TACTILE MENTAL REPRESENTATIONS

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Abbreviations

BA	Brodmann area
BOLD	Blood oxygen level dependent
DMTS	Delayed match-to-sample
EEG	Electroencephalography
ERP	Event related potential
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
IFG	Inferior frontal gyrus
IPS	Intraparietal sulcus
MI	Mental imagery
MVPA	Multi-voxel pattern analysis
PFC	Prefrontal cortex
PMC	Premotor cortex
PPC	Posterior parietal cortex
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SMA	Supplementary motor Area
SVR	Support vector regression
TMS	Transcranial magnetic stimulation
WM	Working memory

Contents

Abstract

The human ability to mentally represent and manipulate information in the absence of sensory stimulation is key for any higher cognitive functions. Empirical neuroscientific research on mental imagery (MI) and working memory (WM) addresses the question of how our brain represents various types of mental contents. Critically, most research stems from studies in the visual modality, leaving open the question of whether findings, models and theories generalize to other modalities.

In my work I focused on the mental representation of tactile contents. To empirically address what brain regions code different types of mental content, two fMRI studies on MI, one WM EEG study and four fMRI WM decoding studies were conducted. We found that posterior parietal regions and primary somatosensory cortex code spatial features of tactile stimuli. In contrast, when participants memorized more abstract stimulus features such as vibratory frequency, intensity or duration, the prefrontal cortex was found to exhibit multivariate parametric codes specific to the mental content. This finding was also replicated in the visual and auditory modalities.

These results support the view that the *abstractness* of a mental representation determines which brain regions exhibit content-specific codes, where the gradient of a*bstractness* stretches from sensory to categorical or parametric content types. This gradient maps onto the hierarchical organization of the cortex. In parallel, predictive brain mechanisms also rely on the hierarchical interaction of bottom-up and top-down processes. I will suggest mechanisms for how these well-established hierarchical processing principles relate to the representation of mental contents.

Zusammenfassung

Die menschliche Fähigkeit, in Abwesenheit von sensorischer Stimulation Informationen mental zu repräsentieren und weiterzuverarbeiten, stellt eine Schlüsselfunktion für höhere kognitive Aufgaben dar. Empirische, neurowissenschaftliche Untersuchungen zur mentalen Imagination und zum Arbeitsgedächtnis beschäftigen sich mit der Frage, wie unser Gehirn unterschiedliche Typen mentaler Inhalte repräsentiert. Hierzu konzentrierte sich die Forschung bisher meist auf die visuelle Modalität. Dies lässt die Frage unbeantwortet, ob sich die Resultate sowie Modelle und Theorien auf andere Modalitäten generalisieren lassen.

Der Schwerpunkt meiner Arbeit liegt auf der mentalen Repräsentation von taktilen Inhalten. Welche Gehirnregionen unterschiedliche Typen mentaler Inhalte kodieren, wurde empirisch in zwei fMRI Studien zu mentaler Imagination, einer EEG Arbeitsgedächtnisstudie sowie vier fMRI Arbeitsgedächtnis-Dekodierungsstudien untersucht. Dabei fanden wir heraus, dass posterior parietale Areale und der primäre somatosensorische Cortex räumliche Eigenschaften taktiler Reize kodiert. Wenn Probanden im Gegensatz dazu abstraktere Reizeigenschaften, wie die Vibrationsfrequenz, Reizintensität oder Reizdauer erinnerten, fanden wir stimulusspezifische, multivariate, parametrische Codes im präfrontalen Cortex. Dieses Ergebnis konnten wir in der visuellen und auditorischen Modalität replizieren.

Unsere Ergebnisse stützen die Sichtweise, dass die *Abstraktheit* von mentalen Inhalten bestimmt, welche Gehirnregionen inhaltsspezifische Codes zeigen. Dabei umfasst die *Abstraktheit* mentaler Repräsentationen sensorische bis hin zu kategorialen oder parametrischen Inhaltstypen. Dieser Gradient bildet sich auf die hierarchische Organisation des Cortex ab. Gleichermaßen basieren prädiktive Gehirnmechanismen auf der hierarchischen Interaktion von *Bottom-up* und *Top-down* Prozessen. Ich werde Mechanismen vorschlagen, wie diese etablierten, hierarchischen Prozessierungsprinzipien in Beziehung zur Repräsentation von mentalen Inhalten stehen können.

List of original articles

This dissertation is based on the following articles:

Schmidt T.T., Ostwald D., Blankenburg F. (2014): Imaging Tactile Imagery: Changes in brain connectivity support perceptual grounding of mental images in primary sensory cortices. NeuroImage, 98:216-224

Schmidt T.T., Blankenburg F. (initial submission November 2017, revision submitted February 2018): The 'tactospatial sketchpad': Decoding the working memory of tactile stimuli with spatial layouts. NeuroImage

Spitzer B., Gloel M., **Schmidt T.T.**, Blankenburg F. (2013): Working Memory Coding of Analog Stimulus Properties in the Human Prefrontal Cortex. Cerebral Cortex, 24(8):2229-2236

Schmidt T.T., Wu Y.-H., Blankenburg F. (2017): Content-specific codes of parametric vibrotactile working memory in humans. Journal of Neuroscience, 37(40):9771-9777.

Wu, Y.-H.*, Uluç I.*, **Schmidt T.T.**, Tertel K., Kirilina E., Blankenburg F. (2017): Overlapping frontoparietal networks for tactile and visual parametric working memory representations. NeuroImage, 166:325-334.

Uluç I., **Schmidt T.T.**, Wu, Y.-H., Blankenburg F. (submitted February 2018) Content-specific codes of parametric auditory working memory in humans. NeuroImage

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1. Introduction

It is a crucial human ability to mentally represent information in the absence of sensory stimulation. This ability is a prerequisite for higher cognitive functions, decision making, and any purposeful behavior. It allows reflecting on oneself, remembering material from the past and simulating the future. It also crucially relates to human consciousness and has therefore attracted philosophers as well as empirical researchers in the field of psychology (Soto and Silvanto, 2014).

In the work comprising my thesis, I took an empirical approach to the question of how our brains temporarily represent mental content. Psychological and neuroscientific research on this matter has been conducted with two types of tasks: mental imagery (MI) and working memory (WM). The literature of both domains contains overlapping conceptual distinctions between two types of mental contents. Despite the use of different terminology, these fall into the dichotomous categories of either sensory or language-dependent contents. It appears that this distinction has had a strong impact on neuroscientific endeavors to identify brain regions that code the content of mental representations. Given that most of the research thus far has been conducted in the visual domain, there are many questions that remain unanswered and many theories without validation across modalities. I therefore set out to add empirical data from the tactile domain to test whether the suggested models can also explain findings across modalities.

I will start by exploring the commonalities and differences of MI and WM tasks and how they constitute a unique window for empirical research into the brain mechanisms underlying mental representations.

1.1 The study of mental content representations

The study of how our brains represent information in the absence of sensory stimulation is dominated by two overarching topics: (1) How are different types of mental contents represented by different neuronal codes? Or formulated differently: What is the nature of the neuronal codes in our brains? (2) What brain regions contain such content-specific codes?

While mental content is *per se* private[1], well designed experiments offer a high degree of control over the material that a person retains. Experimental paradigms developed in the study of MI and WM achieve this by asking participants to perform tasks that necessitate a specific mental representation in order to produce an appropriate behavioral response. Task performance then provides a measure of participants' cooperation and of the extent to which they successfully formed the specified mental representation. Both MI and WM have been defined as the ability to represent and manipulate mental content (Tong, 2013). While the study of both cognitive functions aims at revealing the nature of mental representations, two lines of literature have evolved that rarely cross-reference each other.

What MI and WM tasks have in common is that they both require the participants to mentally represent a specified content. The main difference between MI and WM tasks is, however, that the mental content is either constructed from memory or derived from perception. MI tasks often use cues to instruct participants to retrieve information from long-term memory in order to form a mental image. This image constitutes the content of a mental representation. In contrast, WM research typically applies delayed match-to-sample (DMTS) tasks. Here, one or multiple stimuli are presented to the participant, who encodes and retains task-relevant information during a following delay phase. In this way the content of the mental representation is derived from perception and not from memory. In both tasks, this content is temporarily maintained, and it can be assumed that the simple maintenance of mental content is realized by the same neuronal mechanisms.

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[1] Most aspects of mental states are considered to be accessible only from a first-person perspective. While it appears possible that some facets of mental representations can be inferred (or read out) via physiological measurements, the phenomenal aspects of mental representations cannot. Phenomenal aspects are also referred to as subjective or qualitative experiences and in the philosophy of mind discussed under the concept *Qualia* (Nagel, 1974; Byrne, 2016).

Several additional subtle but important terminological distinctions are discussed within human memory research. The works of Hermann Ebbinghaus (1985) and William James (1890) are considered to be the starting point for the scientific study of human memory. In their work, one finds a distinction between primary and secondary memory, which roughly corresponds to the distinction between the two concepts that we today commonly call WM and long-term memory. The Atkinson and Shiffrin model made such a separation explicit, by distinguishing between (1) a sensory register, (2) a short-term store, and (3) a long-term store of memory (Atkinson and Shiffrin, 1968). The short-term store is thought to receive information from both the sensory register and the long-term store. It is thought to temporarily maintain information and make it available for any mental actions operating on the represented information. Some authors advocate reserving the term short-term memory for the simple temporary storage of information, while WM should refer to both storage and manipulation (Baddeley, 2012). However, the exact distinction depends on the definition, with slight differences among authors (discussed by Cowan, 2009). Today, the terms short-term memory and WM are often used interchangeably.

In an attempt to fuse the terminology used in the MI and WM literature, it was suggested to speak about passive and active / dynamic components of WM, where the first refers to pure maintenance and the latter to the update or manipulation of content (Tong, 2013). In the following, I will consider the following phrases synonymously: short-term memory, (passive) WM, content representation, retention/ maintenance of information / a mental representation / a mental image / content of WM.

1.2 Models and controversies of the representation of mental content

In this chapter, I will provide an overview of historically influential and popular models of how our brains represent mental content.[2] I will start with the so-called *imagery debate,* which dominated the MI literature for decades. This debate concerned the nature of the codes our brains use to represent and process information. Classic behavioral experiments in early cognitive psychology were later supplemented with neuroimaging data to distinguish between *symbolic* and *depictive* codes. Also in the field of WM research multiple psychological models were formulated to account for different types of content representations, for example the extremely influential *Baddeley & Hitch* model that formulates the idea of multiple WM components corresponding to different types of mental content representations.

In both MI and WM, an apparent dichotomy emerged between two types of mental content. Neuroscientific reports also contributed to the view that different types of content are either coded in sensory or prefrontal cortices. Thus far, suggestions for resolving this controversy have mainly been based on studies in the visual domain and evidence from other modalities has been lacking.

1.2.1 The imagery debate

Do our brains function like computers? How should computers be equipped to perform in a human-like fashion? These were, and to some degree still are, central questions in artificial intelligence research. In the development of computer intelligence approaches, it was important to clarify how hard- and software must be structured in order to be – in principle – able to achieve human-like performance. It was suggested that our brains process information in the language of mathematics, which can be expressed in propositional logic (Pylyshyn, 1973, 1981). Just as computers process information in *symbolic codes*, our brain, according to this suggestion, converts perceptual

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[2] Due to the overwhelming interest and amount of work on this key ability of the human brain, such an overview cannot be complete. There are several other big controversies concerning the nature of mental representations which will not be discussed, such as the discussion about the capacity of WM and its relation to measures of intelligence (Miller, 1956; Cowan, 2001; Ma et al., 2014).

information into language-like, symbolic propositions. It would then follow that human reasoning is based on logic-like inferences (e.g., A→B, given that A is true, implies B). Alternatively, it was suggested that the human brain represents information in codes that reflect the physical perceptual properties of objects, as transmitted by the senses (Kosslyn, 1980). It was argued that it is therefore not sufficient for artificial intelligence to use symbolic codes, as these would not have the computational properties to implement human-like intelligence (Tye, 1991; Pearson and Kosslyn, 2013).

Famous psychological experiments presented evidence that mere processing of rules and symbols cannot account for higher human cognition. The study of MI has centrally contributed to this debate. Most famously Shepard and Metzler (1971) demonstrated that mental rotation relies on information represented in analog form. Their participants compared 2-dimensional images of 3-dimensional objects. They had to decide whether two images display the same object at angles of rotation. If objects were mentally represented in symbolic codes, the matching of two objects would require the same amount of computation, regardless of the angle of rotation. However, the authors found that reaction times increased linearly with the angle of rotation, indicating that participants mentally rotate the object by representing the spatial relationships as they are presented in the real world.

Stephen M. Kosslyn performed a series of imagery experiments where participants had to *scan* a mental image to perform spatial judgments (e.g., the *mental island-walk* experiment; Kosslyn et al., 1978). Kosslyn hypothesized that the human brain represents information in so-called analog, pictorial, or *depictive* formats, rather than as symbols. In this view, mental representations directly reflect physical stimulus properties. Mental representations of spatial layouts are based on the actual distance of the real object – e.g. an actual XY-coordinate space. Hence, mental images are not represented in the terms of propositional logic. Instead, they are directly linked to perceptual processes, which automatically code isomorphic properties, in the same way that they usually process information directly obtained from the senses.

1.2.2 Models of content representations in WM

The multicomponent model of WM

Baddeley and Hitch, (1974) used the term WM to assert that the short-term store, described by Atkinson and Shiffrin (1968), should not be considered as a unitary store. Findings on the short-term retention of different types of mental content indicated separate storage mechanisms for different mental content, as some types of content interfere with each other while others do not. Baddeley and Hitch therefore suggested a multi-component model of WM, comprised of: (1) the visuo-spatial sketch pad, (2) the central executive, and (3) the phonological loop. The *Baddeley & Hitch* model was intended to function as a broad theory, where the exact implementation of sub-processes within these components should be worked out as research advances (Baddeley, 2012). The model was later also supplemented by Baddeley with a fourth component: the episodic buffer (Baddeley, 2000).

Due to its general nature the model is broadly consistent with other WM models (for a discussion see Baddeley, 2012), and even today continues to have an impact on current research (Logie and Cowan, 2015). Different WM models strongly vary as to how much they aim to establish direct links between the model and neuronal mechanisms. Within the multicomponent model of Baddeley, it is unclear what type of cerebral counterpart should be expected for *the central executive,* as this component is very abstractly described. On the other hand, multiple recent neuroimaging studies have attempted to map where in the brain visual and/or spatial content is reflected in neuronal activity. These endeavors can be considered as an attempt to identify the neuronal implementation of the visuo-spatial sketchpad. In summary, the basic assertion of a multicomponent model is that content of different types is retained by different neuronal mechanisms.

The role of attention

Nelson Cowan proposed that instead of using distinct buffer systems, as suggested in Baddeley's model, the key function of WM is to make some information temporarily available for conscious access. He suggests that it is attentional mechanisms that act on other systems, e.g., on long-term memory systems, to hold particular WM contents in a temporarily heightened state of availability (Cowan, 1988, 2009; Logie and Cowan, 2015). At first glance, this suggestion seems to be very much in opposition to Baddeley's model. However, Baddeley (2012) and Cowan (2009) both acknowledge their disagreement mainly concerns the terminology, while both models capture well the current state of empirical data.

The study of attentional mechanisms as such appears delicate to me.[3] For the discussion of my empirical work, I agree with the position that it is not meaningful to consider attention and WM as independent psychological constructs (Gazzaley and Nobre, 2012). The argument that activity for which content-specificity can be shown may reflect attentional mechanisms rather than content representation, therefore, appears to be an artifact of terminology. It seems more useful to view content-specific brain activity as representing mental content within distributed networks (Schlegel et al., 2013; Larocque et al., 2014; Lewis-Peacock et al., 2015; Postle, 2015; Lee and Baker, 2016).

1.2.3 Sensory-recruitment versus prefrontal content codes

Based on these psychological models of MI and WM, neuroscientific work has attempted to identify what brain regions code the content of mental representations. Two principal opposing positions

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[3] While much experimental work has been interpreted as assigning the PPC the role of implementing special aspects of attention (e.g. in the somatosensory system by Goltz et al., 2015), one should acknowledge that few psychologists or neuroscientists are satisfied with the current definitions of attention. Most definitions are not much better than the definition offered by William James: *"Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence."* (James, 1890/1950). The fact that the term attention has some commonly-held intuitive meaning has, in my personal view, hindered the development of more adequate terminology that would map much better onto brain function.

have been taken. One position assumes that sensory regions function as a buffer and that content is mainly stored in these regions. The other position states that it is mainly prefrontal regions that exhibit content-specific codes. While neither of these positions has been formulated in an exclusive way, different lines of research have looked for evidence in support of one or the other hypothesis.

In the MI literature, Kosslyn emphasizes the importance of topographically organized brain regions, such as early visual cortices, for implementing a visual buffer (Kosslyn, 2005). He compares their function to a pegboard (rather than a *blackboard*), where different types of local information are represented topographically. Recruitment of sensory regions is consequently seen as evidence for *depictive* codes in the brain, due to their retinotopic organization (Kosslyn et al., 2001). With the rise of positron emission tomography, imagery research started to test for the recruitment of perceptual regions (reviewed in Kosslyn, 2005). As this hypothesis is so central and dominates the imagery literature, most functional magnetic resonance imaging (fMRI) studies also focus on it (a meta-analysis can be found in McNorgan, 2012; a recent review with links to clinical studies in Pearson et al., 2015) and current neuroimaging studies support the importance of perceptual processes for MI (Cichy et al., 2012). However, conflicting reports exist on the role of very early visual cortices (Kosslyn and Thompson, 2003).

In WM research, the view that the prefrontal cortex (PFC) plays a key role in retaining mental content has a long history (a short historic overview can be found in Wang, 2005). Already in the 1930s Jacobsen reported that prefrontal lesions in non-human primates led to deficits in spatial WM abilities (Jacobsen, 1936). Early intracranial recordings in monkeys further demonstrated neuronal activity in the PFC throughout a WM delay phase (Fuster and Alexander, 1971; Kubota and Niki, 1971). Patricia Goldman-Rakic brought together psychological models of human WM with neural recordings from non-human primates to support the view that the PFC comprises central buffer functions for retaining information on spatial layouts during visual WM (Goldman-Rakic, 1987, 1995; Funahashi et al., 1989). The specificity of prefrontal responses to the content of WM was further emphasized by studies on tactile WM. In his seminal electrophysiological investigations Ranulfo Romo found parametric modulations of neuronal firing during the retention of vibratory frequencies in non-human primates (Romo et al., 1999). Finally, human research has also revealed delay activity in prefrontal cortices (discussed in Curtis and D'Esposito, 2003).

On the other hand, it has also been established that WM sometimes activates sensory regions. Different authors have therefore emphasized the crucial involvement of these regions in coding the content of WM (Pasternak and Greenlee, 2005), which is referred to as *sensory-recruitment*. Sensory-recruitment is wholly compatible with Baddeley's multicomponent model. While the model is general enough to not explicitly state how the visuo-spatial sketchpad is implemented, several authors have suggested that visual cortices implement the corresponding information buffers (Baddeley, 2012). However, it remains a hotly debated issue how to evaluate the different lines of experimental evidence (Gayet et al., 2017; Xu, 2017). Multiple recent human fMRI studies identified sensory as well as posterior parietal regions as coding WM content and failed to find such codes in the PFC (reviewed in Lee and Baker, 2016 and D'Esposito and Postle, 2015). These studies presented a serious challenge to the relevance of the PFC for content-coding and put forward the idea of sensory-recruitment.

Different suggestions have been made to explain the apparently contradictory findings on sensory and prefrontal signatures of mental content representations. One perspective is that the role of the PFC is not primarily the representation of content, but rather it is where *cognitive control* functions provide support for information storage (Postle, 2006; Sreenivasan et al., 2014; D'Esposito and Postle, 2015). This view does not ascribe any major functional relevance to the findings of content codes in the PFC.

Another line of argumentation associates different types of mental content with different brain regions.

1.2.4 The relationship of content types and the cortical topography of content representations

From the empirical findings and theoretical discussions, a somewhat dichotomous view of two types of mental content has evolved in both, the MI and the WM literature. However, slightly different terminology has been used. In the MI literature the first type of content has been termed *symbolic* or non-pictorial to refer to information represented in a discrete or digital format. The second type was termed *depictive* and refers to contents in sensory-like formats. The WM literature also makes this distinction when distinguishing between *sensory WM* and the retention of conceptual or language-dependent information (Pasternak and Greenlee, 2005). **Figure 1** summarizes the most prevalent terms from both MI and WM research that reflect the two major classes of content type. A more general taxonomy including the philosophical debate on mental representations can be found in Strasser (2010). Here, the corresponding distinction is between what are termed conceptual and non-conceptual representations, where the former are typically language-dependent.

Psychological and neuroscientific work has been strongly influenced by this distinction, and research in MI and WM has aimed to find evidence for one or the other type of mental content representation. This distinction has been supported by the findings of Lee et al., (2013). In this fMRI study, participants performed a DMTS task in which either the visual appearance or category information of a stimulus was retained. The former was related to occipital regions, the latter to the left PFC.

symbolic	depictive
language-dependent	non-language dependent
verbal	non-verbal
categorical	non-categorical
conceptual	non-conceptual
non-sensory	sensory
non-pictorial	pictorial
non-phenomenal	phenomenal features
	visuospatial
semantic	

Figure 1: Two main classes of mental representations can be found in the literature on MI and WM. Variable nomenclature is used, with slight variations in meaning and precision. Within the two classes the terms are mostly used interchangeably.

An alternative explanation was suggested by Bancroft et al., (2014). They propose that stimulus complexity determines whether the PFC exhibits content-specific codes. Their notion of complexity is strongly related to WM load, as they focus on the number of features that have to be retained. For example, a DMTS task can use detailed images of animals; however, as long as only the animal category (e.g., dog or cat) is memorized, the WM content has low complexity. In contrast, the retention of visual details is considered to be more complex. This notion of complexity does not distinguish between different types of content. The explanation that recruitment of sensory regions is only required with increasing complexity might explain much of the current data. However, it does not address the extent to which participants apply different memory strategies. It is very likely that participants use verbal labels if only a few features have to be memorized. In this case the given data would better be explained in terms of the established dichotomy between verbal and non-verbal codes.

The most general explanation for the findings of content representations in different brain regions was offered by Christophel et al. (2016). They suggested that practically all regions in the brain can represent WM content, and argue against the idea that specific brain regions function as buffers.

In contrast, they suggest that the nature of mental contents follows a gradient of *abstractness*, from sensory-like to language-like or semantic representations. Whether a brain region exhibits content-specific codes mainly depends on the task demands and on the corresponding level of abstractness. Hierarchically lower cortical regions are thought to code sensory-like contents, while more abstract types of information, e.g., language-like codes, are retained by higher order areas. Thereby, their so-called *distributed account of WM* captures the idea of sensory-recruitment and also the finding that the PFC sometimes exhibits content-specific codes. Leavitt et al., (2017) propose a more narrow range of regions that code mental content. They argue that the empirical data do not support the assertion that content-specific activity is distributed over the entire cortex, but instead within a defined subset of regions.

In sum, no final consensus has been reached on the relationship between content type and the brain regions responsible for retaining that content. A distributed account of WM suggests that regions at different hierarchical levels are recruited when different degrees of abstractness must be retained in memory. However, it remains unclear whether abstractness follows a clear gradient, or whether the rather categorical distinction of content types determines the topography of WM. An important empirical shortcoming is that, the discussion is primarily based on research from visual studies. Extending the empirical work to the somatosensory modality will allow us to test the proposed models as overarching accounts independent of modality.[4]

1.3 Mental content representations in the somatosensory system

To allow for a better understanding of information processing within the somatosensory system, I will review the cortical pathway of tactile information processing during perceptual processes. Next, I summarize previous work on tactile MI and WM from non-human primates and humans

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[4] Interestingly, Alan Baddeley has also reflected on the historical development of his model and emphasizes that currently very little is known about the integration of somatosensory information. He furthers stresses that his assumption that information from all sources converge on the visuo-spatial sketchpad is far from definitely established (Baddeley, 2012).

using different recording and data handling approaches. In a short methodological note, I explore the elegance of multivariate analysis techniques for relating brain activity to mental content representations.

