

Fachbereich Erziehungswissenschaft und Psychologie
der Freien Universität Berlin

**Parametric Working Memory of Abstract Quantities on
Multiple Modalities and Formats:
from Frequency to Numerosity**

Dissertation

zur Erlangung des akademischen Grades

Doctor of Philosophy (Ph.D.)

vorgelegt von

Işıl Uluç, MA, MSc

Berlin, 2019

Erstgutachter: Prof. Dr. Felix Blankenburg

Zweitgutachter: Prof. Dr. Dirk Ostwald

Tag der Disputation: 09 May 2019

Acknowledgments

I would like to thank my supervisor Felix Blankenburg for his highly beneficial mentorship and his accessibility. I would also like to thank my second supervisor Niko Busch for his support through my PhD studies. I also would like to thank Berlin School of Mind and Brain and DAAD for their financial and academic support. I am grateful for my cohort in Berlin School of Mind and Brain for their ideas and moral support. I especially thank Esra Al, Dan Cook, Aslı Uluç and Esra Oğuztürk who never left me alone, academically and spiritually. Very special thanks go to Luke Tudge and Monika Graumann for their warm support throughout my PhD. Last but not least I am grateful to my colleagues at the Neuroimaging and Computation Unit (in alphabetical order): Sam Gijzen, Miro Grundei, Jan Herding, Christian Kainz, Evgeniya Kirilina, Jakub Limanowski, Simon Ludwig, Till Nierhaus, Timo Torsten Schmidt, Pia Schröder, Kathrin Tertel, Lisa Velenosi, Alexander Horst von Lautz and Yuan-hao Wu.

Abbreviations

A1	primary auditory cortex
BOLD	blood oxygen level dependent
EEG	electroencephalogram
fMRI	functional magnetic resonance imaging
Hz / kHz	Hertz / kilohertz
IFG	inferior frontal gyrus
IPL	intraparietal lobule
IPS	intraparietal sulcus
MEG	magnetoencephalography
MVPA	multivariate pattern analysis
NHP	nonhuman primate
PFC	prefrontal cortex
PMC	dorsal premotor cortex
S1	primary somatosensory cortex
S2	secondary somatosensory cortex
SVR	support vector regression
TMS	transcranial magnetic stimulation
WM	working memory

Table of Contents

1	Introduction	11
1.1	The underlying mechanisms of working memory maintenance	14
1.1.1	<i>Models of working memory</i>	14
1.1.2	<i>The neuronal underpinnings of working memory</i>	15
1.2	Parametric working memory research	18
1.2.1	<i>Extracellular recordings in nonhuman primates</i>	18
1.2.2	<i>Non-invasive human studies</i>	21
1.3	Approximate numerosity research	23
1.3.1	<i>Approximate number system</i>	24
1.3.2	<i>Numerosity working memory</i>	26
1.4	Aims of the thesis	28
2	Summary of Experiments	29
2.1	Study 1: Parametric auditory versus tactile working memory	29
2.2	Study 2: Visual tactile cross-modal working memory	32
2.3	Study 3: Working memory of approximate numerosities	35
3	General Discussion	37
3.1	Abstract quantity codes in frontal brain regions	39
3.2	Modality independent parametric working memory codes within fronto-parietal network	43
3.3	Modality dependent parametric working memory codes within sensory cortices	45
3.4	Limitations	50
3.5	Outlook	52
	References	54

Abstract

Working memory is central to the complex cognitive functions that are involved in goal-directed behavior. At the core of working memory research, the question remains how and in what format information is retained in the brain. Immense progress has been made using neuroimaging to determine the location of information maintenance using experiments with sensory features, however, it remains unclear how more abstract stimuli are stored.

The aim of this dissertation is to uncover the neural underpinnings of working memory during abstract quantity processing. Specifically, I conducted three functional magnetic resonance imaging (fMRI) studies to address the question of which brain regions represent the abstract quantity content. We found parametric working memory representation of auditory, visual and vibrotactile frequencies distributed across sensory, posterior parietal, and prefrontal cortices. Additionally, the numerosity-specific information is represented in the prefrontal cortex.

These results provide novel insights into how the brain maintains information in working memory and give support to the view that mental representations are distributed across the cortex depending on whether they are maintained as sensory-specific or abstract features.

Zusammenfassung

Das Arbeitsgedächtnis spielt eine zentrale Rolle bei komplexen kognitiven Funktionen, die für zielgerichtetes Verhalten notwendig sind. Eine zentrale Frage in der Arbeitsgedächtnisforschung ist, wie und in welcher Form Informationen im Gehirn gespeichert werden. Mit Hilfe von bildgebenden Verfahren konnte die Neurowissenschaft große Fortschritte erreichen, um festzustellen, an welchem Ort sensorische Stimuli festgehalten werden. Allerdings ist weiterhin unklar, wie abstrakte Stimuli verarbeitet werden.

Das Ziel dieser Dissertation ist, die neuronalen Prozesse zu entschlüsseln, die dem Arbeitsgedächtnis von abstrakter Mengenverarbeitung zu Grunde liegen.

Insbesondere habe ich drei fMRT Studien durchgeführt um die Frage zu beantworten, welche Hirnregionen abstrakte Mengen repräsentieren. Wir fanden parametrische Arbeitsgedächtnisrepräsentationen von auditorischen, visuellen und taktilen Frequenzen über sensorische, posterior parietale und präfrontale Teile der Großhirnrinde verteilt. Des Weiteren wird numerische Information im präfrontalen Cortex repräsentiert.

Diese Resultate liefern neue Erkenntnisse darüber, wie das Gehirn Informationen im Arbeitsgedächtnis speichert.

Sie bestätigen die Sichtweise, dass mentale Repräsentationen über die Großhirnrinde verteilt festgehalten werden. Weiterhin zeigen sie, dass dies abhängig davon ist, ob es sich um sensorische oder abstrakte Merkmale handelt.

List of original research articles

This dissertation is based on the following articles:

Wu, Y. H.*, **Uluç, I.***, Schmidt, T.T., Tertel, K., Kirilina, E., Blankenburg, F. (2018). 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. (2018). Content-specific codes of parametric auditory working memory in humans. *Neuroimage*, 183:254–262.

Uluç, I., Velenosi, L.A., Schmidt, T.T., Blankenburg, F. (under review). Parametric representation of tactile numerosity in working memory. *eNeuro*.

*Shared authorship

1 Introduction

Human beings differ from other animals in their capacity to learn, reason, make decisions, and successfully carry out multiple goals. A central aspect of these cognitive functions is the retention of information over short periods of time. This capacity to briefly maintain information that is currently not present in the environment is referred to as working memory (WM) (Baddeley, 2012). WM is significant for performing more complex executive functions such as reasoning, problem solving and numerical cognition. To get to the root of such complex functions, psychologists and more recently neuroscientists have spent the better part of a century trying to uncover the behavioral and neural substrates of WM.

WM is enabled by a series of processes that make information available for a later use. The information received from the environment is first encoded to a format to be used in WM. This information is then retained for a short period of time. Finally, the information is retrieved – and potentially manipulated – to be used in a goal directed behavior (Baddeley, 2012). The neuronal underpinnings of encoding, manipulation and retrieval processes have been examined together or separately in numerous studies (for a review, see D'Esposito & Postle, 2015). Encoding converts the percept into a format that can be stored in the brain, whereas retrieval refers to re-accessing the information from the memory when needed (Melton, 1963). The core WM function, maintenance, refers to the storage of the necessary information. The information could either be stored in sensory format or alternatively be in an

abstract, independent manner. There is currently much debate about how this maintenance function is implemented in the brain. Relatedly, extracellular recordings in non-human primates (NHP) have revealed activity patterns of neurons in the prefrontal cortex (PFC) which is identified as the main brain region for WM maintenance (Fuster & Alexander, 1971; Kubota & Niki, 1971; for a review see Goldman-Rakic, 1995). Challenging the theory that the PFC is the central region in the WM maintenance, sensory recruitment theory posits that the WM information is maintained in the same sensory areas that encode the memoranda in the first place (Ester *et al.*, 2009). WM research gained significant insights with the development of multivariate pattern analysis (MVPA) methods, which aim to access the information content of the activation patterns across the brain (c.f. Haynes, 2015). With these analysis methods, “state-based” models of WM gained more evidence to support the notion that sensory systems carry content-specific WM information (review D’Esposito and Postle, 2015). More recently, the accumulation of evidence supporting both sides of the debate has led to a hybrid account of WM representations that are distributed across the cortical hierarchy (Lee and Baker, 2016; Christophel *et al.*, 2017). This account suggests that where the information is maintained depends on how abstract the retained feature is (Christophel *et al.*, 2017). In the distributed account, sensory features are likely to be represented in a sensory format. So far, MVPA studies have mainly tested neuronal underpinnings of WM using sensory-specific features of stimuli (Christophel *et al.*, 2017). Therefore, investigation of the underlying maintenance mechanisms

of WM with more abstract features is lacking and will provide significant information for the research.

Among abstract features that are retained in WM to be used for a goal, quantitative information is interesting to investigate as it can be encoded both symbolically and non-symbolically (Piazza et al., 2006) as well as at different levels of abstraction. Think of a biker riding his bike in traffic. He would feel a vibration under his hands coming from the turning wheels. He would also see cars passing by or ahead of him on the road. While biking, he could represent the vibration of the bike as a pure sensation or his speed - a continuous frequency. Moreover, if he has time, he can count the cars and know exactly how many of them are seen ahead. If he does not have enough time, he can eyeball the number of cars, yielding an estimate instead of an exact number. Therefore, stimuli with quantitative features can be represented on a gradient from a pure sensory format to a highly abstract number format, symbolically or non-symbolically. It follows that the investigation of quantity information maintenance in WM would lead to a multi-faceted understanding of its underlying mechanisms.

In this PhD dissertation, I present an investigation into the neural correlates of WM maintenance using abstract quantities as memoranda. Using a well-established WM paradigm – the delayed match-to-sample task (DMTS) – while recording fMRI, I address the question of how abstract quantities are represented in the human brain during WM retention.

1.1 The underlying mechanisms of working memory maintenance

Investigation of WM requires an understanding of how WM functions as well as how the neuronal underpinnings enable the process. To this end, cognitive psychologists have developed models to describe the inner workings of short-term information retention, i.e. WM.

1.1.1 Models of working memory

The most prominent model of WM to date is the multicomponent model of WM (Baddeley & Hitch, 1974; see Baddeley, 2012 for an updated version). For different cognitive models of WM beyond the scope of this thesis, see Atkinson and Shiffrin (1968), Baddeley and Hitch (1974) and Cowan (1999). The multicomponent model (Baddeley & Hitch, 1974) suggests that information that is set to be used in a short time period is stored in our memory by multiple mechanisms, which are controlled by a central attentional component. In particular, it is proposed that visual information is maintained as a visually and spatially retained image, while auditory information, whether verbal or not, is maintained by an articulation-based phonological loop (Baddeley, 2012). The different components in WM storage of auditory and visuospatial information are supported by different sensory processing mechanisms. They can work together without interfering with the processes of the other component. The episodic buffer combines different storage dimensions. This buffer makes information that is integrated from different modalities available to conscious

awareness. Lastly, the central executive is the component that controls the other systems of the WM system and regulates information processing. The central executive encodes, updates, and binds the information entering WM and directs attentional control to the needed component because the processing capacity of WM is limited (Baddeley, 2012). While the multicomponent model explains how WM functions, it does not provide any information about the neuronal mechanisms enabling WM.

1.1.2 The neuronal underpinnings of working memory

Apart from models explaining the functions of WM, neuroscientists also investigate its neural correlates by examining the circuitry that is engaged in WM processes. In this regard, the first significant findings for the underlying brain mechanisms of WM came from electrophysiology studies on NHP, which found sustained neuronal activity during the retention period (Fuster & Alexander, 1971; Kubota & Niki, 1971). Connecting the neural mechanisms to memory maintenance, prefrontal neurons were shown to have memory fields, where the same neuron always codes for the same location (Funahashi et al., 1989). Combining the findings from extracellular recordings from NHPs and human univariate fMRI and positron emission tomography research, Goldman-Rakic proposed that the PFC is central to WM information retention (Goldman-Rakic, 1995). Further evidence for content-specificity of cell activity in the PFC came from WM tasks with quantities such as frequency (Romo et al., 1999) and numerosity (Nieder et al., 2003). NHP electrophysiology studies of parametric

WM have shown that cell spiking activity varies monotonically with the memorized frequency (for a review see Romo and de Lafuente, 2013). Additionally, numerosity WM research found that spike activity of the PFC neurons is tuned to numerosity-specific content during WM retention (for review see Nieder, 2016).

Following NHP studies, human fMRI studies using MVPA methods have revealed results that seemingly contradict earlier findings on WM. Importantly, MVPA is able to detect patterns of activity content distributed across brain regions; the patterns of activity specific to a certain cognitive content (Peacock and Postle, 2012). A number of MVPA fMRI studies found that during the WM retention period, content-specific information about the memorized stimulus can only be decoded from posterior parietal and primary sensory areas, but not from the PFC (D'Esposito & Postle, 2015). Predominantly using visual stimuli as to-be-remembered samples, MVPA studies have shown primary sensory and posterior parietal regions to reflect content-specific WM representations for several stimulus features such as color (Serences, 2009; Christophel et al., 2012), orientation (Harrison & Tong, 2009) and motion (Riggall & Postle, 2012). These findings are commensurate with sensory recruitment theory, which proposes that the same systems and representations responsible for the perception of information also contribute to short term maintenance of that information (Pasternak & Greenlee, 2005; for review see D'Esposito & Postle, 2015).

More recently, the distributed account of WM provided a synthesis of these two seemingly contradictory theories of the neuronal mechanisms of WM (Lee & Baker, 2016; Christophel et al., 2017). According to Christophel and colleagues (2017), instead of one dedicated system or location for WM maintenance, WM representations are distributed across the cortical hierarchy. According to this account, the PFC maintenance and sensory recruitment theories could be seen as compatible with the multicomponent model of WM, having a modular maintenance area in the brain. However, the distributed account of WM seems to be incompatible with the suggestion that there is a designated maintenance location in the brain (Lee & Baker, 2016; Christophel et al., 2017). In particular, the distributed account of WM proposes that the location where WM information is retained depends on the level of abstraction or the functional use of that information (Christophel et al. 2017). Namely, if a sensory feature of the information is used for the behavioral goal, information is maintained in a sensory-specific format and likely in the sensory areas of the brain. In contrast, more abstract stimulus properties are retained in higher cognitive brain regions in a modality and format independent, abstract form (Christophel et al., 2017). Abstract quantity information, which can be represented in different formats according to the functional need, is the optimal feature to test whether WM representations are distributed across the cortex. As tokens of abstract quantities, I used frequency and approximate numerosity for memorized content.

1.2 Parametric working memory research

In introducing the uses of quantities in research on the neural correlates of WM, I will provide an overview of parametric WM research. First, I will start with unimodal and multimodal NHP studies, which were the pioneers of neuronal research of WM using non-symbolic quantities as memoranda. Next, I will go on to explain non-invasive human studies of parametric WM. In doing so, I will point out directions for future work on the topic.

1.2.1 Extracellular recordings in nonhuman primates

The first experiments combining extracellular recordings with psychophysical measurements made use of flutter stimuli (Werner & Mountcastle, 1965; Mountcastle et al., 1967; for a review see Romo & Salinas, 2003). In the pioneering studies of Mountcastle and colleagues, NHPs are required to compare two flutters separated from each other by a time delay. A flutter is a sense of vibration at a frequency between 5 Hz and 50 Hz (Mountcastle et al., 1967). The task requires the subject to compare the perception of the second stimulus to the memory trace left by the first one. The studies investigated the neuronal underpinnings of flutter encoding and retention (Mountcastle et al., 1990). Crucially, this task enables the study of where and how the vibrotactile frequency is retained in the brain while participants keep the first frequency in memory. Moreover, the task is a parametric WM task in the sense that the subject has to remember a scalar analog value of the flutter stimulus, a

continuous parameter (Romo et al., 1999). In their seminal study, Romo and colleagues (1999) also used the vibrotactile variant of this task and recorded from single cells in monkey PFC. This revealed that the firing rates of the right prefrontal neurons during WM maintenance are parametrically modulated as a monotonic function of the remembered frequencies (for review see Romo & de Lafuente, 2013). These findings were also replicated in single and population cell recordings in other studies (Brody et al., 2003; Barak et al., 2010; Hernández et al., 2010). Brody and colleagues (2003) extended the findings of monotonic encoding of the memorized stimulus with a time component. They found that in addition to the parametric coding, firing rates of most neurons in the inferior convexity of the PFC also systematically varied with time. Later, Barak and colleagues (2010) continued this line of research with cell population analysis and showed that the frequency sensitivity of the population state varied over delay period. That is, although sensitivity to memorized frequency decreases around 600 ms after stimulus presentation, it starts to increase after that time point until the end of the delay period. Additionally, testing frequency-selective activity in the primary somatosensory cortex, Salinas and colleagues (2000) showed that the neurons in the primary somatosensory cortex (S1) respond to the stimulus during perception but do not show any significant content-specific activity during retention. The combined results suggest that parametric tactile WM information is maintained in prefrontal brain regions instead of primary sensory ones (Romo & de Lafuente, 2013).

To assess whether this parametric representation in the PFC is specific to the tactile domain, investigation was extended to the auditory modality. In the auditory domain, neural firing rates in the ventral premotor cortex (PMC) have also been shown to reflect the remembered auditory frequency. The firing rate of PMC neurons are similarly parametrically increasing or decreasing as a monotonic function of the remembered frequency (Lemus et al., 2009a). In parallel to tactile studies, auditory WM representations were also investigated in the primary auditory area (A1) (Lemus et al., 2009b). Lemus and colleagues found that A1 was exclusively associated with sensory processes: neuronal activity did not vary with memorized frequency when acoustic flutter stimuli were memorized, extending conclusions from tactile WM studies to the auditory domain.

Parametric WM representations in the frontal regions for both tactile and auditory modalities led to a research question regarding the supramodality of these representations. Vergara and colleagues (2016) addressed the question of whether there is a supramodal code for parametric WM representation. In particular, they investigated whether the same neurons encode tactile and auditory parametric WM regardless of sensory modality, and if so, how. In an auditory-tactile cross-modal DMTS task, NHPs had to memorize the frequency of either an auditory flutter or a tactile vibration and compare it to a test stimulus either of the same or a different sensory modality (Vergara et al., 2016). The study demonstrated that the firing rate of neurons in a substantial part of the pre-supplementary motor area (pre-SMA) uses the same parametric

code while representing WM information for both tactile and auditory frequencies. That is to say, frequencies are represented independently of their sensory modality, by a supramodal parametric WM code in the pre-SMA. This supramodality is argued to be an indicator that a quantity representation is an abstract one since the representation format is not modality dependent and not a sensory one (Vergara et al., 2016). Research on NHPs raised the question of whether the same mechanisms could also be found in humans.

