

**The neural correlates of human vibrotactile working memory:
Converging evidence from functional magnetic resonance
imaging, electroencephalographic and behavioral studies**

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Zusammenfassung

Das Ziel der vorliegenden Arbeit war es, die Mechanismen und die neuronale Implementierung des taktilen Arbeitsgedächtnisses (AG) zu erleuchten. Dazu wurde eine vibrotaktile Diskriminationsaufgabe mit den Methoden der funktionellen Magnetresonanztomografie (fMRT), Elektroenzephalografie (EEG), subliminalen elektrischen Stimulation und Psychophysik untersucht. Eine fMRT-Studie (Studie I) zeigte, dass ein ausgedehntes neuronales Netzwerk mit den einzelnen Aufgabenphasen, Enkodierung, Aufrechterhaltung, und Entscheidung, verbunden ist. Die Analyse oszillatorischer EEG-Aktivität (Studie II) und die selektive Inhibition des primären somatosensorischen Kortex (S1) durch subliminale Stimulation (Studie III) legen nahe, dass S1 nicht an der Aufrechterhaltung der vibrotaktile Gedächtnisrepräsentation beteiligt ist. Das Ausmaß der S1-Aktivierung während der frühen Haltephase hängt vielmehr von der Effizienz, mit welcher Versuchspersonen den vibrotaktile Reiz enkodieren, ab. Außerdem weisen Studie II and III darauf hin, dass bereits der physiologische Zustand von S1 in der Phase vor Beginn eines Versuchsdurchgangs eine einflussreiche Rolle spielt. Während Studie II zeigte, dass S1-Aktivität in dieser Phase, vermutlich durch attentionale top-down Modulation, unter AG-Anforderungen erhöht ist, ergab Studie III, dass eine optimierte bottom-up Verarbeitung in S1 zu einer verbesserten Aufgabenleistung führt. Verhaltensexperimente zeigten, dass Repräsentationen im Langzeitgedächtnis über die durchschnittliche Frequenz der präsentierten Vibrationsreize erheblich die Verhaltensleistung beeinflussen und den Zeitrichtungseffekt verursachen (Studie IV). Die Analyse der fMRT-Daten (Studie V) offenbarte außerdem, dass ein Netzwerk somatosensorischer Areale Informationen über die aktuelle Vibrationsfrequenz und die durchschnittliche Vibrationsfrequenz während der Enkodier- und Haltephase integriert.

Schlagwörter:

Somatosensorik

vibrotaktile

Arbeitsgedächtnis

fMRT

EEG

Abstract

The present dissertation aimed to shed more light on the psychological mechanisms and the neural basis of tactile working memory (WM). For this purpose, a vibrotactile delayed discrimination task was studied using the methods of functional magnetic resonance imaging (fMRI), electroencephalography (EEG), concurrent subliminal electrical stimulation and psychophysics. The fMRI study (Study I) showed that a broad network of brain regions - much broader than known from previous studies in non-human primates - supports the performance of a vibrotactile delayed discrimination task in the different task periods: encoding, maintenance, decision making. The analysis of oscillatory activity over the somatosensory cortex in the EEG study (Study II) and the experiment using subliminal electrical stimulation to locally inhibit the primary somatosensory cortex (S1) (Study III) suggest that S1 does not contribute to the active maintenance of the vibrotactile memory trace. The level of activity in S1 during the early delay period depends on the efficiency with which subjects encode the vibrotactile stimulus. Study II and III also showed that the activation level of S1 in the pre-trial period plays an important role. Study III suggests that, in this task period, S1 activity is up-regulated under WM demands probably reflecting the operation of top-down attentional control. Study III indicates that increasing local inhibition of S1 in the pre-trial period improves performance by facilitating bottom-up processing. Importantly, long-term memory representations of the average frequency of the stimulus set strongly influence performance giving rise to the time-order effect (Study IV). Additionally, the fMRI data (Study V) showed that a somatosensory network integrates information about the current vibrotactile stimulus and the representation of the average vibration frequency during stimulus encoding and maintenance.

Keywords:

somatosensory

vibrotactile

working memory

fMRI

EEG

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe, dass ich mich nicht bereits anderwärts um einen Doktorgrad beworben habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze, und dass ich die zugrunde liegende Promotionsordnung vom 3.8.2006 kenne.

Ort, Datum

Claudia Preuschhof

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List of original publications

This dissertation is based on the following original research articles:

Study I

Preuschhof, C., Heekeren, H. R., Taskin, B., Schubert, T., Villringer, A. (2006). Neural correlates of vibrotactile working memory in the human brain. *Journal of Neuroscience*, 26(51), 13231-9.

Study II

Preuschhof, C., Schubert, R., Schubert, T., Heekeren, H. R. (Under Review: Cerebral Cortex). Rolandic and posterior-parietal alpha rhythms are differentially modulated during vibrotactile working memory.

Study III

Preuschhof, C., Sneve, M. H., Taskin, B., Schubert, T., Heekeren, H. R. (In preparation). Pre-trial subliminal electrical stimulation improves performance in vibrotactile delayed discrimination.

Study IV

Preuschhof, C., Schubert, T., Heekeren. (In preparation). Time-order effect in vibrotactile delayed discrimination: The influence of trial types and response alternatives

Study V

Preuschhof, C., Schubert, T., Heekeren, H. R., Villringer, A. (Under review: *Journal of Cognitive Neuroscience*). Neural correlates of time order effects: Implicit sensory stimulus representations influence vibrotactile delayed discrimination.

List of Abbreviations

ACC	Anterior cingulate cortex
BA	Brodman area
BOLD	Blood-oxygen-level-dependent
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
HRF	Hemodynamic response function
LTM	Long-term memory
M1	Primary motor cortex
PFC	Prefrontal cortex
PMC	Premotor cortex
PPC	Posterior parietal cortex
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex
TMS	Transcranial magnetic stimulation
TOE	Time-order effect
VPL	Ventroposterior lateral nucleus
VPM	Ventroposterior medial nucleus
WM	Working memory

1. Theoretical background

1.1. Introduction

An essential prerequisite for human behavior is the ability to actively maintain representations of information that is no longer available, flexibly update and reorganize this information and use it for guiding actions or thoughts. All these characteristics are subsumed under the psychological construct of working memory (WM) which is assumed to have a limited capacity and operate in a time frame up to several seconds (Baddeley, 03; Fuster, 00; Levy und Goldman-Rakic, 00). WM has been mainly investigated in the visual and auditory modality. However, WM for tactile features is also important for everyday behaviors such as manual object recognition: Imagine you have to find your apartment key in a fully packed handbag without looking. First, it is necessary to activate a mental representation of the tactile features of your key. Then you have to search with your hand through different objects including other very similar keys while maintaining the representation. Finally, you have to recognize the particular key you need. Because tasks like this require complex representations of different stimulus features even within the somatosensory modality and involve a multitude of different processes, a first step in the investigation of tactile WM is to focus on a sub-modality of the somatosensory system and to use a relatively simple sensory WM task. The aim of the present dissertation was to investigate the neural organization of WM for vibratory flutter stimuli in the healthy human brain. For this purpose, a vibrotactile delayed discrimination task was studied using methods of functional magnetic resonance imaging (fMRI), electroencephalography (EEG), concurrent subliminal electrical stimulation and psychophysics.

1.2. The concept of working memory

1.2.1. *Psychological concepts of working memory*

There are many psychological theories about WM and a complete review of these different theories is beyond the scope of the present dissertation (see Miyake and Shah for an overview (99)). Here, only two models are briefly summarized that indicate the range of psychological WM theories and are pertinent for the present dissertation. One influential model that emphasizes the dissociation of maintenance of information and executive processes in WM was developed by Baddeley and Hitch (Baddeley und Hitch, 74; Baddeley, 03; Repovs und Baddeley, 06). This model proposes the existence of multiple specialized compartments which interactively enable WM. A central executive is assumed to control the operation of modality-specific storage systems, the phonological loop and the visuo-spatial sketchpad, which actively maintain memory representations for a limited period of time. Although this model only deals with the storage and processing of phonological and visuo-spatial information, the authors assume that there must also be modality-specific storage systems for the other modalities such as tactile information. Another model was proposed by Cowan (93; 88) who regards WM as the subset of activated representations from long-term memory (LTM). He suggests that a subset of these activated memory representations are in the focus of attention and conscious awareness. The direction of attention is controlled voluntarily by a central executive or automatically by an attentional orientation system initiated by salient or significant stimuli. Because only 3 to 5 unrelated items can be in the focus of attention simultaneously and the activation of representations fades over time, WM capacity is limited.

Besides all theoretical differences, these WM models illustrate important aspects of WM. First, WM involves the active maintenance of information. This can either be information

perceived from the external world or re-activated internal representations. Importantly, the temporarily maintained information is actively protected against decay and from interfering or distracting neural activity. Second, WM is subject to capacity limits regarding the amount of information and the time for which information can be maintained. Third, WM does not only involve the maintenance of these representations but engages executive processes and attention, which serve to re-organize or manipulate the maintained information and determine which information enters WM. Fourth, WM provides a necessary basis for goal-directed behavior and complex cognition. In addition, whereas the model of Baddeley and Hitch stresses the importance of modality-specific storage systems, Cowan's model emphasizes the importance of LTM representations for WM.

1.2.2. Neural basis of WM

For phonological and visuo-spatial information, the dissociation between storage and executive components of WM was confirmed in neuroimaging studies and in studies with brain-damaged patients who suffered from specific neuropsychological symptoms (for review see (Baddeley, 03; Curtis und D'Esposito, 03; Smith und Jonides, 98)). In general, these studies suggest that the storage component of WM is located in those posterior modality-specific sensory or association areas that are also involved in the on-line processing of a specific type of sensory information. Executive processes on the other hand appear to be associated with the activity of brain areas distinct from sensory areas, most importantly the lateral prefrontal cortex (PFC).