1.3.1 The somatosensory system – a short overview

The hierarchical processing of visual information reaching the cortex via the thalamus is well known and discussed in basic undergraduate textbooks (Kandel et al., 2014). The work of Felleman and Van Essen (1991), which includes a visualization of the complex circuitry within the visual system, has achieved substantial fame. It is, however, much less widely-known that the same publication also contains a proposed hierarchy for somatosensory and motor areas (Figure 7 in Felleman and Van Essen, 1991). A schematic representation of the anatomical and hierarchical organization within the somatosensory system is presented in **Figure 2**, summarizing their proposition. Primary somatosensory cortex (SI) subregion Brodmann Area (BA) 3a mainly processes proprioceptive signals. The thalamic afferents transmitting signals from cutaneous receptors innervate BA3b, BA1, and BA2 (Kaas, 1993; Grefkes et al., 2001). Their anterior-posterior gradient reflects their hierarchical organization within SI. Details on SI's and secondary somatosensory cortex's (SII) microstructural organization and anatomical variability can be found in Geyer et al., (1999b, 2000) and Grefkes et al., (2001) and relevant fMRI studies on their functional organization in Eickhoff et al., (2007a), and Martuzzi et al., (2014).

Both in the visual and the tactile system, early sensory cortices directly reflect spatial stimulus properties following a retinotopic or somatotopic organization. Comparable to the well-established phenomenon of orientation coding in the primary visual cortex, orientation-tuned neurons can also be found in SI subarea BA3b (Bensmaia et al., 2008). There is an increase of feature-specific response properties along the hierarchy of somatosensory processing areas (DiCarlo and Johnson, 2002; Sripati, 2006), with primary and SII mostly involved in the processing of simple shape features (Hsiao et al., 2002). This is similar to the organization of the visual system (Yau et al., 2009).

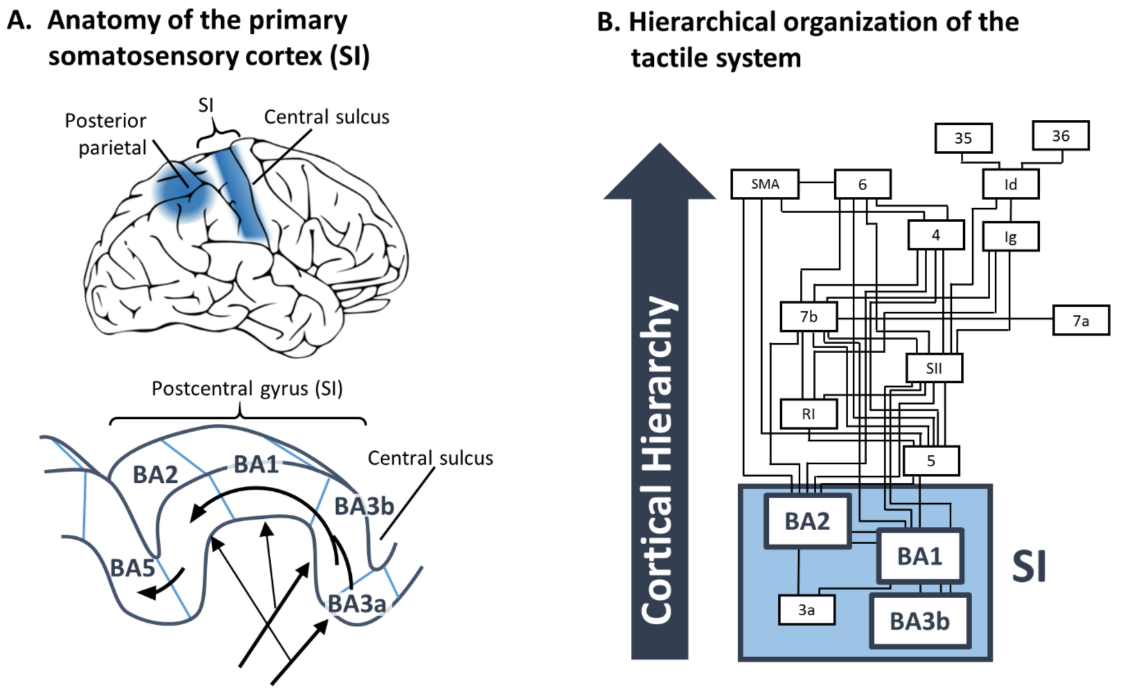

Figure 2: Anatomical and hierarchical organization of the somatosensory cortical system (based on Felleman and Van Essen 1991; Kandel et al. 2014).

While the functional role of separate regions processing higher-level features and their relation to supramodal processes are less well understood (Burton et al., 2008), it has been established that multiple re-mappings, such as from retinotopic to ego- and allocentric coordinate systems, are related to posterior parietal regions (Lloyd et al., 2003; Grefkes and Fink, 2005; Badde et al., 2015; Heed et al., 2015).

1.3.2 Empirical work on the mental representation of tactile content

Previous work on the mental representation of tactile information is mainly found within WM studies and less so in MI. Different methodologies have been used, ranging from non-human primate electrophysiological investigations to several human electroencephalography (EEG), some fMRI and also a few transcranial magnetic stimulation (TMS) studies.

Human fMRI studies of tactile mental imagery

Human neuroimaging work on tactile MI is very limited. McNorgan (2012) summarized the available fMRI imagery studies from different modalities and identified only three tactile studies. In two of these studies, the participants had to imagine somewhat complex properties, e.g., performing a sensory action or haptic/form judgments (Newman et al., 2005; Olivetti Belardinelli et al., 2009). A study by Yoo et al. (2003) was the only one that directly compared a perception condition with an imagery condition. They used brushing stimuli and report time-course data from SI and SII. These showed signal increases in both regions related to imagery. At the time, this study was the only direct human fMRI evidence for sensory-recruitment in tactile MI.

Recently, De Borst and De Gelder (2017) used a multivariate whole-brain searchlight approach in a paradigm where little figures were presented as haptic stimuli. They found some evidence for overlapping representations between perception and imagery in sensory regions.

Non-human primate studies of tactile working memory

The first neurophysiological tactile WM study that gained broad attention was reported by Zhou and Fuster (1996). They obtained intracranial recordings from the SI of monkeys performing a haptic DMTS task. Monkeys had to touch objects with different surface features. They found units with sustained changes in firing frequency throughout the delay period between a sample and a comparison object. This finding was the first evidence that some neurons in SI are involved in haptic WM. Notably, this was a haptic task, which involved grasping the objects. Later WM studies mainly avoided active touch and used stimuli presented without active exploration of objects. Zhou and Fuster (2000) extended the task to include a condition where monkeys were presented with a visual cue corresponding to specific objects. After a delay, monkeys had to match the cue to a tactile object. They found cells that reacted similarly to the visual cue as to the associated tactile object. Zhou and Fuster do not make any link to MI; instead, they only speak about cross-modal associations mediated by higher-order brain regions. However, their data well suit the interpretation that monkeys actively imagined the cued tactile object in order to perform the DMTS task. Activation in SI would correspond to sensory-recruitment during MI. As monkeys are intensively trained in such tasks it is, however, problematic to infer the relevance of such activity for normal cognitive functioning.

Romo et al. (1999) presented a milestone finding for the study of primate WM. Monkeys performed a DMTS task for vibrotactile frequency stimuli, while neuronal firing was recorded from the right PFC. Romo and colleagues identified cells whose firing rate was modulated parametrically (either positively or negatively) by the retained frequency. This study was outstanding in that it showed the direct relationship between the content of WM – the retained frequency – and neuronal behavior. Romo and colleagues proceeded to record from more brain regions in similar tactile tasks to dissociate neuronal activity related to stimulus encoding, stimulus retention, decision making and motor preparations/responses (Hernández et al., 2000; Romo et al., 2004). Two review articles summarize their studies (Romo and de Lafuente, 2012; Romo et al., 2012). In short: they associated the activity of SI neurons with sensory encoding and mnemonic representation, and showed that these are related to the firing behavior of cells in SII, medial, dorsolateral and ventral premotor cortex (PMC), as well as in the PFC. Decision-related activity was additionally coded in the primary motor cortex.

Further evidence for an involvement of the PFC in coding semantic information about stimulus category has been recently reported in a tactile non-human primate study. Rossi-Pool et al., (2016) used stimuli that required the monkeys to memorize categorical information independently of the mere physical properties of a stimulus. To this end, they varied the temporal structure of the tactile stimuli. They found that the dorsal PMC retained categorical information, while SI did not contain WM codes.

In sum, there is conflicting evidence on the role of the SI when either haptic surface features or vibrotactile frequencies are retained. For the latter, a well-defined network of regions has been identified in non-human primates that codes WM content, providing convincing evidence for content-specific codes in the right PFC.

Human EEG studies of tactile working memory

Spitzer et al. (2010) were the first to successfully implement a human EEG version of the vibrotactile WM task as it had been applied in non-human primate studies (Romo et al., 1999). Participants had to memorize the frequency of a vibrotactile stimulus presented to the left index finger and perform a two-alternative forced-choice task after a 1.75s retention period. They tested in the time-frequency domain for induced changes in oscillatory responses during the delay phase. Specifically, they tested for parametric power modulations by the retained frequency and identified content-specific beta-band modulation localized to the right inferior frontal gyrus (IFG). While direct mappings between non-human primate and human anatomy are problematic, this finding suggests that in both species similar neuronal representations can be found within the PFC. In a second study Spitzer and Blankenburg (2011) presented two different vibrotactile frequency stimuli to the different index fingers. By applying a visual retro-cue to select one of the two stimuli for maintenance, they were able to render the retained information independent of encoding processes. The to-be-maintained stimulus property was reflected in right prefrontal beta-band power, while stimulus-specific encoding processes were evident in lateralized alpha signatures over somatosensory cortices. In a third study, Spitzer and Blankenburg (2012) tested whether the identified prefrontal beta-band modulation was specific to the tactile modality. Here, they complemented the vibrotactile paradigm with a visual flicker and an acoustic flutter condition. In all three modalities, they found parametric prefrontal signatures of the retained frequency information. This indicates that the PFC signature is related to a stimulus attribute that is represented in a supramodal fashion. Finally, a study by Ludwig et al., (2016) related prefrontal-beta-band signatures to WM deficits in schizophrenia patients.

Another line of human tactile EEG studies has investigated event-related responses (ERPs). Katus et al., (2015) delivered stimuli to different digits of both hands and cued participants for the memory of a particular stimulus which had to be compared to a delayed test stimulus. As had been shown in visual studies, they demonstrated contralateral delay activity, which indicates an involvement of somatosensory cortices in the coding of tactile WM. In another study they used an extended version of their paradigm in which participants had to switch their focus from one hand to the other. They found that it was the expectation of a target stimulus on one or the other hand that was related to the delay activity, and not the location where the stimulus was perceived (Katus and Eimer, 2015). They supplemented this work with a bimodal tactile-visual task, where they interpret differences in delay activity reflecting separate attentional mechanisms (Katus and Eimer, 2016).

Taken together, the studies by Katus and colleagues provide evidence for content-specific sensory-recruitment, limited by the specificity of ERP analyses. Spitzer and colleagues investigated induced changes in the time-frequency domain. Their work on vibratory frequencies revealed that activity in sensory regions was associated with WM encoding, while the maintenance of WM content was convincingly associated with prefrontal parametric oscillatory responses.

Human fMRI studies of tactile working memory

Few human fMRI studies have addressed the question of which regions exhibit delay activity in tactile WM tasks. Preuschhof et al., (2006) tested for the retention of vibrotactile frequency and found bilateral IFG, supplementary motor area (SMA) and the left IPL. Kaas et al., (2007) tested haptic explored object orientation and Kaas et al., (2013) investigated the retention of surface textures. Delay activity was found in SI, SII, posterior parietal cortex (PPC) and PFC. Li Hegner et al., (2010) compared activation when participants performed a DMTS task either with patterned tactile stimuli or with frequency stimuli. SMA, insula and SII activity was revealed in a conjunction analysis of both conditions. Posterior parietal regions, particularly parts of the intraparietal sulcus (IPS), were activated more strongly in the pattern comparison task. Savini et al., (2012) explored the correlates of a tactile n-back task in which a series of bi-dimensional shaped wood pieces (i.e. triangle, square, oval, cube) were used as stimulus material. They report activity within somatosensory cortices, though without a functional interpretation. Spitzer et al., (2014c) compared maintenance with updating of tactile WM. They found activation in the IFG related to both task conditions, where increased functional coupling between IFG and SI was associated with maintenance.

Taken together these fMRI studies consistently report delay activity in the PFC. Furthermore, the PPC and SI were associated with the retention of surface structure or patterned stimuli.

Human TMS studies of working memory

Two studies tested for an interference with tactile WM by TMS. Auksztulewicz et al., (2011) found a disruption of WM when TMS was applied over the right IFG. Zhao et al., (2017) tested for the effects of TMS applied at different phases of the WM delay phase. They varied the timing of the TMS pulse from 100 to 1900 ms after the onset of a vibrotactile stimulus (200ms) which was then retained for WM. Interestingly, they found that TMS over contralateral SI disrupts WM most strongly during an early phase of WM. This supports the view that SI mainly contributes to the encoding of WM or to a transformation of the sensory code into a WM code stored elsewhere for retention.

1.3.3 Multivariate analysis techniques and their relationship to content-representations

Within the last decade, multivariate analyses methods borrowed from machine learning have been successfully applied to human fMRI data. These approaches are also known as decoding or classification techniques. They aim to identify relationships between multi-voxel activation patterns and task conditions (e.g., experimental trials with different WM content), and therefore termed Multi-voxel pattern analysis (MVPA). This makes multivariate approaches sensitive to the content of WM, which goes beyond tracking of delayed activity (Riggall and Postle, 2012; Tong and Pratte, 2012).

Two milestone publications introduced multivariate analysis techniques to the neuroimaging community. Kamitani and Tong (2005) demonstrated that it was possible to determine which of eight gratings was presented to a participant in trial-by-trial fMRI data. These predictions were based on distributed activation levels of multiple voxels in early visual cortices. Also, Haynes and Rees (2006) demonstrated that stimulus orientation can be decoded from activation patterns in early visual cortices. Impressively, they were able to determine, which of two oriented stimuli was presented, even when masking rendered the stimulus invisible for the participants. Soon afterwards, MVPA was applied to the study of WM. Harrison and Tong (2009) demonstrated that they could reliably predict the orientation of a retained stimulus from activation patterns in visual cortices (V1-V4) during a delay period. This study was the starting point for a series of MVPA fMRI WM studies. However, until the studies described in this thesis, there have been no fMRI MVPA studies that have tested for tactile content representations.

1.4 Overall aim of this thesis

The primary aim of this thesis was to improve the understanding of how the human brain mentally retains information in the absence of sensory stimulation, by empirically investigating mechanisms within the somatosensory system. To this end, I aimed to test how different types of mental contents are represented by different brain networks.

Firstly, I hypothesized that MI of tactile stimuli leads to a recruitment of early somatosensory cortices. I further hypothesized that there is a dissociation between the brain regions storing sensory information as opposed to information about more abstract, but nonetheless non-linguistic, stimulus properties. More specifically, I hypothesized that stimulus features such as the spatial layout of a tactile stimulus are retained by sensory and posterior parietal regions, while the somewhat special stimulus feature of frequency is retained by prefrontal regions.

By additionally testing for frequency-specific activity in the visual and auditory modalities, I aimed to test whether the findings of prefrontal content-codes are modality-specific or supramodal. With the combination of these studies, I seek to bridge a gap between electrophysiological findings in non-human primates and recent MVPA fMRI findings.

Based on the empirical evidence I will suggest that a third class of mental content representations are realized by distinct neuronal mechanisms, namely parametric WM codes for abstract magnitude-like features.

2. Summary and discussion of experiments

In this chapter, I will summarize the seven empirical studies that form the core of this dissertation. The first study is reported including details of the experimental methods, as the given dataset has not been published elsewhere, while studies 2 to 7 are summarized and the corresponding publications are attached.

In **study 1**, we tested N = 19 participants with fMRI, and asked whether the same sensory regions are somatotopically activated during perception and imagery of vibrotactile stimuli. We found body-locus-specific SI activity during MI. Notably, only SI subregion BA2 was active during MI. Perception activated all SI subregions. These data provide initial support for content-specific sensory-recruitment when mentally representing sensory images. The simple nature of the imagined stimuli might have had the consequence that hierarchically lower sensory regions, such as BA1 and BA3b, did not need to be recruited. In **study 2** (Schmidt et al., 2014) we focused on sensory-recruitment during imagery of stimuli with a fine-grained spatial structure. To this end, we used patterned Braille-like vibrotactile stimuli that were presented to the left index finger. The N = 14 participants had to form a detailed mental image to perform a probe-task, which required a fine spatial judgment of the imagined stimulus. The analysis of the fMRI data revealed activation of the same SI subregions during imagery as during perception. Additionally, we found that imagery strongly increased the functional connectivity between the left PFC and the SI finger representation. This coupling might be a direct mechanism of how sensory regions are recruited during MI.

Studies 3 - 7 focused on the mental representations of tactile stimuli in WM. Such representations differ from MI in that their content is not constructed from memory but derived from perception and subsequently maintained. For **study 3**, I developed Braille-like tactile stimuli with an amplitude modulated surface-like texture. These stimuli contained spatial information similar to stimuli previously used in the study of visual WM (Christophel et al., 2012). As MVPA studies have revealed that visuospatial information is jointly coded in posterior parietal and visual cortices, we hypothesized that we could decode tactospatial information from the PPC and from somatosensory cortices. We applied an assumption-free searchlight MVPA approach to the fMRI data of N = 22 participants. In line with our hypothesis, we found similar posterior parietal clusters as reported in the study of visual WM. Additionally, our data support the claim that SI can exhibit WM-related codes.

With the following studies we address the apparent contradiction that most human MVPA studies failed to find content-specific activity in the PFC (Bancroft et al., 2014), whereas data from non-human primates has convincingly demonstrated that the PFC retains such codes (Funahashi et al., 1989; Romo et al., 1999). The following studies bridge this apparent gap by demonstrating that human fMRI MVPA studies can also reveal prefrontal WM codes if abstract stimulus features are retained, such as vibratory frequency.

Study 4 (Spitzer et al., 2014b) addressed in an EEG study (N = 26) the question of whether oscillatory responses in sensory and PFC directly reflect so-called ‘analog stimulus properties’ (i.e., intensity and duration) during WM retention. With **study 5** (Schmidt et al., 2017), we were the first to investigate tactile WM representations with MVPA. With an assumption-free searchlight analysis we tested which brain regions have activation patterns that directly relate to the content of WM. Participants (N = 22 included in the analysis) retained vibratory frequencies in a retro-cue, DMTS, two-alternative forced-choice paradigm. As reported in experiments with non-human primates (Romo et al., 1999) and human EEG experiments (Spitzer et al., 2010), our study revealed that the right PFC exhibits parametric WM codes specific to vibratory frequencies. In **study 6** (Wu et al., 2018) we tested whether such multivariate parametric codes are specific to the tactile modality. In a variation of the initial paradigm, we tested in N = 20 participants for WM codes of frequencies that were either presented as vibrotactile or as visual flicker stimuli. This study revealed overlapping clusters within the right PFC for both conditions. The failure to cross-classify activation patterns between modalities leaves open the question of whether it is the same neuronal populations that code the content or whether decoding relies on different underlying population responses. **Study 7** (Uluç et al. submitted) extended this question to the auditory modality. With the same experimental design as applied in study 5, participants (N = 20 included in the analysis) memorized the frequency of acoustic flutter stimuli. As hypothesized, we found that the right PFC codes frequency-specific information. A conjunction analysis with data from study 5 revealed that the PFC clusters of the two studies overlap.

Study 1: Somatotopic recruitment of SI subregions during simple tactile imagery

Introduction

The study of MI has been dominated by work on visual imagery. Extending this work to the tactile modality is crucial in order to identify which processes and representations are modality-specific and what findings generalize across modalities.

Neuroimaging results have supported the view that retinotopic activation of visual cortices during MI reflect spatial features of mental images (Klein et al., 2004; Slotnick et al., 2005; Naselaris et al., 2015). Furthermore, it has been proposed that the more vivid or detailed a mental image is, the more it recruits regions lower in the hierarchy of the visual cortical pathway (Kosslyn and Thompson, 2003).

In comparison to the visual pathway, the somatosensory system comprises fewer processing stages, a fact that makes it easier to study hierarchy-specific activation (Felleman and Van Essen, 1991; Auksztulewicz et al., 2012). In parallel to visual cortices, early somatosensory cortices have been shown to code stimulus features such as orientation and intensity and are somatotopically organized (see **Section 1.3.1**). It remains an open question, which aspects of SI are involved in tactile MI under different circumstances.

In this fMRI study the perception of tactile stimuli at four different body locations (left/right hands/feet) is compared to MI of the corresponding stimulation. We hypothesized that early somatosensory cortices, in particular SI, would be somatotopically activated during MI. To this end we tested for differences in SI activation between perception and imagery in relation to the hierarchical organization of the activated SI subregions.

Materials and Methods

Participants: N = 19 healthy, right-handed volunteers (mean age: 25.7 ± 3.8; 14 females) without neurological or psychiatric disorder completed the study after written informed consent. The study was conducted according to the Human Subject Guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Freie Universität Berlin.

Experimental paradigm: The experimental paradigm constituted a 2 x 4 factorial design with factors PERCEPTION/IMAGERY and LOCATION: left hand thumb (lH), right hand thumb (rH), left foot big toe (lF), right foot big toe (rF). Vibrotactile stimulation was delivered using four 8-dot piezoelectric Braille-like displays (2 x 4 matrix with 2.5 mm spacing) controlled by a programmable stimulator (Piezostimulator, QuaeroSys, St. Johann, Germany), attached to the four body locations. The vibrotactile stimuli were designed to deliver a clearly perceivable stimulation at fingers and toes with minimal tickling sensation. For 8 seconds a 30 Hz sinusoidal carrier signal was amplitude-modulated with a 2 Hz sinusoidal with alternating elevation of the display’s four rows (**Figure study1-1**). For visual guidance through the experiment, visual cues were presented as a fixation cross, which changed color to blue/green to indicate the PERCEPTION/IMAGERY condition. Color assignment was balanced across participants. Cues indicated where to imagine vibration, or where stimulation occurred to match visual bottom-up stimulation between conditions (upper left = lH; upper right = rH; lower left = lF; lower right = rF; see **Figure study1-1**). During null events the fixation cross remained on the screen, and no stimulus was applied or imagined.

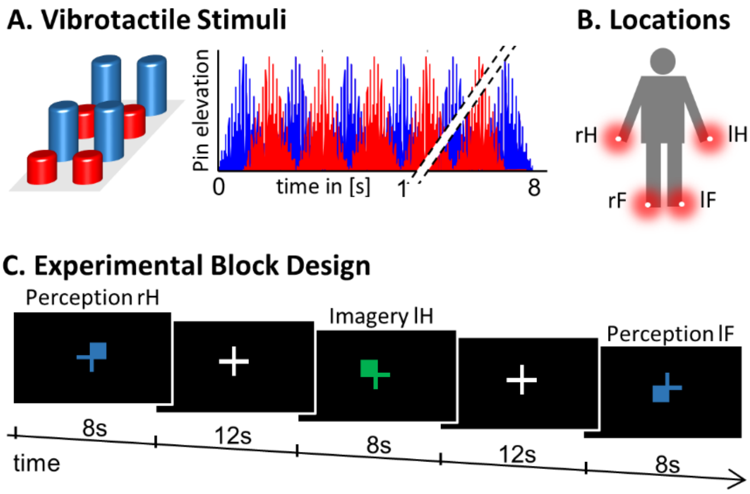

Figure study1-1. Experimental Design
A. Vibrotactile Stimuli were presented on a 2 x 4 pin Braille-like display. **B.** Stimulation modules were attached to four body locations. **C.** The experimental paradigm constituted a fast block design, where a visual color cue indicated where to imagine vibration in the four IMAGERY conditions. For the PERCEPTION condition the visual display was matched, where blue/green indicated IMAGERY/PERCEPTION randomized across participants. Each trial lasted 8 s and was followed by a 12 s inter-trial interval. Each condition was repeated three times in each of the three experimental runs, supplemented with six null-events (8 s fixation) per run.

