Cognitive Representations in the Sensory and Memory Systems of the Human Brain: Evidence from Brain Damage and MEG

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Contents

Abstract

Cognitive representations are constructed internally of events and objects in the outside world. The exact nature of these representations, however, is not fully understood. Studies of cognitive deficits, electromagnetic recordings of brain activity and functional neuroimaging provide complementary means for investigating these representations and their neural basis at multiple levels of analysis. This thesis combined experimental data collected using multiple methods to study cognitive representations and their neural basis in visual information processing and memory. The aim of the thesis was both to collect new empirical evidence to inform current theories of vision and memory, and to use these studies to discuss methodological issues in cognitive neuroscience.

The thesis consists of four empirical studies. Studies I-II investigated how spatial information about the orientation of objects is represented in the visual system. Study I was conducted with an individual with a cognitive impairment in visual processing, patient BC. Experimental results from BC showed that spatial orientation is represented compositionally in the visual system, such that the *direction* of a line orientation's tilt from a vertical mental reference meridian is coded independently of the *magnitude* of angular displacement. Further, the cognitive locus of impairment suggested that these representations are maintained at a supra-modal level. Based on experimental evidence from BC and other patients with cognitive deficits in spatial processing, a theoretical framework, the co-ordinate system hypothesis of orientation representation (COR), was proposed in Study II for interpreting orientation errors.

Studies III-IV investigated the neural basis for the acquisition of new memory representations in the brain. The medial temporal lobe (MTL) is known to be crucial for declarative memory, but how other brain areas outside the MTL interact to support the construction of new memory representations is not fully understood. Study III investigated new memory acquisition in an amnesic individual, LSJ, who has suffered extensive bilateral MTL damage, including the near-complete destruction of the hippocampus. The results showed that non-hippocampal structures can support acquisition of new long-term memory representations in a context cognitively more complex than has previously been demonstrated. Study IV investigated memory acquisition in neurologically healthy adults using whole-head magnetoencephalography (MEG). The results showed that during the acquisition of declarative-memory representations, the feature analysis systems in different sensory modalities interact at a level as early as that of the sensory cortices. Together, the results of Studies III and IV demonstrate that several different non-hippocampal and non-MTL structures interact with the MTL/hippocampal memory system at multiple processing levels to support acquisition of memory representations in the intact human brain. Methodological questions about converging evidence and multiple levels of analysis in cognitive neuroscience are discussed in light of the four empirical studies.

Tiivistelmä

Aivoissa muodostetaan kognitiivisia edustumia ulkomaailmasta. Näiden edustumien luonnetta ei kuitenkaan täysin tunneta. Näitä edustumia ja niiden hermostollista perustaa voidaan tutkia toisiaan täydentävillä keinoilla, joihin kuuluvat kognitiivisista häiriöistä kärsivien yksilöiden kokeelliset tutkimukset, aivojen toiminnan elektromagneettiset mittaukset ja toiminnalliset aivokuvantamismenetelmät. Tässä väitöskirjassa tutkittiin kognitiivisia edustumia ja niiden hermostollista perustaa aivojen näkö- ja muistijärjestelmissä kokeellisen aineiston avulla, joka hankittiin toisiaan täydentävillä menetelmillä. Väitöskirjan tavoitteena oli sekä hankkia uutta empiiristä tietoa näköjärjestelmästä ja muistista että käyttää osatutkimuksia kontekstina metodologisten kysymysten pohtimiseen kognitiivisessa neurotieteessä.

Väitöskirja koostuu neljästä osatutkimuksesta. Osatutkimuksissa I-II selvitettiin, miten avaruudellinen tieto esineiden orientaatiosta on edustettuna näköjärjestelmässä. Koehenkilönä osatutkimuksessa I oli potilas BC, joka kärsii näköinformaation käsittelyyn vaikuttavasta kognitiivisesta häiriöstä. Kokeelliset tulokset potilas BC:ltä osoittivat, että avaruudellinen orientaatio on näköjärjestelmässä edustettuna kompositionaalisesti siten, että viivaorientaation *kallistussuunta* pystysuorasta mielensisäisestä meridiaanista on edustettu *kallistuskulmasta* riippumatta. Häiriön kognitiivinen locus viittasi siihen, että edustumat ovat supramodaalisia eli useita aistipiirejä kattavia. Osatutkimuksessa II potilas BC:n ja muiden kognitiivisista häiriöistä kärsivien potilaiden koetulosten perusteella laadittiin teoreettinen viitekehys, orientaatioedustumien koordinaatistohypoteesi COR, jonka avulla orientaatiovirheitä voidaan tulkita.

Osatutkimuksissa III-IV selvitettiin hermostollisia mekanismeja, joiden varassa uusia muistiedustumia muodostetaan. Mediaalinen temporaalilohko (MTL) tiedetään deklaratiiviselle muistille ratkaisevan tärkeäksi, mutta MTL:n ja muiden aivoalueiden välistä yhteistyötä uusia muistiedustumia muodostettaessa ei täysin tunneta. Osatutkimuksessa III uusien muistiedustumien muodostumista tutkittiin vakavasta muistihäiriöstä

kärsivällä potilaalla LSJ:llä, jolla on laajoja MTL-alueen molemminpuolisia vaurioita ja jonka hippokampus on lähes täydellisesti tuhoutunut. Tulokset osoittivat, että uusien pitkäkestoisten muistiedustumien muodostuminen on mahdollista ei-hippokampaalisten rakenteiden varassa kognitiivisesti monimutkaisemmissa tehtäväympäristöissä kuin aiemmin on osoitettu. Osatutkimuksessa IV muistiedustumien muodostumista tutkittiin neurologisesti terveillä koehenkilöillä käyttämällä magnetoenkefalografiaa (MEG:tä). Tulokset osoittivat, että deklaratiivisia muistiedustumia muodostettaessa eri aistimodaliteettien piirreanalyysijärjestelmät vaikuttavat toisiinsa niinkin varhain kuin sensoristen aivokuorenalueiden tasolla. Kokonaisuutena osatutkimusten III-IV tulokset osoittavat, että ei-hippokampaaliset ja MTL:n ulkopuoliset järjestelmät aivoissa tekevät hippokampuksen ja MTL-alueiden kanssa yhteistyötä useilla eri prosessointitasoilla, kun uusia muistiedustumia muodostetaan.

Kognitiivisen neurotieteen metodologisia kysymyksiä pohditaan väitöskirjan neljän empiirisen osatutkimuksen valossa eri selitystasojen ja toisiaan täydentävien tutkimustulosten näkökulmista.

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Wow, am I actually done soon?

List of original publications

This thesis is based on the following publications:

I Valtonen, J., Dilks, D.D. & McCloskey, M. (2008): Cognitive representation of orientation: A case study. *Cortex, 44,* 1171-1187.

II McCloskey, M., Valtonen, J. & Sherman, J. C. (2006): Representing orientation: A coordinate-system hypothesis and evidence from developmental deficits. *Cognitive Neuropsychology, 23,* 680-713.

III Valtonen, J., Gregory, E., Landau, B. & McCloskey, M. (2014): New learning of music after bilateral medial temporal lobe damage: Evidence from an amnesic patient. *Frontiers in Human Neuroscience, 8,* 694.

IV Valtonen, J., May, P., Mäkinen, V. & Tiitinen, H. (2003): Visual short-term memory load affects sensory processing of irrelevant sounds in human auditory cortex. *Cognitive Brain Research, 17,* 358-367.

The publications are referred to in the text by their roman numerals. The articles are reprinted with the kind permission of the copyright holders.

Abbreviations

ABR	auditory-evoked brainstem response
ANOVA	analysis of variance
BOLD	blood oxygenation level-dependent signal
bpm	beats per minute
CA	cornu ammonis
COR	coordinate-system orientation representation
dB	decibel(s)
DT	difficult-task condition
DTC	difficult-task control condition
DTVP	Developmental Test of Visual Perception
ECD	equivalent current dipole
EEG	electroencephalography
ERF	event-related field
ERP	event-related potential
ET	easy-task condition
fMRI	functional magnetic resonance imaging
HSE	herpes simplex encephalitis
Hz	hertz
ISE	irrelevant sound effect
ISI	interstimulus interval
IT	inferotemporal cortex
LIP	lateral intraparietal area
MEG	magnetoencephalography
MRI	magnetic resonance imaging
MTL	medial temporal lobe
NT	no-task condition
PET	positron emission tomography
PHSV	principal-horizontal/secondary-vertical mapping
PVSH	principal-vertical/secondary-horizontal mapping
SPL	sound pressure level
TMS	transcranial magnetic stimulation

V1	primary visual cortex
VMI	Beery-Buktenica test of Visuo-Motor Integration

1. Introduction: Methods in Cognitive Neuroscience

Cognitive neuroscience aims to understand how the brain enables the mind, to use the words of Gazzaniga and colleagues (2002). For investigating this question, 21st-century cognitive neuroscientists have a vast array of methods at their disposal. In addition to behavioral experiments that can be employed to study, for instance, how objects and events are represented at the cognitive level, electrophysiological tools and functional neuroimaging techniques can be used to record brain activity or its metabolic correlates during cognitive tasks to shed light on the underlying neural processes (for a review of cutting-edge methods, see Gazzaniga & Mangun, 2014). Further, all these methods can be used both in neurologically intact participants and in individuals with acquired or developmental cognitive deficits. Thus, the available range of methods provides an opportunity to study human cognition and brain function from more diverse perspectives than ever before.

All methods are not equally suited for all purposes, however; depending on the question the researcher seeks to address, a given approach can be more informative than others. The relative merits of different methodologies can be a matter of intense disagreement: For example, the contribution of functional neuroimaging to cognitive theories has been under heated debate during the past decade (Bechtel & Richardson, 2010; Caplan & Chen, 2006; Coltheart, 2006a; 2006b; 2010b; Henson, 2005; Jonides, Nee, & Berman, 2006; Loosemore & Harley, 2010; Love, 2015; Mole & Klein, 2010; Page, 2006; Umiltà, 2006; Wixted & Mickes, 2013). Similarly, different authors have disagreed on the relative importance and methods of studying cognitive impairments for understanding cognition and brain function (Caramazza & McCloskey, 1988; Caramazza, 1992; Coltheart, 2010a; Frith, 1998; Kosslyn & Intriligator, 1992; McCloskey, 2001; Patterson & Plaut, 2009). That is, no consensus exists whether the question of how the brain enables the mind should be approached primarily or first from the side of the mind or the brain, or which methods should be preferred for different purposes.

In addition to reflecting the complexity inherent in trying to understand how the mind/brain works, these disagreements about methodology highlight the importance of two things. First, it is essential to understand the assets and limitations of the methodology one uses: being able to select the optimal methodology according to the research question at hand requires an understanding of the rationale and relative advantages and disadvantages of each approach. Second, the debates underscore the value of diverse methods. An uncontroversial view is that converging evidence from multiple methods provides a stronger basis for conclusions than results from any single method alone (e.g., Cabeza & Nyberg, 2000; Chatterjee, 2005; D'Esposito, 2010; Humphreys & Price, 2001; Ochsner & Kosslyn, 2014; Rapp, 2011; Wager & Lindquist, 2011).

In this doctoral dissertation, different methodologies were used in four empirical studies to investigate questions concerning the cognitive neuroscience of visual information processing and memory. The aim of this thesis was both to acquire new experimental evidence about cognitive representations and their neural basis in the intact mind/brain, and also to use these empirical studies to discuss advantages and limitations of different methodological approaches for understanding cognition and brain function.

1.1. Methods in cognitive neuroscience and levels of analysis

Marr (1982) proposed that three levels of analysis are required for understanding any complex computational system. According to Marr's influential tripartite view, these are the *computational* level, i.e., what problems the system is trying to solve and why (sometimes referred to as task analysis); the *algorithmic and representational* level, i.e., the representations and processes the system uses to accomplish these goals; and the *implementation* level, i.e., how these representations and processes are physically instantiated in the brain.

Ultimately, cognitive neuroscience aims to achieve an understanding of the mind/brain that will encompass multiple levels such as the ones proposed by Marr (Ochsner & Kosslyn, 2014). Theories about cognitive processes, such as those formulated in cognitive psychology, can be taken to correspond most directly to the *algorithmic and representational* level (although the levels are not completely independent, see Marr, 1982). In contrast, questions about how these processes are instantiated in the brain (mostly) relate to the *implementation* level. Studies of cognitive deficits and electromagnetic and hemodynamic neuroimaging techniques provide means for approaching multiple levels of analysis in complementary ways.

1.1.1. Experimental studies of patients with cognitive deficits

Since Broca's (1861) investigations of his patient Tan, studies of brain-damaged patients have established the foundation for modern cognitive neuroscience (for a historical perspective, see Selnes, 2001). Early studies of cognitive deficits not only provided evidence that cognitive abilities such as language are not unitary functions (Caramazza & Coltheart, 2006), but in setting up a potential link between specific cognitive deficits and particular locations of brain injuries, also laid the foundational ground for modern neuroimaging methods aiming to localize cognitive functions (D'Esposito, 2010; Rorden & Karnath, 2004). Scientifically perhaps the most influential neuropsychological patient of all time is HM, whose case continued to provide new experimental evidence about the cognitive and neural organization of human memory for more than 50 years until his death. HM was studied in his lifetime by nearly 100 investigators, and Scoville and Milner's (1957) seminal paper documenting his amnesia has been cited almost 2000 times (Corkin, 2002).

The rationale for studying brain-damaged individuals to understand normal cognition and brain function is based on several assumptions, three of which can be considered most essential (Caramazza, 1986; 1992; Coltheart, 2001; Martin & Hull, 2007; McCloskey & Caramazza, 1988; Shallice, 1988). First, the human cognitive system is assumed to be complex and to consist of a number of information-processing components that are functionally (at least relatively) distinct. Second, it is assumed that brain damage can cause impairments in this system without bringing about a qualitatively different organization of function or the formation of entirely new subcomponents. Third, the approach is motivated by the assumption of universality (Caramazza, 1986; Caramazza & McCloskey, 1988), one of the cornerstones of cognitive psychology and cognitive neuroscience (Rapp, 2011). This is the assumption that the functional architecture of the cognitive system is qualitatively invariant across neurologically intact individuals. (For more detailed discussions of assumptions, see Caramazza & McCloskey, 1988; Caramazza, 1992; Coltheart, 2001; McCloskey & Caramazza, 1988; McCloskey, 2001; 2003; Shallice, 1988; and for discussions of concerns relating to the limitations and rationale of neuropsychological patient studies see Kosslyn & Intriligator, 1992; Patterson & Plaut, 2009).

Importantly, the universality assumption does not mean that there are no individual differences; it is clear that there are. However, the cognitive (neuro)scientist is generally interested in the principles of cognition and brain function that are universal to all humans. Practically all studies of brain and cognition regardless of methodology assume that the general cognitive architecture and the underlying principles of brain organization are essentially the same for all humans, and that these universal principles are the subject of investigation in cognitive neuroscience.

Based on the universality assumption, differences in performance among participants in a standard cognitive psychology experiment are not taken to result from fundamentally different cognitive architectures in different individuals, but from random and/or irrelevant sources such as imperfect measurement tools (McCloskey & Caramazza, 1988). Because of this assumption, individual variation among healthy participants in experimental data is treated as noise, and data can be collapsed across subjects to improve the signal-to-noise ratio. Thus, the universality assumption provides one of the methodological foundations for making inferences about experimental data from healthy subjects in cognitive psychology and cognitive neuroscience.[1]

Because the cognitive architecture is assumed to be universal, cognitive theories make predictions not only about the cognitive performance of intact humans, but also about the kinds of cognitive impairment that are possible. Thus, cognitive impairments constitute tests for theories of normal cognition, and can be used to inform these theories. If the assumption of universality is correct, then patients with brain damage can be assumed to have had the same

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[1] It is not clear, however, how potentially non-trivial individual differences should be taken into consideration. This issue will be discussed in section 4, General Discussion.

cognitive system prior to the damage[2], and the researcher can try to make inferences about this system based on experimental data from the brain-damaged individual.

