probability information on performance suggest an effect of PP on the particular subprocess (Sternberg, 1969). Studies using the additive factor logic found an interaction between stimulus probability and stimulus contrast (e.g., Miller and Pachella, 1973). Given that the stimulus contrast has an effect on stimulus encoding, this interaction suggests that probability would also have an effect on stimulus encoding. Others found an interaction between stimulus probability and stimulus-response compatibility, suggesting that

probability has an effect on response selection, provided that stimulus-response compatibility influences response selection (e.g., Hawkin et al., 1973). However, implications of this approach are limited, because the number and nature of the possible processing loci depend on the number and nature of the manipulated variables. Furthermore, the underlying assumption proposes a strictly discrete and sequential order of the processing stages with no temporal overlap, which has been challenged by several researchers (e.g., McClelland, 1979; Miller, 1988). An alternative strategy for investigating the locus of probability effects is obtaining physiological measures as dependent variables which represent ongoing neural activity indicative of particular subprocesses of the information processing chain. Therefore, inferences about subprocesses can be drawn from physiological measures (Coles, 1989). This approach relies on valid mapping between physiological measures and particular subprocesses of the information processing system. Electroencephalogram (EEG)-derived event-related potentials (ERPs) are commonly used as physiological measures to investigate the effects of experimental manipulations.

Two ERP components are indices for different preparatory processes occurring at particular stages of information processing: the contingent negative variation (CNV) and the lateralized readiness potential (LRP). These ERP components are widely used to investigate the influence of advance information. The CNV is a sustained negative potential shift that is recorded over central electrode positions and develops after a warning stimulus (i.e., precue) which is followed by a second stimulus (i.e., imperative stimulus, if it requires a response) after a preparatory interval (foreperiod) (Walter et al., 1964). The CNV is assumed to reflect a state of expectancy or anticipation for the second stimulus (Cohen and Walter, 1966; Loveless and Sanford, 1974; Gaillard, 1977), even when no response is required (van Boxtel and Brunia, 1994a; van Boxtel and Brunia, 1994b). Furthermore, the CNV has been linked to motor and non-motor preparatory processes (van Boxtel and Brunia, 1994a; van Boxtel and Brunia, 1994b; Ikeda et al., 1996). More recent studies suggested that the CNV provides an index of how the motor program is assembled at a higher-order, abstract level of response preparation (Ulrich et al., 1998; Wild-Wall et al., 2003; Leuthold et al., 2004). More generally, the CNV is presumed to, at least partly, reflect premotor, higher-order processes. The LRP is another ERP component which is commonly used to investigate preparatory processes at a later stage (Coles et al., 1988). A lateralized increase of activity in the primary motor cortices due to one-sided limb movement causes a difference in the electrical potential between the electrodes over left and right motor cortex, yielding the LRP. The LRP serves as

an index for lateralized peripheral movement preparation and premature motor activation during the foreperiod preceding an imperative stimulus (de Jong et al., 1988; Coles, 1989).

Both the LRP and the CNV have been frequently used to investigate the influence of advance information and response preparation. The CNV was found to be sensitive to the amount of advance information (Leuthold et al., 1996; Ulrich et al., 1998; Wild-Wall et al., 2003; Leuthold et al., 2004; Jentzsch et al., 2004). The amplitude of the CNV increases with the number of response-relevant movement parameters that are known in advance (i.e., hand, direction, and force). In contrast, the LRP has been found to be sensitive to the information concerning the response hand. When a precue is presented carrying information about the hand with which a subsequent response will have to be executed, an LRP is generated during the foreperiod (Coles, 1989; Leuthold et al., 1996; Ulrich et al., 1998; Wild-Wall et al., 2003; Leuthold et al., 2004). Thus, the hand movement is prepared in advance, as soon as the response hand is determined.

However, the influence of *probability*-based advance information on these ERP components is less known. It seems reasonable that preparation processes would be elicited not only if the stimulus or the response was fully specified before, but also if it was specified with a particular probability less than 100%. With respect to lateralized motor preparation, Miller (1998) found an LRP during the foreperiod for trials with a PP of 0.75 and suggested a motor preparation for highly probable responses. However, in Miller's experiment the probability level remained constant rather than being modulated during the experiment and, thus, a comparison between different PPs during the foreperiod was not possible. A recent study provided evidence that probability information has an effect on the CNV (Smith et al., 2007). The CNV amplitude was found to be higher following a precue indicating the highly probable response side than after a non-informative precue. However, inferences about a parametric influence of probability on the CNV cannot be drawn on the basis of this design.

In sum, it is unclear whether PP influences motor or premotor preparatory processes. A modulation of the LRP or the CNV or both of the components by PP would suggest an influence of probability information on the respective subprocess.