Participants were familiarized with the stimuli as they settled in the scanner to enable imagery already from the first trials.

Each of three experimental runs comprised 24 trials, corresponding to three trials per experimental condition, complemented with 6 null-events. The order of trials was randomized. Stimulus presentation was controlled using custom MATLAB code (The MathWorks, MA) and the Cogent 2000 Toolbox (developed by John Romaya at the LON at the Wellcome Department of Imaging Neuroscience). Visual cues were presented on a screen that was visible from the scanner via a mirror system attached to the head coil.

fMRI data acquisition: MRI data was acquired in 3 runs of 10.5 min on a 3T TIM Trio (Siemens) at the fMRI facility of the Freie Universtät, Berlin. 310 functional images were acquired per run as T2*-weighted gradient-echo EPI: 37 slices; interleaved slice order; no gap; whole brain; TR = 2000 ms; TE = 30 ms; 3 x 3 x 3 mm^3 voxel; flip angle = 90°; 64 x 64 matrix. Additionally a T1-weighted MPRAGE with 176 sagittal slices, TR = 1900, TE = 2.52 ms; 1 x 1 x 1 mm^3 voxel was acquired.

fMRI data analysis: FMRI data were pre-processed with SPM8 (Wellcome Trust Centre for Neuroimaging, Institute for Neurology, University College London, UK). To minimize movement-induced image artifacts each participant's data set was realigned to its mean image. Next, EPI images were normalized to MNI space using unified segmentation (as implemented in SPM8) and re-interpolated to 2 x 2 x 2 mm^3 voxel size. Spatial smoothing was limited to a 5 mm full-width half-maximum Gaussian kernel to preserve a high degree of regional specificity in the group level analysis. Statistical analysis was performed according to a standard general linear model approach. The first level design was specified to model the eight task-conditions as independent regressors, the six null events were split into two independent regressors (to allow independent baseline contrasts in the conjunction analysis) and a run constant. To test for activation shared by PERCEPTION and IMAGERY we computed first-level contrasts of task-condition against null-events, with independent null event regressors for the PERCEPTION and IMAGERY contrasts. Contrast images were forwarded to a second level flexible-factorial design, and condition specific activation overlap was tested against the conjunction null hypothesis (Friston et al., 1999; Nichols et al., 2005). All reported coordinates correspond to MNI space. The SPM anatomy toolbox was used to establish cytoarchitectonical references where possible (Eickhoff et al., 2005, 2006, 2007b). For display purposes we used a mask computed with the anatomy toolbox for bilateral SI and SII (Geyer et al., 1999; Grefkes et al., 2001). Statistical parametric maps are presented at $p < 0.05$, family-wise error(FWE)-corrected at the voxel-level, rendered on a standard 3D brain template using MRIcron (by Chris Rorden; Version 6 6 2013).

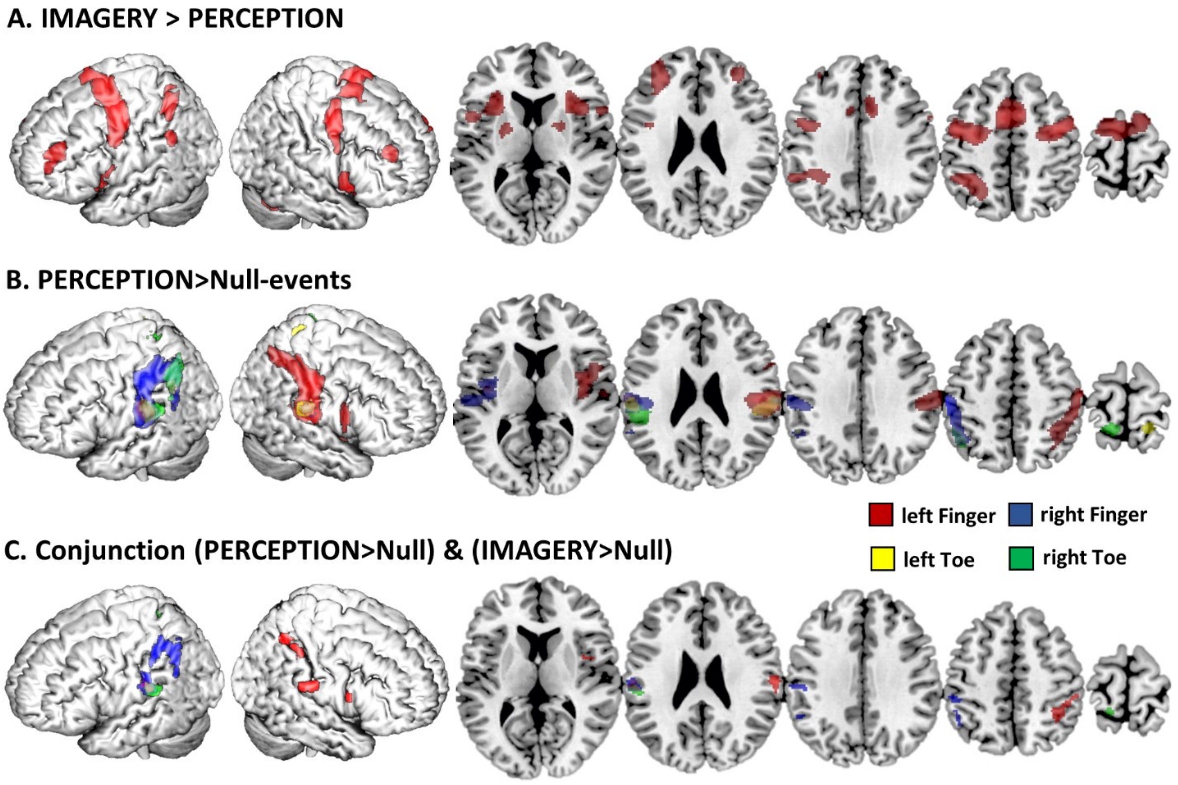

Figure study1-2. Univariate activation differences
A. To depict the network of brain regions that support tactile imagery independent of content, we computed the main effect of IMAGERY>PERCEPTION. The identified network is composed of areas that are known to be modulated by general task demands such as the SMA and the PMC and which were recently associated with rehearsal processes (Fegen et al., 2015) and the medial frontal gyrus. Also bilateral IFG was found, which is well known for its involvement in the processing of vibrotactile stimuli. Furthermore, we found left-lateralized activation in the IPS. **B.** Somatotopic activation in primary and SII during perception revealed by the contrasts of individual stimulation conditions against null events, displayed within an anatomical SI/SII mask. **C.** Overlap in activation between perception and imagery identified by body-locus-specific conjunction analyses, demonstrating that MI indeed recruits SI content-specifically. All results displayed at $p<0.05$ FWE-corrected at the peak level.

Results

To test what brain regions fulfill general support functions during imagery – regardless of content representation – we computed the main effect of IMAGERY > PERCEPTION. This contrast revealed a network comprised of the SMA, bilateral PMC, medial frontal gyrus and IFG, as well as the left IPS (**Figure study1-2**).

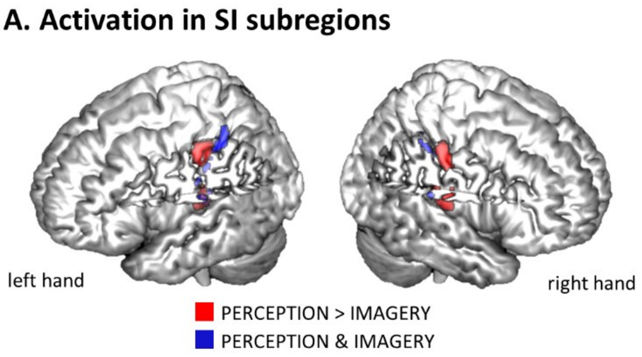

Figure study1-3: Comparison of perception and imagery
Anterior-posterior gradient of activation between perception and imagery To test what areas activate stronger during perception than during imagery, we computed the corresponding contrast for the left and right hand conditions and identified the hierarchically lower SI subregions (BA3b and BA1) to be only activated during perception. Those SI areas that are activated in both conditions – as depicted by the conjunction analysis – appear to be further posterior portions of SI, corresponding rather to the hierarchically higher subarea BA2.

Next, we tested what regions are content-specifically activated during the PERCEPTION condition. For each of the four body loci the contrast against null events was computed on the first-level and on the second-level and contrasted against the other three conditions versus null event contrasts. **Figure study1-2B** displays body-locus-specific activation within SI and SII during stimulus perception.

To test whether the same aspects of SI are activated during IMAGERY and PERCEPTION, we computed locus specific conjunction analyses between PERCEPTION and IMAGERY contrasts against null-events (**Figure study1-2C**). The conjunction for lH, rH and rF revealed clusters within SI ($p < 0.05$ FWE-corrected at the voxel-level). Inspecting the lF condition at $p<0.001$ uncorrected due to strong *a priori* assumptions, a similarly located, contralateral cluster was found as in the rF condition (data not shown).

The well-pronounced activation clusters of the lH and rH conditions allowed us to test for their specificity within SI subregions. To this end, we tested what aspects of SI were activated more strongly for PERCEPTION than for IMAGERY. The results are compared to clusters activated in both conditions, as revealed by the conjunction analyses. **Figure study1-3** shows that BA1 (anterior aspects of the post-central gyrus) is activated only during PERCEPTION. The activation cluster revealed by the conjunction PERCEPTION & IMAGERY was limited to the posterior portion of SI, matching the probability maps of BA2 according to the anatomy toolbox.

Discussion

In this dataset, we found evidence for somatotopic recruitment of SI when participants imagined vibrotactile stimulation at different body locations. This finding contributes to a modality-general perspective of MI and inspires future research by demonstrating that the somatosensory system is well suited for investigations of MI.

The different sub-processes involved in MI are difficult to dissect empirically. The contrast IMAGERY > PERCEPTION reveals activation related to the mental construction process during imagery, while there is no apparent shared activation between the conditions (content). During IMAGERY the participants had to mentally instantiate or mentally create a stimulus representation from memory. This process is expected to require more cognitive resources than perception. This reasoning makes it plausible that the given contrast reveals a network of regions mostly matching the so-called *task-positive*-network, ascribed to engagement and attentional load differences (Kim et al., 2010). As discussed attentional contributions are incremental to imagery (Kosslyn, 2005), and some authors even term imagery processes *reflective attention* (Chun and Johnson, 2011). Future studies are required to clarify the functional role of regions within this network for MI. The contrast IMAGERY > PERCEPTION further revealed a left-lateralized activation cluster in the IPS. We observed a similar lateralization within the decoding results of study 3. To the best of my knowledge at the time of writing this lateralization has not yet been further investigated.

Retinotopic recruitment of visual cortices during visual imagery is considered evidence that our brains produce mental images using depictive rather than symbolic codes (see **Section 1.2.1**). The finding of somatotopic recruitment of SI can be similarly interpreted. There has been scarce previous evidence for this hypothesis, as only a few studies have investigated tactile imagery (see

McNorgan, (2012), and **Section 1.3.2**). Here, we report body-locus-specific activation in SI during imagery, revealed by a conjunction analysis between the IMAGERY and the PERCEPTION condition (**Figure study1-2C**).

The more pronounced activation clusters in the finger regions allowed further investigation of the imagery-induced activation in SI. Finger stimulation activated bigger clusters than stimulation of toes. This was expected, as more cortical surface is responsive to finger than to toe stimulation (Martuzzi et al., 2014). Activation during IMAGERY was limited to subregion BA2, as revealed by the conjunction analysis between PERCEPTION and IMAGERY. During PERCEPTION we found activation clusters spanning all SI subareas (**Figure study1-2B**). The finding of activation only in the highest hierarchical SI subregion during IMAGERY is in line with the suggestion that lower order regions are only activated if fine-grained detailed mental images are generated (Kosslyn and Thompson, 2003). Here, we used simple vibratory stimuli which did not contain any relevant spatial information. Instead, these stimuli delivered standardized, vibratory stimulation to elicit a clear percept. The MI employed in the current paradigm therefore did not require generating a mental image with fine details.

An alternative interpretation of the activation in SI is that SI is activated merely due to the allocation of attention to a particular part of the body. As attention is an incremental aspect of MI this argument does not, however, invalidate the claim that the activation in SI is content-specific.

In summary, we found imagery-induced activation within SI in a tactile MI task. The observation that only the highest hierarchical SI subregion BA2 was activated motivates further studies of tactile imagery with more fine-grained mental images, to see whether a more detailed mental image will lead to a recruitment of SI subregions lower in the hierarchy. A limitation of this study is that no behavioral measure was included to assess whether participants actually performed MI. This limitation was addressed in the design of study 2.

Study 2: Recruitment of primary somatosensory cortex during fine-grained tactile imagery

As described in the introduction, MI has been intensively studied in the visual modality, and research has focused on the question of which aspects of MI rely on the same neuronal mechanisms as perception. Study 1 constitutes initial evidence for the recruitment of sensory cortices during imagery in the tactile modality. However, merely instructing participants to imagine some content lacks experimental control over whether, and to what degree, a mental image is really generated. In study 2 we aimed to address two limitations of study 1: (1) ensure that participants reliably form a mental image, and (2) necessitate the formation of a mental image with fine sensory details. Analogous to the suggestion that has been made in visual research (Kosslyn and Thompson, 2003; Bancroft et al., 2014) we hypothesized that with more detailed sensory imagery, lower regions in the somatosensory hierarchy will be recruited, i.e., all SI subregions.

Within the literature on visual MI, we found an experimental task called ‘Letters in a grid’, introduced by Podgorny and Shepard (1978). We re-designed this paradigm into a tactile fMRI-compatible version. In the visual paradigm a lower-case letter cued participants to imagine a corresponding upper-case letter within a 4 x 5 grid. One cell of the grid was marked with an ‘X’, and participants reported whether this cell was part of the letter or not (**Figure study2-1**).

In our tactile version, we used a 4 x 4 pin Braille-like display, instead of a visual grid. Before the experiment, participants learned to associate a color cue with one of four tactile stimuli. Each tactile stimulus comprised vibrating and non-vibrating pins within the vibrotactile display (**Figure study2-1C**). Participants had to report whether another vibrating pin was part of the imagined stimulus pattern or not. The experiment included a PERCEPTION condition, an IMAGERY condition and a CONTROL condition (**Figure sudy2-1B**).

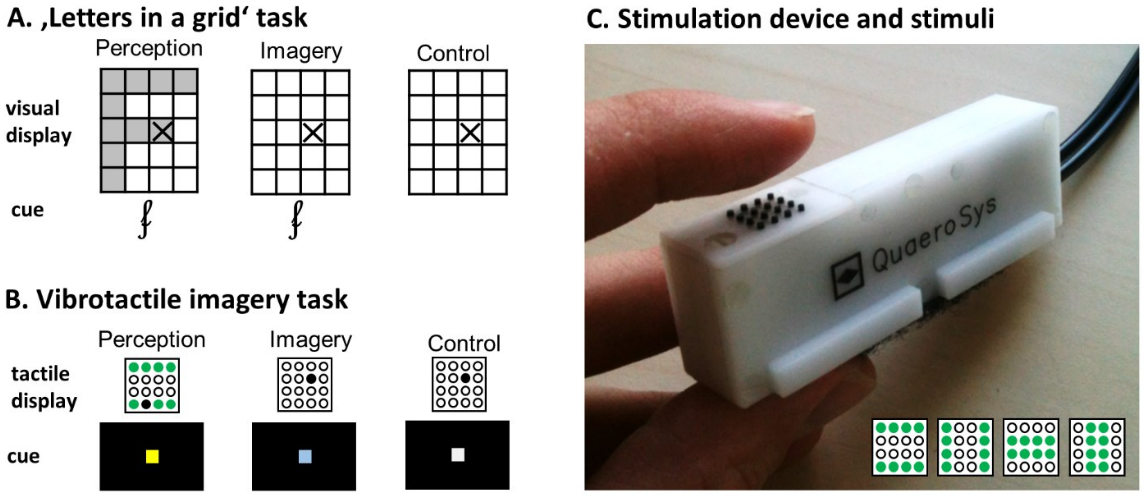

Figure study 2-1: A. Schematic representation of the original 'Letters in a grid' task by Podgorny and Shepard, (1978). **B.** Schematic representation of the vibrotactile imagery task employed in our study. In the imagery condition, participants were presented with visual color cues prompting them to imagine one of four previously learned vibrotactile patterns (green). One probe-pin within the display was vibrating with distinguishable amplitude modulation (black). Participants had to report whether the probe-pin was part of the pattern or was presented outside of the pattern. **C.** An fMRI-compatible piezoelectric stimulation device which was attached to the index finger of the left hand. The predefined four different stimulus patterns are displayed at the bottom right.

This experimental design allowed us to dissociate two types of blood oxygen level dependent (BOLD) activation changes: Changes related to the construction process of the mental image and changes related to the content of imagery. The contrast IMAGERY > PERCEPTION revealed a network of regions previously described as part of the construction network (Buckner& Carol 2007, Hassabis and Maguire 2009, Schacter 2012). This network comprised the retrosplenial cortices, precuneus, and PMC / frontal eye fields. Finding this network activated in a tactile MI task provides evidence for its modality-independent function. In this study we consider activation to be content-specific if it was revealed by the conjunction analysis (IMAGERY > CONTROL) & (PERCEPTION > CONTROL). Such activation is specific to the processing of a tactile pattern and the allocation of the probe pin within this pattern. The CONTROL condition was matched with regards to the physical sensory input to the IMAGERY condition. The conjunction analysis showed clusters in the PPC, including bilateral IPS, as well as a cluster in the lateral occipital cortex. Most interestingly it also revealed a cluster spanning the BA1, BA3b finger representing SI subregions. This finding supports sensory-recruitment in tactile MI (alternatively also termed *'perceptual grounding'* of a mental image).

In addition, we tested for changes in functional connectivity using the psychophysiological interaction approach. Testing for connectivity increases modulated by the contrast IMAGERY > PERCEPTION, we found that the left IFG shows a strong and selective increase in coupling to the identified finger representation in SI. This suggests that a functional connectivity increase between the prefrontal and sensory cortices might be the mechanism of sensory-recruitment during MI.

Together with the findings from study 1, these results support the view that the more detailed a mental image is, the more it causes activation of primary sensory regions. In study 1, MI of simple vibrations led to recruitment of BA2 only, while MI of fine-grained sensory details in this study led to activation of all SI subregions including BA1 and BA3b.

Study 3: The 'tactospatial sketchpad': Tactile working memory of spatial stimulus properties

Visual WM studies have revealed that information about the spatial layout of a stimulus can be decoded from visual and posterior parietal regions (Christophel et al., 2012, 2015). However, nobody had previously used MVPA to decode the spatial layout of tactile stimuli from WM. To make the study of tactile WM comparable to visual WM results, we conducted a study with the same analytical approach as introduced by Christophel et al. (2012).

I developed a set of tactile stimuli to approximate the stimuli used in visual research. As in study 2 the stimuli were delivered to the left index finger on a 4 x 4 pin Braille-like display (**Figure study2-1C**). Each stimulus comprised a surface-like modulation of the vibration amplitudes of the display's pins. For each participant we used a different stimulus set to avoid any stimulus-specific confounds. Each set comprised four maximally different stimuli, one of which had to be memorized in each trial of the experiment. Each trial started with the consecutive presentation of two stimuli. A retro-cue then indicated which of the two had to be retained for a 12-second delay phase. Together with the retro-cue, a vibrotactile mask stimulus was presented to overwrite potential peripheral perceptual residues. After the delay, two comparison stimuli were presented and participants indicated via button-press which of the two matched their WM content. The task was designed to be demanding, by making the comparison stimuli similar enough to the sample stimuli that participants reached only 75% accuracy in a pilot experiment. Participants performed this task in 4 experimental runs of 20 min each during fMRI scanning.

We searched throughout the brain for activation patterns related to WM content using an assumption-free searchlight MVPA approach. We applied the same time-resolved pairwise support vector machine approach as Christophel et al., (2012). In short: First, a finite impulse response model was estimated with regressors for each two-second time bin of the delay phase (six time bins for the 12-second delay) and each WM content (four different stimuli). Within each time bin an independent searchlight analysis (Kriegeskorte et al., 2006) was performed. The accuracy maps resulting from the run-wise cross-validation decoding schema were averaged within time bin for each participant. Accuracy maps were entered into a second-level ANOVA design. We tested with a t-contrast for voxels that display above-chance decoding during the WM delay. We found clusters in the bilateral PPC spanning IPS, BA5 and BA7 ($p < 0.05$ FWE-corrected). We further found a cluster of voxels exhibiting above-chance decoding within the right SI finger representation, when testing with $p < 0.001$ uncorrected, due to our strong *a priori* assumptions.

Our results demonstrate a high overlap of the network coding WM information about spatial layouts in the visual and tactile modality. Overlapping networks do not, however, necessarily entail that it is the same neuronal populations coding the information. Future research is necessary to clarify whether the PPC contains separate systems for tactile and visual information, or whether spatial information is represented in a supramodal format.

In summary, this study demonstrates that the PPC together with SI represents tactile WM content when participants memorize the spatial layout of stimuli. In the famous *Baddeley & Hitch* model, the joint coding of visual layout information within PPC and visual cortices has been identified as the *visuospatial sketchpad*. By analogy with this elegant and evocative name, one could refer to the joint coding of tactile layout information within PPC and SI as the *tactospatial sketchpad*.

Study 4: Parametric vibrotactile working memory codes investigated with EEG

To complement the seminal non-human primate studies of Romo and colleagues (for recent reviews see Romo and de Lafuente, (2012); Romo et al., (2012)), Spitzer and Blankenburg conducted a series of human EEG studies on vibrotactile WM. They found that oscillatory signatures over the right PFC are parametrically modulated by the frequency held in WM (see **Section 1.3.2** and Spitzer and Blankenburg, 2012). Study 4 extends this work by testing whether retention of intensity or duration of a stimulus also induces parametric prefrontal beta-band modulations. Intensity and duration are thought to be represented in a similar fashion to frequency information, namely as abstract, non-sensory, magnitude-like properties (compare Walsh, 2003).

In every trial, participants were presented with a vibrotactile stimulus delivered to the left index finger. One second after stimulus offset, a visual retro-cue instructed them to retain either the intensity or the duration of the stimulus. After a 2.5-second delay a comparison stimulus was presented and participants indicated via button-press whether that stimulus was longer/shorter or less/more intense than the memorized one. The retention of both intensity and duration induced a parametric beta-band modulation over the PFC.

Study 5: Parametric vibrotactile working memory codes investigated with fMRI MVPA

Intracranial recordings in monkeys and EEG studies in humans have provided evidence for parametric WM codes in the PFC (Romo et al., 1999; Spitzer et al., 2010). However, the long standing proposition that the PFC is the main region responsible for coding WM content (Goldman-Rakic, 1995) has been seriously called into question by the failure of human multivariate fMRI studies to decode WM content from the PFC (D'Esposito and Postle, 2015). Instead, MVPA studies have favored the view that sensory and parietal regions maintain WM content. To address this controversy and to bridge the gap between the monkey research and human studies, we investigated with fMRI MVPA where in the human brain content-specific codes for WM representations of vibratory frequency can be found.