One type of inference about normal cognition from cognitive deficits is based on single and double dissociations (Frith, 1998; Shallice, 1988). However, this is only one possible form of evidence in patterns of impaired performance; neither the types of data nor the kinds of inferences are restricted a priori. (For a detailed discussion, see McCloskey, 2003.)

Patients with cognitive deficits are studied both in groups and as single cases. However, because of complications relating to assumptions of group homogeneity, which arguably cannot be ensured *a priori* in cases of cognitive impairment, several authors consider the single-case approach more reliable than aggregating data across subjects (Caramazza, 1986; 1992; Caramazza & McCloskey, 1988; Caramazza & Badecker, 1991; Ellis, 1987; McCloskey & Caramazza, 1988; McCloskey, 1993; Sokol, McCloskey, Cohen, & Aliminosa, 1991; but see also Bub & Bub, 1988; Robertson, Knight, Rafal, & Shimamura, 1993; Zurif, Swinney, & Fodor, 1991).

1.1.1.1. Goals of studying cognitive deficits

To understand how the brain enables the mind, cognitive deficits can be studied for two different purposes. First, impairments offer a window into how cognitive processes are functionally organized. Experimental data from brain-damaged individuals can be studied to understand normal cognitive processes (Coltheart, 2001), most directly corresponding to Marr's (1982) *algorithmic/representational* level of analysis. How information is processed in the human cognitive system is sometimes revealed more clearly when the system has been damaged than when all processes remain intact (McCloskey, 2001). When used for informing cognitive theories only, studies of cognitive deficits aim to identify the locus of the functional lesion within the cognitive system (Caramazza & McCloskey, 1988). For this purpose, knowledge about the neuroanatomical lesion locus is not necessary, because nothing in the logic of

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[2] Studies of cognitive deficits typically also present evidence that the brain-damaged individual was cognitively intact prior to the brain damage.

inference about behavioral patterns of performance hinges on the anatomical locus of injury (Caramazza, 1992; Frith, 1998).

However, in addition to providing evidence about the functional organization of cognition, data from brain-damaged patients also offer a window into how cognitive functions are physically implemented in the brain (Rorden & Karnath, 2004). When brain-damaged individuals are studied for this purpose, neuroanatomical lesion loci are obviously the topic of interest. In practice, many factors limit the usefulness of patient studies for this purpose (Price, Noppeney, & Friston, 2006; Shallice, 1988). For example, lesion loci can be large, diffuse, and brain damage can fail to respect boundaries of anatomical structure or functional interest. At the same time, however, experimental evidence from a brain-damaged patient can establish a causal role for a brain structure in a cognitive function that cannot be established through other methods alone (e.g., Chatterjee, 2005; D'Esposito, 2010).

1.1.2. Electrophysiological methods and functional neuroimaging

Electrophysiological tools and functional neuroimaging techniques provide several methods for studying brain function in living human subjects. Similarly to studies of brain-damaged patients and behavioral experiments with healthy subjects, both electromagnetic and hemodynamic neuroimaging methods also rely on the universality assumption. The methods relevant for the purposes of this thesis are electroencephalography (EEG) and magnetoencephalography (MEG), measuring electric and magnetic brain activity, respectively, and the hemodynamic techniques of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

For investigating questions related to the neural implementation of cognitive functions in the brain, electrophysiological and hemodynamic neuroimaging methods provide several advantages over patient studies. For example, brain regions of interest are not restricted to a particular area (i.e., one that is damaged), but neural activation can be studied in the whole brain. Second, research questions are not limited to the areas that are most susceptible to neural insult. Although brain damage can be caused in different ways, some regions tend to be more vulnerable than others, for example, because of how the system of blood circulation is organized in the brain. Conceivably, this could skew the choice of topics that are studied in patients, whereas neuroimaging methods are less sensitive to vascular anatomy. Third, neuroimaging experiments on healthy participants can be replicated in new samples.

Some authors contend that functional neuroimaging methods can also inform theories of cognitive function at the psychological level (Henson, 2005; Jonides et al., 2006; Love, 2015; Wixted & Mickes, 2013). However, this is under debate (Coltheart, 2006a; 2006b; Loosemore & Harley, 2010; Page, 2006).

1.1.2.1. Electromagnetic measures

The electromagnetic signals generated by synchronized mass-activity of neuronal populations in the brain can be measured non-invasively from the scalp (Baillet, 2011; Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993; Luck, 2014). Electric potential differences created by brain activity can be recorded using EEG. A closely related method, MEG, measures the magnetic fields created by intracellular currents in the brain. The electric and magnetic data can be used to estimate the spatial distribution of the underlying neural sources (Cohen, 1968; Michel et al., 2004).

MEG is thought to be predominantly sensitive to postsynaptic currents in the apical dendrites of large pyramidal neurons (Hämäläinen et al., 1993). MEG mainly records activity from neurons in fissures of the cortex, where dendrites are oriented more or less tangentially to the skull (but see also Papadelis, Leonardelli, Staudt, & Braun, 2012). In source localization, MEG is considered superior to EEG because unlike electric potentials measured by EEG, magnetic fields are not influenced by the physical structures of the skull, the brain, and other tissue between the sources and sensors (Hämäläinen et al., 1993; Leahy, Mosher, Spencer, Huang, & Lewine, 1998).

In both EEG and MEG, the interpretation of the data requires dealing with the inverse problem. That is, the source(s) of a recorded electromagnetic signal cannot be uniquely determined from the measured signal alone, but source models, such as current dipoles, or other estimation techniques are required. One of the limitations of these techniques is that the signal-to-noise ratio is weak, and typically a large number of trials is needed. While the spatial resolution of MEG and especially EEG is limited relative to hemodynamic measures, their temporal resolution is much more precise. Recent methodological advances have provided potential ways of analyzing MEG data for improved spatial resolution (Cichy, Ramirez, & Pantazis, 2015; Stokes, Wolff, & Spaak, 2015), and many sophisticated methods exist also for EEG (Luck, 2014).

1.1.2.2. Hemodynamic methods

In contrast to electromagnetic measures, the hemodynamic neuroimaging techniques PET and fMRI are indirect measures of neuronal activity. They exploit the fact that metabolism and blood flow are enhanced locally when activity in an area of the brain increases (Wager, Hernandez, Jonides, & Lindquist, 2007).

PET is a semi-invasive technique that depends on the injection of radioactive isotope markers into the bloodflow. It is based on measuring local quantities of the metabolic correlates of neuronal activity (Posner & Raichle, 1994). PET can be used to detect local differences in glucose metabolism, oxygen consumption, and regional cerebral blood flow during cognitive activity.

Functional MRI, in contrast, is a newer and currently the dominant functional neuroimaging technique. Most fMRI studies in cognitive neuroscience use the blood-oxygenation-level-dependent (BOLD) signal, which is based on the paramagnetic properties of deoxygenated blood (Ogawa, Lee, Kay, & Tank, 1990; Song, Huettel, & McCarthy, 2006; Wager et al., 2007; Wager & Lindquist, 2011). The BOLD response can be used to measure changes in the ratio of oxygenated to deoxygenated hemoglobin in the blood that accompany changes in neural activity. Spatial resolution is considered the main advantage of fMRI, while its temporal resolution is coarser than that of EEG and MEG. As a non-invasive technique, it also has clear practical advantages over PET (but also some disadvantages, see Raichle, 2006). Over the last two decades, the interest in the use of fMRI has increased dramatically. FMRI has surpassed all other cognitive neuroscience methods in popularity and come to hold a prominent position in research practices (e.g., Cabeza & Nyberg, 2000; Fellows et al., 2005; Raichle, 2006; Wager et al., 2007).

1.2. Cognitive representations and multiple methods

Through empirical examples, this dissertation attempts to demonstrate how different methods in cognitive neuroscience can provide complementary evidence about cognitive representations in visual information processing and memory at multiple levels of analysis. Empirical evidence was used from cognitive deficits and MEG to investigate cognitive representations and their neural basis in visual information processing and memory. The aim was both to collect new experimental evidence about cognitive representations and their neural basis in the intact cognitive system, and to use these studies as a context for discussing relative advantages of different methodological approaches in cognitive neuroscience. In particular, the aim was to evaluate merits and limitations of the single-patient approach, and to discuss how different methods can inform multiple levels of analysis in cognitive neuroscience.

This thesis attempts to show (a) that detailed analyses of impaired performance in brain-damaged individuals can be used to systematize behavioral phenomena theoretically and to guide subsequent research on normal adults, normally developing children and studies using functional neuroimaging, (b) that a single-patient study of a brain-damaged individual can provide a strong form of evidence regarding how cognitive abilities are neurally supported in the human brain, and (c) that MEG, an electromagnetic brain-research technique with excellent temporal resolution, can be used to collect fine-grained evidence about how disparate brain regions interact during cognitive processing.

For this thesis, four empirical studies were conducted (Studies I-IV). Studies I and II are concerned with how the spatial orientation of objects is represented in the visual system. Studies III and IV investigated how the acquisition of new memory representations is neurally supported in the human brain and how different brain regions may interact during this process.

The individual empirical studies will be introduced and discussed first in their theoretical contexts. Finally, methodological questions and implications for future studies will be discussed.

2. Part One: Representation of Object Orientation

We typically take our sensory abilities for granted. Special circumstances excluded, we are mostly able to make sense easily of our everyday environment and to use this information adaptively. Our visual surroundings make sense to us without effort. We can recognize a fallen bike on the sidewalk just as easily as the adjacent one still standing against the fence, and we seldom fumble when reaching for the coffee mug on the kitchen table.

A prerequisite for acting in all these situations is the ability to discern the spatial orientation of the objects we see. Reaching for objects requires accurate perception of the object's spatial orientation; in reading and spelling, the identity of several letters depends on their spatial orientation. Evolutionarily speaking, knowing which way a predator is facing has often been a life-and-death matter. Socially, understanding a situation between two people may hinge on whether they are facing each other or not.

Although we are largely unaware of it, determining the spatial orientation of objects requires enormously complicated computations from the visual system. For any computational system, a demanding enough task would be to learn to recognize a potentially infinite number of objects that can come in any sizes or shapes. For the visual system, however, the task is even more challenging: the pattern of light-intensity reflected on our retinas from any single object can change completely when the same object is perceived from a different viewpoint, but the system needs to recognize it reliably as the same object. Despite the colossal computational demands, the visual system is mostly able to solve these problems rapidly and outside our awareness.

A key concept in the psychological research of perception and memory is cognitive representation. These internal representations constructed of objects and events are not always veridical, but it is these representations that ultimately enable us to act and function in the world, to see, hear and remember. Although we are still far from fully understanding how the human cognitive system meets computational challenges such as the ones related to discerning the spatial orientation of perceived objects, one way to advance our understanding of these processes is by examining the underlying cognitive representations. Our ability to appreciate the different spatial orientations of whole objects depends crucially on the cognitive representations constructed of these objects. Part One of this dissertation aims to understand the nature of these representations and how the spatial orientation of visually perceived objects is processed.

2.1. Orientation processing in the primate visual system

The majority of cells in the primary visual cortex of primates and many other non-human animals are sensitive to spatial orientation. Hubel and Wiesel's (1962; 1968) ground-breaking discovery of simple cells in primary visual cortex that respond selectively to differently oriented edges introduced visual cortical orientation selectivity as a central question for understanding the neurophysiology of vision (e.g., Ferster & Miller, 2000; Ferster, 2003; Shapley & Ringach, 2000; Shapley, Hawken, & Ringach, 2003; Somers, Nelson, & Sur, 1995; Wurtz, 2009).

During cortical processing, the visual system is thought to extract spatial information from a visual scene by means of multiple visual filters, or channels, each of which is sensitive to a narrow band of spatial frequencies and orientations (e.g., Wilson & Wilkinson, 2003). From primary visual cortex V1, visual information is carried in parallel in two divergent visual pathways, both of which carry information about orientation: in a ventral stream projecting to the inferotemporal (IT) cortex, and in a dorsal stream projecting to the posterior parietal cortex (Milner & Goodale, 2006; Ungerleider & Pasternak, 2003). The ventral stream is considered important for visual object recognition, and the dorsal, in contrast, for visual functions that enable reaching for objects and interacting with them. Within the ventral processing stream of macaque monkeys, individual neurons that are sensitive to complex object shapes and their orientations have been identified in the IT area (Gross, Rocha-Miranda, & Bender, 1972; Vogels & Orban, 1994). Similarly, neurons responsive to objects and their orientations have been found in the caudal intraparietal sulcus of the parietal cortex, consistent with the notion that the parietal lobe houses functions related to orientation processing and hand guidance for action (Sakata et al., 1998).

Despite these and many other important findings, however, the available neurophysiological evidence does not directly speak to how the spatial orientation of entire objects is represented. Presumably, computing the orientation of whole objects requires higher-level representations that are not reducible to, for example, the receptive fields properties of single neurons sensitive to simple visual features, such as edges, or even to complex shapes (Corballis & Beale, 1976; Humphreys & Riddoch, 2006; Marr, 1982; McCloskey, 2009; Wilson & Wilkinson, 2003).

2.1.1. Behavioral evidence for orientation processing

In sum, the available neurophysiological evidence does not specify the nature of the higher-order representations needed for discerning the spatial orientation of whole objects. Therefore, important evidence for how the orientation of entire objects is represented in the brain comes from behavioral studies with human children and adults, non-human animals, and individuals with brain damage. In particular, research related to mirror-reflected and obliquely oriented objects has important implications for how the orientation of whole objects is processed. Empirically, both mirror images and oblique orientations of objects have been found demanding to process. Studying the related processing errors can potentially help in understanding how spatial information is represented.

2.1.1.1. Mirror reflections: Developmental evidence

Many animal species and human children up to around the age of seven find it very difficult, and sometimes even impossible, to discriminate between visual stimuli that have been reflected across a vertical axis (Bornstein, 1982; Corballis & Beale, 1976; Walsh & Butler, 1996). For example, Rudel and Teuber (1963) presented children with pairs of stimuli and asked them to indicate which one of the two was “correct”. The assignment was arbitrary, but the experimenter told the children after each trial whether their choice had been correct or incorrect. When the pair consisted of a horizontal and a vertical line (— versus |), even the youngest children, the 3-year-olds, learned to discriminate the stimuli correctly. In contrast, when required to discriminate between two oblique lines that were mirror images of each other (/ versus \ ), the same task proved extremely difficult for the 3-to-5-year-olds, and caused difficulties for many even in the oldest age group, the 6-to-8-year-olds. Similarly, Gregory, Landau and McCloskey (2011) showed that 4-to-5-year-old children had consistent difficulties in orientation-matching tasks, and that the vast majority of their errors involved some of several forms of mirror-image confusion. Even normal human adults need substantially more time when comparing mirror-image obliques than with horizontal and vertical lines (Olson & Hildyard, 1977).

It is not entirely clear why mirror images would be inherently difficult to distinguish. Corballis and Beale (1976) suggest that the brain may employ two mechanisms that could contribute to or explain mirror-image difficulties: *duplication coding* and *reduction coding*. Duplication coding refers to the possibility that the brain constructs and stores object descriptions in several alternate forms, one the left-right mirror image of the other. Several authors have proposed different formulations of duplication-coding accounts for mirror-image difficulties (e.g., Deregowski, McGeorge, & Wynn, 2000; Rollenhagen & Olson, 2000). For example, Deregowski et al. (2000) suggest that the representation of three-dimensional shapes is achieved through duplication coding of two-dimensional images.

Reduction coding, in contrast, refers to the possibility that the brain may store object descriptions that are independent of their left-right orientation. It is often argued that in many environments in the natural world, where biological symmetries are frequent, information about left-right orientation can often be unnecessary for identifying an object. For example, Braine (1978) has proposed that at a cognitive level, the process of visually identifying an object's orientation progresses through three stages, some of which do not carry information about the objects' left-right orientation. The first stage comprises a categorical judgment of whether an object is upright or not. At the second stage, the orientation of a non-upright object is further subcategorized as "upside down" or "sideways", and at the third stage as "left-facing" or "right-facing". Braine contends that left-right confusions occur at the second stage of processing, at which no information about left-right orientation is yet represented. According to her proposal, children confuse left-right orientations until they have reached the level of developmental maturity that the cognitive processing requires at the third stage. Braine's proposal, however, is only concerned with categorical judgments of up, down, left and right, although orientation perception is not a categorical but rather a continuous function. Braine suggests that in addition to categorical three-stage processes, also “relational” judgments of orientation are computed with respect to a spatial frame of reference. How such relations are represented, however, is unclear. It is also not entirely clear why the ability to perform left-right discriminations should necessarily mature developmentally later than that for up-down discriminations.