1.2.2 Non-invasive human studies

Since humans and NHPs are similar in their ability of discriminate frequencies (Romo et al., 1999), paradigms from NHP research can be used in work with humans. Our understanding of how scalar analog values are represented in WM has been extended by using these same paradigms with electroencephalography (EEG) and magnetoencephalography (MEG) in humans (Spitzer et al, 2010; Spitzer and Blankenburg, 2011; von Lautz et al., 2017; Ludwig et al., 2018). In line with NHP findings, human EEG studies also show that brain activity during the retention period in the right lateral PFC is modulated as a monotonic function of the memorized frequency. More specifically, the upper beta signal (20 – 25 Hz) is source-localized to the right inferior frontal gyrus (rIFG) (Spitzer & Blankenburg, 2011). In a similar vein, a recent MEG study (von Lautz et al., 2017) revealed that beta power in the rIFG monotonically increases with the remembered frequency, whereas gamma power monotonically decreases.

Parallel to NHP research, investigation has been extended to multiple modalities in human EEG (Spitzer & Blankenburg, 2012; von Lautz et al., 2019). Spitzer and Blankenburg (2012) presented participants with DMTS tasks using visual, tactile and auditory frequencies. In comparison to typical NHP experiments, human volunteers performed three separate WM tasks, each of them within a particular sensory modality. As in the findings of tactile parametric WM, in all three sensory modalities, upper beta oscillation in the right lateral PFC was parametrically modulated by the remembered frequency. Collectively, these results indicate supramodal frequency representations in the rIFG during the WM retention period in humans just as in NHPs (c.f. Spitzer and Haegens, 2017).

Until recently, human fMRI studies of parametric working memory have been performed with univariate analysis (Preuschhof et al., 2006; Kostopoulos et al., 2007; Spitzer et al., 2014). In line with NHP and human EEG/MEG results, they found sustained BOLD activity in the ventrolateral PFC (vlPFC), PMC, and S2. Although the results of univariate fMRI studies agree with the NHP and human EEG/MEG studies, it remains unclear whether such an encoding is content-specific.

Recently, to address this question, parametric WM research has been extended with an fMRI MVPA study using a vibrotactile WM task (Schmidt et al., 2017). The aim of this study was to identify brain regions that show spatially distributed activity patterns of vibrotactile WM. In agreement with the earlier NHP and human findings, they found frequency-specific information in the rIFG,

SMA and bilateral PMC. Here, the multivariate findings of frequency-specific information for tactile WM provided MVPA research with questions to address on parametric WM using multiple modalities. However, one should note that MVPA fMRI findings do not give any indication of the neuronal signal those brain areas carry. Contrary to NHP and EEG/MEG studies that measure the activity of neurons or neuron populations (Singer, 1999), fMRI measures the blood oxygen level dependent (BOLD) contrast (Logothetis, 2003). In studies related to cognitive functions of the brain, the stimulus-induced hemodynamic response in BOLD contrast is measured, which is not only related to neural activity but also to circulatory and metabolic changes (Logothetis, 2003). The hemodynamic response is also delayed by around two seconds, slowly reaching a plateau after six to 12 seconds and returning to baseline with the same timing (Logothetis, 2003). However, unlike pairwise classification techniques, support vector regression (SVR) analysis depicts the distributed brain activities brain reflecting a parametric change in the memorized content instead of a categorical change, albeit indirectly (Kahnt et al., 2011). Therefore, MVPA reflects brain activity showing parametric content.

1.3 Approximate numerosity research

In addition to parametric WM studies, neural correlates of quantity representations during retention have been investigated for a different presentation format, namely numerosity. In this sense, approximate numerosities, which like frequencies are non-symbolic, are ideal for

researching their WM mechanisms in parallel to the established parametric WM literature. To allow a better understanding of approximate numerosities, I will review the literature on the neural correlates of approximate numerosity perception and point out the potential gaps in our present knowledge.

1.3.1 Approximate number system

Numbers of objects can be perceived by humans in different formats (Piazza et al., 2006). Whereas counting and most algebraic operations rely on language or symbolic representations of precise numbers, the ability to quantify amount, size, length or other analog stimulus properties can be performed non-symbolically, independently of language (Dehaene et al., 1992; Spitzer et al., 2014b). The cognitive system underlying such non-symbolic representations of numerosity has been termed the approximate number system (ANS) (Gallistel & Gelman, 1992; Dehaene, 2011).

While numerosity is a discrete stimulus property, the ANS performs an approximation of a given numerosity and thereby estimates an analog property. In contrast to the symbolic mental representation of numbers as categories, the ANS representation is argued to resemble representation of analog scalar values; e.g. frequencies, stimulus length, intensity (Dehaene, 1997; Piazza et al., 2004; Piazza et al., 2006; Nieder and Dehaene, 2009; Piazza, 2010, Spitzer et al., 2014a). Approximations of numerosities are used when counting or an immediate recognition of a numerosity is not possible.

Specifically, it has been shown that very small numbers can be effortlessly identified without counting and are thus represented as discrete values, a phenomenon which is known as subitizing (Kaufman et al., 1949). If the number of items exceeds the subitizing threshold, counting is required to determine the exact amount. When there is insufficient time for counting, the ANS is thought to approximate the quantity in a fast and efficient manner.

The functional anatomy of the ANS has been extensively characterized by substantial research on NHPs and humans (for reviews see Eger, 2016; Nieder 2016; Knops, 2017). The dominant theory in ANS research proposes a frontoparietal network comprised of vIPFC and the intraparietal sulcus (IPS) in the PPC to be involved in the approximation of quantities (Dehaene et al., 2003; Piazza et al., 2004; 2007; Cantlon et al., 2006; 2009; Jacob and Nieder, 2009; Nieder, 2012; 2016; Knops and Wilmes, 2014). Specifically, in NHPs, the tuning curves of neurons in the PFC and in the PPC respond to certain numerosities (Nieder and Miller, 2004; Nieder and Merten, 2007). These findings suggest that the fronto-parietal network encodes estimated numerosities during perception.

Interestingly, in humans, it appears that the IPS serves as the principal host of the ANS system (Dehaene et al., 2003; Eger et al., 2009 for reviews see Knops, 2017 and Eger 2016). fMRI investigation demonstrates that the IPS responds to perceived numerical stimuli (Jacob and Nieder, 2009; Eger et al., 2009). Additionally, the IPS has been shown to be partially format independent (Arabic numerals vs. sets of dots) in coding numerosities (Eger et al., 2009; for a review

see Knops, 2017). The IPS is not the only region related to the ANS. Piazza and colleagues (2006) revealed a right lateralized frontoparietal network consisting of right intraparietal cortex, right dorsolateral PFC (dlPFC) and right premotor cortex (PMC) for numerosity estimation in humans. Moreover, it has been shown in NHP studies that numerosity is first extracted in the IPS and then amplified in the PFC (Nieder, 2016; Eger, 2016). Hence, the research so far suggests that there is a dedicated fronto-parietal numerosity network in the brain, in which the IPS is the first region to process the number information (Eger, 2016).

1.3.2 Numerosity working memory

The ANS literature is primarily focused on perception. Indeed, only a few NHP studies have investigated WM representations of approximate quantities (for a review see Nieder, 2016). In line with results from ANS perception studies, a fronto-parietal network consisting of the PFC and IPS is shown to exhibit numerosity-selective activity during WM (Jacob et al., 2018). Furthermore, the frontoparietal cortex has been found to code for the memorized numerosity in a supramodal fashion (Nieder, 2012). Unlike parametric WM, the neurons coding for numerosity use a labeled line code tuned to preferred numerosities (Nieder, 2012), instead of a summation code that varies monotonically with the remembered frequency (Romo et al., 1999). Interestingly, in contrast to perception, PFC is more closely linked to numerosity during WM delay (Nieder et al., 2002; Nieder et al., 2003; Nieder and Miller, 2004). In particular, a greater

proportion of numerosity selective neurons in the lateral PFC exhibit stronger tuning to numerosity than those in the IPS during WM retention (Nieder and Miller, 2004; Tudusciuc and Nieder, 2009; Nieder, 2016). Moreover, neurons in the IPS respond to numerosity earlier than those in the PFC, and the latency of IPS neurons is shorter (Nieder and Miller, 2004). Thus, the results indicate a numerosity information flow from the IPS to lateral PFC (Nieder and Miller, 2004).

To the best of my knowledge, only a single study has focused on the WM representation of numerosity in humans, although some approximate numerosity perception studies have used WM-related paradigms during ANS perception studies (e.g., Eger et al., 2009). Spitzer and colleagues (2014) probed the oscillations underlying multimodal WM representations by training participants to estimate numerosity from sequential auditory, visual and tactile stimuli. They identified strong and long-lasting alpha oscillations in the PPC reflecting WM load. Moreover, in line with NHP results, beta-band activity in the right PFC shows numerosity-selective modulation, indicating numerosity representations during WM retention (Spitzer et al., 2014). Therefore, NHP studies and the sole human EEG study both suggest that lateral PFC encodes numerosity information in WM. However, the small number of studies on numerosity WM and the lack of fMRI experiments represent a gap in the literature regarding the location of brain regions coding for numerosity in WM. Importantly, the spatial specificity of fMRI could provide significant insights in investigating the location of numerosity WM mechanisms.

1.4 Aims of the thesis

The primary goal of the work presented in this thesis was to extend the fMRI MVPA research on parametric WM to multiple modalities and other quantity formats. To this aim, together with my colleagues, I conducted fMRI MVPA experiments addressing the following questions: First, in a unimodal and bimodal MVPA analysis, I searched for auditory WM representations in the brain and asked whether there are brain areas carrying information in both tactile and visual domains. Second, with a cross-modal task, I tested for brain regions carrying modality independent WM representations for the frequencies in visual and tactile sensory modalities. Finally, I investigated brain regions underpinning content-specific representations for a higher level abstract quantity: numerosity.

Based on the empirical evidence I collected, I argue that the WM representations are distributed through the cortical hierarchy. I present evidence that that the quantity information that can be represented in both sensory-specific and abstract format will be carried in sensory regions for modality-dependent representations and in higher cortical regions for modality and format independent representations.

2 Summary of Experiments

In this chapter, I summarize the three empirical studies that form this dissertation. In all of the studies a DMTS paradigm is used that is adapted to the needs and research question of the particular study. In the first two experiments, frequencies are used as memoranda, whereas the last study uses tactile numerosities as memoranda. In all of the studies, fMRI data was acquired and analyzed with a searchlight MVPA method. We used an SVR procedure in this analysis.

2.1 Study 1: Parametric auditory versus tactile working memory

The NHP and human EEG and MEG studies probing neural correlates of parametric WM (Spitzer et al., 2011; 2012; Vergara et al., 2016; von Lautz et al., 2017; for a review on NHP research see Romo & de Lafuente, 2013) were extended to multivariate analysis methods in vibrotactile stimuli (Schmidt et al., 2017). In the vibrotactile WM experiment, the DMTS paradigm that was well established in NHPs (for a review see Romo and Salinas; 2003) and humans (cf. Spitzer et al., 2010; Spitzer and Blankenburg; 2011; 2012; von Lautz et al., 2017) were used. Further extending the investigation into another sensory domain, we conducted an auditory WM experiment collecting human fMRI data. We then compared the results of the auditory WM experiment to an earlier tactile WM dataset (Schmidt et al., 2017). Therefore, we searched the unimodal and bimodal frequency-specific representations of WM. In this regard, we explored

the multimodal aspects of parametric WM in addition to the modality-dependent aspects. We thereby investigated whether the vibrotactile WM decoding found in the PFC (Schmidt et al., 2017) in contrast to a large body of visual WM MVPA studies (Serences et al., 2009; Christophel et al., 2012; Harrison and Tong, 2009; Riggall and Postle, 2012) was due to the difference in sensory modality. Another plausible explanation would be that the discrepancy is a result of the quantitative, abstract nature of frequency stimuli.

In Study 1, we conducted a DMTS task with auditory flutters as to be remembered stimuli. Study 1 used the same paradigm that is used in the vibrotactile WM decoding study (Schmidt et al., 2017). In this way, we could directly compare the results of Study 1 to the earlier vibrotactile findings (Schmidt et al., 2017). Similar to the tactile WM study, the experimental design of the auditory WM study comprised the presentation of two sequential auditory flutter samples followed by a retro-cue indicating the to-be-remembered frequency. A constant 1 kHz auditory mask accompanied the retro-cue. The retro-cue paradigm was useful in dissociating WM related activity from sensory residuals (Harrison and Tong, 2009). As in the earlier paradigm, four different auditory frequencies were presented as memoranda equally often in a randomized order. Following a 12 second retention period, two test stimuli were presented in a two-alternative forced choice task. One of the two test stimuli was identical to the sample frequency. The alternative foil was determined with a Weber-Fechner function. I collected 20 human fMRI datasets during this WM task.

In line with the earlier experiment, we used whole brain searchlight MVPA to depict the spatially distributed activity patterns carrying frequency-specific WM content. To this end, we employed a whole brain searchlight protocol, which is an assumption free analysis testing whole brain voxel by voxel for parametric WM representations (Kriegeskorte et al., 2006). To compare the findings of this study with earlier findings from recent parametric working memory MVPA studies, we employed the support vector regression (SVR) that the earlier tactile WM study used instead of a widely used pairwise classification method. The method was employed because SVR predicts the value of a variable continuously rather than a single specific class label. Thus, a linear ordering of values is expected in a successful decoding (Kahnt et al., 2011).

I found a fronto-parietal network comprising right IFG, SMA and bilateral PMC in the PFC and the IPL, the bilateral SPL in the posterior parietal cortex (PPC), and the PCC exhibiting auditory parametric representations during WM retention. Also, clusters in the bilateral superior temporal gyrus (STG) extending into the association auditory areas (TE3, as identified in Morosan et al., 2005) in the temporal cortex showed frequency-selective activity patterns. An additional conjunction analysis across vibrotactile WM data (Schmidt et al., 2017) revealed that prefrontal areas, right IFG, SMA and bilateral PMC code frequency information for not only auditory but also tactile stimuli. Interestingly, the results of our conjunction analysis not only agree with the MVPA data described earlier but also with earlier parametric WM studies of

NHP and human EEG (Vergara et al., 2016; Spitzer and Blankenburg, 2012). Therefore, our results suggest a shared prefrontal network of parametric WM for multiple modalities. Additionally, the content-specific information in the auditory and posterior parietal areas hints at modality specific representations in those brain regions.

2.2 Study 2: Visual tactile cross-modal working memory

Study 1 extended the vibrotactile fMRI MVPA research into another sensory domain. In Study 2, we further investigated the multimodal nature of parametric WM with a visual-tactile cross modal WM task. In this task, participants did not only do a visual-visual or a tactile-tactile task, rather the design allowed us to compare the sample stimulus in one modality to a test stimulus in the other one. Our aim was to test whether PFC, and especially rIFG, carries modality independent frequency-specific WM representations. The cross-modal nature of the task enabled us to further investigate whether these regions use a generalized multivariate WM code across both sensory modalities. We managed this by making sure that the participants did not know which modality to compare the memorized content with. Thus, they were encouraged to use abstract quantity representations instead of sensory-specific ones.

To this end, we again conducted a DMTS task in which a visual flicker and a vibrotactile stimulation were simultaneously presented as sample frequencies.

The presentation of two samples was followed by a retro-cue to indicate the frequency in which modality was to be remembered. Visual and tactile masks were also applied to disentangle the memory related activity from perceptual residues (Harrison & Tong, 2009; Sperling, 1960). A six second delay period was followed by a single visual or tactile test frequency for participants to judge whether the test frequency was higher or lower than the remembered sample. The interesting aspect of the experiment was that the sensory modality of the test frequency did not match the modality of the sample in half of the trials. As a result, the participant could not form a sensory-specific representation already in the retention period to compare with the test stimulus. The order of trials was randomized. This ensured that the participants did not know whether they would compare the sample frequency within its original modality or not. Twenty participants were scanned while performing the WM task. For the sake of consistency and comparability, we used the same whole brain searchlight MVPA with an SVR classifier that we used in Study 1. In this study, we addressed two questions. We first asked whether memorized tactile and visual frequencies were represented in the same brain regions. If that were the case, the second question addressed was: would the neural substrates of memorized tactile and visual frequencies rely on a modality independent WM code? We hypothesized that the frontal regions found in Study 1, i.e. rIFG and SMA, would also represent visual and tactile frequencies irrespective of sensory modality.

In line with the results of Study 1, a conjunction analysis across visual and tactile frequencies revealed a fronto-parietal network consisting of rIFG and pre-SMA

in the PFC and IPL, IPS, SPL in the PPC, and PCC. Additionally, we found bilateral PMC carrying parametric visual WM information. Our findings not only agree with Study 1, the frontal regions coding for both visual and tactile frequencies are also in line with the earlier NHP and human EEG/MEG literature (Vergara et al., 2016; Spitzer et al., 2012). Furthermore, similar to the auditory frequency WM findings in Study 1, we found frequency specific visual and tactile WM representations in their respective sensory areas. It is important to note that in both Study 1 and 2 the sensory areas coded for the frequencies in their respective modalities. These results indicate a modality dependent frequency representation in sensory brain regions.

In addition to within-modality and conjunction analysis, we also conducted a cross-modal classification analysis on the data from Study 2. The aim was to test for a modality-independent WM code for frequency representations. However, our cross-modal classification analysis did not yield any significant results for either tactile-to-visual or visual-to-tactile decoding. These results were unexpected as NHP and human EEG studies found a supramodal parametric WM code in the PFC (Vergara et al., 2016; Spitzer and Blankenburg, 2012). However, the relatively coarse spatial resolution of fMRI data might lead to a lack of access to the information by MVPA that can be easily picked up at the level of single neurons (Ester et al., 2016; see also Leavitt et al., 2017).

All in all, Study 2 agreed with the results of Study 1 and together they suggest a common fronto-parietal network for frequency representations in all three modalities and modality dependent WM coding in sensory brain regions. This

agrees with the account of distributed WM in which the higher cognitive brain regions maintain higher level information (Lee and Baker, 2016; Christophel et al., 2017).

2.3 Study 3: Working memory of approximate numerosities

After our investigation of modality independent parametric WM, we naturally took our investigation to a more abstract quantity format, namely numerosities (see Nieder, 2017). In Study 3, we aimed to discover the brain regions representing approximate numerosity information. As with parametric WM studies, we hypothesized that we would find numerosity-specific information in the PFC.