Multiple previous MVPA studies have limited their analysis to particular regions of interest (Albers et al., 2013). We used a searchlight approach that did not make any *a priori* assumptions about the localization of WM codes throughout the brain (Kriegeskorte et al., 2006). We applied support vector regression (SVR), which allowed us to test whether activation patterns reflect the linear order of increasing frequencies. This approach is considered to be the multivariate equivalent of univariate tests for parametric modulations (Kahnt et al., 2011). That is, a classifier is trained to predict a value (here: the frequency), instead of a class label (see also Fan et al., 2008; Christophel et al., 2015).

We found that information about vibratory frequency is coded in bilateral PMC, SMA and, most interestingly, in the right IFG as part of the PFC. This result bridges the gap between the electrophysiological findings of parametric WM codes in the PFC and the null findings in previous MVPA fMRI studies. We were able to demonstrate that testing for the same type of WM content as in the electrophysiological studies, MVPA for fMRI also reveals PFC WM codes. Previous studies did not reveal the PFC as they tested for different types of WM content. Our findings are in line with the view that the required level of abstraction determines which brain regions encode WM contents.

If this suggestion is true, it should be possible to decode frequency information from the PFC, even if frequency information was presented in other modalities. Studies 6 and 7 set out to test this hypothesis in the visual and the auditory modality.

Study 6: Overlap of parametric vibrotactile working memory with visual working memory

This study set out to test whether the PFC exhibits the same multi-voxel activation patterns when participants retain frequency information derived from either a vibrotactile or a visual flicker stimulus. To this end, we applied a bimodal WM paradigm. In each trial a visual and a vibrotactile stimulus were presented in parallel. A retro-cue indicated which of the two frequencies to memorize. After a delay period, either a visual or a tactile probe stimulus was presented. Participants indicated via button-press whether the probe frequency was higher or lower than the retained frequency. As the sensory modality of the comparison stimulus was independent of the sample stimulus, 50% of the trials were cross-modal comparisons. Using the same SVR searchlight decoding approach as in study 5 we could (1) replicate the finding from study 5 that information is represented in the right PFC, (2) test for overlap in regions that code frequency information derived from vision or touch, and (3) test with cross-classification whether the same multi-voxel activation patterns code information from the two modalities.

Our searchlight analysis revealed above-chance decoding in the right IFG for both conditions. This firstly constitutes a replication of the findings from study 5 and secondly demonstrates that the parametric codes in the PFC are not specific to the tactile modality. Next, we used cross-classification to test whether it is the same activation patterns that code information in visual and tactile trials. To this end, the classifier was trained on data from the one condition and tested on data from the other condition. Only if the activation patterns generalize across modalities would one expect above-chance decoding. We did not find any significant clusters of voxels at $p < 0.05$ FWE-corrected, which does not support the existence of supramodal codes.

We further found above-chance decoding within sensory regions. For visual WM we found information about the encoded stimulus in superior occipital cortex and for tactile WM in SI. This finding is most likely explained by the short retention period of 6 seconds (Note: It was 12 seconds in studies 4 and 5). Due to the sluggish BOLD response, encoding-related activity might leak into the applied contrast.

Study 7: Overlap of parametric vibrotactile working memory with auditory working memory

With this study we complete the picture of modality-specific and modality-independent aspects of frequency retention by extending our work to the auditory modality. The experimental design was identical to study 5. The only difference was that frequency information was presented as acoustic flutter. Most interestingly, SVR whole-brain searchlight decoding revealed activation of the bilateral superior temporal gyrus (including the auditory belt areas), PMC and bilateral IFG. A conjunction analysis with the data from study 5 revealed that the right PFC cluster overlapped between the two studies.

These results are particularly interesting, as auditory information is often considered to be stored by different mechanisms from other modalities. The *Baddeley & Hitch* model, for example, included a separate module for auditory storage, the *phonological loop*. However, in contrast to most auditory WM studies we focused on frequency and not on linguistic material.

3. General discussion

The empirical work presented here addresses the question of which brain regions maintain mental representations of tactile content. This question was addressed empirically in two fMRI studies on MI, as well as in one EEG and four fMRI MVPA WM studies.

The two MI studies revealed evidence for sensory-recruitment when vibrotactile stimuli were imagined. Following up on this initial evidence that SI is crucially involved in the representation of tactile contents, we conducted a series of fMRI MVPA studies to directly test for the content-specificity of activation patterns associated with tactile content representations. The series of MVPA studies presented in this thesis, allowed testing how the nature of the retained information relates to the topography of brain regions that contain content-specific activation patterns. This was addressed by using different tactile stimuli in the studies. Participants had to mentally represent the layout of Braille-like stimuli on the index finger, an exact vibratory frequency, as well as the frequency of visual flicker and acoustic flutter stimuli. Study 3 revealed that retaining information on the layout of a tactile stimulus induces content-specific activation patterns in the PPC and SI. In study 5 – 7 we tested for the retention of frequency information. These studies revealed that right PFC consistently exhibits codes of parametric WM representations in tactile, as well as in visual and auditory, frequency DMTS paradigms.

Based on the consistent finding that the right PFC codes frequency-information, I suggest introducing an additional class of content type: parametric contents. The present findings can be interpreted as consistent with the idea that mental contents can be represented throughout the cortical hierarchy. In addition, the very well-known *predictive coding* framework also strongly draws on the hierarchical organization of the cortex. Our findings therefore inspire speculations on the mechanisms by which content-specific codes at several levels of the hierarchy result from the implementation of principles of predictive processing.

Taken together, our results offer a cross-modal perspective on how the organizational principle of hierarchical coding determines what brain regions exhibit content-specific activity when different material is mentally represented.

3.1 Empirical findings on tactile mental representations

3.1.1 Findings on tactile mental imagery

Following suggestions from the study of MI in the visual domain, the two presented tactile MI studies were designed to test for sensory-recruitment in the tactile system. Further, they allowed testing for the dissociation of content-specific activation from general support functions of MI.

Both studies revealed content-specific activation in SI. While the imagery of simple vibratory stimuli activated higher-order subregions of SI in study 1, the imagery of stimuli with fine-grained details in study 2 recruited the full SI finger representation including BA1 and BA3b as the hierarchically lowest cortical regions in the somatosensory system.

While MI of simple sensations might be directly recalled, more complex information is thought to require a construction process. For example, a visual scene needs to be assembled from different elements such as landscape, humans, houses, plants etc. This process is referred to as the construction of mental images (Buckner and Carroll, 2007; Schacter et al., 2012). A network of brain regions has been described in the context of visual scene construction and spatial imagery (Thompson et al., 2009; Summerfield et al., 2010). The *core* regions of this network are thought to be active across diverse contents and modalities. These regions comprise the retrosplenial cortices, the precuneus, the PPC, and ventromedial PFC (Maguire and Hassabis, 2011), along with the hippocampus if temporal assembly of episodic memory is performed (Hassabis and Maguire, 2007; Hassabis et al., 2007; Addis and Schacter, 2012).

To test what role the construction system plays in tactile imagery, we computed contrasts between imagery and perception conditions in study 1 and study 2. The network of regions activated by MI of simple sensations in study 1 partly overlaps with the construction network. This activation matches well with the results of a recent meta-analysis of neuroimaging data from 42 DMTS WM studies. Independent of the content, these studies displayed consistent activation in SMA, precuneus, aspects of insula cortex and bilateral IFG (Daniel et al., 2016). Most of these regions are also part of the so-called task-positive network, which is activated in diverse cognitive tasks and therefore does not allow for an ascription of a particular functional specificity. In study 2 participants were required to construct a mental representation of a stimulus with spatial layout. Here, we found a clear overlap with the regions described as part of the *core* construction network, indicating the relevance of this network for spatial assemblies regardless of sensory modality.

Both MI tasks that I presented activated the PPC and PMC/frontal eye fields, indicating their domain-general importance for the instantiation of a mental representation. Particularly, the PMC has recently been associated with rehearsal-related processes in WM (Fegen et al., 2015). Our decoding studies further demonstrate that the PMC contains content-specific codes. Future research should address the exact functional relevance of the PMC for the construction and active maintenance of mental contents. Our data support the speculation that the PMC plays a pivotal role in active components of WM, alternatively called rehearsal or refreshment processes (Cisek and Kalaska, 2004; Chun and Johnson, 2011).

3.1.2 Findings on tactile working memory

Our MI studies provide strong support for sensory-recruitment. In both MI studies we found that the activation in sensory regions was specific to the body location where a tactile stimulus was presented, making that activation somewhat content-specific. The rise of MVPA studies gave neuroimaging the methods to demonstrate content-specificity even more directly. By using a WM paradigm that tightly controls the retained mental content, we went on to map the brain regions that exhibit content-specific activation patterns.

Sensory-recruitment in tactile working memory

As summarized in the introduction, it has been hotly debated whether sensory regions are recruited when sensory information is mentally represented (Pasternak and Greenlee, 2005; Cichy et al., 2012; Albers et al., 2013; Xu, 2017). In the tactile modality, conflicting electrophysiological evidence has been presented (see **Section 1.2.3**). The results of our decoding studies also do not completely resolve this debate.

Study 3 demonstrates that SI is involved in WM coding. We found a cluster of above-chance decoding accuracies when testing with a threshold of $p < 0.001$ (uncorrected), across the WM delay. The observed decoding-accuracies dropped relatively quickly after the retro-cue; however, a statistical assessment did not reveal significant differences from the other regions revealed by the same contrast. Taken together, these findings do not clearly establish whether SI represents information throughout the whole WM delay. However, they convincingly demonstrate that SI is involved in the early stimulus encoding phase. Notably, when testing for frequency-coding regions in study 5, we tested across the entire 12-second delay period. In study 6 the contrast of interest was computed over the shorter delay period of 6 seconds. Here, we found SI to contain frequency information. Assuming that content is represented only shortly after stimulus presentation, the sluggish BOLD response would explain above-chance decoding in an early time-window of the delay phase. Importantly, the control analyses shows that this information is encoding-specific and not an artifact of mere stimulus presentation. The results of our MI experiments also do not determine the exact role of SI. While we found SI activity, the MI studies did not require maintenance of sensory details over a longer period.

Taken together, our findings are in line with the view that SI briefly represents information about the content that is to be maintained. This might reflect an encoding-related transformation for storage in higher-order regions (Serences, 2016; Wu et al., 2018). This interpretation agrees with the EEG findings of content-specific alpha-band modulations during stimulus encoding (Spitzer et al., 2010; Spitzer and Blankenburg, 2011). The delay activity in ERP reports could also be interpreted along this line (Katus and Eimer, 2015; Katus et al., 2015; Katus and Müller, 2016). Most convincingly, the TMS study by Zhao et al., (2017) indicates that TMS to contralateral SI affected performance most strongly when applied during stimulus encoding.

The prefrontal cortex and frequency coding

The second major finding from the tactile WM studies presented here is that we found parametric content-specific codes in the PFC when participants retained frequency information. In studies 5 to 7 we used an SVR approach that is considered to be the multivariate equivalent of univariate parametric tests (Kahnt et al., 2011). Parametric codes in the PFC have originally been reported in non-human electrophysiological recordings (Romo et al., 1999) and support a strong argument that the PFC codes WM content (Barak et al., 2010). Spitzer et al. (2010) demonstrated corresponding parametric beta-band modulations in human EEG recordings. Multiple null-findings in human MVPA studies, however, seriously called into question the role of the PFC. However, most research was performed in the visual modality and had focused on the retention of stimulus properties that are very different from frequency information, such as spatial layouts, gratings or visual motion (Lee and Baker, 2016). To resolve this important controversy, we used human fMRI MVPA to test for frequency information in the PFC. Indeed, our assumption-free whole-brain searchlight approach identified a very similar network of regions as the non-human primate studies, including the right PFC (Romo and de Lafuente, 2012; Romo et al., 2012). Therefore, our findings bridge the controversial gap between the electrophysiological and MVPA literature. The reason for the null-findings in most MVPA studies appears to be the different types of stimuli, and consequently the different types of mental content that was retained. Alternatively, one could speculate that these representations are somewhat special to vibratory frequencies. Our studies 6 and 7 have, however, replicated this finding for visual flicker and acoustic flutter. These results demonstrate a modality-independent type of code in the right PFC.

The EEG study reported in this thesis revealed that the PFC also exhibits content-specific signatures for the WM content of intensity and duration of vibrotactile stimuli. This finding supports the view that the PFC codes a more general, more abstract type or magnitude representation. An important line of research suggests that the right PFC is related to the processing of quantity-like stimulus properties. Walsh (2003) termed this function the processing of *abstract magnitudes*. Dehaene et al. (2004) summarized evidence that number processing and approximations depend on the IPS and PFC (See also Viswanathan and Nieder, 2015). It has been suggested that this system also codes for asemantic analog magnitudes, also called numerosity (Nieder and Dehaene, 2009; Knops, 2017). Due to the similarities in the applied stimulus material and the plausibility of the claim that frequency information is retained in an abstract non-sensory type of representation, we and others have argued that frequency can also be considered as an abstract magnitude (Nieder, 2016, 2017). Spitzer et al., (2014a) conducted a WM EEG study to test this hypothesis by testing for WM traces of numerosity. When participants retain the cardinality of stimuli ('how much are there?'), this information is also reflected in prefrontal oscillatory modulations.

In sum, our findings support a dissociation between the representation of spatial layout information and abstract magnitude information. The former are associated with the SI and PPC, the latter with the PFC.

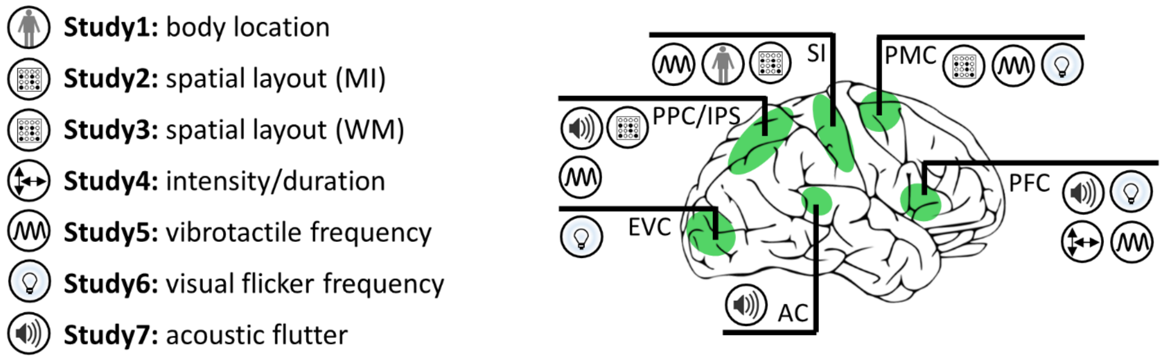

Figure 3: Topography of brain regions found to exhibit content-specific activity for different types of tactile contents. Findings of activations in the early visual cortex (EVC), auditory cortex (AC) and SI provide evidence for sensory-recruitment. The PPC/IPS has been associated with the representation of spatial or layout features. The right IPS also exhibited frequency-specific codes in some of the reported studies. The PMC was found to exhibit diverse content specific codes. The PFC was found to retain information about parametric contents, e.g., frequency information presented in the visual, auditory and somatosensory modalities, as well as the intensity and duration of vibrotactile stimuli.

3.1.3 The topography of tactile mental representations

Different models of WM assign specific WM processes to different brain regions. For example, it has been suggested that sensory cortices fulfill buffer-like functions and that visual cortices implement the psychological construct of a *visuospatial sketchpad* (Baddeley, 2012). Two recent articles review the available studies testing which brain regions exhibit content-specific WM codes (Lee and Baker, 2016; Christophel et al., 2017), and argue that different types of content can be decoded from regions distributed over the entire cortex. This suggestion moves away from the view that particular regions act as buffer-like stores of diverse contents. Most of the evidence for this suggestion stems from visual fMRI studies that used MVPA in DMTS tasks. At the time these studies were summarized, no evidence for codes in the postcentral sulcus had been reported and findings of content representations in the PFC were rare and controversial (Ester et al., 2015). Our work allows for the first time a modality-overarching perspective and shows that aspects of content representations are independent of modality. **Figure 3** schematically summarizes our findings on the topography of tactile WM. While Christophel et al. (2017) have hypothesized that all regions of the brain could retain information, Leavitt et al. (2017) have emphasized that the currently available data imply that only a limited set of regions is used. The findings from our studies overlap with the subset suggested by Leavitt.

3.1.4 Cross-modal perspectives

Comparing our data to findings from visual WM reveals some important parallel (though please note the limitations of direct comparisons between MVPA studies discussed in **Section 3.3**). In study 3 we used an experimental design and analysis approach that had previously been used in visual WM. In a study using visual stimuli with spatial layout, Christophel et al. (2012) identified the PPC and early visual regions as coding the content of visual layout information. We found the PPC and SI to code tactile layout. In line with the catchy nomenclature of Baddeley's multicomponent model, I suggest acknowledging this parallel by introducing the term *tactospatial sketchpad* in addition to the *visuospatial sketchpad*.

It remains an open question for future research whether spatial information is represented by the same neuronal populations in the PPC. Further data are required to decide whether spatial information is mapped into a modality-independent format. Findings on transformations between different coordinate systems have been associated with the PPC, for example transformations from skin-space to external or gaze-centered coordinate systems (Heed et al., 2015). Cross-modal studies of the mental representation of visual and tactile spatial information are required to determine what parts of the PPC process modality-independent contents, and what codes are specific to certain modalities.

Importantly, we did not limit our studies to the tactile modality. Instead we aimed with study 6 and 7 to make a direct link between our findings and visual and auditory research. Here, we also found parametric multivariate WM codes in the PFC. Conjunction analyses with data from vibrotactile frequency maintenance show that PFC clusters overlap. Does this demonstrate that the same code is used across modalities? Is it the same neuronal populations that code parametric information?

These questions are challenging to answer with fMRI data. One possibility for addressing them is with cross-classification. Data from one modality is used to train a classifier, which is then tested with data from the other modality. Only when the mental content is coded by similar neuronal populations that contribute to the activation pattern does one expect above-chance decoding. In study 6 we recorded data in a tactile-visual cross-modal study. Here, we tested for above-chance decoding accuracy with cross-classification. We did not find evidence that the PFC codes are in fact supramodal. As null-findings do not sufficiently prove that supramodal codes do not exist, this question cannot be conclusively answered. Future research will need to reveal whether sensory information is indeed transformed into a common abstract magnitude format that is coded by the same neuronal populations independent of modality.

3.1.5 Introducing an additional class of content type: parametric representations

Based on our empirical findings, I suggest the introduction of a new class of content type. This additional type of mental content is categorically different from the ones predominantly discussed in the MI and WM literature (see **Figure 1**). I suggest that the controversy over content-specific codes in the PFC can be resolved by acknowledging that the gross anatomical distinction between left and right hemispheric PFC is reflected by this new categorization scheme. In addition to the established distinction between (1) sensory-like and (2) categorical contents, I suggest introducing a class of (3) parametric, non-language-dependent representations.

Throughout the *imagery debate*, dichotomous positions on the existence of depictive versus symbolic codes persisted for a long time (see **Section 1.2.1**). Just recently, Pearson and Kosslyn (2015) suggested that this debate could now be ended and acknowledged that the empirical data speak for the existence of both codes. Within the WM literature on the other hand, the Baddeley's multi-component WM model offered an early compromise between these two positions. It describes the visuospatial sketchpad as representing sensory-like contents (the equivalent of depictive codes) and the phonological loop as representing language-dependent contents (the equivalent of symbolic codes). New empirical data, including our studies on the retention of abstract-magnitude (i.e., frequency), challenge this dichotomous distinction. While some authors initially considered vibratory frequency as a sensory-type of information (Romo et al., 1999), Spitzer and colleagues established commonalities with representations of duration and intensity (Study 5) as well as numerosity (Spitzer et al., 2014a). Our studies 4 - 7 consistently revealed the right PFC coding such content types independent of the modality from which the information was derived. This finding stands in contrast with WM studies testing for language-dependent information, which have identified that the left PFC as coding categorical content (Lee et al., 2012, 2013). The left PFC is well known for its pivotal role in language processing, particularly Broca's area (BA44). Additionally, one should note that animals without language abilities are able to perform basic arithmetic operations that require the representation of abstract magnitudes (Nieder, 2009).

In sum, it appears reasonable to distinguish between parametric, abstract-magnitude contents and language-dependent contents. In order to include this previously neglected content type in a general taxonomy (Strasser, 2010), one should distinguish between two classes of conceptual information: the traditional language-dependent categorical class, and a class of parametric magnitude-like representations (**Figure 4**). While the former has been associated with language regions in the left PFC, the latter has now been consistently associated with the right PFC.

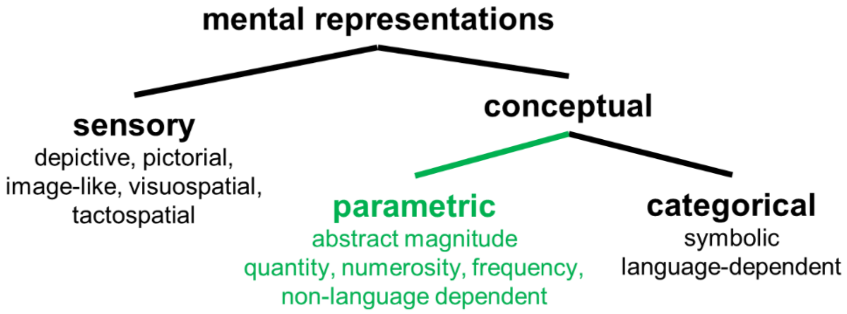

Figure 4: Suggested refinement of the classification of mental representations by supplementing parametric representations as a class of its own.

In addition to this conceptual distinction between different types of mental contents, it has been suggested that different mental contents lie a on a gradient of *abstractness*. This gradient stretches from sensory to abstract mental contents (Christophel et al., 2017). The taxonomy above is not in conflict with this idea. However, it emphasizes the relevance of multiple classes employing parallel gradients of abstractness. It would be problematic to decide whether either parametric or categorical contents are more abstract. On the neuronal level such parallel gradients would correspond to parallel processing streams. The best known example of parallel processing pathways is the *what*- and *where*-pathways in the visual system. Categorically different types of information are processed along these pathways. Within both pathways, however, the hierarchical cortical organization reflects a level of abstractness. Nonetheless, they process categorically different information. The proposed taxonomy is to be understood analogously. Sensory-type information is thought to be represented in hierarchically lower brain regions and more abstract information in higher-order regions. However, the categorical difference between parametric and language-dependent categorical information relates to distinct cortical structures.

3.2 Predictive coding as a framework for content representations

Within the last few decades, the predictive coding (PC) framework has been promoted, most famously in the work of Karl Friston (Friston, 2009, 2010; Friston and Kiebel, 2009). This theory of global brain function has gained notable popularity beyond the neuroscientific community (Hohwy, 2014). Until now, most work on predictive mechanisms has been carried out in the context of action and perception. Very recently, however, Parr and Friston (2017) also proposed how WM might fit into this framework. They suggest WM as a process of evidence accumulation, with the main purpose of optimal policy selection for acting within the environment. Here, I suggest a perspective on predictive coding mechanisms for different types of mental content representations. I focus on how content-related activation might emerge at different hierarchical levels.

My suggestion is based on the parallel between the suggested gradient of abstractness as an organizational principle of WM content in the hierarchically-organized brain and the importance of hierarchical information processing in the PC framework. This parallel inspires speculation about how the representation of mental content could be related to the well-established, evolutionarily old and efficient mechanisms of bottom-up and top-down interactions (Felleman and Van Essen, 1991).