While mechanisms such as duplication or reduction coding may contribute to difficulties with mirror images, some or many duplication coding accounts may also allow competing explanations (McCloskey, 2009). Further and more importantly, these mechanisms alone do not provide an adequate theory of orientation representation in the human brain. Despite the relative problems related to mirror images, humans are also capable of perceiving different orientations and of differentiating between left-right enantiomorphs. Therefore, a level of representation would seem to exist that also represents information about orientation accurately.

In the case of obliquely oriented lines, a still third, alternative account for why mirror images are difficult has been presented. This third account posits that the cognitive representation for an oblique line orientation is more complex than that for a vertical or a horizontal line (Olson & Hildyard, 1977; Rudel & Teuber, 1963; Rudel, 1982). This complexity, however, has not been further elucidated.

2.1.1.2. Mirror reflections: Evidence from brain damage

Further behavioral evidence related to how orientation is represented comes from studies of individuals with cognitive deficits. Studies of brain-damaged individuals have shown that the capability to appreciate the orientation of whole objects can be selectively impaired after brain damage. Selective deficits in perceiving an object’s orientation can occur even when the ability to recognize the object is spared (Cooper & Humphreys, 2000; Best, 1917/Ferber & Karnath, 2003; Fujinaga, Muramatsu, Ogano, & Kato, 2005; Harris, Harris, & Caine, 2001; Karnath, Ferber, & Bülthoff, 2000; Priftis, Rusconi, Umiltà, & Zorzi, 2003; Turnbull, Laws, & McCarthy, 1995; Turnbull, Beschin, & Della Sala, 1997). In a pattern of double-dissociation, patients have also been identified whose object recognition abilities have been severely impaired and who cannot name objects but who are able to perform tasks that require knowledge about their orientation (Turnbull, 1997).

The ability to distinguish between mirror-reflected images can also be selectively impaired after brain damage (Davidoff & Warrington, 1999; Martinaud et al., 2016; McCloskey, 2009; Turnbull & McCarthy, 1996; Walsh, 1996; Warrington & Davidoff, 2000). For example, patient FIM, who had sustained parieto-occipital damage, performed at chance when required to discriminate between mirror-reflected images, but her performance with rotated stimuli was considerably better (Davidoff & Warrington, 2001). Another patient, RJ, studied by Turnbull and McCarthy (1996), was able to name pictures of objects without error, and to distinguish which one of three stimuli differed from the others by a 180-degree rotation, but was unable to pick the odd-one-out when it was left-right reflected. Similarly, Priftis and colleagues' (2003) patient GR was able to determine the correct orientations of objects and to distinguish between rotated stimuli. Despite these spared abilities, GR was profoundly impaired in mirror-image discrimination tasks. These results suggest that the patients had selective deficits in representing the left-right orientation of stimuli, but their ability to process at least some other aspects of object orientation had remained intact.

Impairments in differentiating between mirror images have also been demonstrated with laterally reflected oblique lines. Patient LM, studied by Riddoch and Humphreys (1988), performed without difficulty in matching horizontal and vertical lines to sample, but was severely impaired at matching oblique lines when the distractors were mirror-reflected obliques. Patients MH (Riddoch et al., 2004) and AH (McCloskey et al., 1995; McCloskey, 2004; 2009) were also impaired at differentiating between mirror-reflected oblique lines.

To explain patient FIM's error pattern, Davidoff and Warrington (2001) hypothesized (in a manner consistent with many other *reduction-coding* accounts) that there are two routes to object identification in the intact brain. According to the proposal, one of these routes—the view-independent, or canonical route—uses representations with no information about left-right orientation. In a somewhat similar account, also falling into the *reduction-coding* family, Turnbull and McCarthy (1996) suggested that some processing stages in object recognition seem to carry no information about left-right orientation.

In addition to reduction-coding proposals, some authors have explained mirror-image phenomena by positing abstract coordinate axes and reference frames that, presumably, could house orientation representations. For example, Riddoch and colleagues (2004) suggested that judging the orientation of line stimuli requires “coding concurrent variation along horizontal (x) and vertical (y) coordinates within a frame based on the patient’s body”. Somewhat similarly, Priftis et al. (2003) proposed that patient GR’s problems in mirror-image discrimination resulted from a deficit “in processing the directionality of an object’s intrinsic x-axis.”

Hypotheses based on coordinate-axes and reference-frames seem to have a certain advantage over reduction- and duplication-coding accounts. That is, reduction- and duplication-coding explanations fail to account for how different orientations can be perceived accurately; in contrast, a coordinate-axis account could, in principle, provide a full account of both orientation representation in the normal cognitive system and also of the various types of orientation error that can arise from deficits in processing. None of the previous suggestions, however, have been developed into explicit hypotheses.

2.1.1.3. The oblique effect

The challenges related to mirror-reflected lines may or may not be related to oblique stimuli in general. A well-established body of literature demonstrates that visual stimuli are more difficult to detect if they are presented in oblique rather than in cardinal orientations (Appelle, 1972; Corballis & Beale, 1976; Li, Peterson, & Freeman, 2003; Rudel, 1982; Shen, Tao, Zhang, Smith, & Chino, 2014). This finding, referred to as *the oblique effect,* has been reported across a wide range of various experimental settings both in humans and many non-human animals.

Different neurophysiological accounts have been proposed to explain this anisotropy. For example, Mansfield (1974) suggested that the oblique effect results from a predominance of cortical neurons in V1 with receptive fields responsive to horizontal and vertical as opposed to oblique stimuli. However, it seems unlikely that a neuronally low-level account can explain all the empirical phenomena evidenced with mirror-reflected oblique stimuli. For example, patient LM confused mirror-reflected oblique lines and left-right-reflected letters, but LM's object recognition skills were comparatively better (Riddoch & Humphreys, 1988; Riddoch et al., 2004). That LM was (mostly) able to recognize objects would seem to imply that LM was able to code oblique edges of objects and use this information fairly accurately at least under some conditions. In addition, the oblique effect seems to vary across experimental settings (Heeley, Buchanan-Smith, Cromwell, & Wright, 1997; Li & Westheimer, 1997; Shen et al., 2014; Westheimer, 2003). It therefore seems improbable that all the empirical findings in orientation acuity observed using oblique stimuli could be accounted for in the same way.[3]

2.1.2. Summary

In sum, various intriguing empirical phenomena related to orientation perception have been reported in neurophysiological, neuropsychological and behavioral studies with typically developing children, normal human adults, brain-damaged individuals and non-human animals. Prior research suggests that the orientation of entire objects is computed using higher-order representations that are not reducible to, for example, the receptive fields of simple cells in primary visual cortex. Further, particular empirical phenomena such as mirror-reflection errors suggest that at some processing level, visual information in these higher-order representations is coded in a form that does not distinguish between left and right handedness. The exact nature of these

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[3] Further complicating the issue is that it is not entirely clear whether the difficulties in distinguishing between mirror-reflected oblique lines fall under the broader umbrella of mirror-reflected visual objects in general. Some authors have argued that the visual system may treat lines differently from other shapes (Holmes & Gross, 1984; Walsh & Butler, 1996). According to Walsh and Butler (1996), single lines may lack salient visual features that the visual system can rely on when computing the orientation of entire objects. Nevertheless, whether the visual system treats lines in the same way as more complex objects or not, the cognitive system does seem to code both types of stimuli (at some level of representation) in a form that often leads to mirror-reflection errors at certain stages of normal visual development and in cases of brain damage, and even in normal human adults under particular circumstances. Whether or not the difficulties with mirror-reflected lines and other shapes arise from a single cause or from different causes, the exact nature of the cognitive representations has not been fully explicated for either class of stimuli.

higher-order representations, however, has not been explicitly discussed. Although several authors have suggested general coordinate-based frameworks to account for empirical phenomena such as mirror-image discrimination difficulties after brain damage, the details of such coordinate systems or the exact nature of the underlying orientation representations have not been fully explicated.

2.2. Aims of Part One

The general aim of Part One was to use empirical data to suggest an explicit cognitive-level hypothesis of how the spatial orientation of whole objects is represented in the brain.

The specific aims of Part One were:

- to investigate orientation errors in BC, a young woman with a developmental cognitive deficit affecting orientation perception, to inform hypotheses of how orientation is processed in the cognitive system (Study I), and
- to suggest an explicit hypothesis concerning the nature of orientation representations that can be used as a theoretical framework for discussing and interpreting orientation-related empirical phenomena such as reflection errors (Study II)

2.3. Methods

2.3.1. Participants

Study I investigated orientation errors in BC, a young woman who had acquired extensive bilateral occipital and parietal cortical damage at age three. She presents with a severe developmental deficit in processing visual and spatial information.

2.3.2. Case report

BC is a young left-handed woman, who was 15–16 years old at the time of testing. BC had sustained occipital and parietal damage after a presumed herpes encephalitis infection at age three (for detailed case report, see Study I). A structural MRI at age 5 revealed cortical damage in both left and right occipital regions, intruding into secondary and tertiary occipital and parietal regions in the left hemisphere. An ophthalmologic evaluation at age 14 reported dense right hemianopia and a left visual field of 15–20°. Physical and occupational therapy evaluations at ages 8 and 9 reported that BC had problems related to spatial orientation, such as difficulty replicating postures and walking without a guide.

In the present testing at Johns Hopkins University, BC presented as a young woman of normal intelligence. Her speech was fluent, and she picked up quickly on social cues and expressed herself in an age-appropriate manner. In contrast to her preserved intelligence and language abilities, an extremely profound visuo-spatial impairment was evident both in everyday life and in standardized and experimental neuropsychological testing. BC was often confused about locations within the space in which she was situated. She was able to reach for objects in front of her on the table, but the extent of her impairment was so pronounced that she was unwilling even to try walking unguided along a straight corridor without any obstacles. She had learned to read in Braille, but informal assessment suggested that her reading skills were not at the expected educational level. She was able to write some letters and numbers correctly, but made orientation errors on or was completely unable to write others.

2.3.2.1. Neuropsychological assessment

In the present neuropsychological assessment, BC's performance was profoundly impaired in practically all visuo-spatial tasks on which she was assessed. She was able to name simple geometric shapes such as circles and squares, but could not accurately name line drawings of objects. Her performance was in the 5–6-year-old range on the Boston Naming Test (Goodglass & Kaplan, 1983). On the Developmental Test of Visual Perception (DTVP-2, Hammill, Pearson, & Voress, 1993) assessing a range of visuo-spatial abilities, she scored at a six-year-old level or lower. In the Block Construction Test from the Differential Ability Scales (Elliot, 1990), her performance was at the level of a four-year-old. While she obtained a verbal digit span of 7, she was unable to repeat a visuo-spatial sequence of more than one item on the Corsi Block Span Task (Milner, 1971). BC’s performance was also impaired on the Birmingham object recognition battery (see Table 1, Riddoch & Humphreys, 1993).

Table 1. BC's performance on the Birmingham Object Recognition Battery (Riddoch & Humphreys, 1993).

Test	*Score*
Perception	
Line Length Match A (same/different)	19/30**
large difference	5/5
intermediate difference	3/5
small difference	0/5
identical	11/15
Line Length Match B (same/different)	23/30**
large difference	5/5
intermediate difference	3/5
small difference	2/5
identical	13/15
Circle Size Match A (same/different)	24/30*
large difference	5/5
intermediate difference	4/5
small difference	3/5
identical	12/15
Circle Size Match B (same/different)	25/30
large difference	5/5
intermediate difference	4/5
small difference	4/5
identical	12/15
Object Recognition	
Minimal Feature Match	20/25*
Foreshortened Match	15/25**

* Score 1 SD or more below published control data

** Score 2 SD or more below published control data

Tasks involving drawing proved particularly difficult for BC. Her drawing of a person was at the level of a three-year-old (Fig. 1), and when asked to draw a house, BC gave up after failing to produce a rectangle (Fig. 1). She was able to copy individual lines, but her performance broke down completely with all stimuli of any complexity (Fig. 2). Her age equivalent performance on a test requiring direct copying of visual figures, the Beery-Buktenica Developmental Test of Visuo-Motor Integration (VMI, Beery & Buktenica, 1997), was below that of a five-year-old (for an example, see Fig. 2).

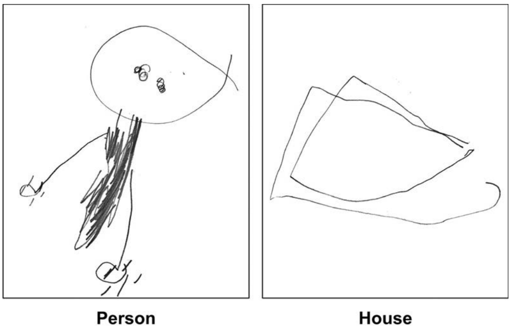

Figure 1. BC's drawings of a person and a house from Study I.

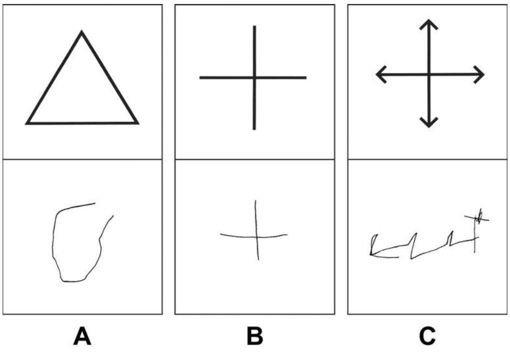

Figure 2. Examples of BC's direct copies from the VMI (Beery & Buktenica, 1997) from Study I.

It is important to note that BC's extreme difficulties with visuo-spatial tasks cannot be attributed to her restricted visual field. Her visual field, albeit limited, is sufficient to support adequate performance in many of the tested tasks. In addition, her performance was equally deficient when stimuli were presented in the auditory or tactile modalities. Her profound difficulties suggest a more global or central deficit affecting the processing of all stimuli with visual or spatial properties. Informally, her deficit could be described as a severe reduction in the resources available for spatial processing.

2.4. Experimental tasks

2.4.1. Experiment 1: Same-different judgments of arrow orientation

Pairs of arrows were presented visually, and BC was asked to judge for each pair whether the orientations of the arrows were the same or different.

2.4.1.1. Stimuli and procedure

Each stimulus consisted of two black arrows printed on white paper. The arrows were composed of a straight line (35 mm in length) and a pointed arrowhead at one end. The two arrows were aligned vertically on the page (90 mm center to center), and each arrow was enclosed within a black circle.

In each trial, BC was instructed to indicate whether or not the arrows were pointing in the same direction.

A total of 124 stimulus pairs were presented. Of these, 40 arrow pairs were identical and 84 discrepant. In the discrepant pairs, the arrows differed in orientation by 30°–180°.

2.4.1.2. Results

The results showed that BC was impaired in detecting orientation differences that would be obvious to a normal observer (see Table 2). She responded correctly to all 40 of the identical pairs. However, she also identified 21% of the discrepant pairs as same, although all the orientation differences were 30° or greater. When the orientation difference between the lines was very large (90°–180°), her responses were mostly correct (93%). In contrast, she detected differences of 30°–60° correctly only in 60% of the trials [$\chi^2(1) = 13.3$, $p < .001$].

Discrepant pairs in which the two arrows were lateral reflections of each other appeared to cause particular difficulty for BC. These were pairs in which, for example, one arrow was tilted 30° clockwise and the other 30° counter-clockwise from the vertical. As shown in Table 2, her accuracy was 83% for non-reflected discrepant pairs, and 86% for up-down reflections. In contrast, she was only 64% correct on the left-right reflected pairs [$\chi^2(1)=3.94$, $p < .05$ for left-right reflected pairs vs. the two other discrepant types combined].