1.3 Neural correlates of prior probability processing

In several single-unit monkey experiments using the visual-saccade task, it has been shown that the firing rate of neurons in motor control areas (superior colliculi, lateral intraparietal sulcus) correlates with the PP of a specific motor action (Basso and Wurtz, 1997; Basso and Wurtz, 1998; Dorris and Munoz, 1998; Platt and Glimcher, 1999). The PP was manipulated

either by changing the number of possible target locations or the relative probabilities of targets appearing at particular locations. Another study in non-human primates revealed that the firing rate of neurons in the dorsolateral prefrontal cortex (DLPFC) increases with increasing PP of the subsequent response indicating an involvement of higher-order areas in PP integration (Quintana and Fuster, 1999). The probability of reward has also been shown to affect the firing rate of neurons in response-specific regions (Platt and Glimcher, 1999; Fiorillo et al., 2003). In monkey studies, the PP concerning decision options is highly intermingled with reward probability and these two factors can hardly be investigated separately.

It is still unclear which brain regions in the human brain are involved in the processing of PP in decision making. It is conceivable that in the human brain, similarly to the non-human primate results, regions related to movement preparation and motor execution are modulated by PP. Response preparation in general involves several parts of a fronto-temporo-parietal network and the basal ganglia (Thoenissen et al., 2002; Toni et al., 2002; Elsinger et al., 2006). The effect of prior, non-probabilistic information was investigated in several studies. In frontal premotor regions, preparatory activity was found to be sensitive to prior information about the subsequent event and the required response (Toni et al., 2001; Thoenissen et al., 2002). Another study found that delivery of prior information enhances neural activity in the pre-supplementary motor area, the primary motor cortex and the inferior parietal lobe (Klaver et al., 2004). However, none of those studies manipulated *probability*-based advance information in a parametrical approach to be able to investigate the exact nature of the relationship between neural activity and PP with respect to response preparation. On the one hand, it is possible that PP also influences on the neural activity of response-related areas. On the other hand, humans might have developed a more abstract decision-making network that is superordinate to response-specific brain regions and allows a more flexible link between perception and action (Heekeren et al., 2004; Rorie and Newsome, 2005; Heekeren et al., 2006). Thus, PP might modulate the neural activity of higher-order areas that are not directly associated with response execution.

In sum, it is unclear which regions are involved in the processing of probability information that is provided in advance of a decision. Single-unit recordings in the monkey brain suggest an involvement of motor-related regions, whereas it is conceivable that in the human brain PP processing and integration occurs in higher-order regions.

1.4 Trial-to-trial fluctuations in prior probability processing

In everyday behavior, environmental conditions and demands as well as intrinsic brain activity vary from situation to situation and from moment to moment. Likewise, the processing of probability information, which is available in advance to making a decision, is affected by many factors dynamically changing over time. In experimental situations as well, a unique pattern of interacting processes occurs in each trial. For example, the instantaneous attentional state influences perception and processing of the probability information. This, in turn, changes expectations of the subsequent stimulus and, consequently, preparatory processes are executed to a greater or lesser extent. It should be noted, however, that processes that vary over trials and fluctuate over time are not considered in conventional EEG and fMRI studies but rather are treated as random noise and eliminated by conventional analysis techniques. In fact, there is growing evidence showing that fluctuations in neuronal activity are not merely noise but instead are functionally relevant signals (Debener et al., 2007). A recent study found that trial-to-trial variations of the P3 amplitude in a probability task are not random noise (Mars et al., 2008). Most of the variation can be better explained by a model accounting for subjective probability fluctuating from trial to trial than by a categorical model that parametrically encodes probability. Thus, trial-to-trial fluctuations in brain activity might represent dynamic modulations of intrinsic probabilistic models of anticipated events (Fox et al., 2006). Attentional fluctuations constitute another likely source for trial-to-trial variability of neural activity (Weissman et al., 2006).

An important question is how trial-to-trial fluctuations affect the integration of probability information and response preparation in decision making. It is still unclear which brain regions represent dynamically fluctuating processes of PP integration.

2 Research questions

The summary of the current research on PP processing suggests that the following major questions remain unresolved:

1. Does PP influence motor or premotor preparatory processes?
2. Which regions in the human brain are involved in the processing of PP?
3. Which brain regions show neural activity underlying trial-to-trial fluctuation in PP processing?

3 Methodological background

3.1 Number comparison task

To investigate PP processing, I employed a probability precueing paradigm (Rosenbaum and Kornblum, 1982) consisting of a number comparison task. In this task, a precue delivers probability information about the imperative stimulus and the response side. Two single-digit numbers are presented consecutively to the left and right of a fixation cross. The participants' task is to decide which of the numbers was numerically larger and to indicate their decision by pressing a button matching the side of the larger number as quickly as possible after the appearance of the second number. The first number (S1) serves as precue and delivers information about the probability of a larger or lower number following S1. Thus, depending on the value of S1, the participant can deduct with a certain probability on which side the larger number will be presented, and consequently the side on which the response will have to be executed. The interval, in which the probability information is provided is called foreperiod. The second number (S2) confirms or disconfirms this expectation.