The basic assertion of PC is that our brains continuously generate predictions about future sensory events. These predictions rely on the interaction between bottom-up and top-down signaling within the cortical hierarchy. Neuronal signals coding sensory predictions are propagated through the hierarchy via top-down connections. Sensory signals that reach the cortex from the sensory organs are propagated via bottom-up connections. If accurate predictions are generated, they match the sensory input signals. If predictions do not match the bottom-up signals, a prediction error is generated. This error signal is used to update the generative model by backpropagation to higher-order regions. The continuous influx of information from our senses requires an equal continuity of predictions. The temporary retention of information during WM has to act against this continual flow of new information. Somehow, the overwriting of information as a result of the continuous sensory influx needs to be overcome in order to temporarily retain information about a specific content. Since hierarchical processing is, however, an evolutionarily old and computationally efficient principle, it is likely that the retention of mental content is realized within the constraints of these processing principles, rather than independently of them.

The cellular microcircuits that form the basis for error-generation and backpropagation within a brain region (within a cortical column) are described in Bastos et al. (2012). Separate neuronal populations are described for receiving bottom-up and top-down inputs and for generating error signals, which are propagated as output signals via long-range connections to the next region. The question is: What additional functional features would it require for this system to allow the retention of information on different hierarchical levels? I conjecture that two mechanisms would suffice: (1) generation of a content-specific top-down signal, and (2) suppressing backpropagation of error signals. The content-specific signal could be generated with different levels of abstraction and propagated through the hierarchy until reaching a region that processes the corresponding levels of abstraction. The content-specific top-down signal would not match sensory input signals, as it carries information about a mental content that is currently not perceived via the senses. Depending on the level of abstraction this top-down signal has, it will generate prediction errors at corresponding hierarchical levels. The energy consuming process of error generation could be the neuronal correlate of the BOLD signal changes assessed with MVPA. The second mechanism is required to avoid the mental content being confused with real sensory input. Of course, such an implementation of mental content representations is just a speculation, and the neuronal mechanisms still require support from empirical evidence. But this model of hierarchical processing of mental content representations would explain several of the empirical findings.

The model can well explain the observation that contents that are memorized in semantic or language-dependent codes lead to content-specific activation in the PFC. On the other hand it can resolve the role of sensory-recruitment. Different MI and WM tasks require mental representations with different levels of detail. These relate to the experience of sensory vividness, and findings from MI suggest that more vivid mental images activate regions lower in the hierarchy (Kosslyn and Thompson, 2003). Our tactile MI studies also support this principle. While imagery of a simple stimulus in study 1 revealed only the hierarchically higher SI subregion BA2, the fine-grained mental contents in study 2 and 3 were passed down to BA1 and BA3b. Interestingly, study 2 also revealed a substantial increase in coupling from the left PFC to SI. This finding could be a correlate of a top-down propagation of mental content information from hierarchically higher to lower sensory regions.

In summary, the findings from our MI and WM studies revealed that mental content is represented at different levels of the cortical hierarchy. One can speculate that the neuronal mechanisms for temporarily retaining mental content are implemented according to evolutionarily old and efficient hierarchical processing principles. One plausible mechanism could be the generation of content-specific top-down signals that cause error signals at different levels of the cortical hierarchy. The specific hierarchical level at which the error is generated will depend on the functional specificity of that brain region.

3.3 Methodological and interpretative limitations

The interpretation of the present data is limited by several methodological concerns. MVPA is known for being more sensitive to fine activation differences than classic univariate analyses (Haynes, 2015). Nevertheless, it is limited by the spatial and temporal resolution of fMRI data. With regards to the spatial resolution, our analyses were limited by voxel sizes of 3 x 3 x 3 mm^3, where each voxel is likely to contain cell populations with highly heterogeneous response properties. The positioning of the voxel-grid for fMRI measurements is not based on the underlying distribution of neuronal populations. Without knowledge of the microanatomical and functional organization, it is not guaranteed that heterogeneous populations are sufficiently separated across voxels to make relevant information accessible (compare the concept of *hyperacuity*, Kriegeskorte et al., 2010). Similarly, it is not known how distributed information is represented. In our analyses we applied a searchlight approach with a spherical, radius = 4 voxels volume-of-interest. We thereby adhered to the empirically-derived standards from previous studies (Kriegeskorte et al., 2006; Christophel et al., 2012; Hebart et al., 2015; Hebart and Baker, 2017). This, however, does not guarantee that the size of our searchlight relates to real underlying distributions of activation patterns. As a consequence of these limitations, it is important to note that decoding accuracies should not be confused with effect sizes (Hebart and Baker, 2017), limiting the interpretative power of MVPA analyses. While these limitations do not invalidate the conclusions drawn from our data, it is important to note that not finding above-chance decoding in a region does not necessarily imply that this region does not contain any content-related information. It is quite possible that a region retains information that is simply not detectable with the given methodology.

Another limitation is the lack of direct comparability across studies. We believe we have addressed this issue as much as possible by adapting an experimental paradigm and analysis approach previously reported in visual WM research. Repeatedly using an identical approach allowed us to combine data from study 5 and study 7 in a conjunction analysis. However, direct comparison with other datasets remains problematic.

Within the last few years the view has been popularized that ‘activity silent’ synaptic mechanisms could contain crucial aspects of WM content (Stokes et al., 2013; Stokes, 2015; Myers et al., 2017). This view suggests that synaptic mechanisms can retain mental content even in a situation when a region is not active, i.e. when neurons are silent and not firing (Stokes et al., 2013; Stokes, 2015). It argues that information is indeed maintained in sensory cortices; however, this information is only accessible for neurophysiologic measurements if corresponding cell populations are activated. For example, drawing attention to the relevant information could activate corresponding neurons that are otherwise silent. For this reason, the presence of information in a particular brain region does not necessarily entail that information is accessible to neuroimaging decoding approaches, nor that it is reflected in cellular firing behavior. Synaptic mechanisms are obviously problematic to investigate with the techniques available for human research. For now, only indirect evidence such as re-activation of WM representations has been provided (Rose et al., 2016), which could also be compatible with alternative explanations. Unfortunately, our data cannot address the interesting question of whether such mechanisms of content retention exist.

3.4 Outlook

Where should research go from this point? The present data call for some direct follow-up research. Firstly, one should test in a human fMRI MVPA study for the representation of categorical information derived from tactile stimuli, as was recently done in non-human primates (Rossi-Pool et al., 2016). Furthermore, the interpretation of frequency information as an abstract quantity would benefit from a comparison study on the retention of numerosity features, as already pioneered with EEG (Spitzer et al., 2014a).

To integrate the research on how our brains mentally represent information into more global theories of brain function, research needs to be extended to include the dynamic interaction of brain networks. To this end, research should shift its focus from the rather passive aspects of information retention towards the active aspects of update and manipulation of mental content. This could be achieved for example by cross-modal MI studies or by a focus on the study of rehearsal or refreshment processes, about which surprisingly little is known (Baddeley, 2012). The regular updating or re-initiating of WM content during rehearsal could constitute a window for an empirical investigation of the dynamics of information representation in dynamically interacting networks. For testing the micro-anatomy of corresponding mechanisms, layer-specific fMRI techniques may soon provide deeper insights. This technical advancement has recently also been applied in WM research (Van Kerkoerle et al., 2017). Improvements in spatial resolution might also allow us to more directly track the individual contributions of separate neuronal populations. In this context the combination of rehearsal paradigms with dynamic causal modelling approaches might allow us to empirically address the role of predictive brain mechanisms in the retention of mental content.

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Study 2

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Title:	The *'tactospatial sketchpad'*: Brain regions that retain the spatial layout of tactile stimuli during working memory
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Abstract

Working memory (WM) studies have been essential for ascertaining how the brain flexibly handles mentally represented information in the absence of sensory stimulation. Most studies on the memory of sensory stimulus features have focused, however, on the visual domain. Here, we report a human WM study in the tactile modality where participants had to memorize the spatial layout of patterned Braille-like stimuli presented to the index finger. We used a whole-brain searchlight approach in combination with multi-voxel pattern analysis (MVPA) to investigate tactile WM representations without *a priori* assumptions about which brain regions code tactospatial information. Our analysis revealed that posterior and parietal cortices, as well as premotor regions, retained information across the twelve-second delay phase. Interestingly, parts of this brain network were previously shown to also contain information of visuospatial WM. Also, by specifically testing somatosensory regions for WM representations, we observed content-specific activation patterns in primary somatosensory cortex (SI). Our findings demonstrate that tactile WM depends on a distributed network of brain regions in direct analogy to the representation of visuospatial information.

Keywords

tactospatial sketchpad, working memory, tactile, vibrotactile, somatosensory, primary somatosensory cortex

1. Introduction

Most information that we explicitly represent in working memory (WM) is derived from the visual and auditory modalities. However, our brains have the capacity to maintain contents derived from all sensory modalities and to represent them in various formats. An important goal of WM research is to identify what types of mental contents are represented by what types of neuronal codes. Of particular interest is which contents are stored in sensory-like formats, and which are transformed to more abstract, non-sensory or symbolic codes that are represented independently of the modality that they were derived from (Christophel et al., 2017). Thus, to establish cross-modal perspectives, studies outside the visual or auditory domain are essential.

To test which brain regions contain information on WM contents, multivariate pattern analysis (MVPA) for fMRI has been instrumental (Haynes, 2015; Norman et al., 2006). The possibility to link activation patterns within a brain region to different WM conditions is the crucial feature that makes MVPA sensitive to the content of WM and thus, it has been applied in studies on various WM contents. When study participants memorized visual features such as orientation (Albers et al., 2013), position (Jerde et al., 2012), motion direction (Christophel and Haynes, 2014; Emrich et al., 2013), or the layout of a stimulus (Christophel et al., 2012; Lee et al., 2013) evidence for stimulus information in early visual and parietal regions was reported. The involvement of visual cortices is viewed as support for *'sensory recruitment'* models of WM that emphasize the importance of sensory regions for coding WM content. The models suggest that sensory regions are re-activated in the absence of sensory stimulation so that the same sensory regions that perform perceptual processing also realize the mental maintenance of WM content (Pasternak and Greenlee, 2005).

The *'sensory recruitment'* account of WM aligns well with the influential *'Baddeley & Hitch'* model, which describes the theoretic construct of a *'visuospatial sketchpad'* as a type of screen on which a mental representation is drawn and stored (Baddeley, 2012). Such sketchpad- or buffer-like representation of visuospatial stimulus features has been speculated to be implemented by retinotopically organized regions, such as early visual cortices (Albers et al., 2013). Aside from WM studies, the study of mental imagery has also built heavily on the assumption that mental content is realized as *'depictive representations'* for which the neuronal activation should reflect the isomorphic or physical stimulus properties in the real world, as for example spatiotopically organized brain representations (Cichy et al., 2012; Harrison and Tong, 2009; Kosslyn, 2005; Schmidt et al., 2014; Tong, 2013). However, recent fMRI MVPA studies suggest that WM representations are not only found in sensory regions but throughout the cortical hierarchy (Christophel et al., 2017; Schmidt et al., 2017). As it is unlikely that a single brain region solitarily implements a particular cognitive function, it is impossible that only visual cortices process the *'visuospatial sketchpad'* or function in isolation buffer-like to store WM content. Nevertheless, it remains a critical question, under which conditions some aspects of mental content representations are realized by sensory cortices.

Early sensory cortices in the visual and the tactile system directly reflect spatial stimulus properties via a retinotopic or somatotopic organization. For example, in line with the well-established orientation coding in the primary visual cortex, orientation tuned neurons can also be found in SI area 3b (Bensmaia et al., 2008). Additionally, feature specific response properties increase in complexity along the somatosensory pathway from the first to the second somatosensory cortex (SII) (DiCarlo and Johnson, 2002; Sripati, 2006) emphasizing the role of SI and SII in the processing of simple shape features (Hsiao et al., 2002), in analogy to the organization of the visual system (Yau et al., 2009). While the functional role of regions processing higher-level features and their relation to attentional supramodal processes are less well understood (Burton et al., 2008), it has been established that multiple re-mappings, such as between retinotopic or ego- and allocentric coordinate systems were related to posterior parietal regions (Grefkes and Fink, 2005). However, it is unclear, in which format or on what level of hierarchical processing, the information regarding the spatial layout of a tactile stimulus in WM is maintained.

Tactile WM has previously been studied with a variety of methods: ranging from recordings of spike activity and local field potentials in monkeys (Romo et al., 1999; Zhou and Fuster, 1996) to human EEG (Spitzer et al., 2013; Spitzer and Blankenburg, 2012) and fMRI studies (Kaas et al., 2013; Preuschhof et al., 2006; Ricciardi et al., 2006; Schmidt et al., 2017; Spitzer et al., 2014). Influential research by Romo and colleagues in non-human primates has revealed that mnemonic representations of vibratory frequency are found predominantly in non-sensory frontal and prefrontal regions (Romo et al., 2012; Romo and de Lafuente, 2012; Romo and Salinas, 2003). However, the quantity-like stimulus feature of vibratory frequency, may be retained in a different manner than spatial, somatotopic stimulus properties. The mental representations of spatial tactile stimulus features have, as of yet, not been investigated with fMRI and MVPA. To close this gap, and to allow a comparison with visual WM studies, we designed Braille-like tactile stimuli with spatial properties similar to recently applied visual stimuli (Christophel et al., 2012) that were presented to the fingertips. We used an assumption-free searchlight approach to map brain regions containing multivariate activation patterns that code corresponding stimulus information during a 12 second WM delay.

'Sensory-recruitment' models would predict that somatotopically organized sensory cortices, i.e., SI and SII, contain content-specific WM codes. Previous work from visual WM suggests that also higher-order brain regions contain content-specific representations as part of a distributed network of WM representations, where WM content is stored in different formats, and correspondingly different brain regions, to flexibly adapt to task requirements (Christophel et al., 2017; Serences, 2016).

2. Material and Methods

2.1 Participants

All participants (N=24, age: 25.5 ± 2.95 years, 15 female) were neurologically intact and right-handed, as assessed by the Edinburgh Handedness Inventory (EHI: 0.81 ± 0.20; Oldfield, 1971). The sample size was motivated by previous WM studies using MVPA (Christophel et al., 2012; Lee et al., 2013). All participants provided written informed consent for the procedure in accordance with protocols approved by the local ethics committee of the Freie Universität, Berlin. Two participants were excluded from the analysis due to low mean performance (57.3 % and 62.5 % correct responses) and chance-level performance (50 %) in at least one run, leaving N=22 participants for the fMRI data analysis.

2.2 Tasks and stimuli

We used a retro-cue WM paradigm wherein the presentation of two spatial tactile sample stimuli was followed by a visual cue, indicating which of the two samples had to be memorized (Figure 1B). Participants performed a two-alternative forced choice task after 12 s delay to indicate which of two test stimuli was identical to the memorized sample. Button-press responses were performed with the middle and index finger of the right hand. The left/right-response mapping was randomized across participants.

Vibrotactile stimuli were delivered to the left index finger using a 16-dot piezoelectric Braille display (4x4 matrix with 2.5 mm spacing) controlled by a programmable stimulator (Piezostimulator, QuaeroSys, St. Johann, Germany). The spatial layout of the vibrotactile stimuli was a composition of pins with different vibration amplitudes (Figure 1A). To enable the classification of stimulus identity in the fMRI analysis, the set of sample stimuli was limited to four. Pins were driven by a 30 Hz sinusoidal amplitude modulation with smoothed stimulus on- and offsets of 700 ms duration. To prevent any stimulus-specific confounds, a unique set of stimuli was created for each participant. This is particularly important as the physiological finger constitution, receptor density as well as skin properties (Sripati, 2006) vary between participants and might alter the perception of spatially distributed vibration intensity. For each participant, four samples were generated that were equidistant in similarity space, defined as correlation coefficient between stimulation amplitude matrices to be between 0 - 0.05. Every stimulus delivered the same amount of physical stimulation by applying vibrotactile stimulation with the same amount of overall pin-amplitudes across the display. After the presentation of two sample stimuli, a 30 Hz mask stimulus consisting of all 16 pins vibrating with maximum amplitude was applied together with the WM retro-cue for 500 ms to overwrite potential peripheral perceptual residues. The WM delay was followed by a two alternative forced choice task, in which the memorized sample stimulus was presented together with a foil stimulus (random, balanced order). To ensure the same difficulty in each trial, a set of 50 foil stimuli per sample stimulus with fixed similarity to the sample (correlation coefficient with sample between 0.5 - 0.75) was composed. In each trial, a random foil for the sample was presented with the sample. The (dis)similarity between sample and foil was chosen based on pilot data with the goal of an overall performance of approximately 75% in the final study. Participants had 1.5 s to respond via button press and indicate which of the two stimuli was the memorized sample (See Figure 1). None of the participants was able to determine how many different stimuli were used in the experiment.

Each experimental run constituted 48 trials with a 12 s WM delay, supplemented by 12 catch trials with a shorter delay of 4 or 8 s. Catch trials were included to motivate the participants to continuously retain a precise stimulus representation throughout the delay phase and discourage any potential alternative memory strategies. Each run started with an 8 s rest phase before the first trial and trials were randomly interleaved with an inter-trial-interval of 3 or 5 s. Trials lasted 17 s, where sample stimuli were presented in the first 2 s, followed by a 12 s delay period and a 3 s two alternative forced choice task (See Figure 1). Each of 6 stimulus pairs was presented equally often in balanced order, where each of the four samples was memorized 12 times. Prior to the fMRI experiment, participants were familiarized with the task by performing 1-2 experimental runs with a different stimulus set on a day before the fMRI experiment.

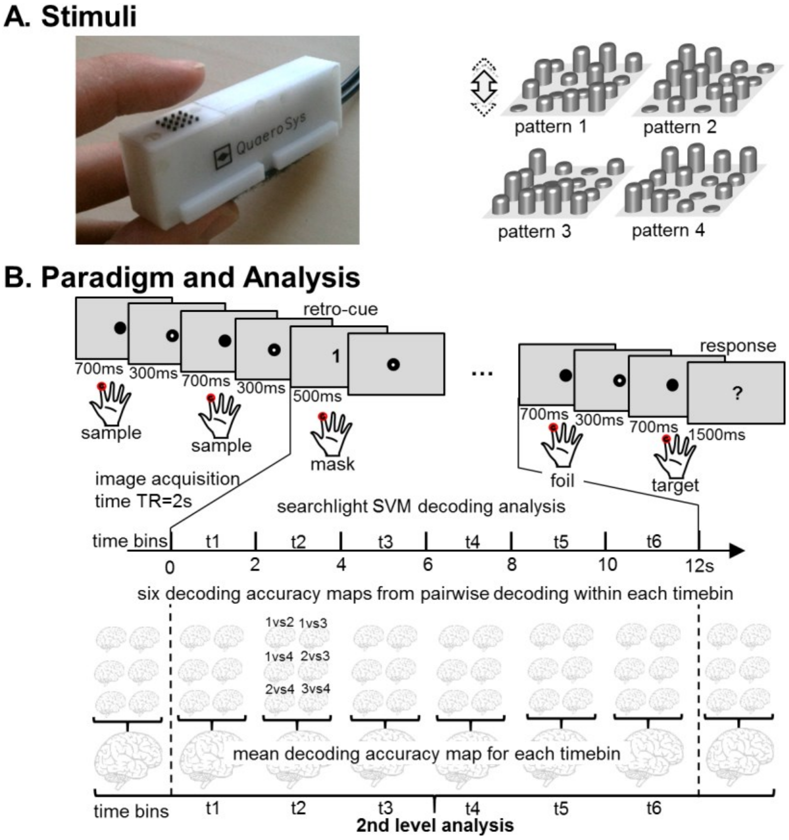

Figure1: Experimental Paradigm

A. Vibrotactile stimuli were presented as patterns of pins on a Braille-like 4x4-pin display, where the spatial pattern constituted pins vibrating with different amplitudes but with the same frequency (30 Hz). The amplitudes were modelled in a surface-like smooth manner, where the four stimuli were equally similar to each other within each stimulus-set. An example stimulus set for one participant is shown. For each participant, an individual stimulus set was created to avoid any potential stimulus specific confounds. **B.** Participants performed a retro-cue delayed match-to-sample paradigm. Each trial started with the presentation of two consecutive vibrotactile sample stimuli to the tip of the left index finger. A mask stimulus (vibration of the full display at maximum intensity) was presented together with a visual retro-cue. The retro-cue (‘1’ or ‘2’) indicated which of the two sample stimuli had to be retained for the 12 second WM delay. After the delay phase, participants were presented with two further stimuli, one of these stimuli was identical to the memorized stimulus (target) and the other stimulus was a slightly changed version of it (foil). Participants indicated with a right-hand button-press (index- or middle-finger) which of the two stimuli was the target. Stimulus combination and response-mapping were randomized and balanced within each experimental run. Image acquisition was time locked to the onset of the WM delay phase and independent decoding analyses were performed within the six 2 s time bins t1 to t6. Data from the time bins before and after the delay phase were additionally analyzed. Whole-brain searchlight analyses with support vector machine (SVM) classification were performed for each stimulus pair, resulting in six decoding accuracy maps per time bin. Averaged, normalized, and smoothed images were used in the 2nd level analysis.

2.3 fMRI data acquisition

MRI data was acquired on a 3 T TIM Trio (Siemens) at the Center for Cognitive Neuroscience Berlin of the Freie Universität, Berlin. Each participant completed 4 experimental runs of 20 min (T2*-weighted gradient-echo EPI: 37 slices; interleaved order; whole brain; TR = 2000 ms; TE = 30 ms; 3 x 3 x 3 mm^3 voxel; 20 % gap; flip angle = 90°; 64 x 64 matrix, 600 volumes per run) and a structural scan (T1-weighted MPRAGE: 176 sagittal slices, TR = 1900, TE = 2.52 ms; 1 x 1 x 1 mm^3 voxel). Trial onsets were time-locked to the functional images. This approach allows a TR-wise analysis of the 12 s WM phase in consecutive functional images as previously applied in the study of visual and tactile WM (Christophel et al., 2012; Schmidt et al., 2017).

2.4 fMRI data processing and searchlight decoding

To preserve the spatiotemporal structure of the fMRI signal, no smoothing, normalization, or slice-time correction was performed before classification, and preprocessing was limited to spatial realignment. All fMRI data processing was performed using SPM8 (Wellcome Trust Centre for Neuroimaging, Institute for Neurology, University College London, London, UK). Furthermore, we used finite impulse response (FIR) models to obtain run-wise beta estimates for each 2 s time bin of the WM delay. High-pass filtered data (cut-off 192 s) was included into a model with a total of 132 beta estimates (4 stimuli x 8 time bins x 4 runs + 4 constants), to model all working memory time bins including one bin before and after the delay period. Beta estimates of each time bin were then used for a whole-brain searchlight-decoding analysis (Kriegeskorte et al., 2006).

All decoding analyses were performed using 'The Decoding Toolbox' (TDT) (Hebart et al., 2015), which provides an interface for applying the computational routines of LIBSVM (Chang and Lin, 2011) to neuroimaging data. We used support vector machine (SVM) classification with a cross-validation scheme for our four experimental runs, as implemented in TDT. In an effort to make our data comparable with previous visual WM research, we used the same SVM classification approach as described in Christophel et al., (2012). We used linear SVM classifiers to distinguish between only two types of activation patterns. Therefore, we implemented a pairwise-classification scheme. For each of the six possible pairs of stimuli (1-2, 1-3, 1-4, 2-3, 2-4, 3-4) an independent whole-brain searchlight analysis was performed and results were averaged. In short, for each pairwise-classification, beta estimates from a 4 voxel radius sphere were extracted for a pair of memorized sample stimuli and z-scaled (normalized) across the samples for each voxel. A classifier was then trained on data from 3 runs and its generalization was tested on the data from the remaining run (leave-one out cross-validation). The center of the searchlight was moved voxel-wise through the brain and thereby whole-brain accuracy maps for each pair of beta maps were derived (reflecting how accurately the classifier can separate the two WM contents). These six accuracy maps were averaged within time bins, normalized to MNI space using unified segmentation (as implemented in SPM8), and smoothed with a 5 mm full-width half-maximum kernel. Mean accuracy maps were entered to a second level ANOVA (repeated measures across time bins). We computed a t-contrast to test decoding accuracies in each voxel against 50 % chance level to determine if a voxel contained information on the stimulus identity across the delay phase. Please note that the chance level is 50% as the chance level of each of the six pairwise-classification steps with a linear SVM is 50% and the resulting accuracy maps were averaged. The t-contrast was computed for time bins t2 - t6 (corresponding to seconds 2-12 of the delay phase, see Figure 1B) to account for the delayed BOLD response and to model only WM time bins after the retro-cue was presented. We report significant voxels at a threshold of $p<0.05$ family-wise error corrected (FWE) at the voxel level if not stated otherwise. All reported coordinates correspond to MNI space. The SPM anatomy toolbox (Eickhoff et al., 2007) was used to provide cytoarchitectonical references where possible.