To make the data more comparable to parametric WM studies, we kept the experimental design – including the WM delay period – as similar as possible to the one used in Study 1, apart from using four numerosities instead of frequencies. To prevent fusion of the single pulses together in the pulse sequences, however, we had to use longer stimuli in Study 3. Additionally, to dissociate the stimulus numerosity from stimulus duration or frequency we used four different stimulus durations in total. In this way we aimed to mitigate the confounds for the WM representations that depend on other quantitative or sensory features of the stimuli such as rhythms, sound patterns or duration. We recorded fMRI data from 30 participants while they performed the numerosity WM task. As before, we used the same multivariate analysis

method to preserve the comparability of results. Using this method, we aimed to localize brain regions maintaining approximate number WM content. Based on previous studies (e.g., Spitzer et al., 2014a; Nieder, 2016; Uluç et al., 2018; Wu et al., 2018), we hypothesized that the content would be represented in frontal regions, specifically the right PFC.

The SVR MVPA analysis revealed numerosity-specific WM responses in the left PMC, left middle frontal gyrus (MFG), left superior frontal gyrus (SFG) extending into bilateral supplementary motor areas (SMA), right SFG extending to the right frontal pole and right MFG extending into the pars triangularis of the right IFG. As in Studies 1 and 2, Study 3 also agreed with NHP studies showing numerosity selective neuronal activity in the PFC. Additionally, we found activation of similar brain regions, i.e. rIFG, SMA and left PMC, to frontal regions of the modality independent parametric WM network in Studies 1 and 2. To conclude, all three studies combined gave us more evidence for the distributed nature of WM mechanisms. Using the most abstract quantity among the three studies, we found only brain areas in the PFC coding for numerosity WM.

3 General Discussion

The goal of my empirical work in the current dissertation was to investigate how abstract numerical quantities are represented in the human brain during WM retention. Here, this question was addressed by three fMRI decoding studies using a delayed discrimination paradigm that has been well-established in WM research (Mountcastle et al., 1990; Romo & de Lafuente, 2013; Nieder, 2016).

Extending earlier parametric WM studies (Romo & de Lafuente, 2013; Spitzer & Blankenburg, 2012; Schmidt et al., 2017), Studies 1 and 2 investigated which brain regions carry frequency information that is presented in auditory, visual and tactile sensory modalities (Wu et al., 2018; Uluç et al., 2018). This was done by testing for content specific, spatially distributed activity patterns across the whole brain from the data that was acquired during either an auditory or a visual-tactile cross modal WM task. First, the data was analyzed within a sensory modality. Then, the results were compared across modalities to test for a shared mechanism maintaining content-specific WM information for all modalities. More specifically, Study 1 addressed the questions of the auditory modality specific aspects of frequency representations. Additionally, in conjunction with an earlier collected dataset (Schmidt et al., 2017), this study set out to identify brain regions encoding not only auditory but tactile parametric memoranda (Uluç et al., 2018). In a further investigation, in Study 2, we tested whether there was a supramodal mechanism coding for frequencies in an abstract manner independent of the sensory modalities (Wu

et al., 2018). To this aim we used a cross modal visual-vibrotactile frequency DMTS task to decode frequency representations. Additionally, we conducted a cross modal whole brain decoding on the collected fMRI data to search for a supramodal parametric code. In Study 3, as a natural next step, we continued our research in a more abstract quantity format, namely approximated numerosities. Study 3 examined which brain regions carried numerosity-selective information during WM maintenance to see if they matched the regions showing parametric WM representations (Uluç et al., under review). Again, we performed a whole brain MVPA searchlight analysis with a SVR procedure to differentiate between four memorized tactile numerosities.

Collectively, our findings indicated distributed representations of WM memoranda maintained across the cortical hierarchy (for a detailed discussion see Lee & Baker, 2016 and Christophel et al., 2017). Specifically, we found sensory modality-dependent information in sensory cortices for frequency-specific content. On the other hand, frequency-specific WM content was represented by a shared fronto-parietal network for auditory, visual and tactile modalities. Furthermore, the same frontal regions, especially right IFG, SMA and PMC, carried both numerosity and frequency memoranda. Here, I will argue that the WM representations of abstract quantities are not found in one brain region, but rather distributed across a network. Also, there is a prefrontal network for the retention of abstract quantities that is independent of sensory modalities or the presentation format of the quantity information. I will argue that this network is a part of a whole brain WM system engaging brain regions

depending on the functional use of the to-be-remembered information. On this account, I will first discuss the brain regions that are shared by both parametric and numerosity WM representations. In this sense, I will explore whether there is an abstract quantity code in WM retention independent of format and modality. Additionally, I will address the question of whether modality dependent frequency representations in sensory areas and modality independent representations in prefrontal and parietal regions show that WM information can be maintained in different representation formats.

3.1 Abstract quantity codes in frontal brain regions

Our major finding in all three studies is that a frontal network comprised of right IFG, SMA and PMC shows content-specific brain activity for WM representations of quantities (Uluç et al., 2018; Wu et al., 2018., Uluç et al., under review). Here, the frontal network is shared by not only multiple sensory modalities but also multiple formats for presenting quantities, i.e. frequencies and numerosities, in all three studies. Said frontal brain regions have also been found in parametric WM studies, the majority of which are NHP and human EEG/MEG studies (Romo and de Lafuente, 2013; Vergara et al., 2016; Spitzer and Blankenburg, 2011; 2012; von Lautz et al., 2017; see also the fMRI MVPA study on vibrotactile WM Schmidt et al., 2017). Additionally, numerosity WM studies of NHPs and human EEG have also shown that same brain regions carry numerosity-specific information (Spitzer et al., 2014a; for a review of NHP studies see Nieder, 2016).

The major findings of our three studies provide compelling evidence for the distributed account of WM. In an account that suggests that sensory cortices encode low-level sensory information and higher cognitive regions represent more abstract, categorical WM content, a frontal network coding for abstract quantities is expected (Christophel et al., 2017). As the values can be represented in a modality and presentation format independent manner, the stimuli are likely stored as abstract quantities (Nieder, 2016; Vergara et al., 2016; Walsh, 2003). In this sense, the stimuli that are used in our studies, i.e. scalar (Romo et al., 1999) and analog (Dehaene, 1992) quantities, are derived from different sensory modalities and presented in different formats. The quantities that are in different sensory modalities and presentation formats permits the possibility of brain forming abstract representations, hence enabling us to address the question of higher level representations.

NHP and human EEG studies also used these abstract quantities to investigate a supramodal code in WM encoding. The notable gap in these EEG and NHP studies is that they cannot provide a spatially fine-grained whole brain approach to discover the locations of WM representations in the brain. Parametric WM research with fMRI MVPA has so far only used vibrotactile frequencies, hence more investigation in other modalities and different quantity presentation formats was needed. As a first step, our results thereby extend the frontal network that is discovered for vibrotactile WM in human fMRI (Schmidt et al., 2017) to auditory, visual and visual-tactile cross modal tasks. Later, the investigation has been taken to another format of presentation

to be tested in not only different modalities but different types of abstract quantities. To this end, we performed a delayed discrimination task with approximate numerosities as to-be-remembered samples. Additionally, there are very few numerosity WM studies even in NHP neurophysiology or human EEG (Nieder, 2016., Spitzer et al., 2014a) and univariate analysis methods that depict overall mean activation instead of the combinatorial aspects of voxel activity has been used (for discussion of multivariate vs. univariate analysis see Haynes, 2015; also Hebart & Baker, 2018). Therefore, we provided spatially finer grained, whole brain human fMRI results in a multivariate analysis format.

The difference of multivariate analysis techniques to univariate ones is that multivariate techniques are sensitive to multidimensional representations, unlike univariate analyses that identify magnitudes of activity in the brain (Peacock and Postle, 2012; Davis et al., 2014). In particular, multivariate techniques are sensitive to the combinatorial aspects of voxel activity (Haynes, 2015). In contrast, univariate analysis methods test for the mean activation of single voxels (Davis et al., 2014). Therefore, MVPA analysis makes it possible to address content-based processing (Haynes, 2015). However, fMRI and the BOLD contrast are indirect measures and represent the activity of large scale neural populations. Therefore, it is difficult to relate such changes to direct neural codes. Thus, caution should be taken when interpreting these results in the neuronal level (Haynes, 2015).

Moreover, the cross-modal classification analysis we conducted between tactile and visual frequencies did not yield any significant results. The lack of

results can be interpreted as distinct mechanisms of frequency maintenance for different sensory modalities. The NHP and EEG studies, however, provide evidence against this interpretation (Spitzer and Blankenburg, 2012; Vergara et al., 2016). Furthermore, fMRI lacks the spatial resolution to enable decoding of the state of a given small populations that might carry the supramodal code that NHP and EEG studies have picked up on (Serences, 2016). But, this explanation does not eliminate the possibility of distinct mechanisms for memorizing frequencies in different sensory modalities.

To be more specific, the shared network for both parametric and numerosity WM does not necessarily show that the code is a result of the same modality and format independent neural code. In fact, it was shown that the neural codes for numerosity and parametric WM are different in nature (Nieder, 2017). More specifically, frequencies are represented in a summation code where the neuronal activity varies with the memorized frequency in a monotonic function. In contrast, the neurons responding to numerosities use a labeled line code, where a neuron that is tuned to a certain numerosity has a maximum discharge rate at that particular numerosity (Nieder, 2017). However, it should be noted that the results are replicated in a human EEG study. As NHP are also extensively trained, both frequency and numerosity information might have been already categorized (Nieder, 2017) and hence the activity of neurons might relate to categorical representations of quantities. Humans, having not been trained as much, might not use other strategies and representations than the established categories. Moreover, it is also noted

that, in NHPs, as much as the neural code could be different for the different value formats, the difference might stem from the different demands of the different WM tasks (Nieder, 2017). Indeed, network simulations propose summation codes in a comparison tasks, and labeled line code in match-to-sample tasks (Verguts, 2007). Hence, our results show similar networks for parametric and numerosity WM, provide more reason to explore the numerosity and parametric WM with tasks that have the same task demands in NHPs in these areas.

3.2 Modality independent parametric working memory codes within fronto-parietal network

Diverging from the numerosity WM results (Uluç et al., under review) in Study 3, parametric WM representations in both Study 1 and 2 were distributed across the cortex also in IPL, IPS and PCC for auditory, visual and tactile frequencies (Uluç et al., 2018; Wu et al., 2018). The results of Studies 1 and 2 show modality independent representations in the parietal regions resulting in a fronto-parietal network for parametric WM (Wu et al., 2018). However, the results regarding parietal regions in the modality independent fronto-parietal network that we found in Studies 1 and 2 do not extend to show any numerosity-specific content. The lack of content-specific representations in the PPC during numerosity WM opens a number of questions as to whether they represent abstract quantity content.

A possible explanation for the said difference in representation in the PPC could stem from the different mechanisms in the maintenance of numerosities and frequencies. As evidence for this hypothesis, numerosity and parametric WM studies found different neuronal codes in NHP studies for WM maintenance of these different quantity formats (labeled line codes for numerosities and summation code for frequencies). However, as explained above, the different task demands might favor different types of codes (Nieder, 2017). Thus, it is not possible to conclusively propose that the different results for frequency and numerosity maintenance in the PPC is due to different codes or neuronal mechanisms in WM representation.

Moreover, ANS perception studies in both NHP and humans do find numerosity selective activity in the PPC (for reviews, Nieder, 2016; Eger, 2016). Notably, during approximate number perception the regions carrying information were the frontoparietal regions comprising LPFC and IPS and IPL (Eger et al., 2009). However, the numerosity-selective activity during retention was observed in the prefrontal neurons rather than the neurons in the PPC (Nieder et al., 2003). On the other hand, one should note that the earlier parametric WM studies have not found frequency-selective brain activity in the PPC either (Romo & de Lafuente 2013; Vergara et al., 2016; Spitzer and Blankenburg, 2011; 2012; Schmidt et al., 2017). However, our studies with both within-modality and cross-modal tasks have found a frontoparietal network shared by visual, tactile and auditory modalities. The discrepancy between the earlier parametric WM studies and our studies could be due to the nature of the task. In Study 1, the

auditory flutters could also be represented in terms of auditory rhythm as well as a pure frequency. In the Study 2 on the other hand, the task is essentially a cross-modal comparison task. Therefore, the task itself is harder and requires vivid representations. In line with this interpretation, it has been shown that the higher level information activated the regions in the PFC during WM retention while the lower level context activated the regions in the PPC (Nee and Brown, 2013).

Additionally, ANS perception studies with spatially and temporally distributed stimuli found stimulus specific perceptual representations in the PPC for spatially distributed stimuli but not for temporally distributed ones (Cavdaroglu & Knops, 2018). Hence, the null findings of numerosity memory content in the PPC might be a result of the presentation of numerosity stimuli temporally instead of simultaneously (Cavdaroglu & Knops, 2018). A similar numerosity discrimination task with spatially distributed stimuli could provide more informative results in this discussion.

3.3 Modality dependent parametric working memory codes within sensory cortices

The account of distributed nature of WM mechanisms for information maintenance (Lee and Baker, 2016; Christophel et al., 2017) is further strengthened by our findings in the Studies 1 and 2 (Wu et al., 2018; Uluç et al., 2018). In Study 3 we used a numerosity that is represented in a more abstract

fashion than the ones in the Studies 1 and 2. In Study 3, the design ensured that participants were not to using the same physical patterns or frequencies but only the approximated numerosity as the WM content. In the earlier two studies, though, vibration or auditory or visual flutter stimuli could also be represented as more sensory features. Thus, in addition to numerosity- and frequency- specific WM representations in the frontal brain regions and parametric WM information in posterior parietal areas, we found frequency representations in auditory, visual and tactile sensory areas for the respective sensory modalities of presented stimuli (Uluç et al., 2018; Wu et al., 2018). Here, the important aspect of our findings is that the frequency-specific representations was decoded from the sensory region of the respective stimulus modality. It should be noted that the modality dependent parametric representations in sensory cortices are very much in line with the sensory aspects of frequency stimuli (Nieder, 2017). Nieder (2017) proposes that the frequencies are relatively sensory properties of stimuli whereas the numerosity is an abstract and absolute. Therefore, the findings of Studies 1 and 2 suggest that the information was represented not only in the PFC as an abstract magnitude but also in sensory cortices, complemented with sensory aspects of the stimuli (see Figure 1 for a schematic summary our findings on the topography of WM of abstract quantities). These representations are modality specific as frequency representations of one sensory modality is decoded only in the respective sensory area. All results of parametric WM experiments considered, the frequency representations during WM retention are shown to

be distributed across the brain and represented in different levels of abstraction.

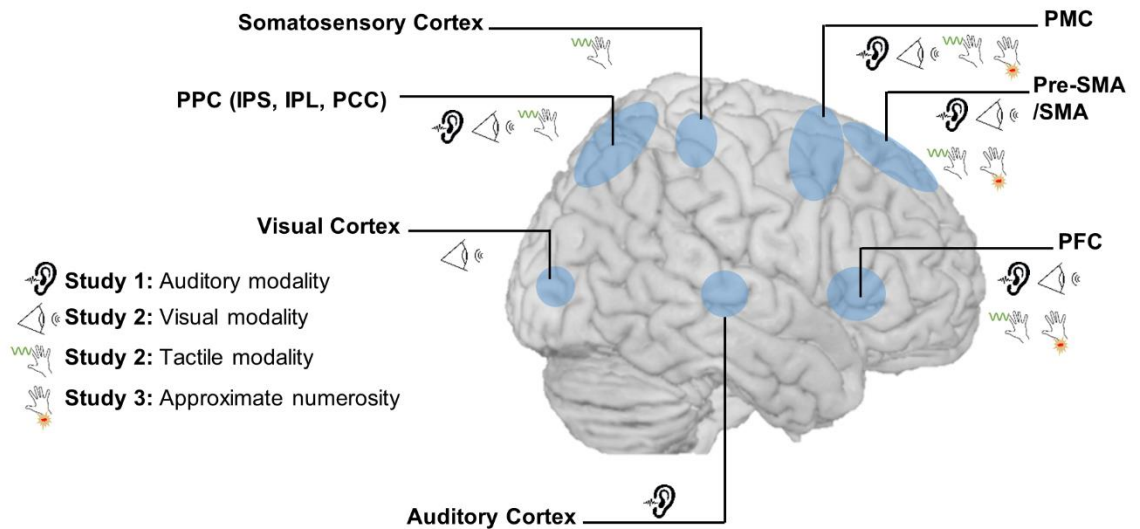


Figure 1: Topography of brain regions that exhibit content-specific activity for different types of abstract quantities. Findings of activations in the visual, auditory and somatosensory cortices provide evidence for modality-specific sensory representations. The IPS, IPL and precuneus exhibited parametric contents in tactile, visual and auditory modalities. The PFC retains information about content-specific representations for all sensory modalities as well as approximate numerosities.

Importantly, the results of Study 1 and 2 showing WM representations in primary sensory areas are in contrast with the findings from NHP and human EEG/MEG studies (Romo & Salinas, 2003; Lemus et al., 2009a; Spitzer & Blankenburg, 2012; von Lautz et al., 2017). A possible explanation for this divergence might come from different task needs in the NHP and human studies. In the NHP electrophysiology WM studies, the training period is quite long making the task rather automatic and resulting in more categorical representations than in the tasks with human participants (Serences, 2016). The result is that the NHPs, when presented with the to-be-remembered

stimulus, use already formed categories rather than getting help from the sensory aspects of the presented stimulus (Serences, 2016). In contrast, human participants – having been subjected to less training than the well-trained NHPs – have less chance to form preconceived categories. Thus, human subjects are expected to use more of other forms of representations during a WM task (Serences, 2016).

Additionally, one should also note Studies 1 and 2 showed content-specific information in higher sensory areas, not in primary sensory areas. To give more detail, NHP studies are limited in their area of investigation while the searchlight decoding studies test the whole brain for the content-specific activity patterns. In this sense, the NHP studies recording single cell activities were mainly focused on the primary sensory areas in parametric WM research. As a result, they did not find any frequency selective spike activity in those primary sensory regions (Lemus et al., 2009a; Lemus et al., 2010). On the other hand, the whole brain searchlight MVPA revealed parametric WM representations not in primary but higher sensory areas (Wu et al., 2018; Uluç et al., 2018). Indeed, neural activity in the secondary somatosensory cortex has been shown to monotonically decrease or increase with the remembered frequency in early stages of the retention period (Hernández et al., 2010). Therefore, the findings of NHP electrophysiology studies may stem from the distinct spatial localizations of their recordings. However, despite the spatial limitations of NHP studies in terms of recording areas, human EEG/MEG studies have not also found any frequency-specific activation in sensory regions

(Spitzer et al., 2010; Spitzer & Blankenburg, 2012; von Lautz et al., 2017). Hence, the lack of evidence in other studies cannot be reduced to only the location of recording. There are, however, other possible explanations for this discrepancy.