These results suggest that in addition to difficulty in apprehending small angular differences, BC may also exhibit a specific tendency to confuse left-right reflected line stimuli. However, the stimuli were not designed to allow systematic comparisons among non-reflected, left-right-reflected and up-down reflected pairs. The next experiments were designed to investigate these issues systematically.

Table 2. BC's accuracy for different pairs in Experiment 1.

Orientation Difference	Trial Type Rotated Correct /Total	 % Correct	 Up-Down Reflected Correct /Total	 % Correct	 Left-Right Reflected Correct /Total	 % Correct
30°	2/6	33%	0/2	0%	0/2	0%
45°	9/12	75%				
60°			3/4	75%	2/4	50%
90°	16/16	100%	10/10	100%	7/10	70%
120°			4/4	100%	4/4	100%
150°			2/2	100%	1/2	50%
180°	6/6	100%				
Total	33/40	83%	19/22	86%	14/22	64%

2.4.2. Experiment 2: Visual reproduction of line orientation

Following the procedure developed by Dilks et al. (2004), a target and a response line were presented on a computer screen, and BC was instructed to match the orientation of the response line to that of the target by turning a dial on the table (see Fig. 3).

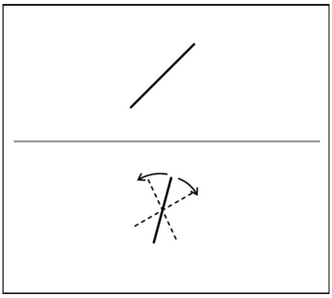

Figure 3. Experiment 2: BC sat in front of a computer screen showing a target line (top) and a response line (bottom). The response line rotated about its center when BC turned a dial on the table in front of her. Adapted from Study I.

2.4.2.1. Stimuli and procedure

BC sat in front of a computer monitor (distance 50 cm). The view on the screen was divided into two sections by a horizontal line. A target line of 6 cm in length and .3 cm in width (visual angle 6.8°) was displayed on the upper half of the screen. A response line of 4.5 cm in length and .3 cm in width (visual angle 5.1°) was presented on the lower half of the screen. The midpoints of the target and response lines were aligned vertically (10.3 cm midpoint to midpoint).

BC was instructed to turn a dial on the table in front of her to make the orientation of the lower (response) line look exactly like that of the upper (target) line. When the dial was turned clock- or counter-clockwise, the response line rotated in the corresponding direction about its midpoint. Both lines remained in view until BC indicated she was satisfied with the result. Because of BC's restricted visual field, the target and response lines were explicitly pointed out to her at the beginning of every trial.

The experiment was conducted in two parts, (a) and (b). In (a), BC was tested with 12 target orientations: -90° (with positive and negative values clock- and counterclockwise from vertical) through +75° in increments of 15°. Three trials were conducted for every target orientation, totaling 36 trials, which were presented in random order. At the beginning of each trial, the response line was 45° or 90° from the target. BC was given three practice trials during which responses were not scored. In part (b), 36 additional trials were presented. Stimuli, design and procedure were identical to (a), except that both the target and response lines were each enclosed within a circle.

2.4.2.2. Results

BC's performance was extremely inaccurate. For illustrative purposes, Figure 4 shows BC's responses in individual trials for all target orientations.

BC's responses can be compared to those of neurologically intact adults and normally developing children, tested by Dilks et al. (2004). Whereas the absolute errors of normal adults range from 1 to 3 degrees (mean absolute error 1.6°, Dilks et al., 2004), BC's errors ranged up to 88°, nearly the possible maximum. BC's mean absolute error was 31° in part (a) of the experiment (range 1°–88°) and 27° in part (b) (range 3°–82°). This is also far poorer than the performance of normally developing children: The mean absolute error of the 10 healthy 5–7-year-old children Dilks et al. (2004) tested at the same task was only 4.8°, with a range of 3.0°–7.0°.

These results show that BC is profoundly impaired at reproducing the orientation of single lines, even when given unlimited time to respond and when the stimulus and response lines remain in view during the task.

Interestingly, the result pattern also suggested that BC's poor performance was not only due to general inaccuracy, but also to a tendency to mirror-reflect the orientation of the line for oblique targets. (See Figure 4.) As the pattern of performance was highly similar in parts (a) and (b) of the experiment, the results were collapsed across (a) and (b). Figure 5 shows BC's responses in a scatterplot, with the target orientation on the x-axis and response orientation on the y-axis. Correct responses fall on the diagonal with a positive slope (solid line in Fig. 5), and mirror reflections on the diagonal with a negative slope (dashed line in Fig. 5).

Across the 60 trials with oblique targets, BC's responses were closer to the target orientation in 55% of trials and closer to the mirror-reflected orientation in 45% of trials. As can be seen in Figure 5, target and response tilt magnitude were correlated across the 27/60 wrong-direction responses BC made for oblique orientations: the response tilt magnitude varied systematically with the target tilt magnitude with a correlation of .63 ($p < .01$). The relationship between target and response tilt magnitude is also evident in the mean tilt magnitudes for each target: for target tilt magnitudes 15°, 30°, 45°, 60° and 90°, the mean response tilt magnitudes were 32°, 32°, 48°, 65° and 70°, respectively. These results demonstrate that BC showed a strong systematic tendency to mirror-reflect the target orientation in reproducing the visually presented line orientations: had the errors in BC's responses been entirely due to random inaccuracy, no systematic relationship between target and response tilt magnitudes such as the one observed should be expected. In contrast, neither the normal adults nor the children tested by Dilks et al. (2004) made any reflection errors in the same task.

In addition to mirror-reflecting oblique orientations, BC was also remarkably imprecise in her responses. This was the case both for responses in which the tilt direction was correct and for those in which it was incorrect. The mean tilt magnitude error in BC's responses was 20.3° for horizontal and vertical targets, and 10.9° for correct-direction responses to oblique targets. For wrong-direction responses, the mean tilt magnitude error from the target's perfect mirror reflection was 15.7°. The level of imprecision in BC's responses is considerable, as both normal adults and normally developing 5–7-year-old children are far more accurate in the same task (mean absolute error 1.6° and 4.8°, respectively, Dilks et al., 2004). Therefore, the results suggest two forms of impairment: a strong tendency to mirror-reflect the target, and greater-than-normal imprecision in reproducing tilt magnitude.

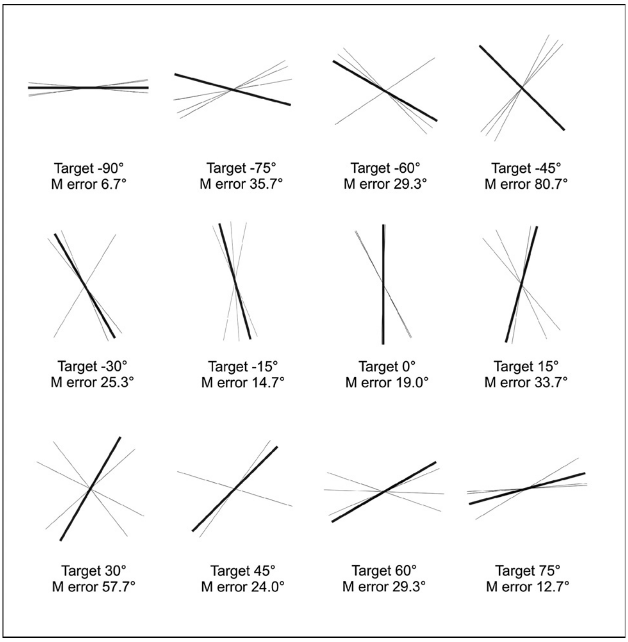

Figure 4. BC's responses in Experiment 2: visual reproduction of line orientation. The thick lines depict the target orientation and the thin lines show individual responses. BC's responses were highly inaccurate, errors ranging up to the possible maximum. The pattern of performance suggests she often mirror-reflected the target. Depicted results are from Experiment 2a. Mean absolute errors are averaged across all three trials per target orientation. Adapted from Study I.

It is unlikely that BC's error pattern could be explained solely by her restricted visual field. The Dilks et al. (2004) study also included a condition in which—unlike in the present experiment—a 5-second delay was introduced after the participant had viewed the target line and before the response line was displayed. Under these conditions, when the participants were not allowed to look back and forth between the target and response lines when adjusting their response, the neurologically healthy adults still made no mirror-reflection errors in the Dilks et al. (2004) study, and even the 5–7-year-old children made very few. The normal adults also remained far more accurate (mean absolute error 3.8°, range 2.0°–5.2°) than BC, even with the delay. Despite being about 10 years younger, the performance of the 5–7-year-olds was roughly comparable in the delay-condition (mean absolute error 15.9°, range 8.1°–21.1°) to BC's under no delay. These results show that merely preventing the subjects from seeing both lines does not introduce the type or degree of error observed in BC's responses. Together, these results strongly suggest that BC's imprecision in reproducing line orientations is both greater than and qualitatively different from that expected solely on the basis of her limited visual field.

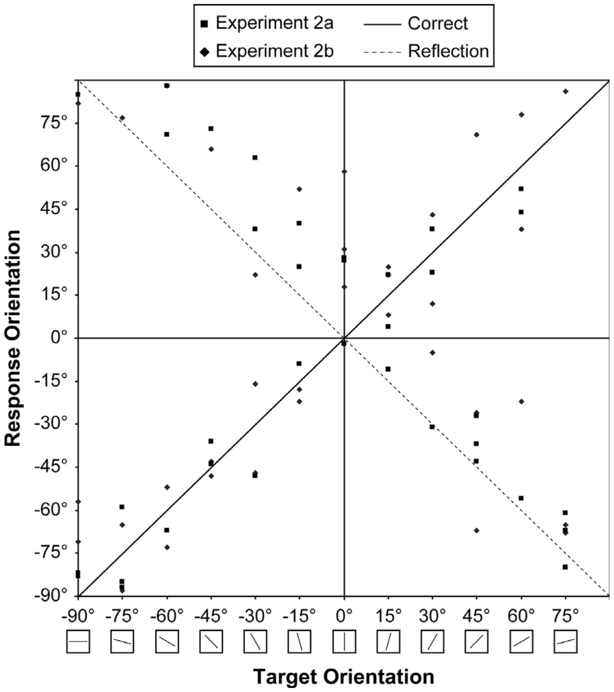

Figure 5. A scatterplot of BC's responses from individual trials (y-axis) as a function of target orientation (x-axis) in Experiment 2. Responses fall along two opposite diagonals: the solid line depicts correct target orientations, and the dashed line depicts the target's mirror reflection. Adapted from Study I.

2.4.3. Experiment 3: Tactile reproduction of line orientation

The previous experiments demonstrated that BC has a tendency to mirror-reflect obliquely oriented line stimuli when they are visually presented. The aim of this experiment was to investigate whether this tendency would extend to the tactile modality. While seated at a table and blindfolded, BC was presented with a fixed wooden stick and instructed to feel it with her hands, and then to rotate a response stick to match the target orientation.

2.4.3.1. Stimuli and procedure

The experiment was conducted in two parts, (a) and (b). The response apparatus consisted of a wooden stick (length 11.5 cm, width 1 cm, thickness 2 mm) mounted to a flat surface with a bolt through its center. When the stick was turned, it rotated about its center.

In part (a) of the experiment, the target was a wooden stick (length 36 mm, width 2 mm, thickness 2 mm) fixed to a flat surface. The target was placed directly in front of BC, and the response apparatus to the left of the target. BC was instructed to turn the response stick to make its orientation match the target. BC felt the target with her right hand and rotated the response stick with her left. The target orientations ranged from -90° through +75° (from vertical, negative values counter-clockwise) in increments of 15°. Each orientation was tested in 1–3 trials, totaling 18 trials.

In part (b), the stick used as the target was identical in size to the response stick. The target was positioned directly in front of BC, as in part (a), but in part (b), the response stick was placed on the table farther away with the midpoints of the sticks aligned. In part (b), BC was instructed to use her (dominant) left hand to feel the stimulus and to adjust the response stick. She was encouraged to go back and forth between the target and response sticks as often as necessary. The target orientations were the same as in part (a), tested in a total of 24 trials. In both parts, she was given unlimited time to respond and was encouraged to readjust her responses until she felt satisfied with the results.

2.4.3.2. Results

BC’s pattern of performance was very similar to that seen in the previous experiments with visual stimuli. The mean absolute error in BC’s responses was

29.0° (range 0°–89°). Examples of her responses are shown in Figure 6, and the scatterplot in Figure 7 shows her responses for all target orientations.

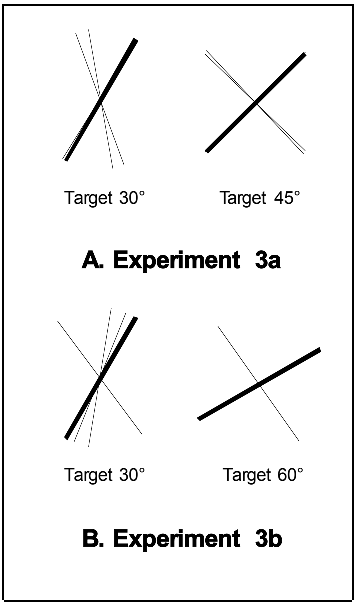

Figure 6. Examples of BC's reflection errors in Experiment 3: tactile reproduction of line orientation. Thick lines depict the target orientation, and thin lines responses in individual trials. The response and target sticks were horizontally and vertically aligned in Experiments 3a and 3b, respectively. Adapted from Study I.

As in reproducing visual line orientations, BC's responses displayed both general imprecision and a tendency to mirror-reflect target orientations. Mirror-reflected responses occurred both in parts (a) and (b) of the experiment. Wrong-direction responses were observed in 41% (12/29) of all oblique-target trials. Among these trials, the correlation between target and response tilt magnitude was .27. In this experiment, the correlation was not statistically significant. However, the finding that the correlation did not reach significance may have been due to a combination of a small number of data points (fewer than half of those in the previous experiment), and a single outlier in which the response was extremely far off target (response -82° for a target of 30°). When this outlier is excluded, the correlation rises to .47.

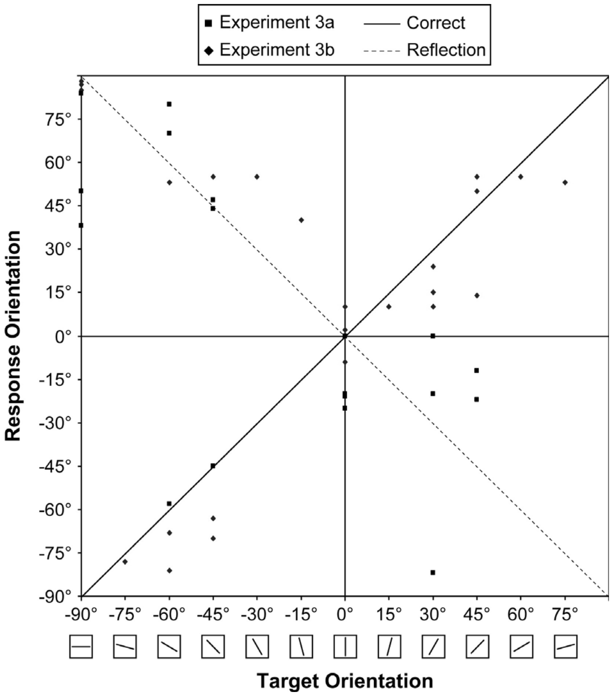

Figure 7. A scatterplot of BC's responses in individual trials (y-axis) as a function of target orientation (x-axis) in Experiment 3. Responses fall along two opposite diagonals: the solid line depicts correct target orientations and the dashed line depicts the target's mirror reflection. Adapted from Study I.

Considering the overall pattern of results (see Figures 6 and 7), the scatterplot suggests that similarly to the pattern seen in the previous experiment, BC was responding to the target's tilt magnitude also when her responses were in the wrong direction. As in the previous experiment with visual stimuli, BC's responses also displayed considerable imprecision in addition to a tendency to mirror-reflect target orientations. The mean absolute distance from target orientation was 13.3° for correct-direction responses, and 18.2° from the mirror-reflected target orientation for wrong-direction responses.