2.5 Control analysis: decoding the non-memorized stimulus

As a control analysis for the specificity of the main analysis, we tested for above-chance decoding accuracy for the non-memorized stimulus. New FIR-models were estimated, with four sets of FIR regressors that modeled those trials where a particular stimulus was presented but not memorized. Thus, each beta image was estimated with equal amounts of data (modelling the same number of trials) as in the original analysis. Beta-images were entered to an identical SVM searchlight and second-level analysis as in the main analysis.

3. Results

3.1 Behavioral performance

Participants successfully memorized the relevant information in the demanding task, as indicated by an overall performance of 76.8 ± 8.6 % (mean ± SD) accuracy. Individual participants' performances across the four experimental runs are displayed in Figure 2. No systematic performance differences were detected across runs. Furthermore, a 2 x 2 repeated measures ANOVA did not reveal any significant differences, or an interaction between the factors, in the performance depending on whether the first or second sample stimulus was memorized (F(1,1) = 0.593, p = .450) nor whether the target stimulus was presented before or after the foil stimulus (F(1,1) = 1.540, p = .228), allowing for unbiased classification. Participants performed with 77.7 ± 10.2 % correct responses in catch trials with shorter delays, indicating that throughout the retention period an equally precise comparison could be performed and not indicating any alternative memory strategies.

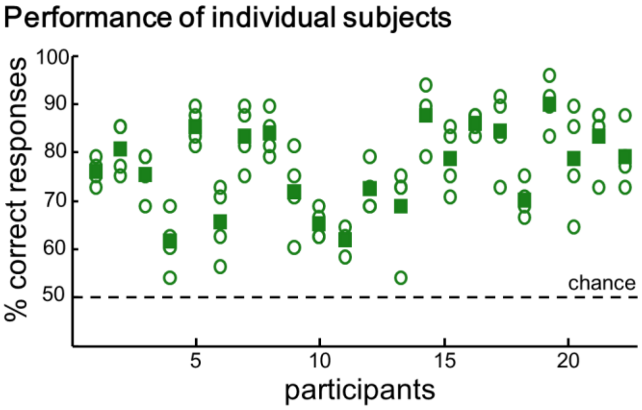

Figure2: Performance in the delayed match to sample task
The difficulty of our WM task was adjusted based on pilot data to approximate 75% correct responses across participants by adjusting the similarity of the foil stimulus to the target stimulus. Consistent performance with relatively low variability across the four experimental runs indicates good cooperation and motivation of the participants. It further demonstrates good discriminability of the stimuli and that it was possible to remember the relevant stimulus information. The performance on an experimental run is shown as a circle; Squares represent each participants' mean performance across the four runs.

3.2 Decoding the spatial stimulus layout

We tested which brain regions represent the spatial layout of the stimuli across the delay period by identifying areas that demonstrated above-chance level decoding accuracies across participants. Therefore, mean-accuracy maps for each participant and every time bin entered a second-level design, within which a t-test against chance was performed ($p < 0.05$ FWE-corrected at the voxel level and a cluster extent threshold of 10 voxel).

As sensory recruitment models suggest that information on the WM content might be represented in sensory regions, we also specifically tested for above-chance decoding accuracies within the right primary and bilateral secondary somatosensory cortices on the more liberal threshold of $p<0.001$ uncorrected. This test revealed a cluster of voxels within the finger-representing region of the right BA1 and BA3b (as depicted by the anatomy toolbox). The results are displayed in red in Figure 3A at a threshold of $p < 0.001$ uncorrected for multiple comparison due to our strong *a priori* assumption.

To assess the temporal unfolding of decoding accuracies within these regions, we plotted the time courses of decoding accuracies throughout the delay as descriptive information of the data (Figure 3B). The time courses show comparable features to those presented in previous WM decoding studies in the visual (Christophel et al., 2012) and tactile modality (Schmidt et al., 2017). Decoding accuracies in all displayed regions increased over the time bins following the retro-cue. Direct comparisons between time-courses were performed with one-way 1 x 5 ANOVAs to test for differences between the five clusters of above-chance decoding within each of the six time bins. None of these revealed significant differences.

Please note that decoding accuracies should not be confused with effect sizes and that even accuracies close to chance can carry useful information (Christophel et al., 2015) as the primary aim of MVPA in neuroimaging is not to optimize the read-out, but to test in an unbiased fashion for the presence of information (Hebart and Baker, 2017).

A control analysis using only correct trials revealed virtually identical clusters of above-chance decoding accuracies, with slightly reduced t-values. A contrast between our main analysis modelling all experimental trials and this control analysis did not reveal any significant differences between the two analyses. Therefore, the exclusion of error trials appears not to affect the main findings of the given report but merely affects the power of the analysis, likely due to the reduced number of trials.

In an additional control analysis, we wanted to test whether activation differences in individual voxels also code information regarding the WM content. Thus, we performed the same MVPA analysis as described above, however, with a decoding searchlight size of 1 voxel radius. This analysis revealed three clusters of voxel: (1) right PPC: peak [20 -66 60], size 85 voxel, $z = 6.50$; (2) left PPC: peak [-38 -50 56], size 55 voxel, $z = 5.94$; (3) right PPC: peak [40 -58 56], size12 voxel, $z = 5.38$ ($p < 0.05$ FWE-corrected, cluster extent threshold 10 voxels). Contrasting the 1 voxel radius analysis against the 4 voxel radius analysis did not reveal any significant voxels, whereas the opposite contrast revealed a posterior parietal network of regions ($p<0.001$ uncorrected) which overlap with the original results. This demonstrates that it is possible to decode more information on the stimulus identity from multivariate activation patterns than from individual voxels, indicating the dependence of the main findings on multi-voxel representations.

Importantly, our study design allowed us to perform an identical MVPA analysis for the non-remembered stimuli as two sample stimuli were presented on each trial and pairs of stimuli were balanced. Decoding the non-remembered stimulus did not reveal any significant clusters. Additionally, testing within each time bin did not reveal any significant clusters of voxels across the delay period. Results of this control analysis are displayed as time courses in Figure 3B (grey) for the information representing clusters from the main analysis.

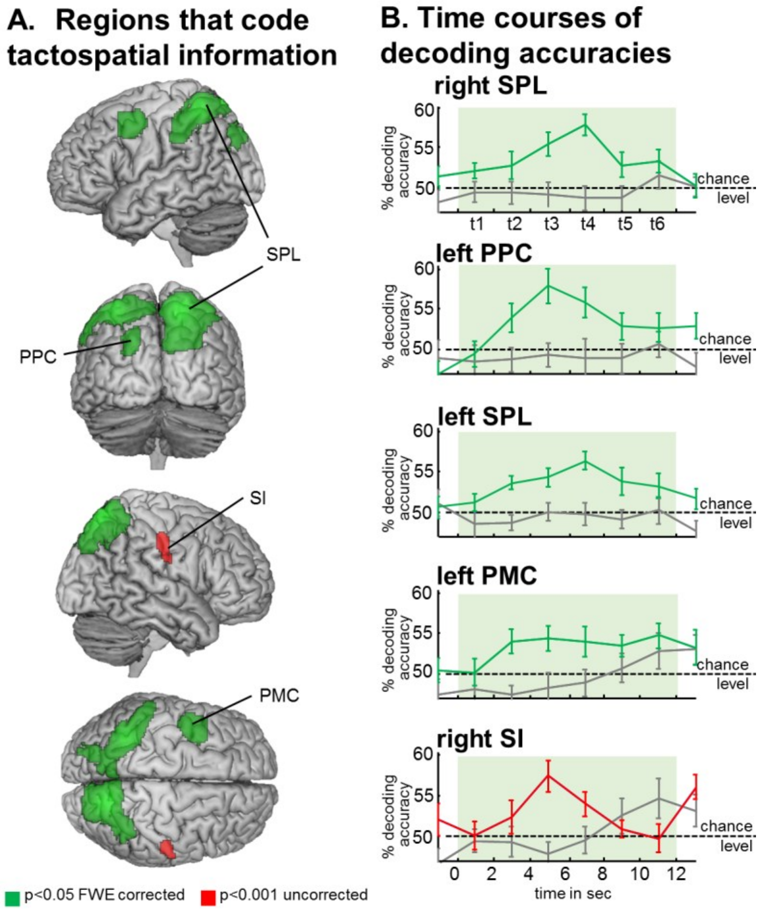

Figure 3: Brain regions coding spatiotactile information during WM
A. A t-contrast testing for above-chance decoding accuracies across the WM delay phase revealed a posterior parietal network supplemented with premotor cortex assessed at $p < 0.05$ FWE corrected (cluster extent threshold 10 voxels). Additionally, to test for the recruitment of sensory regions, decoding accuracies in right primary somatosensory cortex (SI, red) were assessed at $p < 0.001$ uncorrected. This analysis revealed a cluster corresponding to the finger area in right SI. SPM available at: https://neurovault.org/collections/3373/ **B.** To display the temporal unfolding of decoding accuracies across the delay phase, we extracted decoding accuracies for all participants from the peak voxels of the identified clusters (mean ± SEM). Decoding accuracies are displayed in green/red, time courses of the control analysis (decoding the non-remembered stimulus) are displayed in grey. SPL: Superior parietal lobule, PPC: Posterior parietal cortex

Cluster	Anatomical region	Peak MNI X	Y	Z	z-score
Above-chance prediction accuracy across WM delay					
6179	Right SPL	18	-68	60	7.81
	Left SPL	-36	-52	62	6.67
740	Left PMC	-44	2	48	5.29
593	Left PPC	-22	-74	34	5.26
156	Right SI ($p < 0.001$ uncorrected)	54	-18	42	3.40

Table 1: Regions coding information on the memorized tactile stimulus layout
Peak coordinates, cluster sizes and z-scores corresponding to Figure 3A. Above chance decoding accuracies revealed by a t-contrast across the WM delay, assessed with $p<0.05$ FWE corrected at the voxel level. A cluster in the right primary somatosensory (SI) cortex significant at an uncorrected significance level of $p < 0.001$. SPL: Superior parietal lobule; PMC: Premotor cortex; PPC: Posterior parietal cortex.

4. Discussion

The study at hand was designed to test which brain regions code tactospatial information during WM. Our MVPA results demonstrate that WM representations for spatial layouts of tactile stimuli can be found in posterior parietal cortices as well as in the premotor cortex. A similar network was previously identified in the study of visual WM (Bettencourt and Xu, 2015; Christophel et al., 2012), suggesting these representations may be modality independent.

The results at hand indicate that it is mainly hierarchically higher regions that retain tactospatial information throughout the WM delay phase. We also identified SI being involved in the retention, though at a lower statistical threshold. In analogy to visuospatial WM, this speaks in favor of the distributed nature of WM representations, in which lower-level areas may maintain concrete sensory -like information and higher-level areas code more abstract, task-specific information.

4.1 Tactile WM studies and sensory recruitment

The investigation of tactile WM has proven fruitful for studies employing different neurophysiological recording methods, as similar WM tasks can be applied in rodents, monkeys, and humans. In comparison to the visual system, the study of tactile WM benefits from a simpler network organization (Felleman and Van Essen, 1991). Moreover, the possibility to study mental representations of abstract, non-sensory, language-independent features, such as vibratory frequency, has made the somatosensory modality attractive for WM researchers. Early WM studies in monkeys (Romo et al., 1999; Zhou and Fuster, 1996) strongly influenced the view that prefrontal regions code the content of WM. Also, several EEG studies replicated findings showing that parametric codes in human prefrontal regions reflect vibratory frequency for WM delay phases and related them to the representation of abstract quantitative information (Spitzer et al., 2013; Spitzer and Blankenburg, 2012). Finally, human fMRI studies investigated delay activity during vibrotactile WM (Preuschhof et al., 2006; Spitzer et al., 2014), and in a recent study, we localized codes of vibratory frequency to the right prefrontal cortex with MVPA (Schmidt et al., 2017). Taken together, the network that codes information about vibratory frequency has been well described. Further fMRI studies have investigated which brain regions show activity during WM of tactile surface texture (Kaas et al., 2013) and 3-dimensional objects or 2-dimensional surfaces after haptic exploration (Kaas et al., 2007; Ricciardi et al., 2006). However, reports on the mental representation of spatial features of tactile stimuli using MVPA and fMRI have previously been lacking.

'Sensory recruitment' models of WM (Pasternak and Greenlee, 2005) emerged from observations of delay-activity in sensory regions. The models were further compatible with reports from the study of mental imagery about re-activation of perceptual regions during mental reconstruction across all several modalities (McNorgan, 2012; Schmidt et al., 2014; Tong, 2013). Multiple recent MVPA studies support sensory recruitment models by demonstrating that visual stimulus features can be decoded from visual cortices during WM (Christophel et al., 2015; Lee and Baker, 2016). These findings have led to the suggestion that sensory regions could implement a memory buffer for diverse types of visual information (Albers et al., 2013; D'Esposito and Postle, 2015). Evidence for sensory recruitment also exists from tactile studies, when demonstrating delayed EEG activity over somatosensory regions in

WM tasks (Katus et al., 2015; Katus and Eimer, 2015) and recruitment of SI during tactile mental imagery with fMRI (Schmidt et al., 2014).

Based on this literature, we tested in our otherwise assumption-free analysis, for above-chance decoding in right SI and bilateral SII with the more liberal threshold of $p<0.001$, and identified a cluster of voxels in SI (Figure 3A). The comparison of decoding accuracy time courses over the WM delay period did not reveal significant differences between the five regions, while descriptively the representation in SI appears to be shorter lasting than in the other regions. As fMRI measurements rely on the relatively slow evolution of the BOLD response it is problematic to infer details on the temporal evolution and differential contribution of the identified regions. A primarily early contribution of SI could reflect encoding-related information content and would be in line with a recent tactile WM study wherein participants had to memorize vibratory frequencies. In the study, TMS was used to disrupt contralateral SI processes. This intervention had the strongest effect if applied during an early phase of the WM delay (Zhao et al., 2017). Additionally, electrophysiological research supports that sensory regions represent information only briefly after stimulus perception and not throughout the WM delay (Romo et al., 2012; Van Kerkoerle et al., 2017). Further research is required to determine whether the early contribution of sensory regions resemble encoding processes or converting perceptual codes into a different WM code.

Recently it has been suggested that information maintenance during WM may not necessarily need to be reflected in brain activity. It was suggested that so-called “activity-silent” synaptic mechanisms can retain information (Stokes, 2015). A study by Rose et al. (2016) showed that after drawing attention away from a WM content, MVPA decoding accuracies decreased. However, it was possible to reactivate the initial activation pattern, indicating that information was not lost despite the loss of decoding ability. The concept of “activity-silent” representations that can be activated by attention provides an alternative means with which to interpret the temporal pattern of decoding accuracy in SI. Namely, that SI displays content-specific activation patterns only during stimulus encoding, this representation is then changed into a silent state during the WM delay and cannot be decoded even though information is still represented by synaptic mechanisms. However, fMRI might not be a suitable method to test the "activity-silent" representations hypothesis and our study therefore leaves this possibility unexplored.

With a control analysis to decode the non-memorized stimulus, we tested for the specificity of decoding WM content in contrast to perceptual processes. If above-chance decoding during the WM delay was an artefact of the sluggish perception-related BOLD response, it should also be possible to decode the non-memorized stimulus, which was not the case. As revealed from the time courses displayed in Figure 3B, decoding accuracies increased after the retro-cue only for the memorized stimulus in all five identified areas. As stimulus presentation was not temporarily scattered, the design of the present study was not optimized for the investigation of perceptual processes, whereas the control analysis renders the decoding results WM specific.

4.2 Higher-order brain regions coding WM content

Our analysis revealed above-chance decoding throughout the delay period for higher-order regions, such as the intraparietal sulcus (IPS) and the posterior parietal cortex. Particularly, BA5 and BA7 are known to process spatial maps during perception (Andersen et al., 1997; Bremmer et al., 2001; Cohen and Andersen, 2002; Grefkes and Fink, 2005). It appears these regions code the spatial layout throughout the delay period and, interestingly, these regions were also found to code visuospatial WM.

To allow the comparison with visual WM studies we designed our patterned tactile stimuli similar to visual stimuli used by Christophel et al. (2012). Indeed, the regions that contained information in their visual WM study partly overlap for posterior parietal regions. Overall, the clusters identified in our study are located more superiorly than the clusters in Christophel et al. (2012), fitting better to anatomical definitions of BA5 and BA7. The direct comparison with data from the visual WM study with our tactile WM study could be explained by the existence of modality-independent representations in the overlapping regions. Alternatively, it is possible that these regions code both visual and tactile spatial information in a modality specific manner. Future studies are needed to dissect if the apparent posterior-superior gradient from visual to tactile representations reflects the modality-specificity of these regions and which aspects of this network, if any, represent modality-independent information.

The applied experimental design was optimized to have participants mentally retain information of a tactile percept. However, as it is not fully possible in the study of mental representations to gain entire experimental control over participant's strategies to solve a task, one cannot rule out the possibility of mental imagery of visual analogues of the tactile stimuli. Previous research has indicated strong interactions between visual and tactile perception and imagery (Lacey et al. 2010; Lacey et al. 2014; Deshpande et al. 2010). Such interaction could either be explained by interference in supramodal representations (e.g. in the PPC) or by a transformation (imagery) from one modality to the other. Further research is necessary to dissociate the precise roles of the PPC in this interaction between tactile and visual information processing.

The ability to decode the identity of a stimulus from activation patterns in posterior parietal regions does not necessarily imply that it is the spatial stimulus properties that are represented in these regions. Postle (2015) argues that posterior parietal regions rather reflect the *'focus of attention'* than the sensory content of WM. More specifically, the mental representation of stimulus features might recruit attentional mechanisms that elicit activation patterns dissociable between stimuli, while not directly reflecting the stimulus properties as such. In turn, the ability to decode from posterior parietal regions could be viewed as reflecting attentional mechanisms rather than the stimulus property of a spatial layout *per se*. However, the possibility to decode from posterior parietal cortices is unlikely to directly reflect mere attentional mechanism as it was not feasible to decode from these regions when participants retained vibrotactile frequencies in an otherwise identical tactile WM task (Schmidt et al. 2017). The debate of whether it is possible to dissociate attentional mechanisms from mere content representations is as old as the empirical study of mental content representations (Kosslyn, 2005) and it can be argued that it is not meaningful to consider them as independent psychological constructs

(Gazzaley and Nobre, 2012). It is probable that multiple mental codes are able to represent mental content in distributed cortical networks, making it problematic to assign the codes to separate corresponding psychological constructs (Larocque et al., 2014; Lee and Baker, 2016; Lewis-Peacock et al., 2015; Postle, 2015; Schlegel et al., 2013).

4.3 The network coding information in tactile spatial WM: the 'tactospatial sketchpad'

The term *'visuospatial sketchpad'* was put forth by the WM model of Baddeley and Hitch (1979) and has been described similarly as visual working memory, which can be defined as : *"a memory buffer that allows observers to retain visual information for a short period of time when it is no longer viewed"* (Xu, 2017). Over the past years, it has been suggested that mainly sensory visual areas store content of visual WM, suggesting an equation of early sensory regions and the *'visuospatial sketchpad'* (Baddeley, 2012). However, critiques render this view as much too simplistic.

Particularly MVPA studies of variable content-types (Christophel et al., 2017) but also behavioral, TMS and monkey neurophysiology studies (Xu, 2017) have demonstrated that the brain can flexibly represent WM content in formats different from purely sensory codes. A variety of sources of data have emphasized that there is no need for sensory regions to maintain visuospatial information, however, sensory regions are often involved in the representation of such information (Gayet et al., 2017; Leavitt et al., 2017). Gayet et al. (2017) argue that data from visual interference studies (such as Bettencourt and Xu, (2015)), could be explained by assuming that visual WM is stored in sensory areas but observers can flexibly shift between different visual and non-visual memory representations when this serves the current task demands. In line with this view, our finding of WM codes in posterior parietal cortices in combination with SI could be interpreted as the representation of more abstract, non-sensory information in the PPC which can be supplemented with sensory components, if required. Attempting to match neuronal correlates to the functionally described components of the Baddeley & Hitch model, the combined network of parietal regions with early visual regions would thereby constitute the 'visuospatial sketchpad'. Consequently, if tactile sensory features complement an abstract spatial representation by recruiting somatosensory in addition to posterior parietal regions, this network should then be called the ‘tactospatial sketchpad’. This view also concurs with notions from mental imagery (Tong, 2013), where the recruitment of hierarchically lower sensory regions is thought to be modulated by the degree of sensory detail that is supplemented to an abstract mental representation (Kosslyn and Thompson, 2003). While different tasks will require participants to mentally represent more or less vivid sensory representations, it is experimentally challenging to determine the degree to which a mental representation was enriched with sensory components.

5. Conclusion

The idea of a *‘visuospatial sketchpad’* from the *‘Baddeley & Hitch’ WM* model has tempted many researchers to equate sensory cortices with buffers for modality-specific, but highly diverse kinds of mental content. While under some conditions, information appears to be represented in sensory cortices, accumulating evidence indicates that particularly spatial information can alternatively be represented in higher order non-sensory regions. The present finding, of posterior parietal cortices exhibiting activation patterns related to spatial stimulus representations supports the notion of distributed WM representations (Christophel et al., 2015, 2012; Christophel and Haynes, 2014; Ester et al., 2015; Jerde et al., 2012). While both, the visual and the tactile system, have spatiotopically organized early sensory cortices, these regions are not the only buffers to retain spatial information in working memory, emphasizing the flexibility of our brains to represent mental content in a variety of formats.

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Study 4

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Study 5

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Study 6

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Study 7

Uluç I., **Schmidt T.T.**, Wu, Y.-H., Blankenburg F. (submitted February 2018) Content-specific codes of parametric auditory working memory in humans. NeuroImage

Content-Specific Codes of Parametric Auditory Working Memory in Humans

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Keywords:

Working memory, frequency discrimination, auditory, acoustic flutter, parametric, vibrotactile, fMRI, MVPA, abstract quantity

Abstract

Brain activity in frontal regions has been found to represent frequency information with a parametric code during working memory delay phases. The mental representation of frequencies has furthermore been shown to be modality independent in non-human primate electrophysiology and human EEG studies, suggesting frontal regions encoding quantitative information in a supramodal manner. A recent fMRI study using multivariate pattern analysis (MVPA) supports an overlapping multimodal network for the maintenance of visual and tactile frequency information over frontal and parietal brain regions. The study at hand extends the investigation of working memory representation of frequency information to the auditory domain. To this aim, we used MVPA on fMRI data recorded during an auditory frequency maintenance task. A support vector regression analysis revealed working memory information in auditory association areas and, consistent with earlier findings of parametric working memory, in a frontoparietal network. A direct comparison to a similar dataset of vibrotactile parametric working memory revealed an overlap of information coding in prefrontal regions, particularly in the right inferior frontal gyrus. Thereby our findings indicate that the prefrontal cortex represents frequency-specific working memory content irrespective of the modality as has been now also revealed for the auditory modality.