A possible explanation for the difference between human EEG and fMRI findings could be that the information is stored not by a summation code but by distributed firing patterns in sensory cortices. However, it should be noted that we use SVR to search for WM representations in the brain. SVR, as opposed to pairwise classifications methods that search for individual categories, treats the WM content as a continuous variable. Therefore, SVR MVPA also helps uncover parametric representations in the brain.

Contrary to the findings of human EEG/MEG studies, we found frequency information in sensory cortices during WM retention in our studies. The discrepancy between human EEG/MEG and fMRI MVPA results can be explained with a difference in analysis methodology and the different brain signals they measure. Human EEG/MEG studies employ univariate analysis methods reporting a mean activation level (e.g., Spitzer & Blankenburg, 2012; von Lautz et al., 2017). On the other hand, fMRI MVPA studies are sensitive to the combinatorial aspects of voxel activity, thereby enabling the identification of spatially distributed activity patterns (Haynes, 2015). Earlier MVPA WM studies (Serences et al., 2009; Christophel et al., 2012; Harrison & Tong, 2009; Riggall & Postle, 2012) decoded WM information from primary sensory areas, while electrophysiology studies (Lemus et al., 2009b; Salinas et al., 2000) did

not find content-selective activity in these regions, reflecting the aforementioned differences between the studies and their design.

To sum up, we found representations of quantity distributed across the brain, at different levels for different memorized features (see Figure 1 for a summary schematic of all results). Specifically, we identified frontal regions representing abstract quantity memoranda for multiple modalities and presentation formats. Significantly, the structures found as a main combinatory finding of all three studies are commensurate with findings from NHP studies (for reviews see Romo & de Lafuente, 2013; Nieder, 2016) and are also consistent with EEG/MEG studies (cf. Spitzer and Blankenburg, 2012; Spitzer et al., 2014; von Lautz et al., 2017) from both the parametric and numerosity WM domain. That our results span different value formats hints at a shared prefrontal WM network for abstract quantities. Additionally, the WM representations of frequencies were found in the PPC for multiple modalities but not for numerosity. This indicates an additional aspect of frequencies in the PPC that temporally presented numerosities do not share. Last, we found modality dependent representations in the sensory regions for frequencies.

3.4 Limitations

It should be noted that although we use a more sensitive analysis method for the fMRI data, we are still restricted by the limitations of the scanning method in terms of its resolution and the signal it measures. As one single voxel might include more than a million neurons, the information we can decode might be

underestimated at the voxel level (Haynes, 2015). Additionally, different regions of the brain might have different number of neuronal populations exhibiting a specific code, which would be overlooked by the multivariate analysis. Hence the sensitivity of the analysis might be different in distinct brain regions (Haynes, 2015).

Moreover, the signal that fMRI measures is not a direct neural signal but a by-product of the BOLD contrast, which can be affected also by circulatory and metabolic changes. Hence, the conclusions driven from the results of fMRI related analyses are not conclusively about the neural signal, but they are merely indications at a larger scale (Logothetis, 2003).

Moreover, since the non-invasive techniques do not give any information on the actual neuronal code, we cannot conclusively suggest a modality and format independent WM code for abstract quantities. We have shown that both numerosities and frequencies are represented in a parametric fashion. However, we cannot conclude that the regions showing WM representations in different modalities and different formats use the same neuronal code in doing so. On the contrary, it should be noted that our cross modal decoding analysis did not yield any significant results in Study 2. This might be the result of different neuronal codes reflecting numerosity and frequency memoranda. On the other hand, it should be noted that it is prefrontal regions that are subserving representations of frequencies in multiple modalities as well as. The neurons in the PFC have very fine-grained sampling patterns (Serences, 2016). Therefore, the reason we did not have significant cross-classification results

might be a matter of sampling. In conclusion, although NHP and human EEG studies have shown supramodal code for frequency maintenance (Spitzer & Blankenburg, 2012; Vergara et al., 2016), our method so far falls short of revealing supramodal representations in the brain. An interesting avenue for future work would be a replication of the experiment with smaller voxel size and testing for cross-modal decoding to see if smaller sampling affects the results.

3.5 Outlook

The empirical work presented in this dissertation was designed to investigate the neural correlates of WM representing abstract quantities. In doing so, we sought to test the distributed nature of WM representations in the brain. We started with fMRI MVPA research on parametric WM in different sensory modalities. Although the parametric WM research is exhaustively explored in the earlier literature and in our studies, the research in numerosity WM has been rarely explored before and there are still gaps in our understanding. As an obvious next step, the neural correlates of numerosity WM in other sensory modalities should be investigated. This way, more parallels between the parametric WM studies can be built and we can gain a more thorough understanding of the similarities and differences in WM mechanisms of both abstract quantities. Additionally, a parallel in lack of PPC findings between the study on the ANS perception for temporally versus spatially distributed stimuli and our numerosity WM study calls for further investigation in this field with

spatially distributed stimuli. To investigate this, a visual or tactile WM study with spatially distributed stimuli (e.g. visual dots or tactile pins presented at the same time) is required. This extension would provide more insights into the discrepancy between the numerosity and frequency WM representations that we found in the PPC.

Further research will benefit from a shift in focus from using different modalities to different value formats. This shift will provide a more general understanding of magnitudes and how they are processed in WM. In this context, research on different magnitude formats such as duration, speed and intensity (cf. Wimmer et al., 2016; von Lutz et al., 2019) would be beneficial not only to understand WM mechanisms and the distributed nature of WM that has been revealed so far. Additionally, a potentially fruitful future approach would be to combine tasks with different presentation formats, to enable a cross-classification analysis across formats. Another beneficial step would be to conduct intracranial EEG or 7T fMRI studies on quantity WM for finer grained data acquisition.

References

- Atkinson, R.C.; Shiffrin, R.M. (1968). Human memory: A proposed system and its control processes. In Spence, K.W.; Spence, J.T. *The psychology of learning and motivation*. New York: Academic Press. pp. 89–195.
- Baddeley, A. (2012). Working Memory: Theories, Models, and Controversies. *Annual Review of Psychology*, *63*(1), 1–29.
<https://doi.org/10.1146/annurev-psych-120710-100422>
- Baddeley, A. D., & Hitch, G. (1974). Working Memory. *Psychology of Learning and Motivation*, *8*, 47–89. [https://doi.org/10.1016/S0079-7421\(08\)60452-1](https://doi.org/10.1016/S0079-7421(08)60452-1)
- Barak, O., Tsodyks, M., & Romo, R. (2010). Neuronal population coding of parametric working memory. *Journal of Neuroscience*, *30*(28), 9424–30.
<http://doi.org/10.1523/JNEUROSCI.1875-10.2010>
- Brody, C. D., Hernández, A., Zainos, A., & Romo, R. (2003). Timing and neural encoding of somatosensory parametric working memory in macaque prefrontal cortex. *Cerebral Cortex*, *13*(11), 1196–207. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/14576211>
- Cantlon, J. F., Brannon, E. M., Carter, E. J., & Pelphrey, K. A. (2006). Functional Imaging of Numerical Processing in Adults and 4-y-Old Children. *PLoS Biology*, *4*(5), e125.
<https://doi.org/10.1371/journal.pbio.0040125>
- Cantlon, J. F., Platt, M. L., & Brannon, E. M. (2009). Beyond the number domain. *Trends in Cognitive Sciences*, *13*(2), 83–91.
<https://doi.org/10.1016/j.tics.2008.11.007>
- Cavdaroglu, S., & Knops, A. (2018). Evidence for a Posterior Parietal Cortex Contribution to Spatial but not Temporal Numerosity Perception. *Cerebral Cortex*. <https://doi.org/10.1093/cercor/bhy163>
- Christophel, T. B., Hebart, M. N., & Haynes, J.-D. (2012). Decoding the contents of visual short-term memory from human visual and parietal cortex. *Journal of Neuroscience*, *32*(38), 12983–9.
<http://doi.org/10.1523/JNEUROSCI.0184-12.2012>
- Christophel, T. B., T. D., Klink, P. C., Spitzer, B., & Roelfsema, P. R. (2017). The Distributed Nature of Working Memory. *Trends in Cognitive Sciences*, *21*(2), 1–14. <http://doi.org/10.1016/j.tics.2016.12.007>
- Cowan, N. (1999). An Embedded-Processes Model of Working Memory. In A. Miyake & P. Shah (Eds.), *Models of Working Memory*. Cambridge:

Cambridge University Press. pp. 62–101.
<https://doi.org/10.1017/CBO9781139174909.006>

Davis, T., LaRocque, K. F., Mumford, J. A., Norman, K. A., Wagner, A. D., & Poldrack, R. A. (2014). What do differences between multi-voxel and univariate analysis mean? How subject-, voxel-, and trial-level variance impact fMRI analysis. *NeuroImage*, *97*, 271–283.
<https://doi.org/10.1016/j.neuroimage.2014.04.037>

Dehaene, S. (1992). Varieties of numerical abilities. *Cognition*, *44*(1–2), 1–42.
[https://doi.org/10.1016/0010-0277\(92\)90049-N](https://doi.org/10.1016/0010-0277(92)90049-N)

Dehaene, S. (1997). *The number sense: how the mind creates mathematics*. Oxford University Press.

Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three Parietal Circuits for Number Processing. *Cognitive Neuropsychology*, *20*(3-6), 487–506.
<https://doi.org/10.1080/02643290244000239>

D’Esposito, M., & Postle, B. R. (2015). The Cognitive Neuroscience of Working Memory. *Annual Review of Psychology*, *66*, 115–42.
<https://doi.org/10.1146/annurev-psych-010814-015031>

Eger, E., Michel, V., Thirion, B., Amadon, A., Dehaene, S., & Kleinschmidt, A. (2009). Deciphering Cortical Number Coding from Human Brain Activity Patterns. *Current Biology*, *19*(19), 1608-1615.
<https://doi.org/10.1016/J.CUB.2009.08.047>

Eger, E. (2016). Neuronal foundations of human numerical representations. In *Progress in brain research: The mathematical brain across the lifespan* (Vol. 227, pp. 1–27). <https://doi.org/10.1016/bs.pbr.2016.04.015>

Ester, E., Serences, J., & Awh, E. (2010). Global mechanisms of sensory recruitment during working memory maintenance. *Journal of Vision*, *9*(8), 597–597. <https://doi.org/10.1167/9.8.597>

Ester, E. F., Rademaker, R. L., & Sprague, T. C. (2016). How do visual and parietal cortex contribute to visual short-term memory? *eNeuro*, *3*(2). <https://doi.org/10.1523/ENEURO.0041-16.2016>

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1989). Mnemonic coding of visual space in the monkey’s dorsolateral prefrontal cortex. *Journal of Neurophysiology*, *61*(2), 331–349.
<https://doi.org/10.1152/jn.1989.61.2.331>

Fuster, J. M., & Alexander, G. E. (1971). Excitation and Inhibition of Neuronal Firing in Visual Cortex by Reticular Stimulation. *Science*, *133*(3469), 2011–2012. <https://doi.org/10.1126/science.133.3469.2011>

- Gallistel, C. R., & Gelman, R. (1992). Preverbal and verbal counting and computation. *Cognition*, 44(1–2), 43–74. [https://doi.org/10.1016/0010-0277\(92\)90050-R](https://doi.org/10.1016/0010-0277(92)90050-R)
- Goldman-Rakic, P. (1995). Cellular basis of working memory. *Neuron*, 14(3), 477–485.
- Harrison, S. A., & Tong, F. (2009). Decoding reveals the contents of visual working memory in early visual areas. *Nature*, 458(7238), 632–5. <http://doi.org/10.1038/nature07832>
- Haynes, J.-D. (2015). A Primer on Pattern-Based Approaches to fMRI: Principles, Pitfalls, and Perspectives. *Neuron*, 87(2), 257–270. <http://doi.org/10.1016/j.neuron.2015.05.025>
- Hebart, M. N., & Baker, C. I. (2018). Deconstructing multivariate decoding for the study of brain function. *NeuroImage*, 180(Pt A), 4–18. <https://doi.org/10.1016/j.neuroimage.2017.08.005>
- Hernández, A., Nácher, V., Luna, R., Zainos, A., Lemus, L., Alvarez, M., ... Romo, R. (2010). Decoding a perceptual decision process across cortex. *Neuron*, 66(2), 300–14. <http://doi.org/10.1016/j.neuron.2010.03.031>
- Jacob, S. N., & Nieder, A. (2009). Tuning to non-symbolic proportions in the human frontoparietal cortex. *European Journal of Neuroscience*, 30(7), 1432–1442. <https://doi.org/10.1111/j.1460-9568.2009.06932.x>
- Jacob, S. N., Hahnke, D., & Nieder, A. (2018). Structuring of Abstract Working Memory Content by Fronto-parietal Synchrony in Primate Cortex. *Neuron*, 99(3), 588–597.e5. <https://doi.org/10.1016/j.neuron.2018.07.025>
- Kahnt, T., Heinzle, J., Park, S. Q., & Haynes, J.-D. (2011). Decoding different roles for vmPFC and dlPFC in multi-attribute decision making. *NeuroImage*, 56(2), 709–715. <https://doi.org/10.1016/j.neuroimage.2010.05.058>
- Kaufman, E. L., Lord, M. W., Reese, T. W., & Volkman, J. (1949). The Discrimination of Visual Number. *The American Journal of Psychology*, 62(4), 498. <https://doi.org/10.2307/1418556>
- Knops, A., & Willmes, K. (2014). Numerical ordering and symbolic arithmetic share frontal and parietal circuits in the right hemisphere. *NeuroImage*, 84, 786–795. <https://doi.org/10.1016/J.NEUROIMAGE.2013.09.037>
- Knops, A. (2017). Probing the Neural Correlates of Number Processing. *The Neuroscientist*, 23(3), 264–274. <https://doi.org/10.1177/1073858416650153>

- Kostopoulos, P., Albanese, M.-C., & Petrides, M. (2007). Ventrolateral prefrontal cortex and tactile memory disambiguation in the human brain. *Proceedings of the National Academy of Sciences*, *104*(24), 10223–10228. <https://doi.org/10.1073/pnas.0700253104>
- Kriegeskorte, N., Goebel, R., & Bandettini, P. (2006). Information-based functional brain mapping. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(10), 3863–8. <http://doi.org/10.1073/pnas.0600244103>
- Kubota, K., & Niki, H. (1971). Prefrontal cortical unit activity and delayed alternation performance in monkeys. *Journal of Neurophysiology*, *34*(3), 337–347. <https://doi.org/10.1152/jn.1971.34.3.337>
- Leavitt, M. L., Mendoza-halliday, D., & Martinez-trujillo, J. C. (2017). Sustained Activity Encoding Working Memories: Not Fully Distributed. *Trends in Neurosciences*, *40*(6), 328–346. <http://doi.org/10.1016/j.tins.2017.04.004>
- Lee, S.-H., & Baker, C. I. (2016). Multi-Voxel Decoding and the Topography of Maintained Information During Visual Working Memory. *Frontiers in Systems Neuroscience*, *10*(February), 2. <http://doi.org/10.3389/fnsys.2016.00002>
- Lemus, L., Hernández, A., & Romo, R. (2009a). Neural encoding of auditory discrimination in ventral premotor cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(34), 14640–5. <https://doi.org/10.1073/pnas.0907505106>
- Lemus, L., Hernández, A., & Romo, R. (2009b). Neural codes for perceptual discrimination of acoustic flutter in the primate auditory cortex. *Proceedings of the National Academy of Sciences*, *106*(23), 9471–9476. <https://doi.org/10.1073/pnas.0904066106>
- Logothetis, N. K. (2003). The Underpinnings of the BOLD Functional Magnetic Resonance Imaging Signal. *Journal of Neuroscience*, *23*(10), 3963–3971. [doi:10.1523/jneurosci.23-10-03963.2003](https://doi.org/10.1523/jneurosci.23-10-03963.2003)
- Ludwig, S., Herding, J., & Blankenburg, F. (2018). Oscillatory EEG signatures of postponed somatosensory decisions. *Human Brain Mapping*, *39*(9), 3611–3624. <https://doi.org/10.1002/hbm.24198>
- Melton, A. W. (1963). Implications of short-term memory for a general theory of memory. *Journal of Verbal Learning and Verbal Behavior*, *2*(1), 1–21. [https://doi.org/10.1016/S0022-5371\(63\)80063-8](https://doi.org/10.1016/S0022-5371(63)80063-8)
- Morosan, P., Schleicher, A., Amunts, K., & Zilles, K. (2005). Multimodal architectonic mapping of human superior temporal gyrus. *Anatomy and*

Embryology, 210(5–6), 401–406. <https://doi.org/10.1007/s00429-005-0029-1>

Mountcastle, V. B., Talbot, W. H., Darian-Smith, I., Kornhuber, H. H. (1967). Neural basis of the sense of flutter- vibration. *Science* 155, 597–600

Mountcastle, V. B., Steinmetz, M. A., Romo, R. (1990). Frequency discrimination in the sense of flutter: psychophysical measurements correlated with postcentral events in behaving monkeys. *Journal of Neuroscience*. 10, 3032–3044

Nee, D. E., & Brown, J. W. (2013). Dissociable Frontal–Striatal and Frontal–Parietal Networks Involved in Updating Hierarchical Contexts in Working Memory. *Cerebral Cortex*, 23(9), 2146–2158. <https://doi.org/10.1093/cercor/bhs194>

Nieder, A., Freedman, D. J., & Miller, E. K. (2002). Representation of the Quantity of Visual Items in the Primate Prefrontal Cortex. *Science*, 297(5587), 1708–1711. <https://doi.org/10.1126/science.1072493>

Nieder, A., & Miller, E. K. (2003). Coding of Cognitive Magnitude: Compressed Scaling of Numerical Information in the Primate Prefrontal Cortex. *Neuron*, 37(1), 149–157. [https://doi.org/10.1016/S0896-6273\(02\)01144-3](https://doi.org/10.1016/S0896-6273(02)01144-3)

Nieder, A., & Miller, E. K. (2004). A parieto-frontal network for visual numerical information in the monkey. *Proceedings of the National Academy of Sciences*, 101(19), 7457–7462. <https://doi.org/10.1073/pnas.0402239101>

Nieder, A., & Merten, K. (2007). A Labeled-Line Code for Small and Large Numerosities in the Monkey Prefrontal Cortex. *Journal of Neuroscience*, 27(22), 5986–5993. <https://doi.org/10.1523/JNEUROSCI.1056-07.2007>