S1 has the value 1, 3, 5, 7 or 9, and S2 has any integer value between 1 and 9, but never the same as S1. S1 serves as a task-inherent precue predicting the PP of the side of the larger number. The side of the larger number is predicted with a probability of 1.0 with S1 as 1 or 9, with a probability of 0.75 with S1 as 3 or 7, and with a probability of 0.5 with S1 as 5. These trials are referred to as condition PP 1.0, condition PP 0.75, and condition PP 0.5, respectively. In the condition PP 0.75, trials in which the indicated response side turns out to be correct are referred to as valid and trials in which the indicated response side turns out to be incorrect are referred to as invalid. The article Scheibe et al. (2009) provides a detailed description of the task.

Decreasing RTs when expectations are confirmed and increasing RTs when expectations are disconfirmed would indicate that participants use the probability information for preparation during the foreperiod. This approach has several advantages compared to experiments where the participants' expectancy is changed globally in a block-wise fashion (e.g., Miller and Pachella, 1973; Hawkin et al., 1973). By using probability precues, the PP was manipulated trial-to-trial, thus preventing long-term response strategies as they may appear in blocked designs. The probability manipulation is inherent to the number comparison task and thus time-consuming implicit association learning or explicit instructions are not necessary. Furthermore, this approach allows a parametrical gradation of PP. In addition to the

measurement of RT, I measured brain activity during the foreperiod in which PP information is processed using different approaches: electroencephalography and functional magnetic resonance imaging.

3.2 Electroencephalography (EEG)

EEG provides a direct measurement of electrical activity over the scalp. It reflects the variation of voltage measured by electrodes positioned on the skull over certain period of time (Berger, 1929). The EEG signal derives from the summated activity of post-synaptic currents of thousands of pyramidal cells in the underlying cortex that have the same spatial orientation and are activated synchronously. EEG is only sensitive to currents from sources located with a radial orientation to the skull. As the strength of electric fields decreases with increasing distance, deep sources contribute less to the EEG signal than sources near the skull. The temporal resolution is very high (approximately 1 ms), while the spatial resolution is poor. A reconstruction of a unique intracranial current source for a given EEG signal is not possible, as some currents produce potentials that cancel each other out. This is referred to as the inverse problem. However, an electric dipole representing the current sources can be estimated. A dipole analysis identifies the localization, orientation, and strength of a dipole whose potential field at the scalp surface accounts best for the recorded EEG potential at a specified instant, e.g. the peak of an ERP. ERPs refer to averaged EEG responses that are time-locked to the presentation of a stimulus.

ERPs can be used as markers for specific cognitive processes (Coles, 1989). As described above, two ERP components arise during the foreperiod, indicating different preparatory processes: the LRP and the CNV. A lateralized increase of activity in the primary motor cortices due to one-sided limb movement over the contralateral hemisphere causes a difference in the electrical potential between the electrodes over the contra- and ipsilateral motor cortices, yielding the LRP. The LRP during the foreperiod can serve as an index for lateralized peripheral movement preparation and premature motor activation (de Jong et al., 1988; Coles, 1989). The CNV is a sustained negative potential shift that is recorded at central electrode positions and develops during the foreperiod or generally after a warning stimulus followed by a second stimulus (Walter et al., 1964). The CNV provides an index of how the motor program is assembled at a higher-order, abstract level of response preparation (Ulrich et al., 1998; Wild-Wall et al., 2003; Leuthold et al., 2004). In contrast to the LRP, the CNV is presumed to at least partly reflect non-lateralized premotor processes.

As the EEG reflects several simultaneously ongoing processes, many trials have to be conducted and averaged to cause brain activity to be averaged out that is not in the focus of interest. Another approach is to analyze EEG signals at the single trial level. This allows investigation of fluctuations on a trial-to-trial basis.

3.3 Functional magnetic resonance imaging (fMRI)

fMRI is a method to study brain activity non-invasively and indirectly, with a high spatial resolution. The blood-oxygen-level-dependent (BOLD) contrast is employed to indicate local changes in neural activity (Ogawa et al., 1990; Kwong et al., 1992). Neural activity elicits metabolic changes including increased oxygen consumption in the respective brain regions. This increased oxygen consumption leads to an increase of local blood volume and a large rise in local blood flow, the so-called luxury perfusion (Fox and Raichle, 1986; Fox et al., 1988). Through this increased blood flow, vessels in activated brain regions contain an over-supply of oxygenated blood and consequently a relatively low amount of deoxygenated blood. Since deoxyhemoglobin has paramagnetic features, its presence leads to local inhomogeneities of the magnetic field. Due to inhomogeneities a faster decay of the MRI signal occurs. Therefore, active brain regions with a relatively low amount of deoxyhemoglobin show a slower decay of the MRI signal than non-activated brain regions, resulting in an increase of the BOLD signal. In short, fMRI measures the relative absence of deoxyhemoglobin in a given brain region, which is an indicator for local neural activity. Although still a matter of intense research, the BOLD contrast is assumed to mainly reflect neuronal input and local integration processes within a brain region associated with pre- and postsynaptic currents and to a lesser degree neuronal output of a brain region related to action potentials in projection neurons (Logothetis et al., 2001; Viswanathan and Freeman, 2007). The time course of the BOLD response to a brief sensory stimulation is called the hemodynamic response function (HRF). Whereas presentation of the stimulus causes a neural response rising quickly and ending a few hundred milliseconds after presentation of the stimulus, the typical HRF only begins to rise about 2 s after stimulus presentation, reaching a maximum 5–9 s after stimulus onset, and then slowly returns to baseline (for a review, see Logothetis and Wandell, 2004). Due to the sluggishness of the HRF is the temporal resolution of fMRI relatively poor. Depending on the degree of spatial smoothing applied, the spatial resolution of fMRI usually lies between 4 and 12 mm². The exact form of the HRF is different across brain regions and between subjects, tasks and stimulus duration.