Single-unit recording studies to explore the neural correlates of WM in non-human primates used delayed sensory or response tasks, which focus on WM maintenance and place relatively little demand on executive processes. In these studies, stimulus-selective persistent activity during the delay period of WM tasks is considered to be the neurophysiological correlate of stimulus representations maintained in WM (Hebb, 49; Goldman-Rakic, 95). Similar to the findings in human subjects, stimulus-selective delay period activity has been observed in modality-specific brain regions of the posterior association cortex (Chafee und Goldman-Rakic, 98; Fuster und Jervey, 81). In monkeys, however, stimulus-selective activity has also been found in the lateral PFC in delayed-response (Funahashi et al., 93) and delayed matching or discrimination tasks (Sawaguchi und Yamane, 99; Miller et al., 96) suggesting that this region is actively involved in WM maintenance. Importantly, delay-activity was reduced and performance was impaired by cooling-induced transient lesions of the lateral PFC (Chafee und Goldman-Rakic, 00; Fuster et al., 85).

Both, human neuroimaging and non-human single-unit studies, have shown that the PFC seems to be the only brain area with the ability to actively maintain memory representations that survive the appearance of intervening or distracting stimuli (Miller et al., 96; Sakai et al., 02). In addition, the studies in non-human primates suggested a material-specific organization of the lateral PFC with its dorsolateral part associated with the maintenance of visuo-spatial material and its ventrolateral part linked to the maintenance of non-spatial object information (Levy und Goldman-Rakic, 00). These findings agree with anatomical findings showing that modality-specific posterior brain regions are interconnected with distinct sub-regions of the PFC (Petrides und Pandya, 99; Petrides und Pandya, 02; Barbas, 92). They also suggest that modality-specific networks including posterior association areas and lateral PFC conjointly enable the active maintenance of information in WM. Contrary to these findings, results of neuroimaging studies found no evidence of a sub-specialization of the lateral PFC according to the material processed but instead lead to the proposal of a process-specific organization (Frith et al., 91; D'Esposito et al., 00; Petrides, 05).

Although the lateral PFC seems to be crucial for WM, its exact role in the maintenance of information is still under debate (Curtis und D'Esposito, 03; Postle, 05). Humans with lesions of the lateral PFC are relatively unimpaired in delayed sensory or motor tasks (D'Esposito und Postle, 99). Furthermore, it remains unclear what the observed stimulus-selective persistent activity in the lateral PFC reflects. A recent study demonstrated that the majority of task-specific neurons in the lateral PFC are tuned to selective attention to a specific location as opposed to memory for the location (Lebedev et al., 04). Some authors therefore disagree with the view that stimulus representations are maintained in the lateral PFC and assume that persistent activity in this area reflects processes assisting in maintenance such as top-down control (Miller, 00), selective attention (Lebedev et al., 04) or response selection (Rowe und Passingham, 01).

Rather than supporting pure maintenance, it has been suggested that the lateral PFC modulates processing in posterior brain regions and selectively activates task-relevant representations (Duncan und Owen, 00; Kimberg und Farah, 93; Miller, 00; Curtis und D'Esposito, 03; Fuster, 00). Maintenance of stimulus representations is instead supported by a parieto-premotor cortical network (Manoach et al., 03; Rowe et al., 00; Sakai et al., 02) and modality-specific sensory association areas (Pasternak und Greenlee, 05). These authors, therefore, emphasize the function of the lateral PFC in executive control. However, the existence of stimulus-specific delay activity in lateral PFC, which has been observed in various experiments using different stimulus modalities, suggests that the lateral PFC is also involved in WM maintenance, at least in non-human primates. Species differences in brain function might be one reason for the inconsistent findings regarding the role of the lateral PFC in WM. The PFC is the brain region that underwent the proportionally largest increase in the evolution from non-human primates to humans implicating a significant role in complex human cognition (Fuster, 02).

On the other hand, psychological accounts, human neuroimaging studies and single-unit recordings in non-human primates approach the phenomenon of WM from different perspectives. Psychological theories try to provide categorical descriptions of cognitive processes related to observable behavior. Previous approaches for understanding the neural basis of WM might be biased by the attempt to localize theoretically defined psychological constructs in specific brain regions. It is especially tempting to do this when using the method of fMRI. However, processes are implemented in the brain by neural networks and not located in single regions. Furthermore, neuroimaging studies rely on the method of cognitive subtraction and might therefore be more sensitive to specific cognitive processes (Friston et al., 96). In addition, single-unit and neuroimaging studies have a different spatial resolution: whereas neuroimaging studies provide a granular indicator of neuronal activity, single-unit studies can detect stimulus-selective activity in single neurons or populations of neurons. As pointed out by Repovs and Baddeley (06), the different levels of description cannot (yet) be mapped in a 1-to-1 manner but they provide insight into the phenomenon of WM from different perspectives. Maybe new approaches that regard WM as an emergent property of the functional interaction between networks of brain areas provide a promising perspective (D'Esposito, 07; Postle, 06).

The functional interaction between brain regions can only be investigated by exploiting the advantages of different methods including complementary studies in humans and monkeys. In addition, to get a more complete picture of cognitive functions and their neural basis, they have to be studied from different perspectives including psychological and neuroscientific approaches. Therefore, in the present dissertation the same vibrotactile WM that was used in previous studies in non-human primates was investigated with a multi-method approach using fMRI, EEG and behavioral studies in humans.

The above mentioned studies investigated WM for visuo-spatial, visuo-object, phonological or auditory information. However, only a few studies addressed WM for

tactile features which will be further investigated in the present dissertation. According to the emergent property view of cognitive processes, WM for a specific type of sensory information must be implemented in the brain according to the neuroanatomy, physiology, and connections of the modality-specific regions it operates on. As the underlying research of this dissertation refers to somatosensory WM, the neuroanatomy of the somatosensory system will be briefly introduced in the following section before findings regarding vibrotactile WM are discussed.

1.3. The neuroanatomy of the somatosensory system

The somatosensory system conveys information about the outside world that is transmitted via the skin and information about the body itself (for review see (Kaas, 93; Kaas, 04)). It comprises four distinct modalities. *Proprioception* is caused by mechanical displacement of receptors in skin, muscles and joints. *Pain* is produced by noxious stimuli in free nerve endings. *Thermal sensation* is generated by cold and warm stimuli. *Touch* is elicited by the mechanoreceptors of the skin which can be divided into two functional groups. This dissertation only deals with the modality of touch. In touch, rapidly adapting mechanoreceptors, i.e., Meissner and Pacini corpuscles, respond to the onset and offset of a stimulus. They are located in the hairless skin and because of their small receptive fields (2-4 mm) can resolve fine spatial differences. Slowly adapting receptors, i.e., Merkel and Ruffini corpuscles, respond to persistent stimuli. They are located in the subcutaneous tissue and have much larger receptive fields (5 cm). Depending on the specific stimulus features, a tactile sensation is usually a result of a combined activation of different receptor types. In the present dissertation vibrotactile stimuli in the range of 10 to 43 Hz were used. These stimuli have been shown to primarily activate Meissner receptors and elicit a sensation called flutter (Mountcastle et al., 67).

The sensory information from the mechanoreceptors is transmitted to the brain via the dorsal column–medial lemniscal pathway (see Figure 1a): over the dorsal column nuclei the information reaches the spinal cord, and is then transmitted via the dorsal column pathway to the medulla oblongata where the fibers cross to the other side. The information is then transferred via the medial lemniscal pathway to the ventroposterior lateral (VPL) and the ventroposterior medial (VPM) nuclei of the thalamus. From the thalamus, the signal is directly projected to the primary somatosensory cortex (S1) and to a lesser extent directly to the secondary somatosensory cortex (S2).

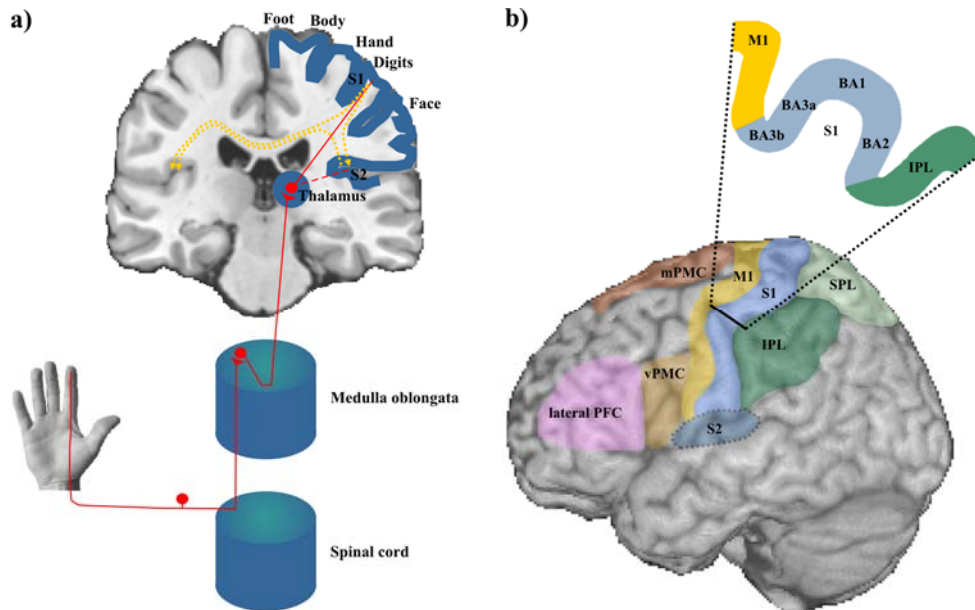


Figure 1. The somatosensory system. a) The somatosensory pathway from the mechanoreceptors to the primary (S1) and secondary (S2) somatosensory cortex. b) S1 comprises the postcentral gyrus in the anterior parietal lobe and contains the Brodman areas (BA) 3b, 3a, 1, 2 (see enlarged cutout). S1 projects to the ipsi- and contralateral S2, the primary motor cortex (M1), the inferior (IPL) and superior posterior parietal lobe (SPL). S2 is located in the upper bank of the Sylvian fissure and projects to contralateral S2, IPL, SPL, the ventral (vPMC) and medial premotor cortex (mPMC) and lateral prefrontal cortex (PFC).