Nieder, A., & Dehaene, S. (2009). Representation of Number in the Brain. *Annual Review of Neuroscience*, 32(1), 185–208. <https://doi.org/10.1146/annurev.neuro.051508.135550>

Nieder, A. (2012). Supramodal numerosity selectivity of neurons in primate prefrontal and posterior parietal cortices. *Proceedings of the National Academy of Sciences of the United States of America*, 109(29), 11860–5. <http://doi.org/10.1073/pnas.1204580109>

Nieder, A. (2016). The neuronal code for number. *Nature Reviews Neuroscience*, 17(6), 366–82. <http://doi.org/10.1038/nrn.2016.40>

Nieder, A. (2017). Magnitude Codes for Cross-Modal Working Memory in the Primate Frontal Association Cortex, 1 *Frontiers in Neuroscience*, 11, 1–7. <http://doi.org/10.3389/fnins.2017.00202>

- Pasternak, T., & Greenlee, M. W. (2005). Working memory in primate sensory systems. *Nature Reviews Neuroscience*, *6*(2), 97–107. <http://doi.org/10.1038/nrn1603>
- Peacock, J. A., & Postle, B. R. (2012). Decoding the internal focus of attention. *Neuropsychologia*, *50*(4), 470–478. doi:10.1016/j.neuropsychologia.2011.11.00
- Piazza, M., Izard, V., Pinel, P., Le Bihan, D., & Dehaene, S. (2004). Tuning Curves for Approximate Numerosity in the Human Intraparietal Sulcus. *Neuron*, *44*(3), 547–555. <https://doi.org/10.1016/j.neuron.2004.10.014>
- Piazza, M., Pinel, P., Le Bihan, D., & Dehaene, S. (2007). A Magnitude Code Common to Numerosities and Number Symbols in Human Intraparietal Cortex. *Neuron*, *53*(2), 293–305. <https://doi.org/10.1016/J.NEURON.2006.11.022>
- Piazza, M., Mechelli, A., Price, C. J., & Butterworth, B. (2006). Exact and approximate judgements of visual and auditory numerosity: An fMRI study. *Brain Research*, *1106*(1), 177–188. <https://doi.org/10.1016/j.brainres.2006.05.104>
- Piazza, M. (2010). Neurocognitive start-up tools for symbolic number representations. *Trends in Cognitive Sciences*, *14*(12), 542–551. <https://doi.org/10.1016/j.tics.2010.09.008>
- Preuschhof, C., Heekeren, H. R., Taskin, B., Schubert, T., & Villringer, A. (2006). Neural correlates of vibrotactile working memory in the human brain. *Journal of Neuroscience*, *26*(51), 13231–9. <http://doi.org/10.1523/JNEUROSCI.2767-06.2006>
- Riggall, A. C., & Postle, B. R. (2012). The Relationship between Working Memory Storage and Elevated Activity as Measured with Functional Magnetic Resonance Imaging. *Journal of Neuroscience*, *32*(38), 12990–12998. doi:10.1523/jneurosci.1892-12.2012
- Romo, R., Brody, C. D., Hernández, A., & Lemus, L. (1999). Neuronal correlates of parametric working memory in the prefrontal cortex. *Nature*, *399*(6735), 470–473. <https://doi.org/10.1038/20939>
- Romo, R., & Salinas, E. (2003). Flutter Discrimination: neural codes, perception, memory and decision making. *Nature Reviews Neuroscience*, *4*(3), 203–218. doi:10.1038/nrn1058
- Romo, R., & de Lafuente, V. (2013). Conversion of sensory signals into perceptual decisions. *Progress in Neurobiology*, *103*, 41–75. <http://doi.org/10.1016/j.pneurobio.2012.03.007>

- Salinas, E., Hernandez, A., Zainos, A., & Romo, R. (2000). Periodicity and firing rate as candidate neural codes for the frequency of vibrotactile stimuli. *Journal of Neuroscience*, *20*(14), 5503–15. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10884334>
- 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. <http://doi.org/10.1523/JNEUROSCI.1167-17.2017>
- Serences, J. T., Ester, E. F., Vogel, E. K., & Awh, E. (2009). Stimulus-specific delay activity in human primary visual cortex. *Psychological Science*, *20*(2), 207–14. <http://doi.org/10.1111/j.1467-9280.2009.02276.x>
- Serences, J. T. (2016). Neural mechanisms of information storage in visual short-term memory. *Vision Research*, *128*, 53–67. <http://doi.org/10.1016/j.visres.2016.09.010>
- Singer, W. (1999). Neuronal Synchrony: A Versatile Code for the Definition of Relations? *Neuron*, *24*(1), 49–65. doi:10.1016/s0896-6273(00)80821-1
- Sperling, G. (1960). The information available in brief visual presentations. *Psychological Monographs: General and Applied*, *74*(11), 1–29. <https://doi.org/10.1037/h0093759>
- Spitzer, B., Wacker, E., & Blankenburg, F. (2010). Oscillatory correlates of vibrotactile frequency processing in human working memory. *Journal of Neuroscience*, *30*(12), 4496–502. <http://doi.org/10.1523/JNEUROSCI.6041-09.2010>
- Spitzer, B., & Blankenburg, F. (2011). Stimulus-dependent EEG activity reflects internal updating of tactile working memory in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(20), 8444–9. <http://doi.org/10.1073/pnas.1104189108>
- Spitzer, B., & Blankenburg, F. (2012). Supramodal parametric working memory processing in humans. *Journal of Neuroscience*, *32*(10), 3287–95. <http://doi.org/10.1523/JNEUROSCI.5280-11.2012>
- Spitzer, B., Fleck, S., & Blankenburg, F. (2014a). Parametric alpha- and beta-band signatures of supramodal numerosity information in human working memory. *Journal of Neuroscience*, *34*(12), 4293–302. <https://doi.org/10.1523/JNEUROSCI.4580-13.2014>
- Spitzer, B., Gloel, M., Schmidt, T. T., & Blankenburg, F. (2014b). Working memory coding of analog stimulus properties in the human prefrontal cortex. *Cerebral Cortex*, *24*(8), 2229–36. <http://doi.org/10.1093/cercor/bht084>

- Spitzer, B., & Haegens, S. (2017). Beyond the Status Quo: A Role for Beta Oscillations in Endogenous Content (Re)Activation. *Eneuro*, 4(4), ENEURO.0170-17.2017. <https://doi.org/10.1523/ENEURO.0170-17.2017>
- Tudusciuc, O., & Nieder, A. (2009). Contributions of Primate Prefrontal and Posterior Parietal Cortices to Length and Numerosity Representation. *Journal of Neurophysiology*, 101(6), 2984–2994. <https://doi.org/10.1152/jn.90713.2008>
- Uluç, I., Schmidt, T. T., Wu, Y.-H., & Blankenburg, F. (2018). Content-specific codes of parametric auditory working memory in humans. *NeuroImage*, 183. <https://doi.org/10.1016/j.neuroimage.2018.08.024>
- Uluç I, Velenosi LA, Schmidt TT, Blankenburg F (under review) Parametric representation of tactile numerosity in working memory. *eNeuro*.
- Vergara, J., Rivera, N., Rossi-Pool, R., & Romo, R. (2015). A Neural Parametric Code for Storing Information of More than One Sensory Modality in Working Memory. *Neuron*, 89(1), 54–62. <http://doi.org/10.1016/j.neuron.2015.11.026>
- Verguts, T. (2007). How to Compare Two Quantities? A Computational Model of Flutter Discrimination. *Journal of Cognitive Neuroscience*, 19(3), 409–419. <https://doi.org/10.1162/jocn.2007.19.3.409>
- von Lautz, A. H., Herding, J., Ludwig, S., Nierhaus, T., Maess, B., Villringer, A., & Blankenburg, F. (2017). Gamma and Beta Oscillations in Human MEG Encode the Contents of Vibrotactile Working Memory. *Frontiers in Human Neuroscience*, 11, 576. <https://doi.org/10.3389/fnhum.2017.00576>
- von Lautz, A. H., Herding, J., Blankenburg, F. (2019). Neuronal Signatures of A Random-Dot Motion Comparison Task. *NeuroImage*, 193, 57-66. <https://doi.org/10.1016/j.neuroimage.2019.02.071>
- Walsh V. (2003). A theory of magnitude: Common cortical metrics of time, space and quantity. *Trends in Cognitive Sciences*, 7, 483–488. <https://doi.org/10.1016/j.tics.2003.09.002>
- Werner, G., Mountcastle, V. B. (1965). Neural activity in mechanoreceptive cutaneous afferents: stimulus–response relations, Weber functions, and information transmission. *Journal of Neurophysiology*. 28, 359–397
- Wimmer, K., Spinelli, P., & Pasternak, T. (2016). Prefrontal Neurons Represent Motion Signals from Across the Visual Field But for Memory-Guided Comparisons Depend on Neurons Providing These Signals. *Journal of Neuroscience*, 36(36), 9351–9364. <https://doi.org/10.1523/JNEUROSCI.0843-16.2016>

Wu, Y.-H., Uluç, I., Schmidt, T. T., Tertel, K., Kirilina, E., & Blankenburg, F. (2018). Overlapping frontoparietal networks for tactile and visual parametric working memory representations. *NeuroImage*, *166*, 325–334. <https://doi.org/10.1016/J.NEUROIMAGE.2017.10.059>

Original publications

Study 1

For Copyright reasons the original publication is not included in this PDF.

Please access the publication via the DOI provided below.

Uluç I., Schmidt T.T., Wu Y.-h., Blankenburg F. (2018). Content-specific codes of parametric auditory working memory in humans. *Neuroimage* 183:254–262.
DOI: <https://doi.org/10.1016/j.neuroimage.2018.08.024>

Original Publications

Study 2

For Copyright reasons the original publication is not included in this PDF.

Please access the publication via the DOI provided below.

Wu Y.-h.*, **Uluç I.***, Schmidt T.T., Tertel K., Kirilina E., Blankenburg F. (2018). Overlapping frontoparietal networks for tactile and visual parametric working memory representations. *Neuroimage* 166:325–334. DOI: <https://doi.org/10.1016/j.neuroimage.2017.10.059>

Original Publications

Study 3

This article may not exactly replicate the final version published.

It is not the copy of record.

Uluç I, Velenosi LA, Schmidt TT, Blankenburg F. (submitted March 2019).

Parametric representation of tactile numerosity in working memory. eNeuro.

1. Manuscript title: Parametric representation of tactile numerosity in working memory

2. Abbreviated title: Tactile numerosity in working memory

3. Authors : Işıl Uluç ^{a,b}, Lisa Alexandria Velenosi^a, Timo Torsten Schmidt ^a, Felix Blankenburg ^{a,b}

^a Neurocomputation and Neuroimaging Unit (NNU), Department of Education and Psychology, Freie Universität Berlin, 14195 Berlin, Germany

^b Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, 10099 Berlin, Germany

4. Author Contributions: IU, TTS, FB and LAV designed the research. IU, TTS and LAV programmed the experimental paradigm. IU and LAV collected the data. IU analyzed the data. IU, TTS and FB interpreted the data analysis. IU wrote the first draft of the paper with further comments from LAV, TTS and FB.

5. Correspondence should be addressed to:

Işıl Uluç

Freie Universität Berlin

Department of Education and Psychology

Neurocomputation and Neuroimaging Unit (NNU)

Habelschwerdter Allee 45 14195 Berlin

isil.uluc@fu-berlin.de

6. Number of figures: 3

7. Number of tables: 1

8. Number of multimedia: 0

9. Number of words for abstract: 161

10. Number of words for significance statement: 117

11. Number of words for introduction: 743

12. Number of words for discussion: 1103

13. Acknowledgements: Authors would like to thank Yuan-hao Wu for his assistance on data collection and Alexander von Lautz for his helpful feedback on this manuscript.

14. Conflict of interest: Authors report no conflict of interest

15. Funding sources: IU was supported by Deutscher Akademischer Austauschdienst and the Berlin School of Mind and Brain. LV was supported by the Research Training Group GRK 1589/2 by the Deutsche Forschungsgemeinschaft (DFG).

Abstract

Estimated numerosity perception is processed in an approximate number system (ANS) that resembles the perception of a continuous magnitude. The ANS consists of a right lateralized frontoparietal network comprising the lateral prefrontal cortex (LPFC) and the intraparietal sulcus. Although the ANS has been extensively investigated, only few studies focus on the mental representation of retained numerosity estimates. Specifically, the underlying mechanisms of estimated numerosity working memory (WM) is unclear. Besides numerosities, as another form of abstract quantity, vibrotactile WM studies provide initial evidence that the right LPFC takes a central role in maintaining magnitudes. In the present fMRI MVPA study in numerosity WM, we designed a delayed-match-to-numerosity paradigm to test what brain regions retain approximate numerosity memoranda. In line with parametric WM results, our study found numerosity-specific WM representations in the right LPFC as well as in the supplemental motor area and the left premotor cortex extending into the superior frontal gyrus, thus bridging the gap in abstract quantity WM literature.

Significance Statement

While the perception of approximate numerosities has been extensively investigated, research into the mnemonic representation during working memory (WM) are relatively rare. Here, we present the first study to localize WM information for approximate numerosities using functional magnetic resonance imaging (fMRI) in combination with multivariate pattern analysis (MVPA). Extending beyond previous accounts that used either a priori brain regions or electrocorticography (EEG) with poor spatial resolution and univariate analysis methods, we employed an assumption-free, time-resolved, whole-brain searchlight MVPA approach to identify brain regions which code approximate numerosity WM content. Our findings, in line with previous work, provide preliminary evidence for a higher level, modality- and format-independent abstract quantitative WM system which resides within the right lateral PFC.

Introduction

Humans can tell whether a hundred people are a larger group than fifty people quite precisely without counting. This ability to quantify amount, size, length or other analog stimulus properties can be performed non-symbolically, independent of language (Dehaene et al., 1992; Spitzer et al., 2014b). Indeed, human babies and several animals are able to approximate a variety of quantities (Nieder, 2005; Piazza et al., 2007, Piazza and Izard, 2009, Nieder and Dehaene, 2009), suggesting a common elemental mechanism, which has been termed the approximate number system (ANS; Gallistel and Gelman, 1992; Dehaene, 2011).

While numerosity is a discrete stimulus property, the ANS allows an approximation of numerosity, resulting in an analog estimation. Thus, in contrast to the symbolic mental representation of numbers as classes or categories, it has been hypothesized that the ANS representation resembles that of continuous quantities or magnitudes such as intensities, lengths, or frequencies (Piazza et al., 2004; Nieder and Dehaene, 2009; Spitzer et al., 2014a). In support of this, neural representations underlying both the ANS and continuous quantities have been shown to be supramodal, implying a representation abstract in nature (Piazza et al., 2006; Spitzer and Blankenburg, 2012; Spitzer et al., 2014; Vergara et al., 2016). Moreover, small numbers can be effortlessly identified without counting, known as subitizing (Kaufman et al., 1949). Thus, these numbers are represented as discrete values. If the number of items exceeds the subitizing threshold, counting is required to determine the

exact amount. When there is insufficient time for counting, the ANS approximates the quantity in a fast and efficient manner.

The functional anatomy of the ANS has been extensively characterized in both human and non-human primates (NHP). A frontoparietal network comprising the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC), specifically the intraparietal sulcus (IPS), is involved in approximating quantities during perception (Dehaene et al., 2003; Piazza et al., 2004; 2007; Cantlon et al., 2006; 2009; Jacob and Nieder, 2009; Knops and Wilmes, 2014). Moreover, the estimated numerosity network has been shown to be right lateralized (Piazza et al., 2006; Dehaene, 2016). The frontoparietal network comprised the right DLPFC, IPS and additionally the right premotor cortex (PMC) confirming right hemisphere dominance for numerosity estimation (Piazza et al., 2006). Particularly in estimated numerosity perception, the IPS has been shown, using both univariate and multivariate analyses of fMRI data, to exhibit stronger numerosity-selective responses than the PFC (Dehaene et al., 2003; Eger et al., 2009).

The ANS literature is primarily focused on perception with relatively few NHP studies extending to investigate working memory (WM) representations of approximate quantities (see Nieder, 2016). As short-term maintenance of information is critical for higher-order cognitive functions such as decision making and reasoning, it is crucial to investigate beyond perception to the maintenance of approximate quantities in WM. In line with results from perception studies of the ANS, neurons in the frontoparietal network were found, specifically in the PFC and IPS, to exhibit numerosity-selective activity

during WM (Jacob et al., 2018). Furthermore, supramodal coding of numerosity memoranda in the frontoparietal cortex has been identified (see Nieder, 2017). Interestingly, in contrast to perception, the proportion of numerosity selective neurons and their tuning strength to numerosity have been more prominent than the ones in the PPC during WM retention. Moreover, neurons in the PFC remained selective and discriminated numerosities better than neurons in the PPC during the WM delay (Nieder and Miller, 2004; Tudusciuc and Nieder, 2009; Nieder, 2016).

To the best of our knowledge, only a single study has focused on the WM representation of numerosity in humans, although some approximate numerosity perception studies used WM-related paradigms (e.g., Eger et al., 2009). Spitzer and colleagues (2014) probed the oscillations underlying multimodal WM representations by training participants to estimate numerosity from sequential auditory, visual and tactile stimuli. They identified strong and long-lasting alpha oscillations in the PPC reflecting WM load whereas, in line with NHP results, beta-band activity in the right PFC showed numerosity-selective modulation.

Nevertheless, whole-brain research regarding the localization of numerosity memoranda in humans is lacking. To this end, we designed a tactile delayed-match-to-numerosity (DMTN) task in combination with whole-brain, searchlight, multivariate-pattern analysis (MVPA) of human fMRI data (e.g., Christophel, 2012; Schmidt et al., 2017; Uluç et al., 2018). Using this analysis approach, we localized brain regions maintaining approximate number content in WM. As per previous studies (e.g., Spitzer et al., 2014a; Nieder, 2016), we

hypothesized that the content would be represented in frontal regions, specifically the right PFC.

Material and methods

Participants

38 healthy volunteers participated in the study. The data of four participants was excluded due to low performance levels ($\leq 60\%$) resulting in data from 34 participants (age: 25.53 ± 5.43 mean years \pm SD, 19 females) being further analyzed. All were right handed according to the Edinburgh Handedness Inventory with an index of 0.82 ± 0.14 (mean \pm SD; Oldfield, 1971). The experimental procedure was approved by the local ethics committee and is in accordance with the Human Subject Guidelines of the Declaration of Helsinki. All participants provided written informed consent before the experiment and were compensated for their participation.