Introduction

The ability to mentally represent information in the absence of sensory stimulation is at the center of cognitive functions critical to consciousness and intelligence. For this reason, the study of working memory (WM) has been the subject of many neuroscientific investigations. One current focus of working memory research is the topographic organization for content-specific information storage in the brain. Many later investigations indicating posterior parietal and sensory cortices as the primary storage sites (reviewed in D'Esposito & Postle, 2014) challenged the initial studies proposing that the prefrontal cortex (PFC) is the primary site of working memory content storage (Goldman-Rakic, 1995). In recent years, accounts supporting both frontal regions and early sensory regions as the neural correlates of WM maintenance have gained evidence, leading to an attempt at integrating both. Hence, the distributed account of WM was introduced suggesting storage of working memory content across the whole cortex. That is, more abstract information is maintained in the higher order association cortices, while more concrete, sensory content seems to be coded in the sensory cortices (Christophel et al., 2017; see also Lee & Baker, 2016; Bancroft et al., 2014).

Experiments that use WM contents that are non-sensory and abstract, while being non-symbolic and not language-like, add to the evidence for this distributed account of WM (Spitzer and Blankenburg, 2012; Schmidt et al., 2017; Wu et al., 2018). Specifically, frequencies have been used as WM memoranda throughout different modalities and species (Romo et al., 1999; Spitzer at al., 2010; Spitzer and Blankenburg, 2011; 2012; Lemus et al., 2009; Vergara et al., 2016; Fassihi et al., 2014). The stimulus property of frequency is here considered to be represented as a type of abstract magnitude, similar to numerosity in a supramodal manner (Walsh, 2003; Spitzer and Blankenburg, 2012; Spitzer at al., 2014). In line with the idea of a distributed account of WM, higher-order regions including lateral prefrontal cortex (lPFC), premotor cortex (PMC), and medial frontal cortex (MFC) parametrically coded for vibrotactile frequency representations (Romo, 1995; Barak et al., 2010; Hernandez et al., 2010; Spitzer et al., 2010; Spitzer & Blankenburg, 2011; Schmidt et al., 2017).

To test whether this parametric representation in frontal regions is specific to the tactile domain or is represented in a supramodal code, research was extended into other modalities. In the auditory domain, Lemus and colleagues (2009) have shown that the firing rate in the ventral PMC neurons reflects the remembered auditory frequency. An additional study indicates the primary auditory cortex (A1) to be rather exclusively associated with sensory processes but not with working memory representations when acoustic flutter stimuli were memorized (Lemus et al., 2009). Further single-cell recordings in non-human primates with a WM task in the tactile and auditory domains (Vergara et al., 2016) have shown that the firing rate of neurons in a substantial part of the pre-supplementary motor area (pre-SMA) use the same parametric code while representing WM information for both tactile and auditory frequencies.

Spitzer and Blankenburg (2012) presented similar results for supramodal coding of frequencies with human EEG recordings. They have shown that upper beta-band oscillations in the right lPFC were parametrically modulated by the to-be-maintained frequencies during tactile, visual, and auditory WM retention, regardless of modality. Recently, the research has been extended to multivariate pattern analysis (MVPA) fMRI in order to study the spatial distributed representation of parametric WM (Schmidt et al., 2017). Expanding the above findings, a recent MVPA study of Wu et al. (2018) has indicated an overlapping frontoparietal network consisting of rIFG, SMA, intraparietal lobule (IPL), intraparietal sulcus (IPS), superior parietal lobule (SPL), and the PCC for the parametric WM representation of both visual and tactile frequencies. Common prefrontal regions foster the view of their multimodal role in representing abstract non-sensory WM contents but leave the investigation for the auditory domain open.

With the current study, we aimed to extend previous fMRI-MVPA research to the auditory domain by testing for the brain topography of frequency-specific memoranda across the brain using an assumption-free whole brain searchlight approach. This allowed us further to directly compare the results of auditory WM to a previously reported tactile WM study with the same paradigm and analysis approach (Schmidt et al., 2017), using a conjunction analysis.

Our study addressed two main questions: (1) whether the results in the tactile and visual domains could also be replicated with auditory frequencies, namely, do frontal brain regions also represent auditory frequency memoranda? (2) are there any brain regions representing maintained frequencies in a multimodal fashion for both auditory and tactile frequencies? We hypothesized that memorized auditory frequencies, as tactile frequencies, are represented in frontal regions including pre-SMA and right lPFC. The finding of WM content in the frontal areas for multiple modalities would support representation in an abstract, sensory-independent, magnitude format, in line with the view that higher-order brain regions code non-sensory contents (Vergara et al., 2016; Spitzer and Blankenburg, 2012; Walsh, 2003).

Material and methods

Participants

Twenty-one healthy right-handed volunteers participated in the study. One participant was excluded due to poor performance (2/4 runs ≤50%) leaving 20 participants (age: 25.65 ± 4.68 years, 10 females, EHI: 0.80 ±0.19) for further analyses. The experimental procedure was approved by the local ethics committee of Freie Universität Berlin and was in line with the Human Subject Guidelines of the Declaration of Helsinki. All participants provided written informed consent before the experiment and received monetary compensation.

Tasks and stimuli

In each trial, the presentation of two auditory sample frequencies was followed by a visual retro-cue indicating which of the two frequencies had to be memorized (Fig. 1). The to-be-remembered samples were taken out of a set consisting of the auditory frequencies 8, 14, 20, and 26 Hz. The two sequentially presented sample stimuli were never of the same frequency. This resulted in a total of 12 possible pairings of sample stimuli (4 frequencies of the first sample x 3 remaining ones of the second one). All stimulus pairs were presented equally often and pseudo-randomized within each run. A retro-cue, namely “1” or “2”, was shown to indicate which of the two sequentially presented samples had to be remembered. A mask, i.e., a stimulus of 1 kHz, was applied for 500 ms concurrently with the retro-cue.

Subjects performed a two-alternative forced choice task after a delay of 12 s. Their task was to indicate which of the two test stimuli was identical to the memorized sample stimulus. Of the two test frequencies, one matched the sample stimulus, and the other, the foil stimulus, was either higher or lower than the remembered sample. The number of higher and lower foils was balanced within each run. To maintain equal difficulty across trials, foil frequencies were adjusted according to the Weber-Fechner law (Fechner, 1966), anchored at the mean sample frequency 17 + 5 Hz (see Schmidt et al., 2017 and Wu et al., 2018). Subjects answered with a button-press of the middle or index fingers of their right hand. The response mapping was counter-balanced across subjects.

The auditory stimuli consisted of auditory flutters with a 1 kHz carrier sine tone, which was amplitude-modulated by a fixed amplitude sine function of the respective stimulus-frequency, as done in Spitzer and Blankenburg (2012). The stimuli were provided at a 48 kHz sampling rate, in mono via the stimulation computer's onboard sound card. The auditory stimuli were presented to both ears by MRI-compatible insert earphones (Sensimetrics Corp., Massachusetts, USA).

Each experimental run consisted of 60 trials. 48 trials had a WM delay of 12 s, supplemented by 12 catch trials with delays of 4 or 8 s. Each of 6 stimulus pairs was presented equally often in a balanced order where each of the four samples were memorized 12 times. Previous to the fMRI experiment, subjects were familiarized with the task using up to two runs of the experiment outside the scanner.

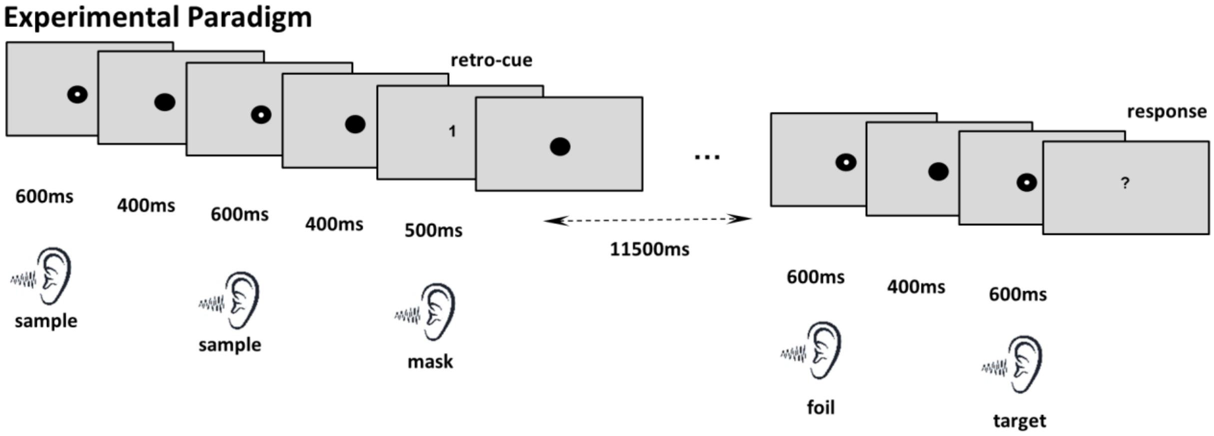


Fig. 1. Experimental design for the auditory task. One trial lasted 17 s. A delayed match-to-sample paradigm was applied, where two sample stimuli (600 ms each with 400 ms SOA) and a mask (500 ms) were consecutively presented. A visual retro-cue simultaneously in time with the mask indicated which of the sample frequencies had to be memorized across a 12 s delay phase. The subjects performed a two-alternative forced-choice task to indicate which of the two target stimuli was identical to the maintained working memory content. The response period was 1 s. Trials were time-locked to the volume acquisition, and images were acquired with a TR of 2 s.

fMRI data acquisition and pre-processing

Functional MRI data were acquired in 4 runs of 20 min each at the Center of Cognitive Neuroscience Berlin, FU Berlin, with a Siemens 3 T Tim Trio MRI scanner (Siemens, Erlangen) equipped with a 32-channel head coil. In each functional run, 600 images time-locked to the onset of the volume acquisition were collected (T2*-weighted gradient-echo EPI: 37 slices; interleaved order; 20% gap; whole brain; TR = 2000 ms; TE = 30 ms; 3x3x3 mm^3 voxel; flip angle = 90°; 64x64matrix). After the last functional run, a high-resolution structural scan (1 mm³) was acquired using a T1-weighted three-dimensional MPRAGE sequence (TR = 1900 ms, TE = 2.52 ms, 176 sagittal slices).

fMRI data preprocessing was performed using SPM12 (Wellcome Trust Centre for Neuroimaging, Institute for Neurology, University College London, London, UK). To preserve the spatiotemporal structure of the fMRI data to be used in MVPA, the preprocessing was limited to spatial realignment to the mean functional image using a six-parameter rigid-body transformation. No smoothing, normalization or slice-time correction was performed. For the univariate control analysis, functional images were realigned to the session mean, normalized and smoothed with a 5-mm FWHM kernel.

Multivariate Pattern Analysis

We used a time-resolved multivariate searchlight analysis (Christophel et al., 2012; Kriegeskorte et al., 2006) to identify brain regions that encode memorized auditory frequencies. To enable the direct comparison to an earlier tactile WM study of Schmidt et al. (2017), the paradigm of our auditory WM task and the SVR MVPA analysis parameters were kept identical between both studies. Accordingly, to obtain run-wise parameter estimates for each time bin of the WM delay, we fitted a general linear model (GLM) with a set of finite-impulse-response (FIR) regressors to each participant's data. A 16 s period started from trial onsets was divided into eight time bins of 2000 ms, including the 12 s WM interval and 2 seconds before and after the WM delay period (i.e., one TR interval). Each of the time bins was modeled with a separate FIR regressor. High-pass filtered data with a cut-off value of 192 s was included in the GLM model with a total of 132 beta estimates (4 stimuli x 8 time bins x 4 runs + 4 constants). Catch trials with shorter WM intervals were not modeled.

All decoding analyses were performed with The Decoding Toolbox (TDT; Hebart et al., 2015). To identify the brain regions encoding the information about the memorized frequency, a searchlight-based multivariate support vector regression (SVR) analysis was performed as implemented in TDT, using the computational routines of LIBSVM (Chang & Lin, 2011). In comparison to support vector machine approaches which treat the classes of stimuli as a categorical variable, SVR predicts the value of a variable in a linear continuum. This approach allowed us to examine whether spatially distributed activity patterns at any location of the brain reflect the parametric change in the memorized auditory frequency.

For each time bin, we separately performed a searchlight decoding analysis using a spherical cluster of 4-voxel radius. The center of the searchlight was moved voxel by voxel throughout the brain. For a given voxel in the brain, parameter estimates corresponding to each WM condition were separately extracted from all voxels within the spherical cluster and stored in pattern vectors. This yielded 16 pattern vectors, each representing the brain activity pattern corresponding to a WM condition of a functional run. These were first z-scaled across all pattern vectors for each voxel. Then, these z-scaled parameter estimates were entered into an SVR model with a linear function (the regularization parameter c was set to 1). We used a leave-one-out cross-validation scheme at the subject-level decoding analysis. The SVR classifier was trained on three runs (12 pattern vectors) and tested on the independent fourth run (4 pattern vectors) for how well it predicts the values of the memorized auditory frequencies. The allocation of training and test runs were iterated until each of the four functional runs was once used as a test run, resulting in four cross-validation folds. The prediction performance from each cross-validation fold was indicated by the Fisher's z-transformed correlation coefficient between the predicted and the actual frequencies. The mean prediction accuracy across all cross-validation folds was assigned to the center voxel of the searchlight and saved for the corresponding locations of a whole-brain accuracy map. The described procedure was repeated for all voxels in the brain and for all time bins. As a result, a whole brain prediction accuracy map was obtained for each of the time bins for each subject. The value of a given voxel in a given prediction map thereby reflects the amount of information about the memorized frequencies that could be read out from the locally distributed brain activity pattern at a given time bin.

The resulting prediction accuracy maps were normalized to MNI space and smoothed with a 5 mm full-width half-maximum (FWHM) kernel. They were then entered into a second-level repeated measures ANOVA group analysis with Subject, Group, and Time as factors. To assess which regions coded the WM content during the WM delay period we computed t-contrasts across the six time-bins for the whole 12 s WM delay and reported voxels with above-chance prediction accuracies at a threshold of $p < 0.05$, family-wise error corrected (p_{FWE}) at the voxel-level for multiple comparisons. Clusters extending a threshold of 30 voxels are reported at coordinates corresponding to MNI space. Cytoarchitectonic references are based on the SPM anatomy toolbox wherever possible (Eickhoff et al., 2007).

Control analyses

To test whether the above-chance decoding results are specific to the WM, we fitted a model with FIR regressors for the non-memorized stimulus. Thereby an identical searchlight decoding procedure was applied as the original analysis.

To show that WM contents were indeed represented across the population of multiple voxels rather than by the modulation of mean activity level, we conducted a parametric univariate analysis. We fitted a standard GLM with regressors for the two stimulus presentations with parametric modulation by the stimulus frequencies, a regressor for the WM delay period with parametric modulation by the retained frequency, regressors for target presentation with parametric modulation, and response. First-level baseline contrasts for the parametric effect of memorized frequencies were forwarded to a one-sample t-test on the second level.

Control analysis: label-permutation tests

To test the specificity of the SVR analysis to the parametric order of the four frequency stimuli, we conducted a label permutation test as described in Schmidt et al. (2017). To this aim, all possible permutations of the frequency-order were computed, and permutations were grouped according to their distance from the original rank order (described in detail in Schmidt et al., 2017). We performed a whole brain searchlight analysis on all possible permutations. We extracted the prediction accuracies from the locations defined using the group-peak voxels of the main analysis for each permutation sample. High prediction accuracy was only expected if the activation patterns in a given brain region represented the correct order of the four frequency labels. Fig. 2D illustrates the graphs for the prediction accuracies for the four distance groups to the linearly ordered labels, averaged across subjects and permutations within the distance group. We tested for a positive correlation between ordering and prediction accuracy for each time bin by calculating Spearman correlation coefficients in each time-bin, and significant effects are reported at $p < 0.05$ in Fig. 2D.

Conjunction analysis with tactile frequency dataset

The paradigm in Schmidt et al. was the same as in the study at hand except that vibrotactile instead of auditory frequency sample were used. Their stimulus set comprised 10, 22, 34 and 46 Hz. Accuracy maps of that study were normalized and smoothed in SPM12 with the same parameters as our main analysis. Consecutively, a second-level conjunction analysis against conjunction null hypothesis was performed to test for overlapping clusters of above-chance prediction accuracy (Nichols, 2015).

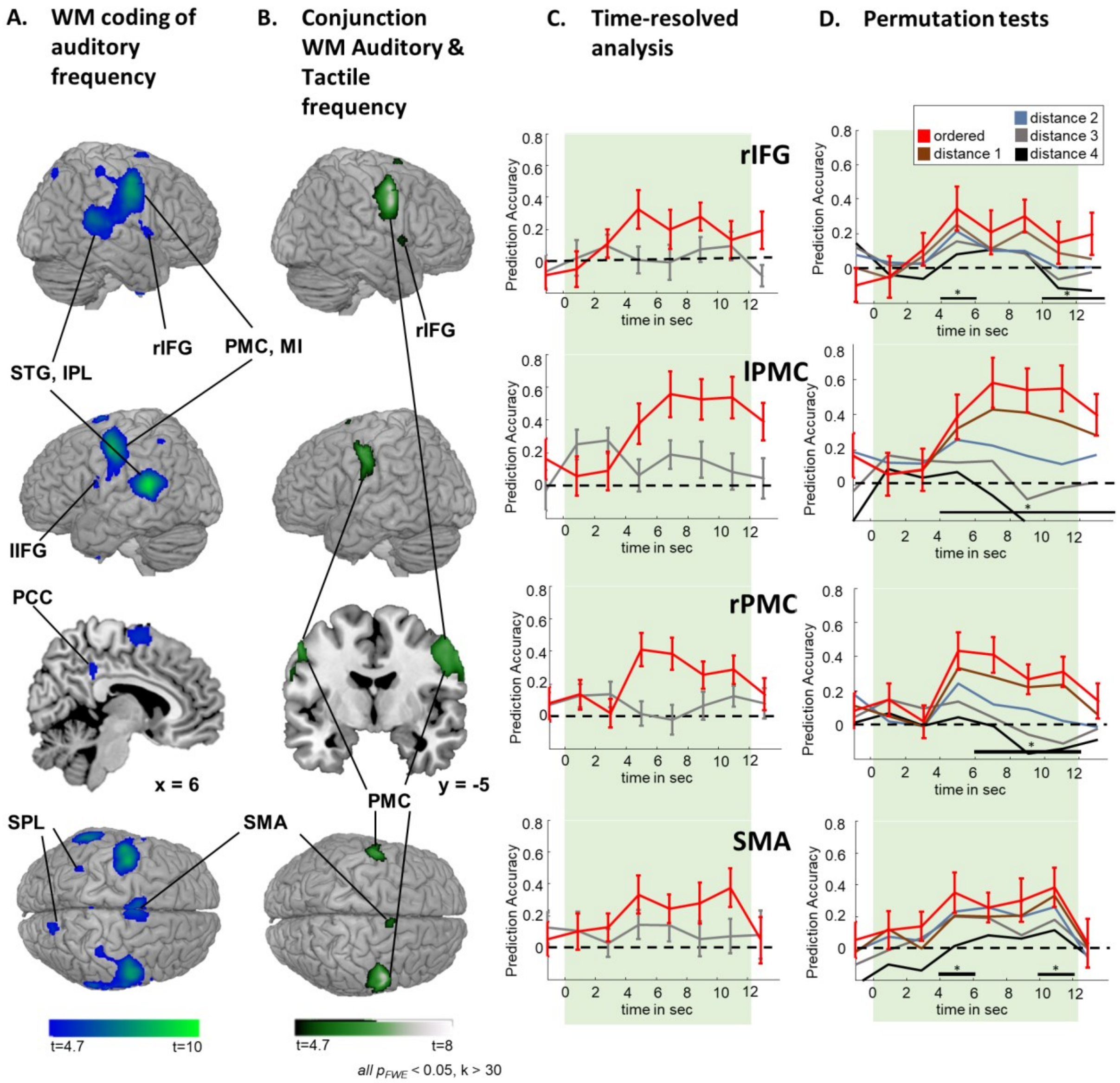
Results

Behavioral performance

Participants (N=20) performed with 66.9 ± 7.5 % (mean ± SD) correct responses in the match-to-sample task across the four experimental runs. To test whether the memory performance differs between the auditory frequencies, we performed a one-way repeated measures ANOVA with four levels, revealing a significant main effect (F(3, 76)=3.5, p=0.0195). Testing for differences in the performance in the frequency comparison of each frequency for presentation of a lower or higher foil revealed that the performance of correct responses is higher for the lower foil of the lowest frequency and the higher foil of the highest frequency when compared to the other conditions. This effect can be ascribed to the fact that the lowest and the highest comparison stimuli are outside the range of presented stimuli, and might therefore, be easier to be distinguished from the other stimuli. Please note, that the behavioral performance during the perceptual choice should not affect in any way the earlier maintenance of the frequencies and thus our MVPA findings.

Multivariate mapping of regions that code the content of WM

A time-resolved searchlight-based SVR analysis was performed to identify the brain regions representing memorized frequency information during WM maintenance. We chose an SVR approach to test the parametric change in activity pattern with the memorized frequencies. This analysis revealed frequency-specific responses in (pre-)frontal brain regions, including the bilateral SMA, opercular part of the right and left IFG, and the bilateral premotor cortex (PMC) during auditory frequency information maintenance. Further, this analysis revealed clusters in the bilateral superior temporal gyrus (STG) extending into the association auditory areas (TE3) in the temporal cortex, the inferior parietal lobule (IPL), the bilateral superior parietal lobule (SPL) in the posterior parietal cortex, the posterior cingulate cortex (PCC) and the right visual area to encode frequency-specific information (Fig. 2A and Table 1A).


A. WM coding of auditory frequency

B. Conjunction WM Auditory & Tactile frequency

C. Time-resolved analysis

D. Permutation tests

Fig. 2. Group-level results. **A.** displays brain regions carrying information about memorized auditory frequencies. **B**. depicts brain regions coding information about memorized frequencies for the tactile and the auditory modality, revealed by a conjunction analysis against a conjunction null hypothesis. All results are displayed at $p_{FWE} < 0.05$, FWE-corrected at the voxel level. All coordinates refer to MNI space. IFG = inferior frontal gyrus, IPL = intraparietal lobule, MI = primary motor cortex, PCC = Posterior cingulate cortex, PMC = premotor cortex, SMA = supplementary motor area, SPL = superior parietal lobule, STG = superior temporal gyrus (STG includes auditory belt areas). **C.** Time courses of prediction accuracy through the WM delay phase for the peak voxel of the four clusters depicted by the conjunction analysis for memorized (red) and non-memorized (grey) stimuli (mean ±SEM). **D.** Results of permutation testing for the clusters in B, in which the same SVR analysis was performed with permuted frequency labels of the data. The divergence of the permutations from the correct linear order of 8, 14, 20, and 26 Hz is expressed as the difference in rank order (see "Materials and Methods"). As expected, since the order of frequencies determines the performance of the SVR, a decrease in the order of frequency labels results in a decreased prediction accuracy. This analysis thereby demonstrates that the linear order of memorized frequencies indeed constitutes the basis for high prediction accuracies in these regions. Bars with an asterisk indicate a significant correlation of order and prediction accuracy for $p < 0.05$. The time courses for the whole clusters depicted in A can be found in the supplement.