3.4 Simultaneous EEG/fMRI recording

The simultaneous application of EEG and fMRI represents a very attractive opportunity for the combined measurement of electrical and hemodynamic activity at high spatial and temporal resolution. Furthermore, simultaneous EEG and fMRI recording offers the possibility to investigate trial-to-trial fluctuations and to identify their underlying brain structures (Debener et al., 2006; Herrmann and Debener, 2008). With a conventional fMRI approach trial-to-trial fluctuations are not considered. We can only look for the average BOLD signal attributed to one condition or one kind of stimulus. Ongoing, event-unrelated activity is treated as random noise and is averaged out by the subtraction logic of fMRI data processing. Also, the traditional approach of ERP analysis does not take into account that neural activity fluctuates between trials, but rather focuses on ERPs averaged over a condition or type of stimulus. Trial-to-trial fluctuations are equally treated as random noise and eliminated through averaging. However, it is possible to determine the EEG signal for each single trial, e.g. the amplitude of the CNV whose magnitude results from a variety of processes. Unfortunately, EEG does not provide the spatial resolution to map underlying processes to particular brain regions. In turn, fMRI allows for spatial mapping of brain activity. To benefit from the virtues of both methods, EEG and fMRI data can be recorded simultaneously enabling an EEG-informed fMRI analysis. With this approach, single-trial ERP amplitudes can be directly related to the BOLD signal. Thus, combining the two methods by simultaneous EEG and fMRI recording holds the benefit of a good temporal as well as spatial resolution. Furthermore, it makes it possible to identify brain regions whose neural activity are underlying the trial-to-trial fluctuations in PP processing.

However, recording an EEG signal inside a MRI system is technically challenging. Magnetic field gradients used during imaging induce an interfering signal clearly visible in the EEG data, which is hard to remove as it is in a similar frequency range to the EEG signal (gradient artifact). When EEG leads move inside the magnet (e.g. through head movements) current is induced and causes artifactual signals as well. In addition, pulsatile movement of blood and the pulsatile movement of electrodes adjacent to large blood vessels in the static magnetic field also cause a signal (ballistocardiographic artifact; Debener et al., 2006). These artifacts have to be extracted accurately from the EEG data prior to further analyses.

In sum, simultaneous EEG and fMRI recording offers the possibility to enrich the significance and the interpretation of processes in a single trial, because the same neural processes are observed from the same brain at the same instant. Single trial EEG and fMRI coupling can be used to predict the fluctuations in BOLD responses in terms of a given EEG component,

thereby correlating spatially distinct activity pattern with temporally distinct neuronal processes.

4 Conducted studies

In the present dissertation, I conducted three studies to answer the research questions described above.

The aim of the behavioral study (Study 1) was to provide evidence for the PP effect on RT in the number comparison task and to examine if the PP effect is present across a broad range of foreperiod durations.

In the EEG study (Study 2) I investigated whether PP modulates premotor or motor preparation by studying the CNV and LRP.

The aim of the simultaneous EEG/fMRI study (Study 3) was to identify the neural correlates of parametrical PP integration (Study 3a). Furthermore, the simultaneous EEG/fMRI study aimed at exploring the underlying brain structures of trial-to-trial variations of PP integration (Study 3b).

The studies refer to the following publications (see Chapter 8):

Scheibe et al. (2009). Electrophysiological evidence for the effect of PP on response preparation. *Psychophysiology* 4(46): 758-770: summarizes the studies 1 and 2.

Scheibe et al. (under review). Effects of parametrical and trial-to-trial variation in prior probability processing revealed by simultaneous EEG/fMRI: reports the results of the studies 3a and 3b.

4.1 Study 1: Modulation of response times by prior probability

The aim of the behavioral study was to provide evidence for the PP effect on RT in the number comparison task. Thus, I explored if participants make use of the probability-based advanced information. Furthermore, I examined if the PP effect is present across a broad range of foreperiod durations. The duration of the foreperiod randomly varied between 70, 210, 500, 1000 or 2000 ms, respectively.