Overall, the pattern of responses closely resembles that observed in the previous experiment with visual stimuli (see Figures 4 and 5). These results suggest that BC's impairments in processing and representing line orientations affect information from both visual and tactile sensory modalities.

2.4.4. Experiment 4: Lines with differentiated ends

Experiments 2 and 3 used stimuli that were identical at both ends. In the case of mirror-reflection errors, however, such stimuli cannot distinguish between lateral and horizontal reflections. That is, an erroneous -45° response to a +45° target could equally result from a lateral mirror-reflection (across a vertical axis), or from a horizontal mirror-reflection (across a horizontal axis). The next experiment was conducted to distinguish between lateral and horizontal mirror-reflection errors.

2.4.4.1. Stimuli and procedure

The stimuli and procedure were the same as in Experiment 2, except that one end of the target and response lines was modified to have a red tip. Each line was enclosed in a circle.

To rule out the possibility that BC's performance might be affected by a particular alignment of the stimulus and response lines on the screen, the experiment was conducted in two parts. In part (a), the target and response were aligned vertically on the screen, and in part (b), horizontally.

The target orientations were -180° through +165° in increments of 15°, totaling 24 orientations. In both parts of the experiment, each orientation was tested in four trials. One trial in part (b) was discarded due to experimenter error. Otherwise stimuli and procedure were identical to those in 2.4.2.

2.4.4.2. Results

As in the previous experiments, BC's responses were extremely inaccurate. The mean absolute error was 27.0° and 31.1° in parts (a) and (b), respectively. As in the preceding experiments, the pattern of results suggested BC's responses were not only generally imprecise, but her errors sometimes took the form of mirror-reflections.

BC's responses to all oblique targets were classified into four categories (see Fig. 8). These were the four possible quadrants defined by the horizontal and vertical axes through the midpoint of the target line and according to the location of the line's red tip. The responses were categorized as 1) correct-quadrant, 2) left-right adjacent quadrant, 3) up-down adjacent quadrant, or 4) opposite-quadrant.

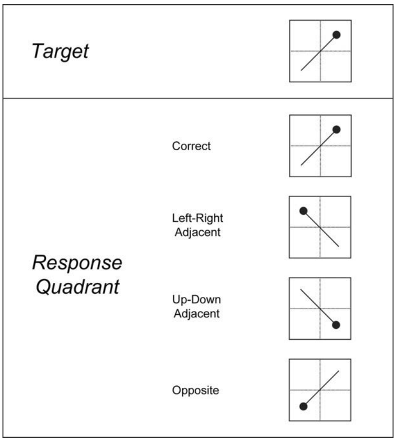

Figure 8. The four categories into which responses were sorted in Experiment 4: correct-quadrant, left-right adjacent quadrant, up-down adjacent quadrant, and opposite quadrant. The black dot at one end of each line shows the location of the red tip. Adapted from Study I.

Table 3 shows the breakdown of responses across these categories in parts (a) and (b) of the experiment. The pattern was virtually identical in the two experiments ($\chi^2 < 1$). Collapsing across (a) and (b), 65% of responses fell into the correct quadrant, 26% into the left-right adjacent and 8% into the up-down adjacent quadrant. Very few responses (1%) fell into the opposite quadrant. These results clearly show BC's responses were sensitive to the location of the target line's red tip: Correct-quadrant responses were more frequent than opposite-quadrant responses (104 vs. 1, $p < .001$ by binomial test), and left-right adjacent responses were more frequent than up-down adjacent responses (41 vs. 13, $p < .001$). That many of BC's responses fell into the left-right adjacent quadrant also suggests that many of her errors may have been lateral (left-right) mirror-reflection errors.

Figure 9 shows BC's responses in all individual trials in a scatterplot. Because one end of the line was marked with a red tip, the maximum possible error was 180° (unlike in the previous experiments, in which it was 90° because the lines' ends were indistinguishable). As in the previous scatterplots, correct responses again lie along the major diagonal with a positive slope (depicted with a solid line). Left-right reflected responses fall along the major diagonal with a negative slope (depicted with a dashed line). Up-down reflections fall along two minor negative-slope diagonals (depicted with a dotted line), which are in the upper-right and lower-left parts of the scatterplot.

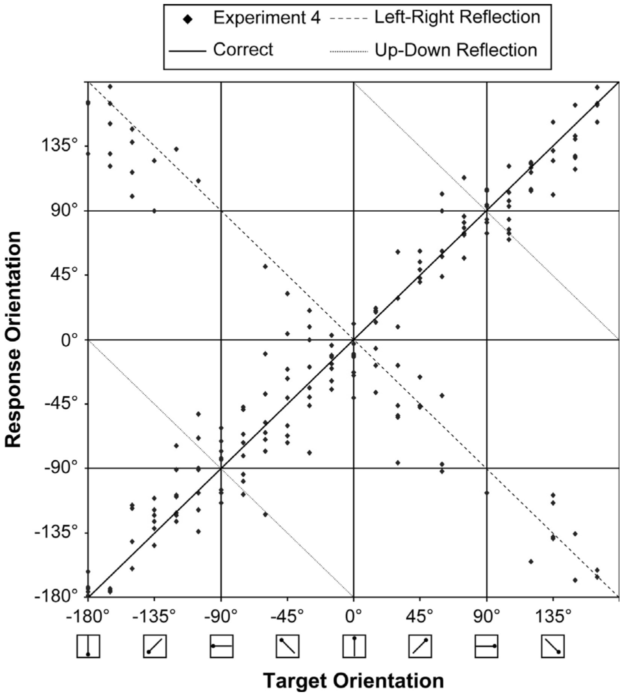

Figure 9. A scatterplot showing BC's responses (y-axis) in individual trials as a function of target orientation (x-axis) in Experiment 4. Responses fall along four diagonals: the solid line with a positive slope (lower left to upper right) depicts correct target orientations, the central falling diagonal (upper left to lower right) depicts left-right reflections, and the two shorter dotted lines with negative slopes depict up-down reflections. The majority of the reflection responses occurred in the left-right direction. Adapted from Study I.

The scatterplot shows that the majority of responses fell along either the correct-response diagonal, or along the left-right reflection diagonal. To further investigate whether the responses on the left-right diagonal were true reflection responses—i.e., ones that were sensitive to the tilt *magnitude* of the target orientation despite being tilted in the wrong *direction*—we calculated the correlation between target and response tilt magnitude across all left-right adjacent responses and the opposite-quadrant responses[4]. The correlation was

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[4] This correlation collapses the upper-left and lower-right quadrants of the scatterplot into a single square region. Including the one opposite-quadrant response as well as left-right adjacent

extremely high, .92 ($p < .001$). This rules out the possibility that the left-right adjacent responses were not sensitive to the target line's tilt magnitude and supports the conclusion that BC often made true left-right reflection errors in her responses.

As in the previous experiments, BC's responses again showed considerable imprecision, both when they fell along the correct-response diagonal and when they fell closer to the left-right reflection of the target orientation. Her mean absolute error was 12.7° for correct-quadrant responses, and 18.1° for left-right adjacent responses (as measured as the mean distance from the target's perfect left-right reflection).

Far fewer of BC's responses fell into the up-down adjacent (8%) than into the left-right adjacent quadrant. The pattern in the up-down adjacent responses makes it unclear whether any of these responses were in fact true up-down reflections. The vast majority of these responses (10/13) involved target orientations only 15° away from horizontal, and the remaining ones (3/13) were responses to targets only 30° away from horizontal. Given the degree of imprecision in BC's responses overall, random imprecision alone could account for these errors. As some of BC's correct-quadrant responses fell off target by as much as 50°, it seems likely that at least some of the responses that fell into the up-down adjacent quadrant resulted from general imprecision. However, it is also possible that some of BC's up-down adjacent quadrant responses were true reflection errors.

In contrast, it is important to note that BC's left-right reflection errors cannot be attributed to random imprecision alone. As can be seen in the scatterplot, left-right reflections occurred not only for orientations close to the vertical axis, but also for orientations that were far from vertical; for example, for targets such as 45°. These errors clearly cannot be interpreted as resulting from random imprecision alone.

In sum, the results confirmed the findings from the preceding experiments showing that BC exhibits imprecision and reflection errors in representing line orientations. The results demonstrate that BC's mirror-reflection errors

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responses ensures that the area is in fact square, and therefore that the correlation could in principle range from -1.0 to 1.0.

predominantly (or perhaps entirely) take the form of lateral reflections (across a vertical axis).

Table 3. BC's responses for oblique targets in Experiment 4, classified according to their location among the four possible quadrants defined relative to the target orientation (correct quadrant, left-right adjacent, up-down adjacent, opposite).

	Experimental condition					
	Vertical alignment		Horizontal alignment		Collapsed	
Response location	N	%	N	%	N	%
Correct quadrant	52/80	65%	52/79	66%	104/159	65%
Left-right adjacent	22/80	28%	19/79	24%	41/159	26%
Up-down adjacent	6/80	7%	7/79	9%	13/159	8%
Opposite quadrant	0/80	0%	1/79	1%	1/159	1%
Total	80/80	100%	79/79	100%	159/159	100%

2.4.5. Discussion

The results of four experiments showed that BC was profoundly impaired in discriminating and reproducing line orientations, and that in addition to general imprecision, her errors involved left-right reflections. The results showed that the reflection errors did not arise from random imprecision, but her responses were sensitive to the target orientation’s tilt magnitude. The pattern of results also indicated that BC’s errors could not be accounted for by attributing them to a visuo-motor impairment. Her responses were consistent across the four experiments, although the visuo-motor requirements differed widely: in same-different judgments the response was verbal, in visual orientation reproduction tasks it was turning a dial to adjust the orientation of the line, and in the tactile task it was turning a wooden stick blindfolded. Across the different tasks, BC’s responses showed imprecision in processing target tilt magnitude, and a strong tendency to mirror-reflect the target, predominantly (or only) in the left-right direction.

BC's reflection errors can be interpreted by assuming that the underlying orientation representations are compositional. The suggestion presented here is that at some level(s) of mental representation, the orientation of a line is represented with respect to a reference axis (e.g., vertical), such that tilt direction and magnitude are represented separately. BC's reflection errors can be interpreted by assuming that she sometimes fails to represent the direction of tilt from a vertical reference axis. Although she is able to encode tilt magnitude, she appears to do so with less than normal precision.

The results from the tactile experiment also showed that BC's deficit affected not only her visual processing, but also her processing of tactile stimuli. This result can be interpreted by assuming that the problem arises at a processing level higher than vision—i.e., at a multi-modal level of representation. Alternatively, the result can be interpreted by assuming that the brain uses visual-like representations in processing the orientation of tactile objects.

The proposal that orientation representations have compositional structure can be seen as making earlier suggestions in the literature more explicit. Rudel and Teuber (1963), Olson and Hildyard (1977) and Rudel (1982) have suggested that oblique line orientations have a more complex representational structure than cardinal orientations. The proposed representational structure is consistent with this suggestion and makes the complexity of obliques and the priority of a vertical meridian more explicit.

The interpretation of BC's orientation errors will be discussed more thoroughly in the context of the representational framework, the COR hypothesis, which will be presented next.

2.5. Representation of orientation: The COR hypothesis

Several authors have discussed orientation errors and their implications for cognitive processing, but these suggestions have not been developed into an explicit theoretical framework of how the orientation of entire objects is represented in the human brain. Such a framework was proposed in Study II.

One of the motivations for constructing a theoretical framework to allow discussion of orientation representations was the observation that when orientation errors occur, they can take one of many forms. Although several qualitatively different orientation errors are possible (see Figures 10 and 11), these are often not differentiated. In many empirical studies of orientation—including the one with BC described above—several different kinds of errors have become conflated.

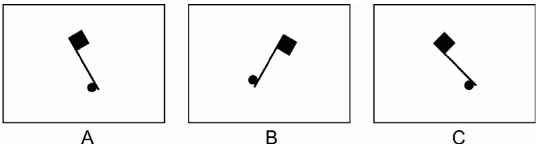

Figure 10. Tilt errors. (A) Stimulus figure. (B) Tilt direction error. (C) Tilt magnitude error. Reproduced from Study II.

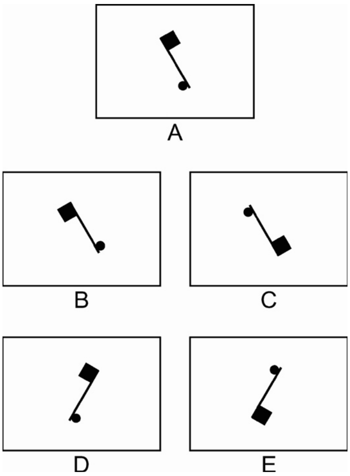

Figure 11. Reflection errors. (A) A stimulus figure can be reflected (B) across the object's principal axis, (C) across the object's secondary axis, (D) across an external vertical axis, (E) or across an external horizontal axis. Reproduced from Study II.

For example, reflecting a simple oblique vertical line across an external vertical axis results in a transformation that looks identical to one resulting from reflection across a horizontal axis, and when rotated 90° clockwise—and even when rotated 90° counterclockwise. Even if one end of the line is distinguished from the other—as in Experiment 4—the stimulus still remains bilaterally symmetric relative to its own principal axis. Bilaterally symmetric stimuli cannot differentiate between tilt direction errors and reflections across an external axis. Similarly, stimuli that are not tilted cannot differentiate between reflections across an object's own axis of elongation and those across an external axis.

Until recently, most authors seem to have assumed that reflection errors always take the form of left-right reflections across an extrinsic vertical axis. Empirically, however, this is clearly not always the case. Gregory and McCloskey (2010) found that adults' errors were not primarily external-axis left-right reflections, but reflections across an object axis. In contrast, young children's mirror-reflections included both object-axis reflections and left-right reflections across an external vertical axis (Gregory et al., 2011).

In most studies that have investigated orientation processing of whole objects—including Study I presented here—the stimuli have been inadequate for differentiating between different types of orientation errors, such as object-axis versus external-axis reflections. One of the suggestions of this thesis is that in future studies of object orientation, it would be useful to choose stimuli complex and asymmetric enough to allow differentiating between the various different types of potential orientation errors. The framework proposed in Study II, *the coordinate-system orientation representation (COR) hypothesis,* aims to help in clarifying the types of spatial relations potentially involved in orientation processing and in systematizing how orientation errors and representations are discussed.

2.5.1. The representation of orientation and spatial location

The COR hypothesis is based on McCloskey and colleagues' prior work on how spatial locations are represented. McCloskey and colleagues (McCloskey, 2004; 2009) proposed that at some level of the visual system, the locations of objects are represented in a mental spatial coordinate system. In this coordinate system, the locations of objects are represented as their distance and direction of displacement along orthogonal axes from an origin.

McCloskey and colleagues' proposal was based on evidence from patient AH, a young woman with a rare developmental visual deficit. In numerous tasks across various different conditions, AH made localization errors that took the form of left-right reflections across a vertical axis. For example, in a task requiring her to reach to an object on the table to the left of her, AH would often reach for an accurate distance, but to the opposite side. When the object was on the far right from her, she would often incorrectly reach far left; when the object was close to her on the left, she often reached near right.

According to McCloskey and colleagues (McCloskey, 2009), AH's location errors can be interpreted within the proposed spatial coordinate system as a selective visual deficit that arises from computations in which the distance of an object along the reference axes is accurately represented whereas the direction of displacement is not. According to the proposed coordinate system, misrepresenting the direction of an object (e.g., 30 cm from a reference point) along a horizontal reference axis (e.g., as RIGHT instead of LEFT) should lead to a reflection error that is sensitive to the object's distance from the origin (correctly 30 cm from the reference point) but in which the direction is incorrect (i.e., to the right instead of left).

In the COR hypothesis, this coordinate system is applied to the representation of object orientation.