Anatomical region	**Peak MNI Coordinates**			**z-score**	**cluster size**
	X	**Y**	**Z**		
A. Auditory WM					
Left STG	-54	-40	16	Inf	1054
Left PMC/MI	-42	-8	48	Inf	1685
Right PMC/MI	54	-6	50	7.55	3863
SMA	-6	2	74	6.45	644
Right STG	52	-40	16	5.72	
Right SPL	18	-72	44	5.51	214
Bilateral PCC	6	-38	40	5.18	206
Left IFG (pars opercularis)	-62	6	18	5.12	47
V I/II	24	-60	8	5.02	62
Right IFG (pars opercularis)	60	10	4	4.99	83
Left SPL	-36	-50	52	4.98	45
B. Auditory WM ∩ Tactile WM					
Right PMC/M1	52	0	36	6.95	1128
Left PMC/M1	-56	-6	46	6.25	380
Right SMA	6	6	66	5.32	124
Right IFG (pars opercularis)	58	10	2	4.87	33

Table 1

Anatomical location and MNI coordinates of brain areas containing information about memorized frequencies during WM delay. All results were reported at a threshold of $p_{FWE} < 0.05$, corrected for multiple comparisons at voxel-level. Areas were, when possible, identified according to the SPM anatomy toolbox (Eickhoff et al., 2005). The table is ordered according to z-values.

Control analyses

As a control analysis, we tested whether the decoded information about cued frequencies was specific to the WM content. Thus, we applied the same searchlight procedure to the un-cued frequency samples. Time courses of prediction accuracies of peak voxels for cued and un-cued frequencies are shown for the clusters from the conjunction analysis in Fig. 2B. The analysis for un-cued auditory frequencies revealed only one cluster in the left lPFC slightly extending into the left IFG ($p_{\mathrm{FWE}} < 0.05$, $k > 30$). However, only a fraction of this cluster overlapped with the cluster on the anterior part of the left PMC for the analysis of WM maintenance ($p_{uncorrected} < 0.001$, $k > 30$). Collectively, the results of our control analysis indicate that our experimental manipulation has successfully suppressed the majority of neural signals related to task-irrelevant information.

In addition to the SVR analysis, we performed label-permutation tests in order to ensure that the observed selective activity patterns to memorized frequencies are specific to the linear change of the frequencies. The prediction accuracy increased with the increasing ordering of the frequency labels during the WM period. Completely unordered labeling yields chance-level prediction accuracy, and the ordered labeling results in the highest prediction accuracy (Fig. 2D).

As a further control, we applied non-parametric permutation tests. Voxels in the correct labeled dataset were considered significant if the rank of their t-statistic was among the highest 5% of the permutation distribution of maximum t-statistics, as performed in Wu et al. (2018). The results of this more stringent non-parametric testing confirms the results of the reported parametric tests by showing highly similar pattern of clusters at a threshold of p_{FWE}.

Finally, we performed a classical univariate analysis to test whether there is evidence that the results of the SVR analysis would be driven by the modulation of the regions' mean activity levels. Assessing the univariate parametric effect for each memorized frequency did not reveal any significant clusters of voxels in the cortex even at $p_{uncorrected} < 0.001$. This result suggests that the frequency-specific brain activity within the regions shown in the SVR analysis stem from multivariate codes across voxel population instead of a univariate parametric effect.

Comparison to the tactile working memory data

We further compared our results to data of a recent tactile working memory study (Schmidt et al., 2017) to identify common brain regions carrying frequency-specific information during working memory retention. Schmidt et al. reported bilateral dorsal premotor cortices (dPMC), a cluster in the supplementary motor area/cingulate cortex (SMA/CC), and a cluster in the rIFG to carry frequency-specific information. A conjunction analysis against a conjunction null hypothesis (e.g., Nichols, 2015) was performed to identify the overlapping brain regions showing frequency-selective activity patterns for auditory and tactile WM tasks. This analysis revealed significant voxels in bilateral PMC/M1, SMA, and rIFG ($p_{FWE} < 0.05$, $k > 30$), demonstrating that these regions carry memorized frequency-information from both sensory modalities (Fig. 2B and Table 1B).

Discussion

The current study has tested with fMRI-MVPA which human brain regions represent auditory frequency information during WM retention and investigates their overlap with the results of a recent tactile WM study (Schmidt et al., 2017). We found frequency-specific WM representations distributed across the bilateral superior temporal gyrus (STG), including TE3 in the temporal cortex, PCC, bilateral IPL and SPL in the posterior parietal cortex (PPC) and the bilateral IFG, PMC, and SMA in the (pre-)frontal cortex. Within these regions, clusters in the temporal and parietal cortices and the PCC represent auditory frequency information, while (pre-)frontal areas, including the rIFG, SMA, and bilateral PMC, code frequency-specific information for both auditory and tactile modalities as revealed by the conjunction analysis.

Working memory codes within the cortical auditory pathway

Our results show frequency representations of auditory WM in the STG and the anterior dorsal plane (planum temporale) within the temporal cortex. This is a well-expected result as recent MVPA studies on auditory WM indicated that the stimulus-specific, non-verbal information could be decoded from the auditory cortex (Linke et al., 2011; Linke and Cusack, 2015; Kumar et al., 2016). Additionally, neurophysiological studies on the hierarchical organization of the auditory cortex have revealed that direct sensory input is received by the core areas (corresponding to primary auditory cortex) and then transferred to the belt areas (corresponding to secondary auditory cortex) (Pandya and Sanides, 1973; Galaburda and Pandya, 1983, Wessinger et al., 2001). Studies on the organization of the human auditory cortex for speech and non-speech sounds found that human auditory cortex was hierarchically organized for different types of stimuli such as pure tones, noise, non-speech and speech sounds (Scheich et al., 1998; Binder et al., 1994; 2000; Wessinger et al., 2001). For example, pure tones only activate the core region of the auditory cortex whereas the auditory belt areas in the STG respond to more complex sounds such as band-passed noise bursts (Wessinger et al., 2001). Pure tone memoranda are represented as activation (Kumar et al., 2016) or suppression (Linke et al., 2011) patterns in the Heschl's Gyrus of the auditory cortex. The temporal frequencies that we use as the to-be-remembered stimuli are more complex sounds than pure tones, similar as the above-mentioned band-pass bursts. As complex sound memoranda are reported to be decodable from the non-core auditory cortex (Linke and Cusack, 2015), it is reasonable to suggest that frequency information in our study is also represented and maintained in the belt areas of the auditory cortex in a sensory-like format. A recent MVPA study on WM of visual and vibrotactile frequencies (Wu et al., 2018) is in line with this suggestion, showing frequency information in sensory brain areas. Here, we extended the vibrotactile and visual frequency MVPA findings to auditory frequencies providing evidence for maintenance of sensory representations in the belt areas such as bilateral STG including TE3 and planum temporale.

The role of posterior parietal regions in coding frequency information

In addition to the regions in the temporal cortex, our results indicate that clusters in IPL, SPL in the PPC, and PCC encode frequency-specific auditory WM information. Although the conjunction analysis with the results of vibrotactile WM does not reveal these regions representing information bimodally, other MVPA findings showed very similar brain areas representing visual and tactile frequency information (Wu et al., 2018). Several studies have shown that the firing rates of posterior parietal regions, which we have also found for frequencies in terms of activation patterns, are associated with numerosity coding (Nieder, 2012; Nieder et al., 2016; for a review see Knops, 2017). It is proposed that the approximate number system in the intraparietal sulcus (IPS) is proposed to be supported by a posterior-superior parietal system (Dehaene et al., 2003). The system is suggested to code for asemantic analog magnitudes (Knops, 2017). Additionally, frequency and numerosity are argued to be closely linked, as both are quantitative features of stimuli (Nieder, 2017). In a visual-tactile frequency WM study, Wu and colleagues (2018) found further evidence for this link by observing visual and tactile frequency WM representations in the PPC. Our results strengthen the evidence that frequency and other quantitative stimulus features such as numerosity are coded in the PPC (Nieder, 2016; Walsh, 2003)

Frequency codes in the (pre-)frontal cortex

Additionally, in line with our hypothesis, we also found (pre-)frontal and frontal regions including PMC, SMA, and rIFG representing auditory frequency memoranda. Earlier reports of related non-human primate and human electrophysiology studies showed that spiking rate and oscillatory activity in the ventrolateral PFC and SMA is parametrically modulated by the memorized content for tactile (Barak et al., 2010; Hernandez et al., 2002; 2010; Romo et al., 1999; Spitzer et al., 2010; Spitzer & Blankenburg, 2011) and supramodal representation (Vergara et al., 2016; Spitzer and Blankenburg, 2012) of frequency information. The recent MVPA studies by Schmidt et al. (2017) and Wu et al. (2018) reinforce these findings for the stimulus-specific information maintenance in the PFC. Our study, extends these results, confirming the rIFG and the SMA to represent also auditory frequency.

Also, the bilateral PMC was revealed by our analysis, as it has been in earlier studies (Romo and Salinas, 2003; Romo and de Lafuente, 2013; Schmidt et al., 2017). Dorsal PMC is suggested to be involved in mental rehearsal, as well as during general retention of short-term memory (Cisek and Kalaska, 2004; Fegen et al., 2015). The information in the PMC may also reflect higher-level magnitude information representation due to the behavioral task demand of using them for decision making and action (see Christophel et al., 2016; Serences, 2016). We also observed that the cluster across the left PMC extends slightly to the left IFG coding for auditory frequency information during WM retention. The left IFG is traditionally attributed to language processing, However, it is also shown that the role of the left IFG is not limited to the language processing, but it is also extended to the rehearsal of pitch (Koelsch et al., 2009; Kumar et al., 2016) and melody generation (Brown et al., 2006). Melody generation activates the opercular part of the bilateral IFG, along with SMA, lateral PMC, and secondary auditory cortices (Brown et al., 2006). It appears plausible that aspects of auditory frequencies share some features with melody, such as rhythm.

A modality-overarching network to retain frequency information

To test for the direct overlap of regions coding for auditory frequencies with those revealed for tactile frequencies, we conducted a conjunction analysis between the results of the present auditory WM experiment and the findings of a recent dataset of vibrotactile WM (Schmidt et al., 2017). This analysis revealed the rIFG, SMA, and the bilateral PMC in the (pre-)frontal cortex (Fig. 2B), which are also consistent with regions found for visual flicker frequencies (Wu et al., 2018). One interpretation of this is that representation of frequency information happens in a format independent of modalities (for a detailed discussion, see Christophel et al., 2017, also Walsh, 2003). Activation in frontal regions during WM retention (Nee & Jonides, 2009; Preuschhof et al., 2006; Ricciardi et al., 2006) has generally been proposed to reflect task-general cognitive functions such as attention, executive control, decision, response mapping, etc. (Gazzaley & Nobre, 2012; Peterson & Posner, 2012; D'Esposito & Postle, 2015; Sreenivasan et al., 2014). Our findings from auditory WM, together with the recent reports on vibrotactile and visual flicker MVPA studies (Schmidt et al., 2017; Wu et al., 2018) indicate that (pre-)frontal cortex indeed also exhibits content-specific codes. Its role might, therefore, go way beyond general cognitive control functions and regions in the PFC such as lPFC can be viewed as part of a modality-overarching system to process abstract magnitudes (Walsh, 2003).

Our study design did not allow to test with cross-classification, if these quantity-like stimulus properties are coded by the same multivariate activation patterns for tactile and auditory modalities. Such an analysis could reveal if the information is indeed coded in a supramodal format, or if the rIFG contains different neuronal populations coding information for different modalities.

Conclusion

In summary, our results are in line with prior findings of parametric WM maintenance of quantitative information in the PFC. This consistent and replicable finding across different modalities supports the suggestion of the PFC regions responding to multiple modalities. Whether this proposed multi-sensory nature of the (pre-)frontal cortex is specific to frequency WM representations or can be generalized to other quantitative formats, e.g., numerosity, needs to be further investigated with MPVA. Our results agree with the account of a distributed nature of WM, which proposes that hierarchically higher cortices maintain information in a more abstract, potentially supramodal format. Hierarchically lower regions represent stimulus information in a more concrete and sensory format (see Christophel et al., 2017).

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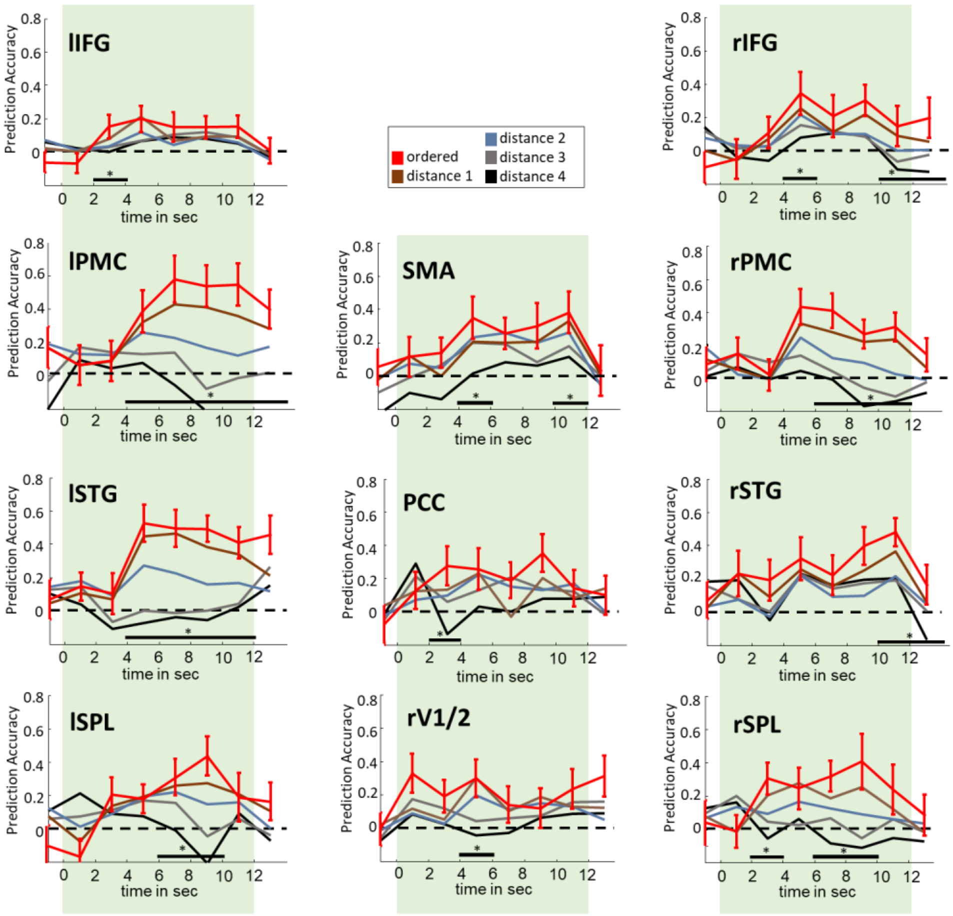
Time-courses of label-permutation tests for all regions



Supp. Fig. 2. Time-courses of decoding accuracies for all identified brain regions. Group-level results for permutation testing for all clusters, in which above chance level decoding accuracy was detected in the main analysis (Fig. 2A). The same SVR analysis was performed with permuted frequency labels of the data. As expected, since the order of frequencies determines the performance of the SVR, a decrease in the order of frequency labels results in a decreased prediction accuracy. Bars with asterisk indicate a significant correlation of order and prediction accuracy for $p<0.05$. This analysis thereby demonstrates that it is indeed the linear order of memorized frequencies that constitutes the basis for high prediction accuracies in the brain regions maintaining auditory frequencies during WM.

Anlage A – Lebenslauf

For reasons of data protection, the curriculum vitae is not included in the online version.

Anlage B – Publikationen

Peer-reviewed Journal Articles – submitted / in review / in revision

14. Uluç I, **Schmidt TT**, Wu Y-H., Blankenburg F (submitted) Content-specific codes of parametric auditory working memory in humans, NeuroImage.

13. **Schmidt TT**, Blankenburg F (in revision): *The 'tactospatial sketchpad': Decoding the working memory of tactile stimuli with spatial layouts.* NeuroImage.

Peer-reviewed Journal Articles – Published

12. McCormick Miller N*, **Schmidt TT***, Blankenburg F, Pulvermüller F (2017): *Verbal labels facilitate tactile perception.* Cognition, 171:172-179.

11. Wu Y-H*, Uluç I*, **Schmidt TT**, Tertel K, Kirilina E, Blankenburg F (2017): *Overlapping frontoparietal networks for tactile and visual parametric working memory representations.* NeuroImage, 166:325-334.

10. **Schmidt TT**, Wu Y-H, Blankenburg F (2017): *Content-specific codes of parametric vibrotactile working memory in humans.* The Journal of Neuroscience, 37(40):9771-9777.

9. Majić T, Jungaberle H, **Schmidt TT,** Zeuch A, Hermle L, Gallinat J (2017): *Psychotherapie mit adjuvanter Gabe von serotonergen psychoaktiven Substanzen – Möglichkeiten und Hindernisse / Psychotherapy with an adjuvant use of serotonergic psychoactive substances – possibilities and challenges.* Fortschr Neurol Psychiatr, 85(07):383-392.

8. Stuke H, Gutwinski S, Wiers C, **Schmidt TT**, Gröpper S, Parnack J, Gawron C, Hindi Attar C, Spengler S, Walter H, Heinz A, Bermpohl F (2016): *To drink or not to drink: Harmful drinking is associated with hyperactivation of reward areas rather than hypoactivation of control areas in men.* Journal of Psychiatry and Neuroscience, 41(3):E24-36.

7. Majić T*, **Schmidt TT***, Gallinat J (2015): *Peak experiences and the after-glow phenomenon: When and how do therapeutic effects of hallucinogens depend on psychedelic experiences?* Journal of Psychopharmacology, (3):1-13.

6. **Schmidt TT**, Ostwald D, Blankenburg F (2014): *Imaging Tactile Imagery: Changes in brain connectivity support perceptual grounding of mental images in primary sensory cortices*. NeuroImage, 98:216-224.

5. Rea E, Rummel J, **Schmidt TT**, Hadar R, Heinz A, Mathe AA, Winter C (2013): *Anti-anhedonic effect of deep brain stimulation of the prefrontal cortex and the dopaminergic reward system in a genetic rat model of depression: An intracranial self-stimulation paradigm study.* Brain Stimulation, 7(1):21-28.

4. Spitzer B, Gloel M, **Schmidt TT**, Blankenburg F (2013): *Working Memory Coding of Analog Stimulus Properties in the Human Prefrontal Cortex.* Cerebral Cortex, 24(8):2229-2236.

3. **Schmidt TT**, Rea E, Klein J, Panagis G, Winter C (2012): *Enhanced reward-facilitating effects of d-amphetamine in rats in the quinpirole model of obsessive-compulsive disorder.* Int J Neuropsychopharmacol, 16(5):1083-91.

2. Klein J, Hadar R, Männer A, Eberhardt C, Baldassarri J, **Schmidt TT**, Kupsch A, Heinz A, Morgenstern R, Schneider M, Weiner I, Winter C (2012) Mapping brain regions in which deep brain stimulation affects schizophrenia-like behavior in two rat models of schizophrenia. Brain Stimulation, 6(4):490-499.

1. Ostwald D, Spitzer B, Guggenmos M, **Schmidt TT**, Kiebel S, Blankenburg F (2012) Evidence for neural encoding of Bayesian surprise in human somatosensation. NeuroImage, 62(1): 177-88.

* shared authorship

Book Chapter

2. **Schmidt TT**, Majić T (2016): *Empirische Untersuchung veränderter Bewusstseinszustände: Definition, Quantifizierung und Forschungsperspektiven.* Handbuch Psychoaktiver Substanzen, Springer Verlag.

1. Majić T, **Schmidt TT**, Hermle L (2016): *Flashbacks und anhaltende Wahrnehmungsstörungen nach Einnahme von serotonergen Halluzinogenen.* Handbuch Psychoaktiver Substanzen, Springer Verlag.

Anlage C –Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt,

- dass ich die vorliegende Arbeit eigenständig und ohne unerlaubte Hilfe verfasst habe,
- dass Ideen und Gedanken aus Arbeiten anderer entsprechend gekennzeichnet wurden,
- dass ich mich nicht bereits anderwärtig um einen Doktorgrad beworben habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze, sowie
- dass ich die zugrundeliegende Promotionsordnung vom 08.08.2016 anerkenne.

Ort, Datum Unterschrift

Anlage D

Erklärung gemäß § 7 Abs. 3 Satz 4 der Promotionsordnung über den Eigenanteil an den veröffentlichten oder zur Veröffentlichung vorgesehenen eingereichten wissenschaftlichen Schriften im Rahmen meiner publikationsbasierten Arbeit

I.	Name, Vorname:	Schmidt, Timo Torsten
	Institut:	Arbeitsbereich Neurocomputation and Neuroimaging
	Promotionsfach:	Psychologie
	Titel:	Master of Science (MSc)

II. **Nummerierte Aufstellung der eingereichten Schriften (Titel, Autoren, wo und wann veröffentlicht bzw. eingereicht):**

1. **Schmidt T.T.**, Ostwald D., Blankenburg F. (2014): *Imaging Tactile Imagery: Changes in brain connectivity support perceptual grounding of mental images in primary sensory cortices*. NeuroImage, 98:216-224
2. **Schmidt T.T.**, Blankenburg F. (initial submission November 2017, revision submitted February 2018): *The 'tactospatial sketchpad': Decoding the working memory of tactile stimuli with spatial layouts.* NeuroImage
3. Spitzer B., Gloel M., **Schmidt T.T.**, Blankenburg F. (2013): *Working Memory Coding of Analog Stimulus Properties in the Human Prefrontal Cortex.* Cerebral Cortex, 24(8):2229-2236
4. **Schmidt T.T.**, Wu Y.-H., Blankenburg F. (2017): *Content-specific codes of parametric vibrotactile working memory in humans.* Journal of Neuroscience, 37(40):9771-9777.
5. Wu, Y.-H.*, Uluç I.*, **Schmidt T.T.**, Tertel K., Kirilina E., Blankenburg F. (2017): *Overlapping frontoparietal networks for tactile and visual parametric working memory representations.* NeuroImage 166:325-334.
6. Uluç I., **Schmidt T.T.**, Wu Y.-H., Blankenburg F. (submitted February 2018): Content-specific codes of parametric auditory working memory in humans. NeuroImage

*shared authorship

III. Darlegung des eigenen Anteils der Schriften:

Die Bewertung des Eigenanteils richtet sich nach der Skala: “vollständig – überwiegend – mehrheitlich – in Teilen” und enthält nur für den jeweiligen Artikel relevante Arbeitsbereiche.

Zu II.1.: Konzeption (überwiegend), Versuchsdesign (überwiegend), Programmierung (vollständig), Datenerhebung (überwiegend), Datenauswertung (überwiegend), Ergebnisdiskussion (überwiegend), Erstellen des Manuskriptes (überwiegend).

Zu II.2.: Konzeption (überwiegend), Versuchsdesign (überwiegend), Programmierung (vollständig), Datenerhebung (vollständig), Datenauswertung (vollständig), Ergebnisdiskussion (überwiegend), Erstellen des Manuskriptes (überwiegend).

Zu II.3.: Datenerhebung (mehrheitlich), Datenauswertung (in Teilen).

Zu II.4.: Konzeption (überwiegend), Versuchsdesign (überwiegend), Programmierung (in Teilen), Datenerhebung (mehrheitlich), Datenauswertung (überwiegend), Ergebnisdiskussion (überwiegend), Erstellen des Manuskriptes (überwiegend).

Zu II.5.: Konzeption (in Teilen), Versuchsdesign (mehrheitlich), Programmierung (mehrheitlich), Datenerhebung (in Teilen), Datenauswertung (in Teilen), Ergebnisdiskussion (in Teilen), Erstellen des Manuskriptes (in Teilen).

Zu II.6.: Konzeption (mehrheitlich), Versuchsdesign (mehrheitlich), Programmierung (in Teilen), Datenerhebung (in Teilen), Datenauswertung (in Teilen), Ergebnisdiskussion (in Teilen), Erstellen des Manuskriptes (in Teilen).