The RT results demonstrated that the PP effect could be provoked using the number comparison task. In line with previous findings (Hick, 1952; Hyman, 1953; Teichner and Krebs, 1974; Posner et al., 1978; Carpenter and Williams, 1995; Reddi and Carpenter, 2000; Sharma et al., 2003; Carpenter, 2004), participants responded faster in trials with a valid precue than when the response side was not precued. They showed the slowest responses in trials with an invalid precue. It can be concluded that participants used the probability information provided by the precue for the preparation of their response. A number of alternative explanations of the PP effect can be ruled out. First, when participants have to determine the numerically larger of two simultaneously presented numbers, RTs decrease with the numerical distance between these numbers (distance effect; Moyer and Landauer, 1967). By performing an analysis comparing trials with the same numerical distance, it can be ruled out that the observed effect of PP is due to a distance effect. Second, the Simon effect assumes that responses are faster when stimulus and response occur at the same location (Simon, 1969). Also, RTs increase with the magnitude of the numbers (magnitude effect; Moyer and Landauer, 1967). In my study, confounding influence of both phenomena were ruled out, because the stimulus response side compatibility and the number magnitude were carefully counterbalanced over conditions and did not act differently on the conditions. Thus, the RT effect can be completely attributed to the manipulation of the PP and its resulting validity.

The PP effect was found with all foreperiod durations. The PP effect in terms of the greatest difference between valid and invalid trials was most pronounced in trials with a foreperiod of 500 ms. The PP effect was smallest in trials with a foreperiod of 70 ms, increased up to a foreperiod of 500 ms, and decreased with further increasing foreperiod duration. This indicates that with increasing time to prepare (i.e., with a foreperiod of more than 500 ms), the preparation was increasingly optimized, so that time loss due to invalid precues was minimized. Overall, RTs were shorter in trials with 210 ms foreperiod compared to trials with 70 ms foreperiod. But even during the 70 ms foreperiod preparatory processes led to faster responses to imperative stimuli that were validly precued and slower responses to invalidly precued stimuli.

Since a robust RT effect of PP was present within all foreperiod durations, I concluded that participants used the probability-based advance information to prepare their responses and apparently integrated PP information into the process of information processing.

4.2 Study 2: Effect of prior probability on response preparation

The results of the behavioral study confirm that PP is integrated into the decision-making process and modulates performance. Behavioral studies attempting to locate this PP effect found that probability-based advance information affects several stages of information processing, including stimulus encoding (Miller and Pachella, 1973; Sharma et al., 2003), response selection (Hawkin et al., 1973), and preparatory processes (Rosenbaum and Kornblum, 1982; Requin et al., 1991). It is still unclear, however, which preparatory processes are induced by probability-based advance information modulating performance. In the EEG experiment, I investigated the influence of PP on specific motor and premotor preparatory subprocesses as indicated by the CNV and LRP. While the foreperiod LRP reflects preparatory processes on a motor stage, the CNV indicates preparation processes occurring on a stage prior to lateralized motor preparation. Furthermore, I identified the underlying neural sources during the preparatory period by dipole source localization. To control for premature muscular activation of the response finger, EMG was recorded additionally.

As in Study 1, I found a robust behavioral effect of PP. During the foreperiod a CNV was elicited with the amplitude parametrically increasing with increasing PP. This gradual CNV modulation indicates that probability-based advance information had a parametrical influence on premotor preparatory processes. In contrast, an LRP during the foreperiod only emerged if the precue provided reliable information about the following stimulus and the response hand. In the other PP conditions, no LRP evolved during the foreperiod, indicating that motor preparation is not influenced by PP. The conclusion of a premotor locus of probability integration is further confirmed by the earlier onset of the LRP in those trials with precues containing highly probable, valid information, as compared to trials with non-informative precues. The interval between precue and LRP onset is assumed to reflect premotor processing time, whereas the interval between LRP onset and response execution indicates motor processing time (Leuthold et al., 1996; Masaki et al., 2004). Thus, the onset difference of the stimulus-locked LRP between the two conditions with and without probability-based preparation indicates an influence of PP on processes occurring prior to motor activation. Moreover, there was no onset difference of the response-locked LRP, confirming that PP does not influence motor processes. This strongly supports the hypothesis of a premotor locus of PP integration. The EMG data showed that no precue-related muscular activity of the response hand occurred during the foreperiod, ruling out premature movements of the thumb muscles. The source localization results revealed a dipole located in the anterior cingulate

cortex (ACC) during the preparation period, whereas no motor sources were found. The dipole activity increased parametrically with the increasing amount of advance information. This confirms the notion of a parametrical influence of probability-based advance information on premotor preparatory processes at a cognitive, higher-order level as already shown by the electrophysiological results, whereas I did not find evidence for preparation at a peripheral motor level.