Stimuli

Tactile stimuli consisted of trains of square-wave electric pulses ($200 \mu\text{s}$) delivered via a pair of surface-adhesive electrodes attached to the participant's left wrist. A constant current neurostimulator (DS7A, Digitimer Ltd.) was used to deliver the stimuli. Subjects reported tactile sensations radiating to the thumb, index, and middle finger, verifying stimulation of the median nerve. Individual sensory thresholds were determined for each participant. The stimulus intensity was then adjusted to a target value of approximately 200% of the sensory threshold (mean: 6.42 mA, SD: 1.20 mA).

A to-be-remembered stimulus sequence comprised either 7, 9, 11, or 13 pulses. In order to dissociate stimulus length and perceived pulse frequency (spacing of tactile pulses) from the numerosity of pulses, the duration of the stimulus varied, and the inter-pulse-intervals were randomized. To this end, we

defined four stimulus durations (960, 1020, 1080 and 1140 ms). Each duration was subdivided into 60 ms slots, resulting in 17, 18, 19 and 20 slots, respectively. The temporal distribution of the pulses was then randomized across the slots (see Figure 1A for illustrative stimuli). Within each run, each numerosity was presented in a short (17 or 18) and a long (19 or 20) duration resulting in 24 different numerosity-duration pairings (4 numerosities x 2 durations/run x 3 uncued numerosities). The different durations were balanced across runs. This stimulus design ensured that participants had to memorize the stimulus numerosity since they could not use the temporal density of the pulses or the stimulus length as WM memoranda to solve the task.

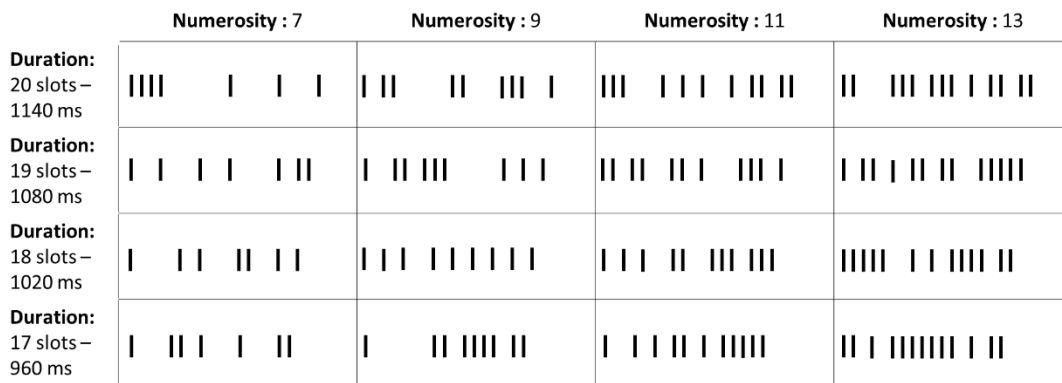
Task

We employed a DMTN paradigm in which participants remembered the estimated numerosity of a stimulus. Each trial began with the presentation of two pulse sequences with different numerosities. Next, a retro-cue (“1” or “2”) indicated which of the two numerosities had to be remembered. To ensure the dissociation between perceptual processes and the memory-related activity, a mask consisting of the longest duration (1140 ms) with a pulse in each of the 20 slots, was applied simultaneously with the onset of the retro-cue. Following a 12 s retention phase, two test stimuli were presented and a two-alternative forced-choice was given. Neither of the test stimuli were identical to the encoded stimulus, however, one had the same numerosity while the duration and the frequency were different. This ensured that participants used the approximated numerosity of the stimulus instead of some other stimulus feature to correctly match the test with the remembered stimulus. The

numerosity of the alternative stimulus was 3 pulses \pm the target stimulus. To ensure that the number of pulses in each stimulus was above the general subitizing threshold of 4 (Lechelt, 1975; Philippi et al., 2008; Schmidt et al., 2014), the lower alternative stimulus for the lowest to-be-remembered numerosity (7), was set to five. After the second target stimulus, participants had 1.5 s to indicate, via button-press with their right middle or index finger, which of the two stimuli had the same numerosity as the encoded stimulus (see Figure 1B for experimental design). Furthermore, the response mapping was counter-balanced across participants. In total, a trial lasted 21 s and an experimental run, consisting of all possible stimulus pairings presented equally often (12 pairings x 4 presentations = 48 trials) in a randomized order, with inter-trial intervals of 1.5 or 3.5 s, lasted 18.7 minutes. Four experimental runs were collected for each participant, resulting in a total recording time of 74.8 minutes.

Prior to the fMRI experiment, each participant was familiarized with the timing and structure of the task by performing up to two experimental runs outside the scanner.

A.



B.

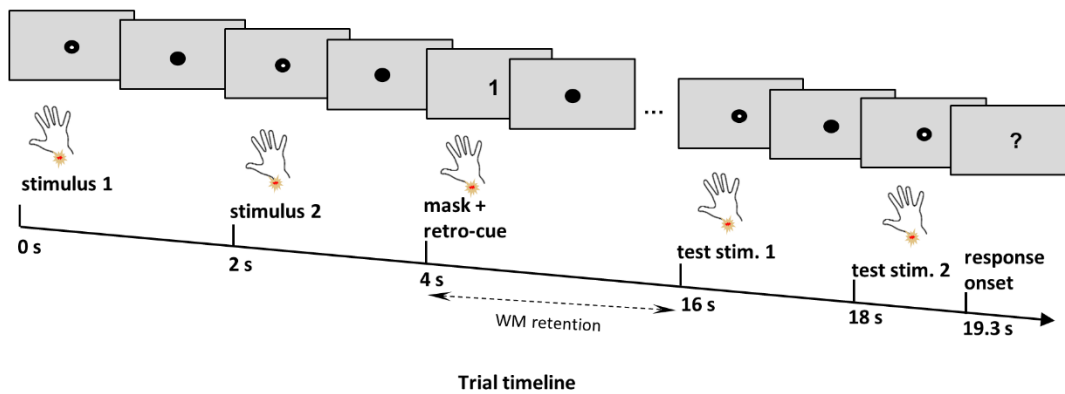


Figure 1. Sample pulse sequences and experimental paradigm **A.** Sample Stimuli. Pulse sequences of 7, 9, 11 and 13 were used as experimental stimuli. For each numerosity, there were four different durations (960, 1020, 1080 and 1140 ms), where each duration was subdivided into 60 ms slots. The distribution of pulses to slots was randomized for each stimulus presentation. The first and the last slot of each stimulus always contained a pulse. The stimuli displayed are for illustrative purposes. **B.** Experimental paradigm. A delayed-match-to-numerosity task was employed, where two sample stimuli and a mask were presented consecutively. A visual retro-cue presented simultaneously with the mask indicated which of the numerosities should be retained for the 12 s delay. After the delay, participants performed a two-alternative forced-choice, indicating which of the two test stimuli had the same numerosity as the cued stimulus. The response period was 1.5 s. Please note that the stimulus duration and inter-stimulus-interval changed depending on the stimulus duration, but the onset of each event was locked to coincide with the onset of an image acquisition.

Number naming test assessing countability

Subsequent to the fMRI session, we applied a number naming task to ensure that participants were unable to count the number of pulses employed in the stimulus set. Participants were asked to try to count the number of pulses. The stimuli ranged from 1 to 15 pulses with 5 different duration and

temporal pulse distribution combinations of each numerosity tested, resulting in 75 trials. The counting test was performed after fMRI data acquisition so as to prevent biasing the participants towards counting the pulses in the main experiment.

To ensure that the presented numerosities were above participants' subitizing thresholds, we calculated the mean performance for each numerosity across participants and calculated each average estimated numerosity. We then compared the slope of accuracy for estimating numerosities with earlier studies that calculated subitizing thresholds for tactile stimuli (Lechelt, 1975; Philippi et al., 2008; Spitzer et al., 2014a). We performed a linear trend analysis using linear regression to determine whether the distance between the true and estimated numerosity scales with increasing true numerosity in a linear fashion.

fMRI data acquisition and pre-processing

fMRI data were acquired in 4 runs, with a Siemens 3 T Tim Trio MRI scanner (Siemens, Erlangen) equipped with a 32-channel head coil. In each run, 565 images were collected (T2*-weighted gradient-echo EPI: 37 slices; ascending order; 20% gap; whole brain; TR = 2000 ms; TE = 30 ms; 3 x 3 x 3 mm³; flip angle = 70°; 64 x 64 matrix). After the last functional run, a high-resolution structural scan was recorded using a T1-weighted MPRAGE sequence (1 x 1 x 1 mm³; 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). Functional images were slice-time corrected and spatially

realigned to the mean image. In order to conserve the spatiotemporal structure of the fMRI data for the multivariate analyses, no smoothing or normalization was performed. For the univariate control analysis, functional images were normalized to MNI-space and smoothed with an 8 mm FWHM kernel.

First Level Finite Impulse Response Models

A time-resolved, multivariate searchlight analysis (Kriegeskorte et al., 2006, Schmidt et al., 2017) was used to identify brain regions encoding memorized numerosity information. First, a general linear model (GLM) with a set of finite-impulse-response (FIR) regressors was fit to each participant's data to obtain run-wise parameter estimates of each WM content (numerosity value of 7, 9, 11 or 13). A single FIR regressor was estimated for each fMRI image or 2 s time bin (1 TR), thus, the 20 s trial was divided into 10 time bins. We additionally included the first five principal components accounting for the most variance in the cerebrospinal fluid (CSF) and white matter signal time courses respectively (Behzadi et al., 2007), and six head motion regressors, as regressors of no interest. Hence, the GLM model comprised a total of 228 beta estimates: $(4 \text{ numerosities} \times 10 \text{ time bins} + 5 \text{ CSF regressors} + 5 \text{ white matter regressors} + 6 \text{ motion regressors}) \times 4 \text{ runs} + 4 \text{ constants}$. Moreover, the data was filtered with a high-pass filter of 128 s. The resulting parameter estimates were used for the MVPA performed with The Decoding Toolbox v. 3.52 (TDT) (Hebart et al., 2015).

Multivariate Pattern Analysis

For the decoding of memorized numerosity information, a searchlight-based multivariate analysis using a support vector regression (SVR) approach was performed with the computational routines of LIBSVM (Chang and Lin, 2011), as implemented in TDT. SVR MVPA (see Kahnt et al., 2011 for more discussion; Schmidt et al., 2017) considers the variable of interest (memorized numerosity) as a continuous data vector with multiple independent variables (multi-variate BOLD activities) as opposed to the commonly used support vector machine approach that treats the variable of interest as a categorical object. This means that the SVR MVPA approach seeks a linear continuum for the numerosities in which their distance is proportional to the distances of the rank order.

We analyzed each time bin independently by implementing a searchlight decoding analysis with a spherical searchlight radius of 4 voxels. For a given voxel, z-scaled parameter estimates (across samples) corresponding to each WM condition were extracted from all voxels within the spherical searchlight for each run. This yielded 16 pattern vectors (4 WM contents x 4 runs), each corresponding to the BOLD activity pattern for a specific WM condition of a functional run. We then fitted a linear function to these pattern vectors such that the multivariate distribution for the different numerosities follows a linear mapping of numerosities. The z-scaled parameter estimates were entered into an SVR model with a fixed regularization parameter c that was set to 1.

We used a leave-one-run-out cross-validation scheme for the subject-level decoding analysis. The SVR classifier was trained on three runs (12 pattern

vectors) and tested on the data of the independent fourth run (4 pattern vectors) for how well it predicted the values of the remaining run. The allocation of training and test runs was iterated so that each of the four functional runs was used as a test run once, resulting in four cross-validation folds. The prediction performance from each cross-validation fold was reported by a Fisher's z-transformed correlation coefficient between the predicted and the actual numerosity information estimate. The mean prediction accuracy across cross-validation folds was assigned to the center voxel of the searchlight, and the center of the searchlight was moved voxel by voxel through the brain, resulting in a whole-brain prediction accuracy map. Consequently, we obtained one prediction accuracy map for each time bin for each participant, where the prediction accuracy reflects how well a linear ordering according to the associated numerosities could be read out from the locally distributed BOLD activity pattern at a given voxel location and time.

Next, prediction accuracy maps were normalized to MNI space and smoothed with an 8 mm FWHM kernel. They were then entered into a second-level, repeated measures ANOVA analysis with subject and time (time bins) as factors. To assess which brain regions exhibit WM content-specific activation patterns during the delay period, we computed a t-contrast across the 6 time bins corresponding to the 12 s WM delay (time bins 3-8). The results are presented at $p < 0.05$ family-wise error correction (FWE) at the cluster level with a cluster-defining threshold of $p < 0.001$. Cytoarchitectonic references are based on the SPM anatomy toolbox where possible (Eickhoff et al., 2005). Presented images, e.g. surface projections with applied color scales were

created using MRIcron version9/9/2016 (McCausland Center for Brain Imaging).

Control analyses

In the first control analysis, we examined whether the decoded numerosity information during WM retention was specific to WM or could be assigned to perceptual residues. To this aim, we defined a second, first-level model with FIR regressors for the non-memorized stimulus. We then implemented the identical searchlight decoding procedure as the main analysis. Thus, this control analysis tested for the presence of numerosity information of the non-memorized stimulus.

Next, we conducted a parametric univariate analysis to ensure that the decoded information in the main analysis is not due to the modulation of mean activity level. To this end, we fitted a standard GLM with 4 HRF-convolved regressors: one regressor to capture WM processes, a parametrically-modulated regressor for the numerosity content of the WM memoranda as well as 8 (4 numerosities x 2 (sample, test)) additional parametrically-modulated regressors for each sample and test stimulus. First-level baseline contrasts for the parametric effect of memorized numerosity were forwarded to a second-level one-sample t-test.

Finally, to test the specificity of the SVR analysis to the parametric order of the four numerosities, we performed exhaustive whole-brain SVR searchlight analyses for all possible permutations of numerosity labels. In order to achieve this, we computed distance rank order as a sum of the absolute difference of adjacent ranks (e.g., 11, 13, 7, 9 numerosity, is distance 5 ($|3-4|+|4-1|+|1-2|$))

for all possible permutations of the numerosity-order. Then, the permutations were grouped according to their distance from the original rank order. We used 12 instead of 24 permutations as the distances of rank order permutations are symmetric. Including the permutation with the correct linear order, the 12 permutations are aggregated into five classes depending on their distance from the correct linear order. Then, for each permutation analysis, we extracted the prediction accuracies of the group-peak voxels that are defined in the original analysis. For statistical assessment, we calculated the mean prediction accuracy across related time bins (WM time bins 3-8) for each peak voxel for each distance group (Figure 3B).

Results

Behavioral performance

Participants (n=34) performed with $65.36 \pm 3.29\%$ (mean \pm SD) accuracy in the demanding DMTN task across the four experimental runs (see Figure 2A). To test whether the behavioral performance differed for the four numerosity values, we performed a one-way repeated measures ANOVA with four levels, one for each numerosity. This test revealed a significant main effect ($F(3,135)=7.52$, $p<0.001$). Post-hoc t-tests (Bonferroni-corrected for multiple comparisons) between performances were significant for numerosity values 7 and 13 and 9 and 13 ($p < 0.05/6$; see Figure 2A). This is expected because we did not control for the Weber-Fechner effect except for the lowest numerosity (which we did due to subitizing concerns). As a result, as the numerosity increases, it becomes more difficult to differentiate between the sample and

alternative stimuli, thus resulting in a lower performance for high numerosities (Fechner, 1966) but is unlikely to affect WM processing.

Behavioral performance on number naming test assessing countability

To test whether participants were able to count the numerosities employed in the current study, participants performed an additionally number naming test. Previous research in tactile numerosity indicated the subitizing threshold for comparable stimuli to be 4 pulses (Lechelt, 1975; Philippi et al., 2008; Spitzer et al., 2014a). The approximation of the subitizing threshold identified in the present study is in line with these reports (Figure 2B). As expected, participants' perceptual accuracy decreased with increasing numerosity and performance decreased to 50% when more than 3 pulses were presented. Similarly, the distance between the true and estimated numerosity increased with increasing numerosities ($p < 0.001$, linear trend analysis) (Figure 2C).

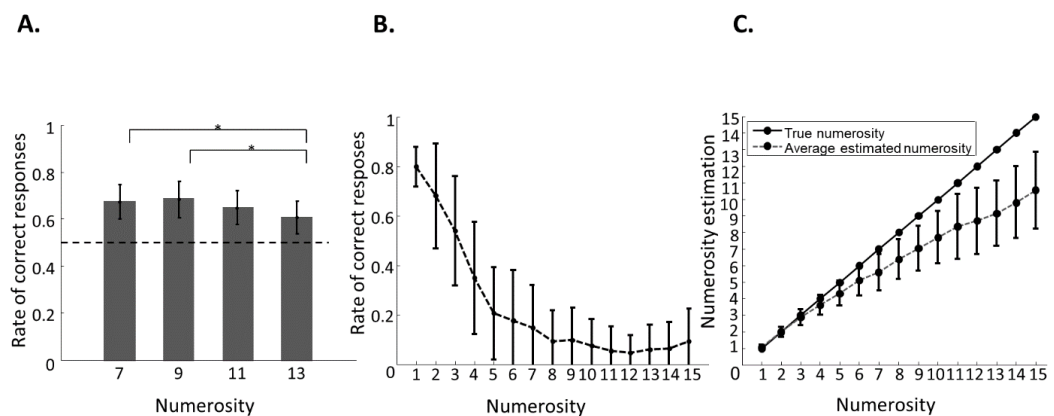


Figure 2. **A.** Mean rate of correct responses across participants ($n = 34$) for different numerosities in main WM DMTN task. The figure shows that the WM performance decreases with increasing numerosity. Error bars represent standard deviation (SD). Asterisks indicate statistical significance for pair-wise t-tests, Bonferroni corrected for multiple comparisons ($p < 0.05/6$). **B.** Mean performance across subjects for estimated numerosity in number naming task (mean \pm SD). **C.** True numerosities vs. mean numerosity estimations (error bars show SD).

Multivariate mapping of regions that code numerosity as WM content

The time-resolved, searchlight-based multivariate regression analysis was performed to identify brain regions representing estimated numerosity memoranda. The SVR MVPA analysis for the WM retention period revealed numerosity-specific responses in the left PMC, left middle frontal gyrus (MFG), left superior frontal gyrus (SFG) extending into bilateral supplementary motor areas (SMA), right SFG extending to the right frontal pole and right MFG extending into the pars triangularis of the right IFG. Results are reported at $p < 0.05$, FWE-corrected at the cluster level with a cluster-defining threshold of $p < 0.001$ (Figure 3 and Table 1).