2.5.2. The coordinate-system orientation representation hypothesis

The COR hypothesis assumes that, unlike location representations, orientation representations involve relationships between different reference *frames*. The COR hypothesis assumes that at some level(s) of representation in the visual system, the orientation of an object is cognitively represented as a relationship between (a) an object-centered frame of reference and (b) a second external reference frame.

This proposal assumes that an object-based representation first defines how the component elements of an object are arranged. The object's principal axis of elongation and a secondary axis, orthogonal to the principal axis, define an object-centered reference frame. The arrangement of all the object's component elements is specified according to this reference frame, and this arrangement within the frame forms the object-based representation. The location and tilt of all object parts are defined in this frame in relation to the principal axis of elongation. By definition, however, this object-based representation carries no information about the entire object's orientation, as orientation must be defined in relation to an external reference frame. In contrast, the object-based representation does determine whether any object parts are tilted in relation to the principal axis of elongation.

The orientation of an object in relation to the outside world is defined through a second reference frame *external* to the object. This external reference frame could be defined in relation to the viewer's body or, for example, the direction of gravity. The COR hypothesis does not make explicit claims as to how the axes of this external frame are defined; for present purposes, the only crucial assumption is that an external frame with orthogonal axes is used (referred to here as "vertical" and "horizontal"). It is further assumed that both axes are assigned a polarity, such that one end can be referred to (arbitrarily) as positive and the other end as negative.

Given the object-based representation and an external reference frame, the orientation of an object can now be defined as a relation between these two frames. This relation is specified based on three parameters:

1) *Axis correspondence:* the correspondence between the object axes and the axes of the external reference frame,
2) *Polarity correspondence:* the relation between the polarity of the object axes and the polarity of the axes of the external reference frame, and
3) *Tilt:* the object's tilt relative to the axes of the external reference frame.

Axis correspondence defines which axes of the object correspond to each external axis in the representation. In a two-dimensional object, there are two possible mappings: the principal axis of elongation can be represented in relation to the external vertical axis (a principal-vertical/secondary-horizontal mapping, PVSH) or, alternatively, in relation to the external horizontal axis (a principal-horizontal/secondary-vertical mapping, PHSV).

In the example in Figure 12, the principal axis of the object-based frame is mapped onto the external frame's vertical axis, and the secondary object axis onto the external frame's horizontal axis.

Polarity correspondence defines how the polarity of each object axis is related to the polarity of the axes of the external reference frame—in essence, whether or not they correspond. A *positive polarity mapping* refers to a relation in which the object's axis polarity value (e.g., positive) corresponds to that of the external axis polarity value (e.g., positive). In contrast, a *negative polarity mapping* refers to a relation in which the object's axis polarity value (e.g., positive) does not correspond to that of the external axis (e.g., negative).

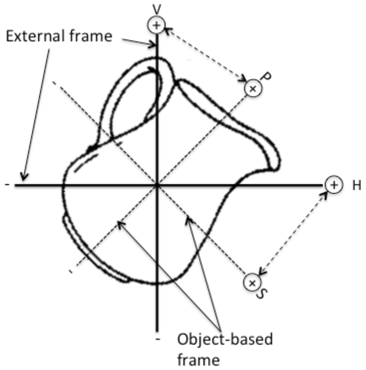

Figure 12. A principal-vertical/secondary-horizontal mapping. The object's principal axis is mapped onto the vertical axis of an external reference frame, and the object's secondary axis onto the horizontal axis of the external frame. In this example, both polarity mappings are positive (i.e., the polarity values of the object axes correspond to those of the external axes. The object's tilt is represented in relation to the vertical external axis; the object-based frame does not carry information about the object's orientation in space. The line-drawing of the pitcher is adapted from Snodgrass & Vanderwart (1980).

The *tilt* component designates the tilt of the object's axes in relation to the corresponding external axes. It is assumed that tilt direction and tilt magnitude are represented independently, by dictating both the direction and magnitude of the angular displacement between the object's principal axis and the corresponding external axis.

For example, the orientation representation of a tilted pitcher (see Fig. 12) would look something like this. In this example, the open end of the pitcher (the "top") along the primary axis of elongation in the object-based representation is assigned a positive value (+) and the closed end (the "bottom") a negative value (-). (In an everyday setting, the open end would typically be upwards and the closed end down, as when placed normally on a table, which is why they are referred to as the "top" and the "bottom". However, the object-based representation would not carry any of this information; this level of representation is only concerned with the configuration of the object's parts within the object.) Let us assume a vertical external reference frame with one end assigned a positive value (+) (e.g., with respect to the force of gravity) and the other end a negative value (-). In the example shown in Figure 12, the principal axis of elongation of the pitcher is mapped onto the vertical external frame, and the polarity correspondence is positive: the positive pole of the object's primary axis is mapped onto the positive pole of the external vertical axis.

In this example, the secondary axis of elongation in the object-based representation is defined such that the end with the lip of the pitcher is assigned a positive value (+), and the end with the handle is assigned a negative value (-). As shown in Figure 12, the secondary axis is mapped to the horizontal axis of the external frame, and the polarity correspondence is positive. The pitcher is also slightly tilted clockwise with respect to the external frame's vertical axis. Arbitrarily designating clockwise as the positive direction, the tilt component of the representation could be referred to as something like TILT DIRECTION +, and TILT MAGNITUDE 45°.

Taking all the previous parameters into consideration, the whole orientation representation for the pitcher would look something like this:

AXIS CORRESPONDENCE: PVSH

POLARITY CORRESPONDENCE
- PRINCIPAL: +
- SECONDARY: +

TILT
- DIRECTION: +
- MAGNITUDE: 45°

After this relation between an object-centered reference frame and an external frame has been established, this (new) representation can then be used for action. However, using the representation will typically (or perhaps always) involve relating the original reference frame to a *new* external frame. For example, drawing a perceived object involves relating the external stimulus frame to a frame relevant for the response, such as a frame defined by the sheet of paper on which one draws the picture of the object. The assumption is that exactly as in the first relation between the object-centered frame and the external frame, the same relations—axis correspondences, polarity correspondences and tilt—will now have to be specified again, this time between the first external (e.g., gravity-defined) frame and the second external frame (e.g., the stimulus sheet). The assumption is that processing of spatial information often involves a progression through several different reference frames.

Given these assumptions, orientation errors in spatial processing could arise from failures in the construction or use of any of the representations relating reference frames to each other, or in the construction or use of any of the representation components.

2.5.3. Orientation errors and the COR hypothesis

The COR hypothesis predicts different types of errors depending on which component or processing level is misrepresented. These can be illustrated using the examples in Figures 10 and 11.

As discussed earlier, misrepresentations of tilt direction and tilt magnitude should result in the kinds of errors shown in Figures 10B and 10C, respectively. In contrast, polarity correspondence errors lead to different types of errors. A polarity correspondence error relating an object-based frame's secondary axis to an external frame's horizontal axis should result in an object-axis (left-right) reflection (Fig. 11B). Such errors differ from reflections across the object's secondary axis (Fig. 11C), which result from a polarity correspondence error in relating the object's principal axis to the vertical axis of an external frame. A still third kind of reflection error is a reflection of the whole figure across an external vertical axis through three-dimensional space, resulting from a polarity correspondence error between the horizontal axes of two external reference frames (Fig. 11D). Fourth, a polarity correspondence error in relating the vertical axes of two external frames should result in a reflection of the whole stimulus figure across an external horizontal axis (Fig. 11E).

Using this framework, the performance of BC and other patients with cognitive deficits can be interpreted in tasks that involve the processing of spatial orientation.

2.5.3.1. Interpreting BC's and other patients' performance

As noted before, patient BC's performance suggested that her responses involved both inaccuracy and left-right reflections. Within the COR framework, it can be assumed that BC represented the tilt of the object's principal axis relative to a vertical external axis, and that she very frequently misrepresented tilt direction.

The left-right reflection errors can be interpreted as a deficit in representing the direction of tilt in relating object and external reference frames. The few up-down reflections BC may have made for target orientations near to the horizontal can be interpreted by assuming that she represented these orientations relative to an external horizontal axis. When tilt is specified relative to an external horizontal axis, a misrepresentation of tilt direction should not lead to left-right but to up-down reflections. (However, it is not clear whether BC made true up-down reflection errors, or whether these responses could be explained by imprecision alone; for details, see Studies I and II).

Alternatively, it is also possible that BC's reflection errors could have arisen from polarity correspondence errors in relating two external reference frames to each other. A deficit in representing polarity correspondence between two external frames should result in a mirror-reflection of the whole object across an external axis through three-dimensional space (Figures 11D and 11E). In contrast, a tilt-direction error should result in a rotation of the object in the picture plane (see Fig. 10B). However, to distinguish between these possibilities, one would need empirical data with stimuli that are not bilaterally symmetrical about the principal object axis, as both classes of error look identical with simple line stimuli. Unfortunately, tasks with stimuli that involved any degree of complexity resulted in BC's performance breaking down completely.

A key point, however, is that the COR hypothesis makes such distinctions explicit. With participants from whom such empirical data can be collected, the proposed framework helps in distinguishing between different error types and interpreting them. For example, the performance of patient AH can be interpreted as resulting from a deficit in representing polarity correspondences between object and external reference frame axes, especially in relating a secondary object axis to an external reference frame axis (see Figure 13). In direct copying tasks, AH frequently made orientation errors in which a whole object was left-right reflected (McCloskey, 2009)[5]. Within the COR framework, such errors can be interpreted as polarity correspondence errors. These errors could arise either from erroneous mapping between the object-centered representation and an external frame, or from erroneous mapping from one external reference frame to another.

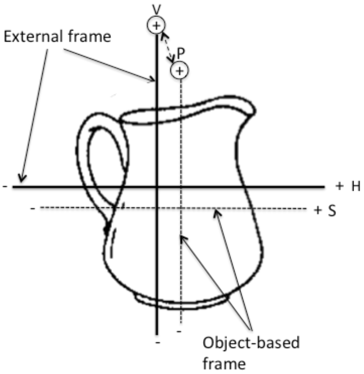

Figure 13. A representation in which all axes have been assigned polarities, but polarity correspondence is not specified between the object's secondary axis and an external reference frame's horizontal axis. The line-drawing of the pitcher is adapted from Snodgrass & Vanderwart (1980).

Differentiating between object-to-external versus external-to-external polarity correspondence errors is not always possible because, as noted before, both confusions lead to identical errors with stimuli that are not tilted. However, McCloskey and colleagues also tested AH with tilted stimuli, thus, providing a basis for further differentiating between such errors. For example, in direct copying tasks, AH frequently reflected the stimulus across its principal axis of elongation (see Study II). Such errors provide important empirical evidence for object-based representations (for a further discussion of this issue, see McCloskey, 2009). Within the COR framework, these errors can be interpreted as a deficit in representing polarity correspondence between the secondary axis of the object-centered frame and an external reference frame. (For a more detailed discussion of all orientation error types in AH's

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[5] Although such deficits clearly are rare, an extremely similar case has been reported in the literature. Pflugshaupt and colleagues (2007) recently identified a patient, PR, whose orientation deficit is strikingly similar to AH's.

performance and evidence from other patients with developmental deficits, see Study II and McCloskey, 2009).

Analogously to the above errors in brain-damaged patients, mirror-reflection confusions have also been demonstrated in typically developing children and under specific conditions, also in neurologically normal human adults. As noted before, Gregory and McCloskey (2010) found that the reflection errors adults made were primarily reflections across an object axis, while young children made both object-axis and external-axis reflections (Gregory et al., 2011). According to the COR hypothesis, the object-principal-axis errors observed in both adults and children can be interpreted as a failure to represent polarity correspondences between object secondary axes and external axes. The external vertical axis errors, observed in children but not in adults, can be interpreted according to Gregory et al. (2011) as a difficulty in the process of assigning polarity representations consistently to the poles of external horizontal axes. Presumably, the children's representations of left and right could be less well-differentiated than adults' representations, which could cause the children to assign polarity representations inconsistently to external horizontal extrinsic axes, giving rise to extrinsic vertical-axis reflection errors.

Finally, in interpreting BC's performance, the results showed that in addition to the left-right (and possibly some up-down) reflections, her responses were clearly also very imprecise. The imprecision in BC's responses can be interpreted by assuming that her representations of tilt magnitude are noisier or much more imprecise than those of neurologically intact subjects. Interestingly, prior research indicates that such a deficit is also neurophysiologically plausible. Damage to the inferotemporal cortex can cause a deficit in monkeys resulting in imprecise orientation discrimination. Holmes and Gross (1984; Walsh & Butler, 1996) found that macaque monkeys with IT cortex lesions were able to discriminate normally between stimuli that were rotated 60° or 120°, but failed to discern smaller orientation differences of 30° or 45°. Although the degree of imprecision is not identical, these results demonstrate that brain damage can, in some cases, lead to imprecision in orientation discrimination tasks.

2.6. General discussion

In Part One of this dissertation, orientation representation was investigated in an individual with cognitive impairments in orientation processing, patient BC (Studies I-II). A theoretical framework was proposed for discussing reflection errors and the representation of object orientation, the Coordinate-system Orientation Representation (COR) hypothesis, and it was demonstrated that this coordinate system could be used to discuss and to interpret orientation errors made by patient BC and other patients with deficits in orientation processing (Study II), as well as also by neurologically intact adults and typically developing children (Gregory & McCloskey, 2010; Gregory et al., 2011).

Orientation representation has previously been discussed in the literature in terms of reference frames and relations between such frames (e.g., Braine, 1978; Davidoff & Warrington, 2001; Humphreys & Riddoch, 2006; Riddoch & Humphreys, 1988; Riddoch et al., 2004; Turnbull & McCarthy, 1996). Some authors have explicitly argued that orientation judgments require the ability to represent the object and its axes in relation to an external coordinate frame such as one's body (Humphreys & Riddoch, 2006; Priftis et al., 2003; Riddoch et al., 2004). Others have suggested, in a similar fashion, that the recognition of object orientation would seem to depend on a process aligning an object-centered representation with an object-external representation, such as one related to the eyes (Harris et al., 2001). While these suggestions are consistent with the COR hypothesis, none of these prior suggestions have, however, been developed into explicit hypotheses of how orientation is represented at a cognitive level, and what the underlying assumptions are about the cognitive processes that relate such object- and external frames with each other. The COR hypothesis is an attempt to explicate the parameters that an orientation representation needs to define, and to provide a theoretical framework within which orientation errors can be classified and interpreted.

For example, prior studies (Turnbull, Driver, & McCarthy, 2004) have shown that the ability to judge orientation differences in the picture plane (2D rotations) can be dissociated from the ability to discriminate between them in the depth plane (3D rotations). The COR hypothesis provides an explicit framework for interpreting such dissociations. Further, other studies have shown that knowledge about some orientations—most notably, the upright—can be preserved when the ability to judge other orientations has been lost after brain damage (Harris et al., 2001; Karnath et al., 2000; Turnbull et al., 1995; Turnbull et al., 1997). With the COR hypothesis, results from these and other various studies can be discussed and interpreted using the same theoretical framework. In fact, recent work has begun to apply the COR hypothesis to investigating how the canonical orientation (uprightness) of stimuli is represented and how it affects the processing of spatial information (Hatfield, Gregory, & McCloskey, 2015).

The COR hypothesis may also help explain previous findings. For example, Harris et al. (2001) studied patient EL, who was impaired in judging many orientations of objects rotated in the picture plane, but performed remarkably well with objects that were upright. According to the COR hypothesis, the processing of orientation information begins with defining axis correspondences and polarity correspondences between axes. EL's performance can be interpreted by assuming a locus of deficit in representing tilt (either tilt magnitude or both direction and magnitude), with a preserved ability to represent axis and polarity correspondences. EL was not tested using mirror-reflected stimuli, but from the viewpoint of the COR hypothesis, this would be an interesting possibility to follow (see also Hatfield et al., 2015).

Similarly, Turnbull and McCarthy's (1996) patient RJ could not tell an image from its left-right mirror image but was able to differentiate between upright and upside-down images. In COR, this pattern of performance can be interpreted by assuming that the patient was able to represent the object's principal axis in relation to an extrinsic vertical axis, but that the representation failed to specify the polarity correspondence between the object's secondary axis and an extrinsic horizontal axis (see Fig. 13). Such a representation would enable one to differentiate between upright and inverted objects, but not to distinguish between left-right enantiomorphs.