S1 is located in the postcentral gyrus of the anterior parietal lobe and consists of four cytoarchitecturally distinct regions (see Figure 1b): Brodmann areas (BA) 3a, 3b, 1 and 2. The subregions of S1 are functionally specialized: whereas neurons in 3a and 2 respond predominantly to proprioceptive stimulation, neurons in BA 3b and 1 are primarily activated by mechanical stimulation. In primates, BA 3b contains the largest representation of the finger with the finest resolution (Blake et al., 02). S1 neurons primarily represent physical properties of stimuli.

Most thalamic projections end in BA 3b and 3a. BA 1 and 2 receive much less direct thalamic inputs but receive their main input from BA 3a and 3b. Each of the S1 subregions contains a complete somatotopic map of the entire contralateral body. Recently, evidence for an ipsilateral representation has been found (Iwamura, 00; Palva et al., 05). Body parts that are more sensitive to touch (e.g., fingers and lips) are represented by a relatively larger area of this map resulting in the so-called homunculus. S1 is reciprocally connected with S2 and the primary motor cortex (M1) (Kaas, 93).

S2 is located in the upper bank of the Sylvian fissure (see Figure 1b) and smaller in size than S1. S2 neurons have receptive fields which are larger and bilateral. S2 exhibits a somatotopic representation of the ipsi- and contralateral body but with much less detail than S1. S2 is reciprocally connected with the ipsilateral S1 and via the corpus callosum with the contralateral S1 and S2. S2 receives a small direct input from the VPL. S2 projects to inferior and superior posterior parietal cortex (PPC) and lateral PFC (Cipolloni and Pandya, 99; Carmichael and Price, 95) (see Figure 1b). PPC contains neurons with tactile and multimodal receptive fields and projects to the premotor cortex (PMC), the lateral PFC and the insular cortex (Friedman et al., 86; Kaas, 93; Petrides and Pandya, 84; Breveglieri et al., 06; Geyer, 04; Seltzer and Pandya, 80; Preuss and Goldman-Rakic, 89). Most experimental data hint towards a serial processing of information from S1 to S2 (Allison et al., 89a; Allison et al., 89b; Hari et al., 84). However, some studies were able to demonstrate the existence of parallel direct pathways to S1 and S2 (Barba et al., 02; Karhu

und Tesche, 99). Whereas lesions of S1 impair the localization and detection of tactile stimuli, lesions of S2 lead to more complex impairments including disturbed shape and roughness processing, temperature perception, and nociception (Freund, 03; Duncan und Albanese, 03). PPC is implicated in even more complex tactile processing including attention and memory, multi-modal processing and somato-motor programming (Burton und Sinclair, 00; Jeannerod et al., 94; Driver und Vuilleumier, 01). Lesions of PPC can cause the syndrome of tactile neglect and apraxia (Vallar et al., 03; Binkofski et al., 01).

1.4. Previous research on vibrotactile working memory

1.4.1. *Single-unit studies of vibrotactile working memory in non-human primates*

Several studies in monkeys and humans investigated WM for vibrotactile information in the range of flutter frequencies. Romo and colleagues (Hernandez et al., 00; Hernandez et al., 02; Romo et al., 99; Romo et al., 02b; Romo et al., 02a; Romo und Salinas, 03; Romo et al., 04; Salinas et al., 00) conducted a series of studies in which neural activity from single units in S1, S2, PFC, medial and ventral PMC was recorded while monkeys were performing a vibrotactile delayed discrimination task. A similar version of their task was used in all experiments of the present dissertation. In the vibrotactile delayed discrimination task, two vibrotactile stimuli differing in vibration frequency were applied to the monkeys' index finger separated by a delay ranging from 6 to 8 s. After the second vibration was applied, the monkeys had to indicate which of the two vibrations had the higher frequency. This task comprises different epochs: *encoding* of the vibrotactile stimulus, *maintenance* of this stimulus over a delay period and finally *decision making* comprising the comparison of the first with the second vibrotactile stimulus.

The authors found that the majority of S1 neurons *encoded* the frequency of the vibrotactile stimuli in the periodicity of the firing pattern but about one third of S1 neurons modulated their firing rate as a function of the stimulus frequency. The firing rate of these later neurons was parametrically modulated by the frequency of the vibrotactile stimulus, i.e., the neurons fired more frequently with increasing vibration frequency. Discrimination performance only decreased slightly when aperiodic vibrations with irregular intervals between single pulses were applied. This finding indicates that the periodicity of spikes cannot be the necessary code for performing the task. Even when electrical current pulses with different frequencies were used to intracranially stimulate S1 instead of applying peripheral vibrotactile stimulation, monkeys still correctly performed the delayed discrimination (Romo et al., 00). Moreover, S1 neurons in the macaque brain show higher firing rates during active discrimination than during passive vibrotactile stimulation (Salinas et al., 00). Together, these results show that the neural representation necessary and sufficient to perform the vibrotactile delayed discrimination task is a firing rate code that parametrically encodes the frequency of the vibration stimulus. In addition to S1, neural activity in S2, lateral PFC, medial and ventral PFC also parametrically represents the vibration frequency during the presentation of the first and the second vibration.

During the *maintenance* period of the task, Romo and colleagues found neurons that varied their firing rate parametrically depending on the frequency of the first vibration in S2, lateral PFC, ventral and medial PMC. Notably, no delay activity was found in S1. Whereas in S2 only neurons with early delay activity were found, delay-related neurons in PMC only showed stimulus-modulated firing rates in the late delay period. Lateral PFC was the only region where neurons with sustained firing rates during the entire delay period were observed. Interestingly, while S1 neurons only exhibited positively monotonic tuning curves, the firing rate of the delay-related neurons in these other regions increased or

decreased as a monotonic function of the frequency of the first vibration. For S2 neurons it has been shown that the existence of two populations of neurons with opposite tuning functions enhances the fidelity of the neural representation by reducing noise and enhancing signal strength (Romo et al., 03). Periodicity was almost absent in S2 and could not be identified in PFC or PMC. Similarly to S1, sustained firing in these regions was reduced during passive stimulation and the firing rate elicited by the second vibration stimulus correlated with behavioral performance. Taken together, these findings suggest that S2, PFC and PMC are part of the neural circuitry mediating the maintenance of the vibrotactile memory trace whereas S1 seems to generate the neural representation of the stimulus, i.e., translating a periodic into a firing rate code. Furthermore, the physiological basis of the somatosensory memory trace seems to be represented parametrically by the firing rate of neurons and not categorically. It is important to note that this was the first time that a firing rate code had been linked to a sensory memory representation.

Neurons in S2, lateral PFC, medial and ventral PFC exhibit activity patterns that reflect the evolution of the behavioral *decision*. During the presentation of the second vibration some neurons responded at a rate that exclusively reflected the frequency of the first or the second vibration. However, the majority of neurons modulated their response according to the difference between the first and the second vibration. Accordingly, about half of these neurons fired with a higher rate when the first stimulus had a higher frequency than the second whereas the other half showed the opposite pattern. The sign of this difference correlates with the monkeys' behavioral response indicating that the observed modulations of firing rate are indeed functionally relevant. Together, these findings indicate that the firing pattern of neurons in these brain regions becomes gradually correlated with the monkey choice during the presentation of the second vibration. This indicates that these neurons reflect and are crucially involved in the comparison process gradually evolving into the decision. The outcome of this decision-making process is transferred to M1 which generates the overt behavioral response. The decision related activity occurs earliest in ventral PMC followed by PFC, medial PMC and then in S2. Therefore, it has been suggested that the decision process in this task might be initiated and controlled by the ventral PMC, continued and amplified by lateral PFC and medial PMC, and its result sent as an "efference copy" to S2. The finding that two oppositely tuned populations of neurons integrate neural evidence over time leading to a final decision is similar to results of single-unit recordings in PPC and PFC of monkeys performing a visual discrimination task (Kim und Shadlen, 99; Shadlen und Newsome, 01).

In summary, these studies imply that a cortical network of somatosensory, prefrontal and motor areas provides the neural basis necessary for performing the vibrotactile delayed discrimination task. These studies revealed three important aspects related to the neural basis of cognitive processes. First, performance is conjointly realized by a distributed neural network. Except for S1 and M1, activity of neurons reflects the entire sequence of processing steps, i.e., encoding, maintenance and decision making that link sensation and action in the task. Second, different conceptually defined cognitive processes (e.g., encoding, maintenance, decision making) are not located in distinct brain regions. Specialization of a specific brain region is in fact a result of the relative strength with which it contributes to specific process. Third, neural activity does not proceed in separate steps but develops gradually in the involved brain regions to enable task performance.

Although these single-unit studies revealed important insight regarding the neural implementation of vibrotactile WM, brain activity was only studied in a few pre-selected brain regions. Therefore, it remains an open question which additional brain regions are part of the neural network supporting vibrotactile WM. For instance, in the visual modality it has been shown that the sustained maintenance of information and decision making is implemented in posterior modality-specific association areas (Pasternak und Greenlee, 05;

Gold und Shadlen, 07). However, Romo and colleagues did not record in the PPC which represents an important association area of the somatosensory system. In the present dissertation, fMRI was used to study the whole brain when subjects performed a vibrotactile delayed discrimination task (Study I).

1.4.2. Human studies on vibrotactile working memory

Comparative psychophysical studies in humans and monkeys have shown that both species have similar abilities to discriminate between vibrotactile frequencies (Mountcastle et al., 90).