4.3 Study 3a: Neural correlates of prior probability processing

Brain regions which are parametrically influenced by PP have not yet been systematically investigated using brain imaging methods relying on the BOLD signal like fMRI. I conducted a simultaneous EEG/fMRI experiment and applied the number comparison task to investigate brain structures which underlie the processing of probability based advance information. I analyzed the fMRI data separately to identify brain regions which are parametrically modulated by PP information. For this analysis, first, the high PP condition was contrasted with the medium PP condition ($PP\ 1.0 > 0.75$); second, the medium PP condition was contrasted with the low PP condition ($PP\ 0.75 > 0.5$). By calculating a conjunction analysis, I searched for regions that were activated in both contrasts. The conjunction analysis revealed, that the BOLD signal in a region in the posterior part of the medial frontal cortex (pmFC) increased parametrically with increasing PP. The activated region is located in the border zone between Brodmann areas 8, 6 and 32. It corresponds to the region which is commonly referred to as rostral cingulate zone (RCZ; Picard and Strick, 2001; Ridderinkhof et al., 2004). This is in line with the ACC result of the dipole analysis in the previous EEG study (Study 2 of this dissertation), as the ACC is part of the RCZ. The functional role of the pmFC is frequently described as performance monitoring and cognitive control signaling the need of behavioral adjustments (Ridderinkhof et al., 2004; Ullsperger and von Cramon, 2004a; Heekeren et al., 2008). Probability information enhanced activity in this region in a parametrical fashion signaling the need for response preparation and initiation of behavioral adjustment depending on the PP. If the probability is high for one response side (PP 1.0), then preparatory processes have to be initiated to perform with maximum efficiency. If the probability is low (PP 0.5), there is no need for behavioral adjustment, because action can only be initiated when more information is available.

4.4 Study 3b: Trial-to-trial fluctuations in prior probability processing

The EEG and fMRI findings of Study 2 and Study 3a indicate the parametrical integration of PP into the decision-making process at a premotor stage and the involvement of the pMFC. However, these findings rely on the mean CNV amplitude while the trial-to-trial variability in the CNV amplitude was not included in the analysis. Considering the parametrical influence of PP on the mean CNV amplitude, the single-trial amplitude of the CNV might carry additional information about the processing of the PP and interactions with ongoing brain activity. Recent studies suggest that ongoing fluctuations in several ERPs are not random noise, but rather reflect specific intrinsic and extrinsic processes (Debener et al., 2005; Eichele et al., 2005; Debener et al., 2006; Fox et al., 2006; Weissman et al., 2006; Mars et al., 2008). Trial-to-trial variability of brain activity is not taken into account by conventional ERP or fMRI techniques but rather treated as random noise and eliminated. EEG and fMRI have to be combined to identify brain regions whose activation is underlying a trial-to-trial fluctuation in PP processing. Therefore, I simultaneously recorded EEG and fMRI data and conducted an EEG-informed fMRI analysis. This approach allows for relating single-trial CNV amplitudes directly to the BOLD signal.

By calculating a correlation analysis with CNV amplitude and RT, I demonstrated that the single-trial CNV amplitude correlated with RT, with high CNV amplitudes followed by short RT. This confirms that the CNV signifies preparatory processes resulting in an adjustment of behavior. I found a network of mainly frontal, parietal, and striatal regions representing the trial-to-trial fluctuations in CNV amplitude during the preparation period in which PP information is processed. Parts of this network, namely, the left DLPFC, the right inferior frontal gyrus (IFG), and the right inferior parietal lobule (IPL), showed activations, that exclusively represented the contributions of PP to CNV amplitude fluctuations. Activations in frontal, parietal and striatal regions which fluctuate together with the CNV amplitude probably represent general response preparation processes that are independent of PP information (Toni et al., 2001; Thoenissen et al., 2002; Klaver et al., 2004; Monchi et al., 2006). In contrast, the DLPFC, IFG, and IPL were involved in the processing and integration of PP information on a trial-to-trial basis. Fluctuating activity of lateral prefrontal and parietal regions might be attributed to the representation of trial-specific attentional effort, depending on the probability information (MacDonald, III et al., 2000; Weissman et al., 2003), and the integration of PP information to plan the upcoming response (Gold and Shadlen, 2001; Sugrue et al., 2005).

5 General discussion

The integration of PP into the process of decision making is essential for efficient everyday behavior. The probability information that is available in advance permits the preparation of actions. In a dynamically changing environment, the extraction and processing of probability information and subsequent preparation provides a mechanism for a dynamical adjustment of behavior. In the present dissertation, I investigated preparatory processes that are influenced by PP and the neural correlates of PP integration. Furthermore, in view of the varying situations that influence PP availability in everyday life, I shed light on the neural basis of those fluctuations in PP processing.