As the COR hypothesis is in many ways to be considered a preliminary suggestion, several avenues for future research suggest themselves. For example, prospects for research could include empirically investigating how external reference frames are defined. Empirical evidence so far does not clearly indicate whether external axes are defined according to, for example, the force of gravity, the viewer's head and/or body, or, perhaps under special circumstances, the walls of a room. Similarly, the neural mechanisms that support the representation of external reference frames—however they are defined—are a promising direction for further investigation. For example, the lateral intraparietal (LIP) area is known to be important for updating spatial information from the eyes and for supporting retinally defined representations relative to the viewer (Duhamel, Colby, & Goldberg, 1992). In the close vicinity, in the lateral anterior intraparietal sulcus, neurons have been identified that are sensitive to the orientation of three-dimensional objects (Sakata et al., 1998), which may be related to how the parietal cortex supports the ability to guide hand actions targeted at objects in space. Despite these and other interesting findings, however, the neural basis for how different external frames are defined, chosen and used in relation to objects is not understood. Further research will hopefully elucidate these mechanisms in more detail.

More generally, many questions related to the neural mechanisms that support orientation representations of whole objects are still open and lend themselves to further study. Many interesting findings related to the neural basis of orientation processing have been reported (e.g., Ferster & Miller, 2000; Ferster, 2003; Furmanski & Engel, 2000; Gaffan, Harrison, & Gaffan, 1986; Gross et al., 1972; Holmes & Gross, 1984; Hubel & Wiesel, 1962; Hubel & Wiesel, 1968; Kravitz, Saleem, Baker, & Mishkin, 2011; Ling, Pearson, & Blake, 2009; Rollenhagen & Olson, 2000; Somers et al., 1995; Ungerleider & Pasternak, 2003; van der Zwan, Leo, Joung, Latimer, & Wenderoth, 1998; Vogels & Orban, 1994). The neural basis of orientation processing has been investigated in brain-damaged patients (e.g., Harris et al., 2001; Karnath et al., 2000; Martinaud et al., 2016; Riddoch et al., 2004), animal models (Walsh & Butler, 1996), and in neuroimaging work with normal adults (Faillenot, Sunaert, Van Hecke, & Orban, 2001; Shikata et al., 2003). Despite these and many other important studies, neither the neural mechanisms that support orientation representations of whole objects, nor the dynamics that give rise to the different orientation error types are yet fully understood. For example, the parietal cortices are often implicated in discussions of orientation processing, as many patients with orientation deficits have sustained damage to the parietal areas (Humphreys & Riddoch, 2006; Martinaud et al., 2016; Walsh, 1996, but this is not the case with all patients (e.g., McCloskey, 2009; Pflugshaupt et al., 2007). Integrating the findings across different studies has proven challenging.

One goal of the present discussion has been to show that the processing of orientation may employ several kinds of representations comprising several different subcomponents. These may in turn depend on different neural substrates. Previous studies have often been conducted using heterogeneous materials that are often inadequate for distinguishing among all possible error types. This limits the conclusions that can be drawn across studies, and may partly explain why integrating the different findings from previous studies has been difficult. For example, if a tilt-direction-component deficit might arise from a particular kind of injury that can be anatomically localized, would the neural locus be different for a tilt-magnitude deficit, or for deficits resulting in object-principal-axis or object-secondary-axis reflections? To tease apart these components, one needs to use stimuli that do not conflate the different error types. Hopefully, an explicit cognitive-level theoretical framework such as the COR hypothesis could provide a cursory map for informing such research in the future, both in imaging and behavioral work with intact adults and with individuals with cognitive deficits.

Promisingly, recent neuroimaging work has begun to apply the COR hypothesis in exactly this manner to investigate the neural representation of object orientation. Hatfield et al.'s (2014; under review) results suggest that object-axis reflections may elicit more similar patterns of neural responding than external-axis reflections in object-selective areas in the lateral occipital complex, consistent with how object-axis reflections are more easily confusable behaviorally. Also consistently with the COR hypothesis, a recent study of patients with parietal damage suggests that the abilities to differentiate mirror-reflected and rotated stimuli are both cognitively distinct and supported by (at least partly) separate neural processes (Martinaud et al., 2016).

Finally, still another possibility for future research, not specifically conjoined to the COR hypothesis, is related to symmetry perception. The human visual system is particularly sensitive to bilateral visual symmetries, and some phenomena related to orientation processing might be pertinent for how symmetries are detected. For example, the orientations of local element pairs affect how global symmetries are perceived (Saarinen & Levi, 1995). In addition, some visual properties of symmetry axes seem to be processed similarly as those of line orientations, and some authors have suggested that both orientation and symmetry encoding might be neurally supported by similar mechanisms (Treder, 2010; van der Zwan et al., 1998). Like mirror images, visual symmetries are also detected across external or object axes, and the percept of symmetry with respect to the vertical seems to emerge especially quickly and effortlessly under a wide range of conditions (Herbert & Humphrey, 1996; Treder, 2010). The detection of bilateral symmetry may be involved in how visual input is organized and segregated into figure and ground (Driver, Baylis, & Rafal, 1992). An interesting suggestion is that biological preferences for symmetric patterns in animals might have evolved to facilitate object recognition from different orientations (Enquist & Arak, 1994). If symmetry detection plays such an important role in primate vision, perhaps possible connections between symmetry perception and orientation representation might also be useful to investigate further.

3. Part Two: The Neural Basis for the Acquisition of New Memory Representations

Like vision, human memory relies on cognitive representations constructed of objects and events in the outside world. What are the brain mechanisms that enable us to acquire new memory representations? For example, how does the brain support our ability to learn to perform new tasks? How do different processing modules in the brain work in concert to support the acquisition of new memories for facts and events?

Part Two of this dissertation is concerned with these questions. In particular, Part Two aims to investigate how structures outside the medial temporal lobes (MTL) in the brain contribute to learning when new memory representations are acquired.

The different brain structures that support the acquisition of new memories are typically investigated in isolation from each other, which is often a fruitful approach. However, rapidly mounting evidence indicates that in learning, many different brain mechanisms localized in various brain regions act in concert to support learning in an adaptable and versatile manner (Barredo, Oztekin, & Badre, 2015; Buckner & Wheeler, 2001; Henke, 2010; Nadel & Peterson, 2013; Poldrack et al., 2001; Reber, 2013; Simons & Spiers, 2003; Squire & Wixted, 2011). Thus, it is sometimes beneficial to examine cognitive processes and their neural basis in the context of the cognitive modules and brain mechanisms with which they normally interact. In fact, Shohamy and Turk-Browne (2013) suggest that "the most fertile ground for discovery in cognitive psychology and neuroscience lies at the interface between parts of the mind and brain that have traditionally been studied in isolation".

Therefore, in order not to restrict the focus of study to an isolated mechanism alone, Part Two aimed both to shed light on the brain mechanisms that support learning, and to examine how MTL- and non-MTL-based brain mechanisms interact during the acquisition of new memory representations. Part Two employed both behavioral experiments and magnetic recordings of brain activity to collect empirical evidence through different but complementary methods. The brain dynamics of interest were studied both in a brain-damaged amnesic individual and also in neurologically healthy participants.

3.1. The medial temporal lobe, the hippocampus and human memory

Since Scoville and Milner's (1957) landmark study of patient HM, the medial temporal lobe (MTL) has been known to be critical for the acquisition of new long-term memories. In an attempt to alleviate HM's difficult epilepsy, sections of his MTL areas were surgically removed. After the resection, HM developed a severe deficit in the ability to form new *declarative memories,* memories that can be intentionally retrieved (Corkin, 2002; Eichenbaum, 2013; Scoville & Milner, 1957; Squire, 2009). The link between the MTL and memory function has later been corroborated in studies with other amnesic patients, such as RB, GD and EP (Insausti, Annese, Amaral, & Squire, 2013; Preston & Wagner, 2007; Squire & Knowlton, 2000; Stefanacci, Buffalo, Schmolck, & Squire, 2000; Zola-Morgan, Squire, & Amaral, 1986) and in experimental work with rodents and monkeys (Eichenbaum, 2000; Squire & Zola-Morgan, 1991; Squire & Knowlton, 2000; Squire, Stark, & Clark, 2004; Squire & Wixted, 2011; Suzuki & Amaral, 2004).

A structure of particular importance for declarative memory within the MTL is the hippocampus. The hippocampal region[6] consists of the subicular complex, the CA fields and the dentate gyrus. The hippocampus lies at the top of a processing hierarchy, receiving projections from the entorhinal cortex, which in turn receives its input from the perirhinal cortex, the parahippocampal cortex and other direct projections (Squire & Zola-Morgan, 1991; Squire et al., 2004; Suzuki & Amaral, 2004). Through the perirhinal, parahippocampal and entorhinal cortices, the hippocampus is wired to receive neural input from all parts of the neocortex, and it is thought to integrate information from all sensory modalities (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Squire & Knowlton, 2000; Suzuki & Amaral, 2004).

The hippocampus, together with other MTL structures (and the diencephalon), is thought to comprise the neural basis for declarative learning

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[6] The hippocampal *region* is not to be confused with the hippocampal *formation,* which refers to the hippocampal region together with the entorhinal cortex.

(for reviews, see Eichenbaum, 2000; Gabrieli, 1998; Preston & Wagner, 2007; Squire & Knowlton, 2000; Squire et al., 2004; Squire & Wixted, 2011). While the functions of the hippocampus are complex and their optimal conceptualization still under debate (Henke, 2010; Moscovitch et al., 2006; Nadel & Peterson, 2013; Shohamy & Turk-Browne, 2013; Verfaellie, LaRocque, & Keane, 2012), a large body of evidence from both human amnesic patients and non-human animals shows that the hippocampus is critical for the formation of new declarative memories (Eichenbaum, 2000; Mishkin, 1978; Rempel-Clower, Zola, Squire, & Amaral, 1996; Squire & Zola-Morgan, 1991; Zola-Morgan, Squire, & Ramus, 1994). Already in HM's case, Scoville and Milner (1957) regarded the lost hippocampal tissue as the prime suspect for causing his amnesia, as the removed MTL areas included large parts of the hippocampus. Although HM was the first well-documented patient study to suggest an important role for the hippocampus in supporting long-term memory, this conclusion was not warranted on HM's performance alone. HM's lesion included not only parts of the hippocampus, but also the amygdala and the adjacent parahippocampal areas (Corkin, 2002), leaving the relative contributions of the different structures unclear. The first thoroughly documented neuropsychological study demonstrating the critical role of the hippocampus in humans was Zola-Morgan and colleagues' (1986) investigation of patient RB, who developed moderately severe anterograde amnesia following an ischemic episode. RB's MTL damage was localized to the CA1 subfield of the hippocampus, demonstrating that a lesion limited to the hippocampus alone (or only one of its subfields) is enough to impair memory function. These results were later corroborated in other patient studies (Rempel-Clower et al., 1996).

The hippocampus has traditionally been held to be critical for both *semantic memory,* the ability to learn new factual knowledge about the world, and *episodic memory,* the ability to acquire new memories about life events (Squire & Knowlton, 2000; Squire et al., 2004; Squire & Wixted, 2011). However, Henke (2010) has argued that this may not be the optimal way to conceptualize memory processes in relation to hippocampal involvement. Instead, Henke proposes that several other factors, such as flexibility of retrieval and the number of trials needed for learning are more essential. While both semantic and episodic memory acquisition are profoundly disrupted by hippocampal damage, evidence also shows that some learning of new semantic memories is possible even when the hippocampus is damaged, albeit very slowly over numerous repetitions (Hamann & Squire, 1995; Holdstock, Mayes, Isaac, Gong, & Roberts, 2002; Kitchener, Hodges, & McCarthy, 1998; O'Kane, Kensinger, & Corkin, 2004; Tulving, Hayman, & Macdonald, 1991). According to Henke (2010), the hippocampus is critical for the rapid encoding of associations that can be flexibly retrieved cued by different contextual demands.

In addition to the hippocampus, the entorhinal, perirhinal and parahippocampal cortices also contribute to declarative memory. Larger MTL lesions result generally in more severe memory impairments than if the damage is restricted to fewer structures (Corkin, 2002; Gabrieli, 1998; Rempel-Clower et al., 1996; Squire & Zola-Morgan, 1991; Squire et al., 2004; Squire & Wixted, 2011). For example, HM's lesion extended to the parahippocampal gyrus. Consistent with the notion that non-hippocampal MTL areas are also important for memory function, his memory impairment was markedly more severe than RB's, whose MTL damage was limited to the CA1 subfield only.

3.2. Memory function supported by non-MTL-structures

All memory functions are not equally affected by MTL damage. For example, HM did not lose his ability for all learning after his MTL resection. Despite his severe deficits in tasks such as memorizing word lists, his performance showed gradual improvement after repeated trials in various other tasks such as mirror drawing, in which he was asked to trace the outline of a figure through a mirror without being able to see his hand (Corkin, 1968; 2002; Milner, 1962). In addition to simple motor tasks such as mirror drawing and rotary pursuit, HM and other amnesic patients have also shown improvement after repeated trials in perceptual priming tasks, classical conditioning, and habituation experiments (Corkin, 1968; 2002; Eichenbaum, 2000; Milner, 1962; Squire & Knowlton, 2000; Stefanacci et al., 2000), corroborating that MTL damage does not impair learning completely in all tasks.

The learning observed in various tasks with MTL-damaged patients is probably not supported by a single unified neural mechanism, however, but instead by several different ones. As Reber (2013) points out, it has proven extremely difficult to determine what different non-MTL-supported learning tasks have in common. Typically, non-MTL-supported learning processes are investigated in settings that do not require voluntary retrieval[7] of the learned material and in which learning is expressed implicitly through performance. Other common denominators have been difficult to find. Thus, these "other" types of learning are often collectively referred to as *non-declarative* learning—an umbrella term referring to several different non-MTL-based memory systems.

Different authors have suggested several candidates for brain mechanisms that could support non-declarative learning in various tasks. For example, evidence suggests that the neostriatum—the caudate nucleus and the putamen—and the cerebellum can support at least some forms of learning required in simple motor tasks (Eichenbaum, 2000; Knowlton, Mangels, & Squire, 1996; Woodruff-Pak, Papka, & Ivry, 1996). The cerebellum is also considered important for certain forms of conditioning that do not depend on the MTL/hippocampal memory system (Weiss & Disterhoft, 2015). For perceptual priming effects, in contrast, neocortical regions have been implicated (Cave & Squire, 1992; Schacter & Buckner, 1998; Tulving & Schacter, 1990). More generally, a widely entertained notion is that multiple regions of the neocortex participate in memory function by maintaining a distributed neural record of the initial sensory experiences that can be reactivated later (Buckner & Wheeler, 2001; Danker & Anderson, 2010). As an example of such a reactivation-based memory system, the primary sensory cortices, such as primary auditory cortex, seem capable of housing at least some forms of non-MTL-based memory representations related to sensory processing (Grosso, Cambiaghi, Concina, Sacco, & Sacchetti, 2015; Polley, Steinberg, & Merzenich, 2006; Weinberger, 2007a; Weinberger, 2007b).

Importantly, evidence indicates that the brain mechanisms that support declarative and non-declarative memory interact depending on task demands. Poldrack et al. (2001) used functional MRI to show that with an identical set of

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[7] Complicating the issue further, see Henke (2010) for a convincing argument that voluntary retrieval many not be the best basis for classifying memory processes.

stimuli, the relative engagement of the MTL and the basal ganglia changed depending on whether declarative or non-declarative aspects of the cognitive task were emphasized, respectively. According to the authors, this suggests that structures in these brain regions compete during the acquisition of new memories, and that this competition is dependent on task demands. Complex interactions between declarative and non-declarative memory systems have also been reported in the context of relatively simple forms of learning such as conditioning (Weiss & Disterhoft, 2015). Thus, although distinct and dissociable memory systems such as those supporting declarative and non-declarative memory do exist in the brain, they do not operate in isolation from each other, but in a dynamic and interdependent fashion.