More recent behavioral studies in humans using a similar vibrotactile delayed discrimination task indicate that WM for flutter stimuli follows the somatotopic organization of S1 and S2 (Harris et al., 06; Harris et al., 02; Harris et al., 01). At short delays (< 1 s) subjects were more accurate at comparing vibrations delivered to the same finger than vibrations delivered to the corresponding finger of the opposite hand. Also, accuracy decreased as the distance between the stimulated fingers of one hand increased for shorter (1 s) but not longer (2 s) delays. An interference vibration delivered between the first and the second vibration had the most disruptive effect on accuracy when delivered to the same finger as opposed to different fingers. These results suggest that for shorter delay periods, performance in a somatosensory WM task mirrors the somatotopy and lateralization of processing in S1, whereas at longer delays performance reflects the broader somatotopic and bilateral organization of S2. In addition, disruption of neural activity in S1 using a single pulse of transcranial magnetic stimulation (TMS) impaired performance at short retention intervals (300, 600 ms) but not longer ones (Harris et al., 02). Based on the behavioral effects in their studies, the authors suggested that S1 seems to contribute to human vibrotactile WM for early or short delay periods whereas S2 supports WM for later phases or longer delay periods. However, this interpretation is in contrast to the single-unit studies in non-human primates which did not find delay activity in S1 (Romo und Salinas, 03). Besides possible species differences, these inconsistent results could also be due to differences in experience with the task: whereas the human subjects were unfamiliar with the task before the experiment, the monkeys received extensive training over months probably leading to a more efficient encoding of the vibrotactile stimulus. Recently it has been suggested that these results can also be explained by the adaptation of S1 neurons having an effect on processing in downstream areas involved in early maintenance, possibly S2 (Harris et al., 06; Romo und Salinas, 03). However, early delay activity in S1 was also found in a tactile pattern WM task using single-unit recordings in monkeys (Zhou und Fuster, 96). Thus, the contribution of S1 for the active maintenance of the vibrotactile memory trace during the early part of the delay period remains unclear.

An earlier neuroimaging study on vibrotactile WM using positron emission tomography found higher activity in S2, ventrolateral PFC and PPC during a WM compared to a control condition (Klingberg et al., 96). However, because a continuous discrimination task was employed, activation could not be related to different task periods. Only recently, have the first fMRI studies emerged which used the vibrotactile delayed discrimination task in human subjects (Preuschhof et al., 06; Pleger et al., 06; Li et al., 07; Kostopoulos et al., 07; Burton et al., 07).

Together, the studies in humans suggest 1), that the role of S1 for the early maintenance of vibrotactile stimuli is still vague, and 2), that there might be an additional contribution of PPC but its relative contribution in the different task periods is still unclear. The role of S1 for the active maintenance of the vibrotactile memory trace was further investigated in the present dissertation using neuroscientific methods with adequate temporal resolution: EEG

(Study II) and subliminal stimulation (Study III). As mentioned above, additional brain regions associated with vibrotactile WM were identified using fMRI (Study I).

1.4.3. Time-order effects in vibrotactile working memory

In many studies investigating the discrimination of stimuli varying in quantity (magnitude), the so-called time-order effect (TOE) has been found (Hellstrom, 85; Helson, 64; Fechner, 60). The typical behavioral pattern related to this effect is an interaction between stimulus magnitude and the time-order of stimulus presentation, i.e., whether the stimulus of low or high magnitude was presented at the first (standard stimulus) or at the second (comparison stimulus) position of the trial. For low magnitude stimuli, accuracy increases when the comparison stimulus is of lower magnitude than the standard stimulus. For high magnitude stimuli, accuracy increases when the comparison stimulus is higher than the standard stimulus. Theoretical accounts (Hellstrom, 85) predominantly place the source of the TOE into perceptual and mnemonic processes as opposed to processes taking place during the decision stage of the task (Masin und Fanton, 89; Masin und Agostini, 91; Masin, 95). Hellström formulated a comprehensive theory that regards the TOE as a side effect of stimulus weighting processes and the effect of a general reference level which is influenced by the stimulus set, context and background information (Hellstrom, 03; Hellstrom, 00; Hellstrom, 85). Similarly, it has been shown that memory for magnitudes is influenced by prior stimuli and determined by regression to the mean of the stimulus set (Huttenlocher et al., 00; Sailor und Antoine, 05). Important insights regarding development of the TOE come from experiments comparing the method of constant stimuli (where an explicit standard and a comparison stimulus have to be compared) and the method of single stimuli (where the comparison has to be judged in relation to the mean of the stimulus set) (Nachmias, 06; Morgan et al., 00). These experiments showed, that independent of the method used, an average standard close to the arithmetic mean of the stimulus set is used by the subjects. Importantly, the generation of this average standard seems to be an implicit, automatic process and only requires the first 10 to 20 trials of the experiment (Morgan et al., 00). Performance in magnitude discrimination, therefore, seems to be influenced by implicit stimulus representations that are based on average information about previous stimulus input. Sinclair and Burton (96) observed the TOE in a vibrotactile delayed discrimination task using a very broad range of standard frequencies (50, 100, 200 Hz) and relatively high differences between standard and comparison frequency. The existence of the TOE indicates that tactile frequency discrimination is influenced by activated LTM representations. However, it remains an open question whether the TOE can also be found when only frequencies within the flutter range are used. In addition, it is not clear how robust this effect is. Therefore, in the present dissertation the TOE was investigated when only flutter frequencies were used. To investigate the robustness of the TOE, task parameters were manipulated (Study IV). Furthermore, the neural correlates of the associated representations remain elusive and until now no study has addressed the neural correlates of the proposed stimulus weighting processes leading to the TOE. To address this issue a parametric fMRI analysis was conducted (Study IV).

2. Summary of research questions

The summary of the current research on vibrotactile WM suggests that three major questions are still unresolved:

1. Which brain regions support the performance of the vibrotactile delayed discrimination task during the different task periods in the human brain?

For this purpose, an fMRI study was performed using the vibrotactile delayed discrimination task (Study I).

2. *What is the role of S1 for actively maintaining the vibrotactile memory trace in the early delay period?*

To address this issue, an EEG study was conducted to study the time course of S1 activity as indicated by the rolandic rhythms over the somatomotor cortex with a sufficiently high temporal resolution (Study II). In addition, the method of concurrent subliminal stimulation was used to selectively inhibit processing in S1 (Study III).

3. *How is the performance of a vibrotactile WM task influenced by implicit LTM representations that are reflected by the TOE?*

To answer this question, initial behavioral experiments were conducted to further investigate the TOE in vibrotactile WM (Study IV). The fMRI data from Study I were, then, re-analyzed to study the neural representations associated with the TOE (Study V).

3. Methodological background

Two methodological premises largely influenced the proposal for this dissertation. First, the quest for the neural basis of tactile WM should start with the investigation of a relatively simple task manipulating only specific stimulus features and involving few cognitive processes. Second, to get a complete understanding of tactile WM, converging evidence provided by different methods and integration of findings over species is necessary. Therefore, in all experiments of this dissertation a vibrotactile delayed discrimination task was employed which has been used in previous studies using the methods of single-unit recordings in non-human primates and behavioral experiments in humans. In the present dissertation, this task was studied using complementary methods: fMRI, EEG, subliminal electrical stimulation and psychophysics. The task and the neuroscientific methods will be introduced in the next sections.

3.1. Vibrotactile delayed discrimination task

In all experiments of this dissertation (Study I to V), subjects performed a vibrotactile delayed discrimination task (Figure 2) similar to that previously used in primate (Romo et al., 99) and human studies (Harris et al., 02). The specific task parameters are described in more detail in the different manuscripts related to this dissertation. In general, each trial began with a warning tone indicating that the next pair of vibrations would appear. After a couple of hundred ms, the first vibrotactile stimulus (standard stimulus) was applied to the distal phalanx of the subjects' right index finger followed by a delay varying between 100 and 4100 ms. After the delay, the second vibrotactile stimulus (comparison stimulus) was applied to the identical location as the standard stimulus. With the exception of study IV where the trial types and the response alternatives were varied, the subjects had to decide if the comparison stimulus had a higher or a lower frequency than the standard stimulus. They had to indicate their choice by pressing one of two response buttons. All vibrations lasted 1000 ms. The frequency of the first vibration varied on a trial to trial basis ranging from 10 to 43 Hz. The frequency of second vibration was depending on the experiment either 1, 3 to 7 Hz higher or lower than the first frequency. In the fMRI (Study I and Study V) and EEG (Study II) experiments, two No-WM control conditions were also applied. The trial structure of these control conditions was identical to the WM condition but the vibration frequencies within one trial were identical. The vibrotactile delayed discrimination task can be sub-divided into different task periods: *encoding* (ranging from the beginning of the standard vibration to its end), *maintenance* (ranging from the end of

the standard vibration to the beginning of the comparison vibration), and *decision making* (starting with the beginning of the comparison vibration and ending with the subjects' response).

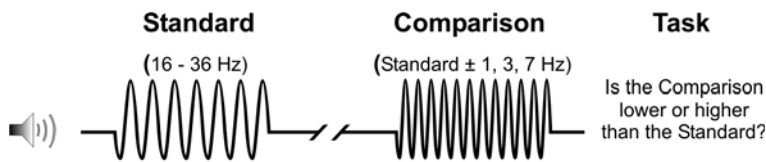


Figure 2. The vibrotactile delayed discrimination task. After a warning tone, two vibrotactile stimuli are presented successively to the subject's index finger. The subject has to discriminate between the two vibration frequencies.