For the investigation of PP processing, I used a number comparison task. PP information about the response side was delivered by a precue during a preparatory interval. Using this approach, PP was manipulated differently for each trial instead of being manipulated blockwise, permitting an analysis of trial-to-trial fluctuations. The probability precue elicited the preparation of the response, as shown by the parametrical modulation of RT depending on PP (Study 1). As frequently described in the literature, RT decreased with increasing PP (Hick, 1952; Hyman, 1953; Teichner and Krebs, 1974; Carpenter and Williams, 1995; Reddi and Carpenter, 2000; Sharma et al., 2003; Carpenter, 2004). Thus, the number comparison task proved to be suitable to elicit the PP effect on RT.

The EEG study (Study 2) revealed a parametrical effect of PP on the CNV during the foreperiod, which is an indicator for premotor response preparation (Ulrich et al., 1998; Wild-Wall et al., 2003; Leuthold et al., 2004). In contrast, the LRP during the foreperiod was only enhanced if the response side was precued with certainty, ruling out motor preparation due to graded PP. EMG data showed that no precue-related muscular activity of the response hand was occurring during the foreperiod. Response preparation at a premotor stage is further confirmed by the earlier onset of the LRP in those trials with precues containing highly probable information as compared to trials with non-informative precues, because the interval between precue and LRP onset is assumed to reflect premotor processing time (Leuthold et al., 1996; Masaki et al., 2004). Furthermore, a dipole was located in the ACC with its activity parametrically modulated by PP. From these EEG results can be concluded, that PP influences premotor response preparation in a parametrical fashion.

With fMRI I investigated which brain regions are parametrically modulated by PP (Study 3a). I found that the BOLD signal in the pmFC increased with increasing PP. In the EEG-informed fMRI analysis (Study 3b), the CNV amplitude was correlated with the BOLD signal

in a network consisting of frontal, parietal and striatal regions reflecting general preparatory processes independently of PP. Parts of the network, namely, the DLPFC, the right IFG, and the right IPL, showed activations, which exclusively represented the contributions of PP to the CNV amplitude fluctuations.

Together, these results suggest that the processing of probability information in a number comparison task occurs at a premotor stage and includes different processing mechanisms, namely, parametrical and trial-to-trial modulation. The parametrical modulation of the CNV by PP as well as the prolonged interval between precue and LRP onset (when probability information was high in contrast to non-informative) suggest that probability information provokes preparation processes at a premotor processing stage. The location of the dipole in the ACC further emphasizes the involvement of higher-order premotor structures in the processing of PP. In the pMFC, the BOLD response was parametrically modulated by PP, which is in line with the graded dipole activity in the ACC depending on PP. The pMFC is involved in evaluative processes and performance monitoring signaling the need for behavioral adjustment (Ridderinkhof et al., 2004; Ullsperger and von Cramon, 2004a; Heekeren et al., 2008). This matches the parametrical activation in this region, because the probability precue task requires monitoring concerning behavioral adjustment during the foreperiod. Depending on the probability information delivered by the precue preparation processes were initiated. The knowledge of PP enables the adjustment of performance to optimize the achievement of action goals. If the probability is high for one response side (PP 1.0), then preparatory processes have to be initiated to perform with maximum efficiency. If the probability is low (PP 0.5), there is no need for behavioral adjustment, because any action can only be initiated if more information will be available. In accordance to these results, it has been shown that when the need for behavioral adjustment is high, indicated by a high informative content of negative feedback, the RCZ shows a stronger response than when negative feedback is less informative (Jocham et al., 2009). This supports the hypothesis that activity in the pMFC reflects the degree to which the PP information of the precue is used to guide the subsequent decision. In a similar vein, Rushworth and colleagues (2004; 2007; 2008) postulate that the MFC has a central role in action selection and response preparation. They state that this region does not select individual actions but instead selects superordinate sets of action selection rules and is involved in anticipatory preparation. Activity of the MFC is enhanced in tasks that include conflict (Botvinick et al., 2001; Carter and van Veen, 2007), decision uncertainty (Volz et al., 2005), and error processing (Holroyd and Coles, 2002; Ullsperger and von Cramon, 2004b). Similarly to the number comparison task, these

conditions demand enhancement of cognitive control and performance monitoring. The pmFC belongs to the RCZ (Picard and Strick, 2001; Ridderinkhof et al., 2004) which is the human equivalent of the cingulate motor area (CMA) in the monkey brain (Ridderinkhof et al., 2004). The anatomical location of the RCZ is suitable for integration of actions and outcomes. This region is closely interconnected with the motor system. The monkey CMA projects to and receives afferents from primary and secondary motor cortices (Hatanaka et al., 2003). The CMA also shows projections to the striatum (Takada et al., 2001) and to motor neurons of the spinal cord (He et al., 1995).

Thus, the parametrical modulation of pmFC activity by PP confirms the assumption of a premotor locus of PP integration as already suggested by the EEG findings. PP does not modulate neural activity in response-specific brain regions as indicated by monkey studies (Basso and Wurtz, 1997; Basso and Wurtz, 1998; Dorris and Munoz, 1998; Platt and Glimcher, 1999). The pmFC evaluates the probability information and, depending on the PP, signals other brain regions that a behavioral change is needed to regulate task performance in an adaptive fashion.