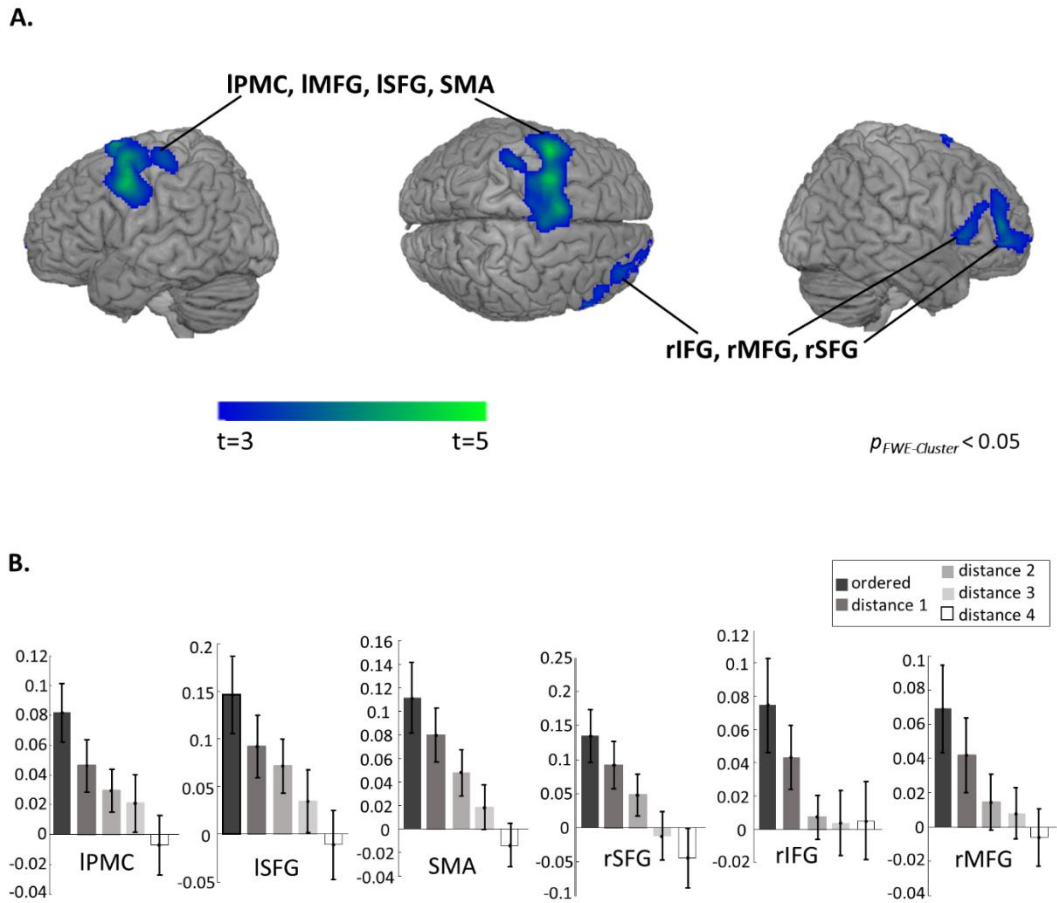


Figure 3. A. Brain regions coding information for the memorized estimated numerosities. Group level results of a t-contrast testing the 12 s WM delay for above chance prediction accuracy. Brain regions carrying information about memorized scalar magnitudes are: IFG = inferior frontal gyrus, MFG = middle frontal gyrus, PMC = premotor cortex, SMA = supplementary motor area, SFG = superior frontal gyrus. **B.** Results of the label-permutation tests. 5 bars are shown for each brain region, respectively. Each bar displays the mean prediction accuracy estimated from the distance to correct order groups. The shade of the bar color, ranging from black to white, depicts the different distance to correct ordering. Black bars indicate the mean prediction performance of the group with the correct linear order, while white bars represent the mean prediction accuracy derived from the most linearly unordered data. Brain regions tested for label permutation are: IFG = inferior frontal gyrus, MFG = middle frontal gyrus, PMC = premotor cortex, SMA = supplementary motor area, SFG = superior frontal gyrus. Error bars indicate standard error of the mean.

Table 1. SVR MVPA results for tactile numerosity WM task

Anatomical label and MNI coordinates of brain areas depicting memorized numerosity information during WM. All results are reported at $p_{FWE-Cluster} < 0.05$ with a cluster-defining

threshold of $p < 0.001$. Mean prediction accuracy over the delay period is reported. Areas were, where possible, identified using the SPM anatomy toolbox (Eickhoff et al., 2005). IFG = inferior frontal gyrus, MFG = middle frontal gyrus, PMC = premotor cortex, MI = primary motor cortex, SMA = supplementary motor area, SFG = superior frontal gyrus.

Cluster size	Anatomical region	Peak MNI coordinates			z-score	Prediction accuracy
		X	Y	Z		
4557	Left PMC/MI	-50	2	52	4.78	0.082
	Left SFG	-28	0	60	7.74	0.146
	SMA	-6	10	74	4.48	0.114
1342	Right SFG	32	50	10	4.17	0.135
	Right IFG (pars triangularis)	60	24	2	4.17	0.075
	Right MFG	40	50	30	3.69	0.069

Control analyses

To test, if the identified decoded information is indeed specific to the memorized numerosity representation, we applied the same searchlight procedure to the non-memorized numerosity stimulus. This analysis did not reveal any clusters with above-chance prediction accuracy at $p_{\text{FWE-Cluster}} < 0.05$.

Additionally, we conducted a univariate parametric analysis to test whether the decoding results could be due to differences in activation strength between WM contents. A second level t-test revealed no significant voxels at $p_{\text{FWE-Cluster}} < 0.05$, thus providing evidence for the multivariate nature of the numerosity representations identified in this study rather than the modulation of univariate mean activity.

Finally, we performed label-permutation tests in order to ensure the specificity of the linear ordering of stimuli in the SVR MVPA. Higher prediction accuracies were expected when the activation patterns in a given brain region represented the correct order of the four numerosity labels, and it was

expected to decrease with the distance from the correct ordering. As expected, the prediction accuracy during WM was the highest for the true-labelled data and decreased with increasing distance from the correct ordering (Figure 3B).

Discussion

The current study, to our knowledge, is the first to identify brain regions that code approximate numerosity WM content using human neuroimaging methods. Thus, this study extends the extensive literature on ANS perception to the maintenance of mental representations which can be used for higher-order cognitive functions. We employed a well-established, whole-brain, searchlight, DMTN paradigm to identify representations of tactile approximate numerosity memoranda. Specifically, we employed an SVR technique, which in contrast to support vector machines, treats the retained WM content as a continuous variable and thus predicts the ordering of content along the variable, rather than a singularly specific class label. Consequently, an above-chance prediction accuracy in a brain region means that the content-specific activation patterns follow a linear ordering according to the associated numerosity. Our searchlight analysis identified a distributed network spanning the left PMC, bilateral SFG, bilateral SMA and right MFG extending into right IFG. Therefore, these regions contain linearly-ordered, multivariate WM representations of the numerosities.

Our results are in line with previous numerosity WM studies in NHPs and human EEG which have established the central role of the PFC. Indeed, previous uni- and multimodal studies have identified content-specific representations in the PFC (Nieder and Miller, 2004; Tudusciuc and Nieder, 2009; Nieder, 2016; Spitzer et al., 2014a; Jacob et al., 2018). More specifically, in humans, parametric modulation of upper-beta oscillations in the right lateral PFC has been shown to reflect analog numerosity estimation which has been derived

from discrete sequences, both within and between stimulus modalities (Spitzer et al., 2014a). Thus, the numerosity representations in the PFC are likely to be supramodal in nature. However, those studies used either electrophysiological recordings from an a priori brain region or EEG and have employed univariate data analysis methods. The present study extends the literature on numerosity WM in two ways: firstly, to whole-brain fMRI data, and secondly to multivariate data analysis methods, specifically the SVR MVPA. The benefits of multivariate over univariate analysis methods have been well-established (e.g., Haynes, 2015). Multivariate analysis techniques are sensitive to the combinatorial aspects of voxel activity, thereby enabling the identification of spatially distributed representations (e.g., Haynes, 2015; Hebart and Baker, 2018). Thus, our results agree with and extend the previous NHP and human EEG numerosity WM findings to whole-brain, spatially distributed activity patterns, suggesting that estimated numerosity WM content is maintained in the LPFC (Nieder et al., 2002; Nieder and Miller, 2003; 2004; Tudusciuc and Nieder, 2009; Nieder, 2016; Spitzer et al., 2014a).

It should be noted that we used temporally distributed tactile numerosity stimuli as the WM memoranda, namely the numerosity was presented as a sequence of pulses. Evidence exists for potential differences in perceptual processing of spatially- and temporally-distributed numerosities, where spatially-distributed stimuli appear to be processed in parietal regions while temporarily-distributed stimuli do not (Cavdaroglu and Knops, 2018). In line with the finding of Cavdaroglu and Knops (2018), we used temporally distributed stimuli and did not find any evidence of WM representations in

posterior regions. On the other hand, our results also agree with numerosity WM findings in NHPs that suggest frontal rather than parietal coding for spatial numerosity stimuli during WM retention (for review, see Nieder, 2016). A future direct comparison of our results with spatial numerosity stimuli is necessary to test for differences determined by the stimulus types.

Moreover, while the literature relating to numerosity WM is limited, there is extensive work exploring the WM representation of abstract quantities more generally. Specifically, the frequency discrimination task has been systematically explored in a multitude of modalities with a wide range of methods (e.g., Romo et al., 1999; Spitzer et al., 2010; Lemus et al., 2009; Spitzer & Blankenburg, 2011; 2012; Fassihi et al., 2014; Vergara et al., 2016; von Lutz et al., 2017; Schmidt et al., 2017; Wu et al., 2018; Uluç et al., 2018). Numerosity and frequency share several traits, particularly they are both abstract magnitudes which may be represented in a supramodal fashion (Spitzer and Blankenburg, 2012; Vergara et al., 2016; Nieder, 2016; Miller, 2003). However, whether their underlying WM representations are maintained by a shared network has yet to be explored. The present study provides an initial step towards resolving this question by providing the first evidence that frequency and numerosity WM representations are maintained in overlapping brain regions. We identified numerosity-specific WM content in the right IFG, SMA and left PMC which is in agreement with results from frequency studies also using an fMRI-MVPA approach in humans (Schmidt et al., 2017; Wu et al., 2018; Uluç et al., 2018). Uni- and multimodal research in both NHPs and humans has identified frequency-specific content in the right LPFC and SMA thereby

suggesting the WM representations are modality independent in nature (e.g., Romo et al., 1999; Hernandez et al., 2002; 2010; Barak et al., 2010; Spitzer et al., 2010; Spitzer & Blankenburg, 2011; 2012; Vergara et al., 2016; Schmidt et al., 2017; Wu et al., 2018). However, the explicit relationship between frequency and numerosity still needs to be explored, particularly with respect to the underlying neural codes of numerosity and frequency representations (see Nieder, 2017).

Additionally, we identified numerosity-specific content in the left PMC. Previous findings from frequency WM fMRI-MVPA studies identified abstract quantity information in the PMC (Schmidt et al., 2017; Wu et al., 2018; Uluç et al., 2018). Moreover, the dorsal PMC has been shown to represent abstract numerical rules, such as comparison and calculation (Gruber et al., 2001; Eger et al., 2003; Nieder, 2005). This is in line with the present task which required the comparison of numerical quantities, suggesting representation of task-relevant, numerosity-specific information to be used in numerical comparison.

In summary, the data at hand is in line with the suggestion of a domain general, abstract magnitude processing system. This abstract processing system can be identified by multivariate WM representations of tactile numerosity stimuli within the right PFC. Taken together with previous findings which found WM representations of tactile frequency (Spitzer et al., 2010; Spitzer and Blankenburg, 2012; Spitzer et al., 2014a; Schmidt et al., 2017; Wu et al., 2018), visual flicker frequency (Spitzer and Blankenburg, 2012; Spitzer et al., 2014a; Wu et al., 2018), and auditory frequency (Spitzer and Blankenburg 2012, Uluç et al., 2018), and the reports of number coding (Nieder et al., 2002;

Nieder and Miller, 2003; 2004; Tudusciuc and Nieder, 2009; Nieder, 2016) in the PFC, the present study provides additional evidence suggesting that the PFC is capable of representing both analog quantities as well as parametric stimulus properties as frequencies. Thus, we provide preliminary evidence for a higher level, modality- and format-independent abstract quantitative WM system which resides within the PFC.

References

- Barak, O., Tsodyks, M., & Romo, R. (2010). Neuronal population coding of parametric working memory. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*(28), 9424–30.
<http://doi.org/10.1523/JNEUROSCI.1875-10.2010>
- Behzadi, Y., Restom, K., Liu, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101.
<http://doi.org/10.1016/j.neuroimage.2007.04.042>
- Cantlon, J. F., Brannon, E. M., Carter, E. J., & Pelphrey, K. A. (2006). Functional Imaging of Numerical Processing in Adults and 4-y-Old Children. *PLoS Biology*, *4*(5), e125. <https://doi.org/10.1371/journal.pbio.0040125>
- Cantlon, J. F., Platt, M. L., & Brannon, E. M. (2009). Beyond the number domain. *Trends in Cognitive Sciences*, *13*(2), 83–91. <https://doi.org/10.1016/j.tics.2008.11.007>
- Cavdaroglu, S., & Knops, A. (2018). Evidence for a Posterior Parietal Cortex Contribution to Spatial but not Temporal Numerosity Perception. *Cerebral Cortex*. <https://doi.org/10.1093/cercor/bhy163>
- Chang, C.-C., & Lin, C.-J. (2011). LIBSVM. *ACM Transactions on Intelligent Systems and Technology*, *2*(3), 1–27.
<http://doi.org/10.1145/1961189.1961199>
- Christophel, T. B., Hebart, M. N., & Haynes, J.-D. (2012). Decoding the contents of visual short-term memory from human visual and parietal cortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *32*(38), 12983–9.
<http://doi.org/10.1523/JNEUROSCI.0184-12.2012>
- Christophel, T. B., T. D., Klink, P. C., Spitzer, B., & Roelfsema, P. R. (2017). The Distributed Nature of Working Memory. *Trends in Cognitive Sciences*, *21*(2), 1–14. <http://doi.org/10.1016/j.tics.2016.12.007>
- D'Esposito, M., & Postle, B. R. (2015). The Cognitive Neuroscience of Working Memory. *Annual Review of Psychology*, *66*, 115–42.
<http://doi.org/10.1146/annurev-psych-010814-015031>
- Dehaene, S. (1992). Varieties of numerical abilities. *Cognition*, *44*(1–2), 1–42.
[https://doi.org/10.1016/0010-0277\(92\)90049-N](https://doi.org/10.1016/0010-0277(92)90049-N)
- Dehaene, S. (1997). *The number sense : how the mind creates mathematics*. Oxford University Press.

- Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three Parietal Circuits for Number Processing. *Cognitive Neuropsychology*, 20(3-6), 487–506. <https://doi.org/10.1080/02643290244000239>
- Dehaene, S., Molko, N., Cohen, L., & Wilson, A. J. (2004). Arithmetic and the brain. *Current Opinion in Neurobiology*, 14(2), 218–224. <https://doi.org/10.1016/J.CONB.2004.03.008>
- Diester, I., & Nieder, A. (2007). Semantic Associations between Signs and Numerical Categories in the Prefrontal Cortex. *PLoS Biology*, 5(11), e294. <https://doi.org/10.1371/journal.pbio.0050294>
- Dormal, V., Dormal, G., Joassin, F., & Pesenti, M. (2012). A common right fronto-parietal network for numerosity and duration processing: An fMRI study. *Human Brain Mapping*, 33(6), 1490–1501. <https://doi.org/10.1002/hbm.21300>
- Eger, E., Sterzer, P., Russ, M. O., Giraud, A.-L., & Kleinschmidt, A. (2003). A Supramodal Number Representation in Human Intraparietal Cortex. *Neuron*, 37(4), 719–726. [https://doi.org/10.1016/S0896-6273\(03\)00036-9](https://doi.org/10.1016/S0896-6273(03)00036-9)
- Eger, E., Michel, V., Thirion, B., Amadon, A., Dehaene, S., & Kleinschmidt, A. (2009). Deciphering Cortical Number Coding from Human Brain Activity Patterns. *Current Biology*, 19(19), 1608–1615. <https://doi.org/10.1016/J.CUB.2009.08.047>
- Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage*, 25(4), 1325–35. <http://doi.org/10.1016/j.neuroimage.2004.12.034>
- Fassihi, A., Akrami, A., Esmaeili, V., & Diamond, M. E. (2014). Tactile perception and working memory in rats and humans. *Proceedings of the National Academy of Sciences of the United States of America*, 111(6), 2331–6. <https://doi.org/10.1073/pnas.1315171111>
- Fechner, G. (1966). *Elements of Psychophysics*. New York: Holt Rinehart & Winston.
- Gallistel, C. R., & Gelman, R. (1992). Preverbal and verbal counting and computation. *Cognition*, 44(1–2), 43–74. [https://doi.org/10.1016/0010-0277\(92\)90050-R](https://doi.org/10.1016/0010-0277(92)90050-R)
- Gruber, O., Indefrey, P., Steinmetz, H., & Kleinschmidt, A. (2001). Dissociating Neural Correlates of Cognitive Components in Mental Calculation. *Cerebral Cortex*, 11(4), 350–359. <https://doi.org/10.1093/cercor/11.4.350>