3.2. Functional magnetic resonance imaging

fMRI was used in Study I and V. It is a method to study brain activity non-invasively. It is important to emphasize that fMRI does not measure neuronal activity directly. fMRI employs the blood-oxygen-level-dependent (BOLD) contrast to indicate local changes in neural activity (Kwong et al., 92; Ogawa et al., 90). Neural activity associated with information processing leads to metabolic changes including increased oxygen consumption in the respective brain regions. Mediated by physiological mechanisms that are still not completely understood, 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 et al., 88; Fox und Raichle, 86). As a result of this increased blood flow, vessels in activated brain regions contain an over-supply of oxygenated blood and consequently a relatively low amount de-oxygenated blood. Because deoxyhemoglobin has paramagnetic features, its presence leads to local inhomogeneities of the magnetic field. Inhomogeneities lead to a faster decay of the MRI signal. Therefore, active brain regions which exhibit a relatively low amount of deoxyhemoglobin show a slower decay of the MRI signal than non-activated brain regions resulting in an increased BOLD signal. In brief, fMRI measures the relative absence of deoxyhemoglobin in a given brain region which, mediated over hemodynamic coupling and the associated BOLD response, is an indicator for local neural activity (Logothetis und Wandell, 04). Although still an issue of intense research, the BOLD contrast is assumed to reflect mainly 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., 01; Viswanathan und Freeman, 07).

The time course of the BOLD response to a brief sensory stimulation is called the hemodynamic response function (HRF). Whereas the neuronal response to the stimulus rises quickly and ends a few hundred ms post-stimulus, the typical BOLD response only begins to rise at about 2 s and reaches a maximum at 5–9 s after stimulus onset and then slowly returns to baseline (for review see Logothetis and Wandell (04)). In some instances the BOLD response has an initial dip and a post-stimulus undershoot. The slow HRF causes the relatively poor temporal resolution of fMRI. The exact form of the HRF differs across brain regions and between subjects as well as tasks. It also depends on the stimulus duration. To model brain activity in fMRI analyses usually a canonical HRF is used (Friston et al., 95). Depending on the degree of spatial smoothing applied, the spatial resolution of fMRI lies usually between 4 and 12 mm². For group analyses, functional maps are normalized to a structural brain template using coordinates according to the Talairach or the Montreal Neurological Institute standards (Evans et al., 93; Talairach und Tournoux, 88). For illustrating purposes, the relatively low-resolution functional activation maps are usually super-imposed on high-resolution structural MRI images.

3.3. Electroencephalography

EEG was used in Study II. In contrast to fMRI, EEG provides a direct measure of neuronal activity and has a temporal resolution in the range of ms but a lower spatial resolution. Surface EEG reflects voltage differences between electrodes positioned on the skull (Berger, 29). The EEG signal is composed of summated activity of post-synaptic currents of thousands of pyramidal cells in the underlying cortex that have the same spatial orientation and are synchronously activated (for review see Barlow (93)). EEG is only sensitive to currents from sources located with a radial orientation to the skull. Because the strength of electric fields falls off with increasing distance, deep sources contribute less to the EEG signal than sources near the skull. Neuronal oscillatory activity, which can be recorded with EEG, is caused by complex interactions between inhibitory and excitatory mechanisms either on the level of single neurons mediated by intrinsic membrane properties or on the level of networks mediated by local inhibitory interneurons and feedback loops (Singer, 93; Lopes da Silva, 91). Oscillatory activity can be related to functionally distinct brain rhythms that are defined by a characteristic frequency and spatial distribution. These rhythms seem to reflect different states of brain functioning and specific aspects of information processing. Whereas synchronous oscillation in the beta (15 - 25 Hz) and gamma (25 - 120 Hz) frequency range seem to reflect binding of locally distributed stimulus and memory representations (Gray et al., 89; Singer, 99; Tallon-Baudry, 03; Fries, 05), oscillations in the theta (4 - 8 Hz) and alpha (8 - 14 Hz) frequency range have been linked to long-range thalamo-cortical and cortico-cortical connections and top-down attentional control (Palva und Palva, 07; Klimesch et al., 05; von Stein und Sarnthein, 00). In addition, oscillatory activity over modality-specific sensory cortices indicates the functional state of these brain regions (Hari et al., 97; Pfurtscheller und Lopes da Silva, 99; Berger, 29). Specifically, the modulation of the rolandic rhythms, which can be recorded over the somatomotor cortex and lie in the alpha and beta frequency range, are an indicator of somatosensory activation with a power increase reflecting active processing or readiness to process somatosensory stimuli and a power increase indicating somatosensory inhibition (Hari et al., 97; Pfurtscheller et al., 97).

3.4. Subliminal electrical stimulation

Subliminal electrical stimulation was used in Study III. As opposed to fMRI and EEG, subliminal electrical stimulation is not a method for measuring brain activity. However, by influencing the physiological state of S1, it affects performance in tasks depending on the integrity of S1. Subliminal electrical stimulation of the finger has been demonstrated to selectively enhance inhibition of S1 as reflected by effects on a physiological and behavioral level (Taskin et al., 08; Blankenburg et al., 03). Thalamo-cortical afferents activate both excitatory glutamatergic principal cells and fast-spiking GABAergic inhibitory interneurons in layer IV of S1. These interneurons again inhibit the same principal cells that are activated by the thalamo-cortical afferents. Thalamo-cortical input activates the inhibitory interneurons more strongly than excitatory principal cells leading to powerful and efficient local feedforward inhibition (Swadlow, 02; Bruno und Simons, 02; Gibson et al., 99; Inoue und Imoto, 06; Gil und Amitai, 96). The physiological effects underlying subliminal stimulation are either caused by a preferential activation of feedforward inhibitory interneurons due to their lower spiking threshold (Gil und Amitai, 96) or by synaptic mechanisms (Cruikshank et al., 07). Whatever process is involved, at a functional level such a strong inhibitory network reduces the likelihood or even prevents cortical target neurons to reach threshold when sensory input is weak or not optimal (Swadlow, 03).

4. Empirical studies

In this section the 5 studies the present dissertation is based on will be briefly summarized. While the first three studies aimed to contribute additional evidence regarding the neural network supporting vibrotactile WM, the goal of the last two studies was to investigate the role of the TOE and associated LTM representations in vibrotactile WM.

4.1. Neural correlates of human vibrotactile working

4.1.1. *Study I: Neural correlates of vibrotactile working memory in the human brain*

In the first study, fMRI was used to further investigate the neural network supporting vibrotactile WM in the human brain. Whereas single-unit recordings only allow studying neural activity in pre-selected brain regions such as S1 or lateral PFC, fMRI enables the investigation of the functioning of the whole brain in healthy human subjects. Therefore, fMRI provides the opportunity to identify additional regions that are part of the vibrotactile WM network. As the study by Klingberg and colleagues suggested, the PPC might also be involved in vibrotactile WM (Klingberg et al., 96). This suggestion is supported by studies using phonological and visuo-spatial WM in which association areas of the PPC have also been found to play a role (Smith und Jonides, 98). In addition, it has been shown that the recruitment of sensory brain regions in WM tasks depends on the length of the delay period. While ultra-short delay periods have been shown to be associated with activation of sensory brain regions, tasks with longer delay periods additionally recruit the lateral PFC (Cornette et al., 02; Pasternak und Greenlee, 05).

In this fMRI study, an event-related design was used to separate brain activity related to the different phases of the vibrotactile delayed discrimination task (encoding, maintenance, decision making). To identify the specific regions of the network crucially involved in WM functions, a WM condition was compared to a control condition which did not require maintaining the vibrotactile stimulus in WM. In addition, trials with short (100 ms) and long (4100 ms) delay periods were compared.

A distributed network of brain regions was associated with the performance of the vibrotactile delayed discrimination task. When activity in the WM condition was compared to activity in the control condition, only a few areas remained significantly activated. During *encoding*, consistent with neurophysiological data in monkeys and behavioral studies in humans, S1 and the ventral PMC exhibited increased activity. Because the ventral PMC (Broca's area) supports language processes in humans (Friederici, 02), its activation could indicate that the encoding of a vibrotactile stimulus in human subjects includes verbal processes. *Maintenance* of a vibrotactile memory trace evoked activity in PMC and lateral PFC. *Decision making* caused activation in S1, S2, PMC, and lateral PFC. However, human vibrotactile WM recruited additional areas. *Decision making*, in particular, activated a much broader network than known from the studies in non-human primates. *Maintenance* and *decision making* additionally activated the inferior PPC. The activation of the PPC is consistent with a previous study (Klingberg et al., 96) but now could be related to the maintenance and decision making periods of the task. This is in line with findings that link activity in the PCC to the active maintenance of information and decision making in other modalities (Gold und Shadlen, 07; Smith und Jonides, 98). Although the different task components evoked activity in distinctive neural networks, there was considerable overlap of activity, especially regarding maintenance and decision making, indicating that similar neural mechanisms are required for the sub-processes related to these task components.

Also, the comparison of short and long delay trials revealed specific activation patterns: While long delay trials had more anterior activation peaks in the lateral PFC and recruited the PPC, the opposite pattern was found for short delay trials. Short delay trials caused more posterior activation of the lateral PFC extending into premotor areas, while the parietal activation extended into S1. The finding that short delay trials are associated with increased levels of activity in S1 indicates that primary sensory regions are more crucial for performing a WM task with extremely short delay periods and confirms WM studies in the visual modality (Cornette et al., 02). However, due to the low temporal resolution of fMRI, this S1 activity can not be associated with a specific task period. Therefore, methods with a better temporal resolution than fMRI are required to investigate the role of S1 for the maintenance of the vibrotactile memory trace in the delay period.

Together, the fMRI study showed that a much broader network than previously studied supports the performance during the different periods of the vibrotactile delayed discrimination task. The finding that the PPC supports maintenance and decision making is of particular interest because posterior modality-specific association areas have also been implicated for sustained maintenance and decision making in other modalities (Pasternak und Greenlee, 05; Gold und Shadlen, 07). This indicates structural similarities in the neural organization of WM between modalities.