In addition to the parametrical modulation of neural activity by PP, I investigated trial-to-trial fluctuations in PP processing. The relationship of single-trial CNV amplitude and RT demonstrates that the CNV amplitude reflects response preparation in the precuing task. First, I identified regions in which activity covaried with the CNV amplitude. Second, I searched for regions reflecting the proportion of CNV variance solely attributable to PP. Neural activity in a network of frontal and parietal regions and the putamen (part of the striatum in the basal ganglia) fluctuated from trial to trial depending on the single trial CNV amplitude. Response preparation in general involves several parts of a fronto-parietal network and the basal ganglia (Thoenissen et al., 2002; Toni et al., 2002; Elsinger et al., 2006). In frontal premotor regions and the inferior parietal lobe, preparatory activity is sensitive to prior non-probabilistic information about the subsequent event and the required response (Toni et al., 2001; Thoenissen et al., 2002; Klaver et al., 2004). The putamen also plays a role in unspecific preparation mechanisms and planning behavior (Monchi et al., 2006). Thus, the activations of frontal, parietal, and striatal regions that fluctuate together with the CNV amplitude represent general response preparation processes that are independent of the PP information. In contrast, activations in the DLPFC, IFG, and IPL were related exclusively to PP induced CNV fluctuations indicating that those regions are involved in the integration of PP information for response preparation on a trial-to-trial basis. A very similar configuration of activated areas in the dorsal frontal and parietal cortex is known to be involved in cue processing in anticipation

of a stimulus, irrespective of the modality of the cue (Corbetta and Shulman, 2002; Peelen et al., 2004). Lateral prefrontal regions regulate the current focus of attention through their interaction with parietal areas. The DLPFC contributes selectively to the establishment of an attentional set for task-relevant information during cue processing (Weissman et al., 2003). Other authors state that the left DLPFC is engaged during the preparation period by regulating and actively maintaining the attentional demands of the task (MacDonald, III et al., 2000). Activity fluctuation in these areas may therefore represent trial-specific attentional effort, depending on the probability information. In line with the finding that DLPFC activity correlated directly with fluctuating PP processing, single-unit recordings in monkeys revealed that the firing rate of neurons in the DLPFC increases with increasing PP of the subsequent response (Quintana and Fuster, 1999). While the prefrontal cortex plays an important role in attentional executive control, parietal regions are recruited when stimulus-response associations can be prepared in advance (Corbetta and Shulman, 2002). Primate studies with two-alternative forced-choice tasks have shown that neurons in the lateral intraparietal area integrate information from multiple sources and encode the likelihood ratio concerning the subsequent selection between the two decision alternatives (Gold and Shadlen, 2001; Sugrue et al., 2005). Thus, fluctuations of activation in parietal regions may be attributed to the integration of information from different sources including PP information when planning the upcoming response.

Taken together, the results of the present dissertation indicate that several subprocesses are involved in the integration of PP information during the decision-making process and the initiation of action preparation. After sensory features of probability information are processed in the primary visual cortex, the PP is integrated with information from other sources in parietal regions. This is a dynamical process and presumably depends on factors that are present in this moment of time, e.g. subjective expectations due to prior trials. Trial-specific attentional fluctuations associated with activity in prefrontal regions also contribute to the dynamical processing of PP. Information is then transferred to premotor regions, that are connected to response-execution areas. The pMFC has a control function, that evaluates and monitors the need for behavioral adjustment independently of attentional fluctuations and initiates response preparation. As soon as enough information is available, the response is executed. It can be concluded from the present data that two distinct mechanisms are involved in the integration of PP. A superordinate cognitive control regulates behavioral adjustment and response preparation independently of the current state of the system, while instantaneous

factors, like the actual attentional state, affect PP processing and response preparation dynamically.

To provide further evidence for these considerations, the interplay of the parametrically modulated pMFC and dynamically modulated prefrontal and parietal regions has to be elucidated. Furthermore, one might get more insight into the topic of PP processing and response preparation by investigating processes and underlying brain activity when PP information turns out to be invalid and demands a reorganization of response preparation.

6 Conclusion

The results of this dissertation suggest that:

- PP parametrically modulates preparatory processes at a central premotor level
- PP parametrically modulates neural activity in the pMFC and affects the evaluation and monitoring regarding behavioral adjustment
- DLPFC, IFG, and IPL are involved in the trial-to-trial fluctuations in PP processing dynamically regulating attentional control and the integration of information from multiple sources

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, dass ich

- die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe,
- mich nicht bereits zu einem anderen Zeitpunkt oder an einer anderen Fakultät um einen Doktorgrad beworben habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze,
- und die zugrunde liegende Promotionsordnung vom 3.8.2006 kenne.

Ort, Datum

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