- Haynes, J.-D. (2015). A Primer on Pattern-Based Approaches to fMRI: Principles, Pitfalls, and Perspectives. *Neuron*, 87(2), 257–270. <https://doi.org/10.1016/J.NEURON.2015.05.025>
- Hebart, M. N., Görden, K., & Haynes, J.-D. (2015). The Decoding Toolbox (TDT): a versatile software package for multivariate analyses of functional imaging data. *Frontiers in Neuroinformatics*, 8. <http://doi.org/10.3389/fninf.2014.00088>
- Hebart, M. N., & Baker, C. I. (2018). Deconstructing multivariate decoding for the study of brain function. *NeuroImage*, 180(Pt A), 4–18. <https://doi.org/10.1016/j.neuroimage.2017.08.005>
- Hernández, A., Zainos, A., & Romo, R. (2002). Temporal Evolution of a Decision-Making Process in Medial Premotor Cortex. *Neuron*, 33, 959–972. [https://doi.org/10.1016/S0896-6273\(02\)00613-X](https://doi.org/10.1016/S0896-6273(02)00613-X)
- Hernández, A., Nácher, V., Luna, R., Zainos, A., Lemus, L., Alvarez, M., ... Romo, R. (2010). Decoding a perceptual decision process across cortex. *Neuron*, 66(2), 300–314. <http://doi.org/10.1016/j.neuron.2010.03.031>
- Hyde, D. C., Boas, D. A., Blair, C., & Carey, S. (2010). Near-infrared spectroscopy shows right parietal specialization for number in pre-verbal infants. *NeuroImage*, 53(2), 647–652. <https://doi.org/10.1016/J.NEUROIMAGE.2010.06.030>
- Jacob, S. N., & Nieder, A. (2009). Tuning to non-symbolic proportions in the human frontoparietal cortex. *European Journal of Neuroscience*, 30(7), 1432–1442. <https://doi.org/10.1111/j.1460-9568.2009.06932.x>
- Jacob, S. N., Hahnke, D., & Nieder, A. (2018). Structuring of Abstract Working Memory Content by Fronto-parietal Synchrony in Primate Cortex. *Neuron*, 99(3), 588–597.e5. <https://doi.org/10.1016/j.neuron.2018.07.025>
- Kahnt, T., Heinzle, J., Park, S. Q., & Haynes, J.-D. (2011). Decoding different roles for vmPFC and dlPFC in multi-attribute decision making. *NeuroImage*, 56(2), 709–715. <https://doi.org/10.1016/j.neuroimage.2010.05.058>
- Kaufman, E. L., Lord, M. W., Reese, T. W., & Volkman, J. (1949). The Discrimination of Visual Number. *The American Journal of Psychology*, 62(4), 498. <https://doi.org/10.2307/1418556>
- Knops, A., & Willmes, K. (2014). Numerical ordering and symbolic arithmetic share frontal and parietal circuits in the right hemisphere. *NeuroImage*, 84, 786–795. <https://doi.org/10.1016/J.NEUROIMAGE.2013.09.037>

- Knops, A. (2017). Probing the Neural Correlates of Number Processing. *The Neuroscientist*, 23(3), 264–274. <https://doi.org/10.1177/1073858416650153>
- Kriegeskorte, N., Goebel, R., & Bandettini, P. (2006). Information-based functional brain mapping. *Proceedings of the National Academy of Sciences of the United States of America*, 103(10), 3863–8. <http://doi.org/10.1073/pnas.0600244103>
- Lee, S.-H., & Baker, C. I. (2016). Multi-Voxel Decoding and the Topography of Maintained Information during Visual Working Memory. *Frontiers in Systems Neuroscience*, 10(February), 2. <http://doi.org/10.3389/fnsys.2016.00002>
- Lechelt, E. C. (1975). Temporal numerosity discrimination: intermodal comparisons revisited. *British Journal of Psychology*, 66(1), 101–8. <https://doi.org/10.1111/j.2044-8295.1975.tb01444.x>
- Lemus, L., Hernández, A., & Romo, R. (2009). Neural encoding of auditory discrimination in ventral premotor cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 106(34), 14640–5. <https://doi.org/10.1073/pnas.0907505106>
- Mock, J., Huber, S., Bloechle, J., Dietrich, J. F., Bahnmüller, J., Rennig, J., Klein, E., Moeller, K. (2018). Magnitude processing of symbolic and non-symbolic proportions: an fMRI study. *Behavioral and Brain Functions*, 14(1), 9. <https://doi.org/10.1186/s12993-018-0141-z>
- Nieder, A., Freedman, D. J., & Miller, E. K. (2002). Representation of the Quantity of Visual Items in the Primate Prefrontal Cortex. *Science*, 297(5587), 1708–1711. <https://doi.org/10.1126/science.1072493>
- Nieder, A., & Miller, E. K. (2003). Coding of Cognitive Magnitude: Compressed Scaling of Numerical Information in the Primate Prefrontal Cortex. *Neuron*, 37(1), 149–157. [https://doi.org/10.1016/S0896-6273\(02\)01144-3](https://doi.org/10.1016/S0896-6273(02)01144-3)
- Nieder, A., & Miller, E. K. (2004). A parieto-frontal network for visual numerical information in the monkey. *Proceedings of the National Academy of Sciences*, 101(19), 7457–7462. <https://doi.org/10.1073/pnas.0402239101>
- Nieder, A. (2005). Counting on neurons: the neurobiology of numerical competence. *Nature Reviews Neuroscience*, 6(3), 177–190. <https://doi.org/10.1038/nrn1626>

- Nieder, A., Diester, I., & Tudusciuc, O. (2006). Temporal and Spatial Enumeration Processes in the Primate Parietal Cortex. *Science*, 313(5792), 1431–1435. <https://doi.org/10.1126/science.1130308>
- Nieder, A., & Dehaene, S. (2009). Representation of Number in the Brain. *Annual Review of Neuroscience*, 32(1), 185–208. <https://doi.org/10.1146/annurev.neuro.051508.135550>
- Nieder, A. (2012). Supramodal numerosity selectivity of neurons in primate prefrontal and posterior parietal cortices. *Proceedings of the National Academy of Sciences of the United States of America*, 109(29), 11860–5. <http://doi.org/10.1073/pnas.1204580109>
- Nieder, A. (2016). The neuronal code for number. *Nature Reviews Neuroscience*, 17(6), 366–82. <http://doi.org/10.1038/nrn.2016.40>
- Nieder, A. (2017). Magnitude Codes for Cross-Modal Working Memory in the Primate Frontal Association Cortex, *Frontiers in Neuroscience*, 11, 1–7. <http://doi.org/10.3389/fnins.2017.00202>
- Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, 9(1), 97–113. [http://doi.org/10.1016/0028-3932\(71\)90067-4](http://doi.org/10.1016/0028-3932(71)90067-4)
- Philippi, T. G., van Erp, J. B. F., & Werkhoven, P. J. (2008). Multisensory temporal numerosity judgment. *Brain Research*, 1242, 116–125. <https://doi.org/10.1016/j.brainres.2008.05.056>
- Piazza, M., Izard, V., Pinel, P., Le Bihan, D., & Dehaene, S. (2004). Tuning Curves for Approximate Numerosity in the Human Intraparietal Sulcus. *Neuron*, 44(3), 547–555. <https://doi.org/10.1016/j.neuron.2004.10.014>
- Piazza, M., Mechelli, A., Price, C. J., & Butterworth, B. (2006). Exact and approximate judgements of visual and auditory numerosity: An fMRI study. *Brain Research*, 1106(1), 177–188. <https://doi.org/10.1016/j.brainres.2006.05.104>
- Piazza, M., Pinel, P., Le Bihan, D., & Dehaene, S. (2007). A Magnitude Code Common to Numerosities and Number Symbols in Human Intraparietal Cortex. *Neuron*, 53(2), 293–305. <https://doi.org/10.1016/J.NEURON.2006.11.022>
- Piazza, M., & Izard, V. (2009). How Humans Count: Numerosity and the Parietal Cortex. *The Neuroscientist*, 15(3), 261–273. <https://doi.org/10.1177/1073858409333073>

- Piazza, M. (2010). Neurocognitive start-up tools for symbolic number representations. *Trends in Cognitive Sciences*, 14(12), 542–551. <https://doi.org/10.1016/j.tics.2010.09.008>
- Roitman, J. D., Brannon, E. M., & Platt, M. L. (2007). Monotonic Coding of Numerosity in Macaque Lateral Intraparietal Area. *PLoS Biology*, 5(8), e208. <https://doi.org/10.1371/journal.pbio.0050208>
- Romo, R., Brody, C. D., Hernández, A., & Lemus, L. (1999). Neuronal correlates of parametric working memory in the prefrontal cortex. *Nature*, 399(6735), 470–473. <https://doi.org/10.1038/20939>
- Romo, R., & de Lafuente, V. (2013). Conversion of sensory signals into perceptual decisions. *Progress in Neurobiology*, 103, 41–75. <http://doi.org/10.1016/j.pneurobio.2012.03.007>
- 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. <http://doi.org/10.1523/JNEUROSCI.1167-17.2017>
- Spitzer, B., Wacker, E., & Blankenburg, F. (2010). Oscillatory correlates of vibrotactile frequency processing in human working memory. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 30(12), 4496–502. <http://doi.org/10.1523/JNEUROSCI.6041-09.2010>
- Spitzer, B., & Blankenburg, F. (2011). Stimulus-dependent EEG activity reflects internal updating of tactile working memory in humans. *Proceedings of the National Academy of Sciences of the United States of America*, 108(20), 8444–9. <http://doi.org/10.1073/pnas.1104189108>
- Spitzer, B., & Blankenburg, F. (2012). Supramodal parametric working memory processing in humans. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 32(10), 3287–95. <http://doi.org/10.1523/JNEUROSCI.5280-11.2012>
- Spitzer, B., Fleck, S., & Blankenburg, F. (2014a). Parametric alpha- and beta-band signatures of supramodal numerosity information in human working memory. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 34(12), 4293–302. <https://doi.org/10.1523/JNEUROSCI.4580-13.2014>
- Spitzer, B., Gloel, M., Schmidt, T. T., & Blankenburg, F. (2014b). Working memory coding of analog stimulus properties in the human prefrontal cortex. *Cerebral Cortex*, 24(8), 2229–36. <https://doi.org/10.1093/cercor/bht084>

- Tudusciuc, O., & Nieder, A. (2009). Contributions of Primate Prefrontal and Posterior Parietal Cortices to Length and Numerosity Representation. *Journal of Neurophysiology*, *101*(6), 2984–2994. <https://doi.org/10.1152/jn.90713.2008>
- Uluç, I., Schmidt, T. T., Wu, Y.-H., & Blankenburg, F. (2018). Content-specific codes of parametric auditory working memory in humans. *NeuroImage*, *183*. <https://doi.org/10.1016/j.neuroimage.2018.08.024>
- Vergara, J., Rivera, N., Rossi-Pool, R., & Romo, R. (2015). A Neural Parametric Code for Storing Information of More than One Sensory Modality in Working Memory. *Neuron*, *89*(1), 54–62. <http://doi.org/10.1016/j.neuron.2015.11.026>
- von Lautz, A. H., Herding, J., Ludwig, S., Nierhaus, T., Maess, B., Villringer, A., & Blankenburg, F. (2017). Gamma and Beta Oscillations in Human MEG Encode the Contents of Vibrotactile Working Memory. *Frontiers in Human Neuroscience*, *11*, 576. <https://doi.org/10.3389/fnhum.2017.00576>
- Walsh V. (2003). A theory of magnitude: Common cortical metrics of time, space and quantity. *Trends in Cognitive Sciences*, *7*, 483–488. <https://doi.org/10.1016/j.tics.2003.09.002>
- Wiener, M., Turkeltaub, P., & Coslett, H. B. (2010). The image of time: A voxel-wise meta-analysis. *NeuroImage*, *49*(2), 1728–1740. <https://doi.org/10.1016/J.NEUROIMAGE.2009.09.064>
- Wu, Y., Uluç, I., Schmidt, T. T., Tertel, K., Kirilina, E., & Blankenburg, F. (2018). Overlapping frontoparietal networks for tactile and visual parametric working memory representations. *NeuroImage*, *166*, 325–334. <https://doi.org/10.1016/J.NEUROIMAGE.2017.10.059>

Legends

Figure 1. Sample pulse sequences and experimental paradigm **A.** Sample Stimuli. Pulse sequences of 7, 9, 11 and 13 were used as experimental stimuli. For each numerosity, there were four different durations (960, 1020, 1080 and 1140 ms), where each duration was sub-divided into 60 ms slots. The distribution of pulses to slots was randomized for each stimulus presentation. The first and the last slot of each stimulus always contained a pulse. The stimuli displayed are for illustrative purposes. **B.** Experimental paradigm. A delayed-match-to-numerosity task was employed, where two sample stimuli and a mask were presented consecutively. A visual retro-cue presented simultaneously with the mask indicated which of the numerosities should be retained for the 12 s delay. After the delay, participants performed a two-alternative forced-choice, indicating which of the two test stimuli had the same numerosity as the cued stimulus. The response period was 1.5 s. Please note that the stimulus duration and inter-stimulus-interval changed depending on the stimulus duration, but the onset of each event was locked to coincide with the onset of an image acquisition.

Figure 2. **A.** Mean rate of correct responses across participants ($n = 34$) for different numerosities in main WM DMTN task. The figure shows that the WM performance decreases with increasing numerosity. Error bars represent standard deviation (SD). Asterisks indicate statistical significance for pair-wise t-tests, Bonferroni corrected for multiple comparisons ($p < 0.05/6$). **B.** Mean performance across subjects for estimated numerosity in number naming task (mean \pm SD). **C.** True numerosities vs. mean numerosity estimations (error bars show SD).

Figure 3. **A.** Brain regions coding information for the memorized estimated numerosities. Group level results of a t-contrast testing the 12 s WM delay for above chance prediction accuracy. Brain regions carrying information about memorized scalar magnitudes are: IFG = inferior frontal gyrus, MFG = middle frontal gyrus, PMC = premotor cortex, SMA = supplementary motor area, SFG = superior frontal gyrus. **B.** Results of the label-permutation tests. 5 bars are shown for each brain region, respectively. Each bar displays the mean prediction accuracy estimated from the distance to correct order groups. The shade of the bar color, ranging from black to white, depicts the different distance to correct ordering. Black bars indicate the mean prediction performance of the group with the correct linear order, while white bars represent the mean prediction accuracy derived from the most linearly

unordered data. Brain regions tested for label permutation are: IFG = inferior frontal gyrus, MFG = middle frontal gyrus, PMC = premotor cortex, SMA = supplementary motor area, SFG = superior frontal gyrus. Error bars indicate standard error of the mean.

Table 1

Anatomical label and MNI coordinates of brain areas depicting memorized numerosity information during WM. All results are reported at $p_{FWE-Cluster} < 0.05$ with a cluster-defining threshold of $p < 0.001$. Mean prediction accuracy over the delay period is reported. Areas were, where possible, identified using the SPM anatomy toolbox (Eickhoff et al., 2005). IFG = inferior frontal gyrus, MFG = middle frontal gyrus, PMC = premotor cortex, MI = primary motor cortex, SMA = supplementary motor area, SFG = superior frontal gyrus.

Anlage A – Lebenslauf

2014 - 2019	PhD Student Graduate School: Berlin School of Mind and Brain, Berlin Neurocomputation and Neuroimaging Unit (NNU), Freie Universität Berlin
2012 - 2014	Master Student Middle European Interdisciplinary Master's Programme in Cognitive Science Universität Wien, Vienna, Austria
2004 - 2007	Master Student Institute of Social Sciences Department of Philosophy, Bogazici University, Istanbul, Turkey
1999 - 2004	Bachelor Student Department of Philosophy, Bogazici University, Istanbul, Turkey

Anlage B – Publikationen

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

3. **Uluç I**, Velenosi LA, Schmidt TT, Blankenburg F (under review) Parametric representation of tactile numerosity in working memory. eNeuro.

Peer-reviewed Journal Articles – Published

2. **Uluç I**, Schmidt TT, Wu Y-H., Blankenburg F (2018) *Content-specific codes of parametric auditory working memory in humans*. NeuroImage, 183:254-262.
1. Wu Y-H*, **Uluç I***, Schmidt TT, Tertel K, Kirilina E, Blankenburg F (2018): *Overlapping frontoparietal networks for tactile and visual parametric working memory representations*. NeuroImage, 166:325-334.

* shared authorship

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: Uluç, Işıl
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. **Uluç I.**, Schmidt T.T., Wu Y.-H., Blankenburg F. (2018): *Content-specific codes of parametric auditory working memory in humans*. NeuroImage 183:254-262.
 2. Wu, Y.-H.* , **Uluç I.***, Schmidt T.T., Tertel K., Kirilina E., Blankenburg F. (2018): *Overlapping frontoparietal networks for tactile and visual parametric working memory representations*. NeuroImage 166:325-334.
 3. **Uluç I**, Velenosi L.A., Schmidt T.T., Blankenburg F. (under review) *Parametric representation of tactile numerosity in working memory*. eNeuro.

*shared authorship

III. Darlegung des eigenen Anteils der Schriften:

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

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

Zu II.2.: Konzeption (in Teilen), Versuchsdesign (in Teilen), Programmierung (in Teilen), Datenerhebung (mehrheitlich), Datenauswertung (in Teilen), Ergebnisdiskussion (in Teilen), Erstellen des Manuskriptes (in Teilen).

Zu II.3.: Konzeption (großteils), Versuchsdesign (mehrheitlich), Programmierung (mehrheitlich), Datenerhebung (mehrheitlich), Datenauswertung (großteils), Ergebnisdiskussion (großteils), Erstellen des Manuskriptes (mehrheitlich).

IV. Die Namen und Anschriften nebst E-Mail oder Fax der jeweiligen Mitautorinnen oder Mitautoren:

- zu II.1.: Yuan-hao Wu, Arbeitsbereich Neurocomputation and Neuroimaging,
Fachbereich für Erziehungswissenschaft und Psychologie, Freie Universität
Berlin, Habelschwerdter Allee 45, 14195 Berlin.
E-Mail: yuan-hao.wu@fu-berlin.de
- Timo Torsten Schmidt, Arbeitsbereich Neurocomputation and Neuroimaging,
Fachbereich für Erziehungswissenschaft und Psychologie, Freie Universität
Berlin, Habelschwerdter Allee 45, 14195 Berlin.
E-Mail: titoschmi@zedat.fu-berlin.de
- Katrin Tertel, Arbeitsbereich Neurocomputation and Neuroimaging,
Fachbereich für Erziehungswissenschaft und Psychologie, Freie Universität
Berlin, Habelschwerdter Allee 45, 14195 Berlin.
E-Mail: kathrintertel@posteo.de
- Evgeniya Kirilina, Arbeitsbereich Neurocomputation and Neuroimaging,
Fachbereich für Erziehungswissenschaft und Psychologie, Freie Universität
Berlin, Habelschwerdter Allee 45, 14195 Berlin.
E-Mail: kirilina@zedat.fu-berlin.de
- Felix Blankenburg, Arbeitsbereich Neurocomputation and Neuroimaging,
Fachbereich für Erziehungswissenschaft und Psychologie, Freie Universität
Berlin, Habelschwerdter Allee 45, 14195 Berlin.
E-Mail: felix.blankenburg@fu-berlin.de
- zu II.2.: Yuan-hao Wu, s.o.
Timo Torsten Schmidt, s.o.
Felix Blankenburg, s.o.
- zu II.3.: Lisa Alexandria Velenosi, Arbeitsbereich Neurocomputation and
Neuroimaging, Fachbereich für Erziehungswissenschaft und Psychologie, Freie
Universität Berlin, Habelschwerdter Allee 45, 14195 Berlin.
E-Mail: lisa.velenosi@fu-berlin.de
- Yuan-hao Wu, s.o.
Timo Torsten Schmidt, s.o.
Felix Blankenburg, s.o.