4.1.2. Study II: Rolandic and posterior-parietal alpha rhythms are differentially modulated during vibrotactile working memory

As mentioned in the introduction, single-unit recordings in monkeys as well as behavioral and TMS studies in humans produced inconsistent results regarding the importance of S1 in the early delay period (Harris et al., 02; Romo und Salinas, 03). The fMRI study (Study I) revealed that S1 is crucially involved in the encoding of the standard stimulus and that S1 is more important for short WM trials as compared to long WM trials. However, due to the low temporal resolution of fMRI it is not possible to disentangle activity during the encoding of the standard stimulus and the early delay period. Therefore, in the second study the excellent temporal resolution of EEG was used to shed light on the role of S1 in the early delay period.

The rolandic alpha and beta rhythms over the somatomotor cortex indicate the physiological state of the underlying cortex with low power indicating active processing or readiness to process somatosensory stimuli and high power indicating low levels of activity (Hari et al., 97; Pfurtscheller et al., 97). In addition, high levels of alpha power over a brain region have been suggested to reflect the functional inhibition of this region during cognitive processing (Klimesch et al., 07). This functional inhibition could serve either to keep out new sensory information that could be further transmitted to areas actively maintaining the memory trace and thus interfering with the maintenance process or to shut-down irrelevant areas in order to devote processing capacity to areas actively involved in maintenance (Jokisch und Jensen, 07; Tuladhar et al., 07; Klimesch et al., 07).

In this study, EEG was recorded to investigate the dynamics of the rolandic rhythms during the encoding and maintenance phase of the vibrotactile delayed discrimination task. Based on the functional inhibition account, a reduction of rolandic rhythms over the somatomotor cortex during the delay period, representing maintenance of the vibrotactile memory trace, was hypothesized. A second question concerned the role of S1 during the early delay period. It was expected that if the neural representation of the vibrotactile stimulus is being maintained or still actively processed (consolidated) in S1 during the early delay, the rolandic rhythms, especially the alpha component, should still be suppressed over contralateral somatomotor cortex during this time period. To investigate if S1 activity is differentially modulated when subjects have to retain the memory trace for a short as

opposed to longer delay, again two different delay lengths (370 ms and 4070 ms) were used.

Vibrotactile stimulation led to the typical modulation of the rolandic alpha and beta rhythms over contralateral somatomotor cortex with initial power suppression and a significant post-stimulus power increase which was stronger in the beta than in the alpha frequency band. In addition, during the middle portion of the delay period alpha power over the somatomotor cortex significantly increased over baseline levels. In light of the functional inhibition hypothesis, this could be interpreted as relative inactivation of the somatosensory cortex during memory retention. Across all subjects, the rolandic rhythms were not significantly modulated during the first second of the delay period. However, power was still reduced compared to baseline. Also, when compared to low performing subjects, higher performing subjects exhibited higher alpha amplitudes over contralateral somatomotor cortex during the late encoding period and the early delay period. In addition, high performers reached their alpha peak earlier than low performers. This suggests that the divergent findings in humans and monkeys might be caused by differences in encoding efficiency. Due to faster and more efficient encoding in high performing or trained subjects, consolidation of the neural code might already be finished during stimulus presentation and the memory trace is already maintained in other brain regions. The most pronounced effect for the rolandic alpha rhythm is a reduction of baseline power before the upcoming standard stimulus in the WM compared to a No-WM condition. This might reflect a tonic up-regulation of the activation level of contralateral S1 caused by sustained attention.

Concurrently, with the rolandic alpha suppression during stimulation, an alpha power increase was present at posterior parietal sites. This posterior parietal alpha power remained increased during the entire delay period indicating that posterior parietal and occipital visual areas are functionally inhibited during the active maintenance of a vibrotactile stimulus. In addition, the posterior alpha power increase was accompanied by a prefrontal alpha power increase. Higher prefrontal alpha power was also found during the encoding and early delay period of long as compared to short WM trials probably reflecting increased executive demands when a vibration frequency has to be maintained for a longer time. Therefore, simultaneous increases at prefrontal and posterior parietal sites might reflect top-down control by a fronto-parietal network (Palva und Palva, 07).

In summary, somatosensory and visual brain regions seem to be functionally inhibited during the delay period of the vibrotactile WM task. Concerning the question regarding the role of S1 during the early delay period, this study indicates that S1 is not involved in active maintenance of the vibrotactile stimulus. The activation level of S1 during the early delay period depends on the efficiency of stimulus encoding. Top-down attentional control probably up-regulates the activation level of S1 under WM demands in order to optimize task performance.

4.1.3. Study III: Pre-trial subliminal electrical stimulation improves performance in vibrotactile delayed discrimination

The results of Harris and colleagues (02), who applied TMS to contralateral S1, indicate that S1 supports the maintenance of vibrotactile information during the early delay period. However, the results of the EEG study (Study II) indicated that S1 does not actively maintain the memory trace and that the level of activity in S1 during the early reflects ongoing consolidation processing in untrained or low performing subjects. The effects of TMS are not very localized and not specific concerning the type of neurons affected (Siebner und Rothwell, 03). In contrast, subliminal electrical stimulation leads to weak but selective inhibition of S1 (Taskin et al., 08; Blankenburg et al., 03). Therefore, it can be

used to further investigate the proposed ongoing memory consolidation during the early delay period. In addition, Study II indicated that pre-trial activity of S1 plays an important role for task processing. However, the question remains whether a manipulation of the physiological state of S1 affects performance in the vibrotactile discrimination task.

To address these issues, subliminal stimulation was applied concurrently during the pre-trial, encoding and early delay period of the vibrotactile delayed discrimination task. To prove that the efficiency of a subliminal train of pulses lasting only 1 s could produce similar effects on detection-threshold as continuous stimulation (Blankenburg et al., 2003; Taskin et al., 08), an initial pilot experiment using a modified non-blocked version of the previous detection experiment was conducted. In the pilot experiment, subliminal stimulation raised the detection threshold for subsequent weak electrical stimuli confirming and extending the results of previous studies in which block-wise subliminal stimulation was used (Taskin et al., 08; Blankenburg et al., 03). In contrast, when subliminal stimulation was applied in the pre-trial period of a vibrotactile delayed discrimination task, performance improvements were observed. There is converging evidence that the detection of weak stimuli and the processing and encoding of strong stimuli are associated with different physiological brain states (Nicoletis, 05). It has been suggested that subliminal electrical stimulation reduces background noise in S1 (Blankenburg et al., 03). This facilitates the encoding of the upcoming strong vibratory stimulus. In the case of the weak electrical stimuli in the pilot experiment, the reduction of noise levels prevents mechanisms of stochastic resonance. Stochastic resonance has been shown to improve the detection of weak stimuli (Collins et al., 96; Collins et al., 95). When subliminal stimulation was applied during the early delay period, performance impairments were observed for a subgroup of subjects who received (defined by the slope of their psychometric function) the strongest subliminal stimulation. For this subgroup the results are in line with results by Harris and colleagues (02) who found that single pulses of TMS, when applied over contralateral S1 during the early delay period, disrupted performance in the vibrotactile delayed discrimination task. The effect of subliminal stimulation during the early delay period depends on the intensity of subliminal stimulation possibly reflecting the level of inhibition achieved. Therefore, the present study indicates that relatively strong subliminal stimulation interferes with the ongoing processing of a fragile vibrotactile stimulus representation in S1 during the early delay period.

In summary, study III indicates that the memory representation is still consolidated but not actively maintained in S1 during the early delay period confirming the results of the EEG study (Study II). Furthermore, this study confirms the finding of Study II regarding the importance of the physiological state of S1 in the pre-trial period. However, whereas in Study II top-down modulation enhances the activity in S1, here less noisy bottom-up processing facilitates performance.

4.2. Time order effects in vibrotactile working memory: the influence of long-term memory representations on task performance

4.2.1. Study IV: Time-order effect in vibrotactile delayed discrimination: The influence of trial types and response alternatives

The TOE phenomenon has been found consistently in psychophysical experiments in various modalities (Hellstrom, 85). In the tactile domain, the TOE has already been reported for vibrotactile discrimination (Sinclair und Burton, 96). Burton and Sinclair used a wide frequency range with standard frequencies of 50, 100, and 200 Hz including flutter and higher frequency vibrations. In addition, the difference between standard and

comparison stimuli in their study was quite large ranging from 14 to 46 Hz difference which makes it more likely that subjects categorize the second stimulus as high or low instead of discriminating between the stimuli (Hernandez et al., 97). It remains an open question whether the TOE can be also found when only frequencies within the flutter range are used. In addition, it is not clear how changes in task parameters affect the TOE. In this series of behavioral experiments, the TOE was investigated in more detail. An initial experiment was carried out to determine whether the TOE can be found in vibrotactile delayed discrimination tasks when only stimuli in the range of flutter frequency (i.e., 10 - 50 Hz) are used. To prevent the subjects from using categorical judgments to solve the task, 6 standard frequencies and smaller frequency differences between standard and comparison stimulus ranging from 1 to 7 Hz were used. Three further experiments were conducted to investigate whether the TOE is affected by manipulations of the trial types and response alternatives available to the subject. Depending on the experiment, the trial types and response alternatives were symmetrical (e.g., "comparison stimulus is higher", "comparison stimulus is lower", and "both stimuli have the same vibration frequency") or asymmetrical (e.g., "comparison is higher", "both stimuli have the same vibration frequency").

Despite the variation in trial types and the available response alternatives, the TOE was consistently found in all 4 experiments. In addition, the magnitude of the TOE increased with increasing delay length and decreasing frequency difference between the two stimuli. Together, these results confirm that the TOE is a robust phenomenon in tasks involving the discrimination of magnitudes even within the range of flutter frequency. The independence of the TOE from the response alternatives and the pattern of results suggest that subjects implicitly use information about the average vibration frequency when performing the task. The question remains: In which period of the vibrotactile delayed discrimination task does average information affect task performance leading to the TOE? Whereas decisional accounts of the TOE assume that average information is used during the decision making process (Allan, 79; Masin und Fanton, 89), sensory accounts propose that the current standard vibration is integrated with the average vibration during encoding and maintenance (Hellstrom, 85; Helson, 64).

4.2.2. Study V: Neural correlates of time order effects: Implicit sensory stimulus representations influence vibrotactile delayed discrimination

This study aimed to identify the brain structures that are related to the generation of the TOE in the vibrotactile delayed discrimination task using fMRI. Perceptual accounts of the TOE suggest that it results from weighting processes during the encoding and maintenance of the standard stimulus (Hellstrom, 85). These weighting processes seem to reflect the integration of the sensory evidence provided by the standard stimulus and the weighted average of all stimuli presented previously. To identify brain regions that are involved in this assumed weighting process, the data from the first fMRI study (Study I) were re-analyzed. First, brain regions in which the BOLD response varies parametrically with the deviation of the vibration frequency of the standard stimulus from an assumed implicit average frequency were identified. To do this, the absolute value of the difference between the standard frequency and the arithmetic mean of the stimulus set was calculated with higher values reflecting larger deviations of the standard vibration from the mean vibration. The resulting values were then used as a parametric regressor in the subsequent fMRI analysis. The weighting processes leading to the TOE affect the difficulty of the subsequent decision. This is indicated by the finding that accuracy is determined by the time-order in which the stimuli are presented. To additionally identify regions showing a

parametric modulation of the BOLD signal depending on the difficulty of the decision during the decision period, a second parametric regressor was used. The values of this parametric regressor were calculated by subtracting the comparison frequency from the mean frequency.

Brain activity in S1 and S2, the thalamus and the ventral PMC showed a parametric modulation during the encoding period, while the PPC showed a corresponding pattern during the maintenance period. Importantly, the BOLD signal in S2 during encoding and PPC during maintenance predicted individual differences in the size of the TOE providing the necessary link between the theoretical assumption of this integration process and actual behavior. The only region showing an effect of decision difficulty was the anterior cingulate cortex (ACC). The ACC has been associated with detection and monitoring of response conflicts, uncertainty and error detection (Braver et al., 01; Barch et al., 01; Ridderinkhof et al., 04; Botvinick et al., 99; Yoshida und Ishii, 06). Supporting this view, the reaction time pattern reveals that in addition to lower accuracy, subjects showed increased response times for decisions where the un-preferred time-order had to be judged. This suggests that subjects experience a conflict about their decision in trials when, in the case of the un-preferred time-order, information provided by the first vibration and the average information diverges.

Together, this study indicates that vibrotactile decision making is influenced by implicit LTM representations of the average vibration frequency. The neural network related to somatosensory processing seems to weight information about this average and the current standard frequency before the comparison period which supports perceptual accounts of the TOE. In addition, the present neural and behavioral data suggest that this conflict processing is an important factor accompanying the decision process in magnitude discrimination tasks in addition to earlier perception-related processes.

5. General discussion

The ability to actively maintain tactile information is a prerequisite for complex behaviors such as object recognition. Tactile WM is crucial for blind people who predominantly rely on their tactile sense in everyday life, e.g. for reading Braille writing. Moreover, the tactile modality is being increasingly applied as an additional channel to provide information in environments with visual and acoustic information overload, e.g. in a cockpit. However, as opposed to WM for visuo-spatial or phonological information, WM for tactile stimuli has been largely neglected by psychological and neuroscientific research. The present dissertation, therefore, aimed to shed more light on the mechanisms and the neural basis of tactile WM. This dissertation was guided by two methodological premises. First, the investigation of the neural basis of tactile WM should start with a relatively simple task manipulating only specific stimulus features and involving few cognitive processes. Second, to get a complete understanding of tactile WM, converging evidence provided by different methods and integration of findings over species is necessary. Therefore, in all experiments of this dissertation a vibrotactile delayed discrimination task was employed which has been used in previous studies using the methods of single-unit recordings in non-human primates and behavioral experiments in humans. Our experiments aimed to add evidence according the neural network supporting the same task in humans.

5.1. The neural network supporting vibrotactile WM

First, this dissertation addressed the question of which neural network is related to vibrotactile WM. In *Study I*, fMRI was used to identify the brain regions supporting task performance in the vibrotactile delayed discrimination task. A distributed network including S1, S2, ventral and medial PMC, lateral PFC and PPC exhibited increased

activity during the different task periods (encoding, maintenance, decision making). This network is similar to - but comprises more brain regions - than the network previously studied in non-human primates. However, although distinct patterns of brain activity could be related to the different task periods, it is not clear which specific function the respective regions have for vibrotactile WM. Studies manipulating specific task processes might elucidate this issue further. For instance, two recent studies demonstrated the importance of the lateral PFC for cognitive control in vibrotactile WM. One study confirmed that the difficulty of the decision in vibrotactile WM depends on Weber's law and demonstrated that the activity of the lateral PFC increases with increasing decision difficulty (Pleger et al., 06). A second study showed that active retrieval of information about vibrotactile stimuli is accompanied by an increased connectivity between lateral PFC with S2 and PPC (Kostopoulos et al., 07).

The EEG study (*Study II*) showed that, in addition to brain regions activated during the maintenance of vibrotactile stimuli, the parieto-occipital and primary somatosensory cortex seem to be functionally inhibited during the delay period. It has been suggested that the function of this inhibition is to prevent task irrelevant and possibly interfering information from entering the brain regions actively maintaining the memory trace (Klimesch et al., 07). In addition, the EEG study showed that alpha power was increased during the delay period at prefrontal and posterior parietal sites. Prefrontal alpha power was further modulated by delay length. Neural synchronization in the alpha frequency range between PFC and PPC has been suggested to reflect the functioning of a global neural workspace controlling cognitive processing including WM (Palva und Palva, 07). The interaction between brain regions has not been investigated in this dissertation. However, in future studies the manipulation of task demands could be related to the amount of synchronization or coherence between brain regions as in indicator of fronto-parietal top-down modulation. In addition, the analysis of oscillatory activity between brain regions is a promising correlate of actively maintained memory representations (von Stein und Sarnthein, 00).

5.2. The role of S1 in vibrotactile WM

While it is accepted that S1 is crucial for the encoding of vibrotactile stimuli into WM, it is still unclear what role this brain region plays for the active maintenance of tactile information. The EEG experiment (*Study II*) and the experiment using concurrent subliminal stimulation (*Study III*) addressed this issue and suggested that the activation level of S1 is still enhanced during the early delay period. In the EEG study, the amplitude of the rolandic rhythms over the contralateral somatomotor cortex was still reduced compared to the pre-trial baseline and only reached its maximum during the middle portion of the delay period. Concurrent subliminal stimulation, previously shown to inhibit S1, impaired discrimination performance when applied during the early delay period for subjects receiving relatively high levels of subliminal stimulation indicating that S1 activity during this period is functionally relevant. In addition, the performance comparison between high and low performing subjects in the EEG study suggested that the inconsistent finding between human subjects and monkeys might be related to the velocity and efficiency with which subjects can encode the vibrotactile stimulus. This interpretation further implies that S1 is not actively involved in the maintenance of the vibrotactile memory trace but instead that some subjects still consolidate the representation of the vibrotactile stimulus during the early delay period.

In both studies the clearest finding regarding the role of S1 for vibrotactile WM was found in the pre-trial periods. The lower amplitude of the rolandic rhythms in WM compared to the control condition probably reflects anticipatory attention associated with a tonic up-

regulation of S1 in the WM trials. The results of the study applying concurrent subliminal stimulation additionally suggest that reducing the background noise in S1 by increasing local inhibition improves performance. This performance improvement might indicate that lower levels of noise in S1 before the first stimulus is applied prepares S1 to process the upcoming stimulus and subsequently facilitates encoding. Linking the two studies, it has been shown that increasing inhibition abolishes alpha-like oscillations and bursting activity in the rat somatosensory "barrel" cortex and that this physiological state is beneficial for faithful encoding as opposed to stimulus detection (Nicolelis, 05; Swadlow, 03). Our data might also suggest that subliminal stimulation reduces synchronous alpha activity in S1. In the pre-trial period this would reflect enabling a physiological state related to increased anticipation and decreased noisy background activity which is beneficial for performance. Further studies could investigate the relationship between oscillatory activity over the somatomotor cortex and the effects of subliminal stimulation.

Together, the results of this dissertation regarding the role of S1 in vibrotactile WM suggest that S1 is not actively involved in the maintenance of the WM trace but that the physiological state of S1 is dynamically regulated to optimize task performance. The proposed dependence of S1 activity during the early delay period on the subjects' encoding efficiency could be tested by training subjects in the vibrotactile delayed discrimination task and analyzing changes in performance and S1 activity over time.

5.3. The role of implicit LTM representations in vibrotactile WM

Already Cowan (93; 88) emphasized the importance of activated LTM representations for WM. More and more behavioral evidence suggests that in magnitude discrimination tasks, implicit LTM representations about the average value of the stimulus set presented during the experiment influence task performance giving rise to the TOE (Sinclair und Burton, 96; Hellstrom, 85; Masin und Fanton, 89). Results of the behavioral experiments of this dissertation indicate that the TOE is a robust phenomenon in vibrotactile discrimination tasks independent of specific task parameters (*Study IV*). The fMRI data (*Study V*), additionally suggest, that during the presentation and delay period current sensory evidence provided by the vibrotactile standard stimulus is integrated with the representation about the average stimulus. The somatosensory cortices and the PPC, which have been shown to be involved in encoding and maintaining the vibrotactile stimulus, are associated with this integration process. These results provide neural evidence for sensory accounts that explain the TOE by assimilation or integration processes (Helson, 64; Hellstrom, 85). In addition to this pre-decisional source, it could be that in trials where the sensory evidence about the first stimulus is weak or completely lost, subjects could base their discrimination on the average representation only (Masin und Fanton, 89). The study was not designed to decide between pre-decisional and decisional accounts of the TOE but it shows that the TOE at least partly results from pre-decisional processes. Further studies are necessary to disentangle the relative impact of these implicit LTM before and during decision making. Interestingly, the subjects were not aware that they used average information. Therefore, it seems that the TOE in vibrotactile discrimination is another example of how average or prototype information implicitly influences behavior (Hellstrom, 85).

5.4. An integrated model for vibrotactile working memory

I would like to conclude by integrating the findings of this dissertation and previous studies on vibrotactile WM (see Figure 3).

The neural *representation format* of the frequency of vibrotactile flutter stimuli in WM is a firing rate code, i.e., the neuronal firing rate parametrically varies depending on the

frequency of the presented vibration. This firing rate code is a unique feature of vibrotactile WM and substantially different from representation formats for object or spatial information; whereas object WM has been reported to rely on a categorical code with neurons selectively firing for a specific object or color (Fuster und Jervey, 81), spatial WM has been demonstrated to rely on a code that is tuned to a specific location with neurons firing maximally for the preferred location and decreasing firing rates with increasing location from the preferred location (Funahashi et al., 89). S1 generates the rate firing code and is, therefore, crucially involved in the *encoding* of vibrotactile information into WM. In humans, this encoding process is supported by verbal processes. The findings of this dissertation indicate that the vibrotactile WM trace is not actively maintained in S1. This is in line with findings in the visual and auditory modality where modality-specific storage of stimulus features is supported by the modality-specific sensory associated cortex but not primary sensory cortex (for an extensive review see (Pasternak und Greenlee, 05)). The tactile posterior association areas actively maintaining the vibrotactile memory trace are S2 for maintenance in the early delay period and the PPC for sustained maintenance. This suggests that the neural structure of WM is similar for the different modalities with stimulus encoding in primary sensory brain regions and maintenance in a distributed network including the modality-specific posterior association cortex. However, during the early delay period, activity in S1 can still be enhanced reflecting ongoing consolidation processes. The occurrence of S1 activity during the early period is related to encoding efficiency which depends on the subjects' ability and training. From S1, the rate code is transmitted to S2 and the inferior PPC. Both regions convey the information to lateral PFC and PMC. All these regions exhibit increased activity during vibrotactile stimulation which is parametrically modulated by vibration frequency. The existence of two populations of neurons with positively and negatively modulated firing rates in these regions increases the fidelity of the memory representation. The *maintenance* of a vibrotactile memory trace and vibrotactile *decision making* are supported by a distributed network of overlapping brain regions including S2, the PPC, the lateral PFC, and the ventral and medial PMC. The decision process evolves gradually in these brain regions and is realized by neurons encoding the difference between both vibrations.

Together, many brain regions conjointly enable vibrotactile WM. In addition, there is a gradual specialization of brain regions rather than an absolute specialization. Whereas the inferior PPC with its close connections to the somatosensory cortices might be relatively more important for the sustained maintenance of the vibrotactile memory trace, the PMC as an interface between sensory and motor regions might be especially suited to initiate the comparison process evolving into a decision. On the other hand, the lateral PFC is involved in active maintenance and decision making but its major role is the *control* of ongoing information processing in the other regions. The *control function of lateral PFC* during vibrotactile decision making is reflected by increased connectivity of lateral PFC with S2 and with the inferior PPC during active memory retrieval and by increased activity of the lateral PFC with increased task difficulty determined by Weber's law.

LTM representations reflecting the average vibration frequency heavily influence vibrotactile WM. First, in somatosensory brain regions sensory evidence about the current vibration is integrated with this average representation during stimulus encoding and maintenance. Additionally, the average information is used as a standard for the decision process when sensory evidence about the first vibration is weak or lost.

The physiological state of S1 in the pre-trial period determines the vibrotactile WM performance. On the one hand, top-down modulation in form of spatial selective attention towards the target finger primes S1 and facilitates subsequent processing. On the other hand, less noisy thalamo-cortical bottom-up processing also facilitates task performance.

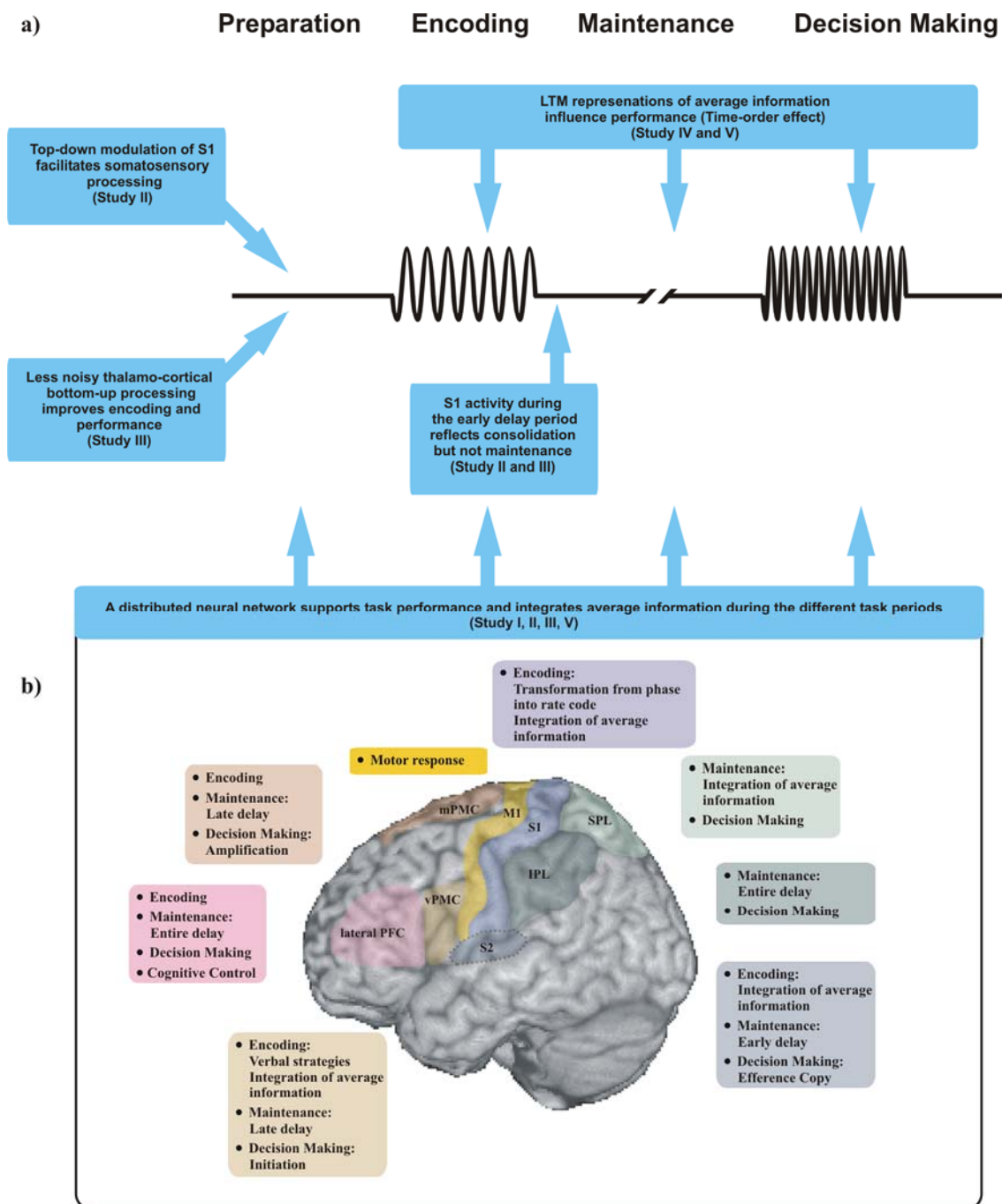


Figure 3. An integrated model of vibrotactile WM. a) summarizes the major claims of the different studies of this dissertation. b) shows the main regions of the neural network related to the different task periods. Please note that neural network supporting vibrotactile WM is much broader than depicted here. Abbreviations: S1, primary somatosensory cortex; S2, secondary somatosensory cortex; M1, motor cortex; mPMC, medial premotor cortex; vPMC, ventral premotor cortex; PFC, prefrontal cortex; IPL, inferior parietal lobe; SPL, superior parietal lobe.

Of course, WM for vibrotactile information lacks obvious ecological validity. However, I believe that the vibrotactile delayed discrimination task provides a useful model for studying the neural basis of the multitude of processes linking perception and action as well as known psychophysical phenomena such as the TOE or Weber's law that commonly contribute to WM. At a later stage, this knowledge can be used to study more complex cognitive activities such as Braille reading or tactile object recognition which heavily relies on the interaction between the different somatosensory modalities and motor functions.

6. Conclusion

The results of this dissertation contribute to the existing literature on vibrotactile WM by suggesting that:

- A broad network of brain regions - much broader than known from previous studies in non-human primates - supports the performance of a vibrotactile delayed discrimination task. In particular, the PPC is involved in active maintenance and decision making.
- S1 does not contribute to the active maintenance of the vibrotactile memory trace. The level of activity in S1 depends on the efficiency with which subjects encode the vibrotactile stimulus.
- The physiological state of S1 in the pre-trial periods reflects task demands and influences performance.
- LTM representations, that give rise to the TOE, influence neural processing and performance in vibrotactile delayed discrimination.

Together, this dissertation supports the view that convergent evidence by complementary experiments in humans and monkeys, as well as the application of multiple methods, can help to elucidate the cerebral organization of cognitive functions in the primate brain.

7. Literature

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