3.3. Aims of Part Two

In sum, prior research has established that the MTL/hippocampal memory system is crucial for the rapid acquisition of new declarative memories, and that damage to the MTL area, or even to the hippocampus alone, can impair the ability to form new declarative memories. In contrast, many types of non-declarative learning are not equally dependent on the integrity of the MTL/hippocampal system.

While the MTL/hippocampal memory system has been studied in considerable detail, many questions remain concerning the non-MTL- and non-hippocampally supported memory systems. For example, non-MTL-based learning mechanisms have typically been investigated using tasks that are relatively (or extremely) simple. Thus, it is unclear whether non-MTL- and non-hippocampally-based learning mechanisms can support learning in tasks that are cognitively complex.

Another question that has not been fully investigated concerns how the MTL/hippocampal system interacts with other brain systems to support learning. For example, prior research has shown that brain structures dedicated to sensory processing participate in memory function, at least to some extent (Buckner & Wheeler, 2001; Danker & Anderson, 2010; Polley et al., 2006), and that the hippocampus and the MTL also contribute to sensory processing (Barense, Ngo, Hung, & Peterson, 2012; Nadel & Peterson, 2013). How do sensory processing modules interact with the MTL/hippocampal system when new memories are acquired? This potential interaction has currently not been investigated in detail.

The general aim of Part Two of this dissertation was to use empirical data collected using complementary methods to explore some of the brain mechanisms outside the MTL/hippocampal system that support the acquisition of new memories.

The specific aims of Part Two were:

- to use behavioral data from a brain-damaged individual to investigate whether non-hippocampal structures alone can support the acquisition of new memory representations in music performance, a cognitively complex context that requires motor control (Study III)
- to use recordings of brain activity from neurologically intact adults to investigate whether the process of new declarative-memory acquisition affects the neural processing of irrelevant sensory information in a non-MTL region—human auditory cortex (Study IV)

3.4. Study III

3.4.1. Can non-hippocampal structures support complex learning?

As outlined earlier, simple motor tasks can be learned through rote repetition despite hippocampal damage. However, an unresolved question is whether new learning is possible without the hippocampus in a cognitively complex context that requires motor control. The cognitive complexity of the learning process itself seems to critically affect whether the MTL and the hippocampus are involved. That is, the more processing modules the learning requires, the more likely the learning is to engage the hippocampus (Henke, 2010). Potentially, this might mean that new learning that requires motor control might not be possible after hippocampal damage if the learning context is complex.

A prime example of a complex task that requires precise motor control is music performance. Playing music has been described as one of the cognitively most complex forms of skilled serial action that human beings can perform (Altenmüller & Schneider, 2009; Palmer, 1997). However, music performance has been studied considerably less in cognitive neuroscience than music recognition (for reviews of the cognitive neuroscience of music, see Levitin & Tirovolas, 2009; Peretz & Zatorre, 2005; Zatorre, Chen, & Penhune, 2007). Reasons for this relative imbalance include technical difficulties in neuroimaging complex motor behavior and the lack of neuropsychological research patients who would present with both suitably focal brain lesions and special abilities for music performance.

Despite the inherent complexity involved in music performance, learning to play a new piece of music has sometimes been equated with “procedural”, “non-declarative” or “motor learning” in the psychological research literature (Cavaco, Feinstein, van Twillert, & Tranel, 2012; Cowles et al., 2003; Crystal, Grober, & Masur, 1989; Simmons, 2012), implying that new learning for music performance would not depend on the hippocampus. These terms, however, may not be entirely applicable to complex skills such as music performance. Stanley and Krakauer (2013) have recently argued convincingly that what HM acquired in simple motor tasks such as mirror drawing was not a motor *skill* but improved motor *acuity* – only one component of complex motor skills such as music performance. Therefore, in contrast to how the results from HM and other amnesic patients have often been interpreted, complex skills such as music performance are probably not adequately operationalized by motor acuity tasks (see Study III introduction, Beatty et al., 1999; Stanley & Krakauer, 2013).

Consistent with the difference between motor skill and motor acuity, the ability to improve one’s performance in simple motor acuity tasks does not guarantee the capability to learn to play new music (Beatty et al., 1999), suggesting that the hippocampus may be critical for the learning of new music for performance. Unlike the repetition of well-rehearsed motions, sight-reading novel music requires the execution of novel combinations of motor movements in an order one has never encountered before. Unlike the simple motor tasks in which HM showed improvement after repetition, sight-reading difficult new musical material poses large cognitive demands, including a high short-term memory load, because music is played under strict hierarchical time constraints (Furneaux & Land, 1999; Kinsler & Carpenter, 1995; Lehmann & Kopiez; Palmer, 2006; Sloboda, 1984).

Is the learning of new music possible in the absence of the hippocampus? Only two previous studies have investigated the learning of new music in amnesic patients with hippocampal damage. Modest learning was reported in both studies (Cavaco et al., 2012; Cowles et al., 2003). Unfortunately, however, both studies left open the possibility that the observed learning was supported by remaining hippocampal tissue. In both patients, either some hippocampal tissue remained, or the extent of the hippocampal damage was unreported.

Indirect evidence suggests that both hippocampal and non-hippocampal structures normally contribute to learning when new memories are acquired for music performance. First, the hippocampus is important for both the learning of single items and for the ability to form new associations between unrelated items (Eichenbaum, 2000; Henke, Weber, Kneifel, Wieser, & Buck, 1999; O'Kane et al., 2004; Schapiro, Gregory, Landau, McCloskey, & Turk-Browne, 2014; Squire et al., 2004; Stark, Bayley, & Squire, 2002). Second, sight-reading novel pieces of music requires the ability to integrate information related to pitch, rhythm and meter and sensory information from the visual, auditory and tactile modalities. The hippocampus is likely to be recruited especially when the context is complex and when task demands require that information is integrated from many sources (Henke, 2010; Nadel & Peterson, 2013; Squire & Knowlton, 2000). Third, sight-reading music poses high short-term memory demands, and tasks that pose high short-term memory demands have been shown to recruit the hippocampus (Axmacher et al., 2007; van Vugt, Schulze-Bonhage, Litt, Brandt, & Kahana, 2010). Fourth, the hippocampus has been implicated in memory tasks that involve the learning of novel melodies (Watanabe, Yagishita, & Kikyo, 2008), and MTL damage has been shown to impair the ability to learn new melodies (Wilson & Saling, 2008). Fifth, neuroimaging studies show that the hippocampus is engaged when complex temporal sequences are learned during motor performance (Robertson, 2007; Schendan, Searl, Melrose, & Stern, 2003). Some authors contend that the hippocampus supports the learning of higher-order temporal associations in practiced sequences (Albouy et al., 2008; Schendan et al., 2003), suggesting that the integrity of the hippocampus may be essential for the learning of new music for music performance.

In sum, it is currently an open question whether the hippocampus is critical for learning to perform a new piece of music, or whether at least some learning can be supported by non-hippocampal structures alone. To investigate this, Study III examined the learning of novel pieces of viola music through sight-reading in an amnesic patient whose hippocampus has been bilaterally nearly completely obliterated. Study III investigated whether LSJ could show learning for new pieces of music after practice despite her extensive anterograde amnesia and extensive bilateral MTL damage.

Unlike the patients in previous studies (Cavaco et al., 2012; Cowles et al., 2003), LSJ has virtually no intact hippocampal tissue. Therefore, any learning potentially observed in her performance cannot be attributed to remaining hippocampal tissue. Thus, her rare case of brain damage and selectively spared ability to play and sight-read music offer a unique opportunity for investigating whether new learning for music performance is possible without the hippocampus. Further, unlike in previous studies, novel viola pieces were used that were specifically composed to control for factors affecting musical complexity. In addition, unlike in previous studies, performance was evaluated before and after practice, both immediately and 14 days later, with detailed note-by-note analyses and subjective whole-piece performance judgments by a group of string instrumentalists.

3.4.2. Methods

3.4.2.1. Participants

LSJ is a newly-identified amnesic patient who has suffered extensive bilateral MTL damage, including the near-complete bilateral destruction of the hippocampus, after a herpes simplex encephalitis (HSE) infection. Before her illness, LSJ was a skilled amateur musician. Her ability to play the viola and to sight-read music have been spared after the brain damage.

Case report. LSJ contracted HSE at age 57; during the time of the study, she was 62 years old. Prior to her illness, she was a successful professional illustrator and a trained amateur musician.

Structural MRI revealed extensive bilateral damage to the MTL and anterior temporal damage in the left hemisphere (Figure 14). A volumetric analysis of the MTL region (Table 4, Schapiro et al., 2014) showed that the hippocampus had been eliminated bilaterally nearly completely: 4% of hippocampal tissue remained in the left hemisphere and 0% in the right.

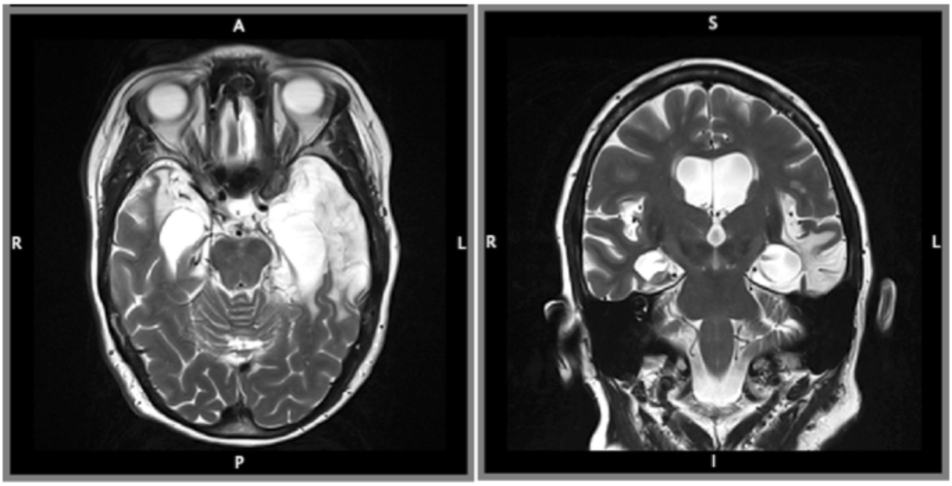

Figure 14. Magnetic resonance images of patient LSJ's brain: axial (Right) and coronal (Left) view.

Table 4. Remaining brain volume in patient LSJ by MTL region (Schapiro et al., 2014).

MTL Region	**Remaining volume relative to age-matched controls (N=4)**	
	Left (%)	**Right (%)**
Hippocampus	4	0
Parahippocampal cortex	12	62
Entorhinal cortex	0	43
Perirhinal cortex	2	50

In sharp contrast to LSJ's largely spared intellectual and musical capabilities (see Study III for details), LSJ presents with extremely severe anterograde and retrograde amnesia. On the Wechsler Memory Scale III, she scored in the severely impaired range on all subscales except for working memory, which showed milder impairment (for details, see Study III, for full neuropsychological profile see Gregory, McCloskey, & Landau, 2014). Thorough interviews failed to identify memory for even a single episode of her life prior to her illness (Gregory et al., 2014). She did not remember anyone from the research group despite meeting the researchers several times for hours at a time, and showed no recollection of tasks she had completed only a moment ago. In conversation, she discussed everyday topics enthusiastically and expressively but appeared to forget the conversation immediately if her attention was drawn elsewhere.

3.4.2.2. Stimuli

Three new semi-classical pieces of viola music were composed (A, B and C). Special care was taken to control for various factors that affect a piece's complexity (e.g., hand position changes, accidentals, clef and key signature changes). The factors matched across the three pieces are shown in Tables 5 and 6. (For details, see Study III.)

3.4.2.3. Procedure

LSJ practiced playing two of the pieces (A and B) in two different sessions during the same day (see Figure 15). Piece A was practiced in Session 1, and Piece B in Session 2. Piece C served as a control and was not practiced.

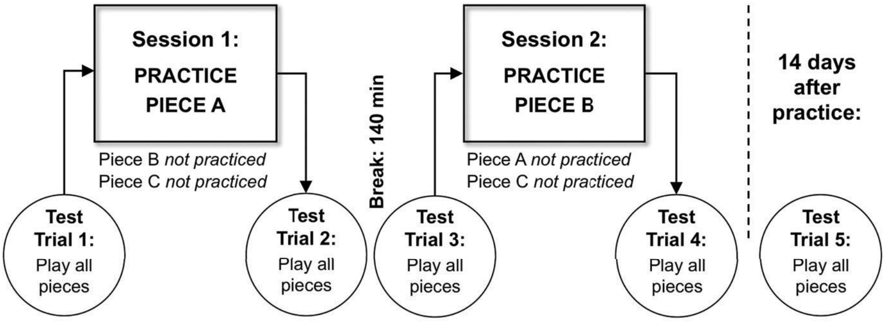

Figure 15. Study design. Two practice sessions were conducted during the same day, in which LSJ practiced two pieces on the viola. Piece A was practiced in Session 1, and Piece B in Session 2. LSJ's performance on all pieces was evaluated at a tempo of 144 bpm in test trials before and after each practice session, and 14 days after practice. Adapted from Study III.

During each practice session, LSJ completed 32 *practice trials* in which she played material from the piece on the viola at increasing tempos with a metronome. The practice material included both short segments of the piece as well as whole-piece performance trials. Each practice session lasted approximately an hour. (For details, see Study III.)

Table 5. Number of notes by duration and clef in Pieces A, B and C.

Note type	Piece		
	Piece A	Piece B	Piece C
Dotted quarter notes	1	1	1
Eighth notes	145	145	145
Half notes	15	15	15
Quarter notes	80	78	80
Quarter triplets	6	6	6
Whole notes	1	1	1
Total	248	247	248
Quarter notes in treble clef	8	8	8
Half notes in treble clef	4	4	4
Eighth notes in treble clef	16	16	16
Total number of notes in treble clef	28	28	28
Total number of notes in alto clef	220	219	220
Total	248	247	248

Table 6. Type and number of other musical events matched across Pieces A, B and C.

Musical event	Piece		
	Piece A	Piece B	Piece C
Quarter-note double-stops	4	4	4
Half-note double-stops	6	6	6
Eighth-note double-stops	2	2	2
A# accidentals	1	1	1
D# accidentals	3	3	3
Bb accidentals	2	2	2
Quarter-note slurs	6	6	6
Eighth-note slurs	52	52	52
Harmonics	2	1	1
Notes played with 4th finger	6	6	5
String crossings	119	119	119
Hand position shifts	4	4	4
Notes played in third position	24	24	21

Test trials, in which LSJ played all three pieces in their entirety at a tempo of 144 beats per minute (bpm), were administered immediately before and after each practice session and again after a 14-day delay period.

In all practice and test trials, LSJ was presented with the sheet music and instructed to play it to the best of her ability, without interruption, and according to the metronome.

Not even once did LSJ show any recollection of ever having encountered the same sheet music before when she was presented with any of the pieces or segments of them.

3.4.2.4. Note-by-note analyses

LSJ's performance in test trials was evaluated with two methods: *note-by-note analyses* and *subjective performance ratings* by experienced string players (violinists and violists).

In note-by-note analyses, two independent coders scored the number of notes LSJ played correctly from audio recordings of intact whole performances. Both coders were skilled amateur musicians. The first coder was blind to test trial, but not to which pieces had been practiced. The second scorer was blind to both test trial and practiced pieces, and was otherwise not involved with the study.

One point was awarded for every note that was played correctly according to pitch, relative rhythm, note duration, and the metronome-dictated tempo. Zero points were given for notes in which any of these aspects were incorrect.

When an error occurred that caused all subsequent notes to be misaligned (e.g., a skipped or an extraneous note), coders indentified the next first run of four consecutive notes that were played correctly to avoid penalizing all subsequent notes after a single error. This four-note run was used to establish a new meter with respect to the metronome, and coding was resumed from (and including) this four-note string.

The performances were scored in three blocks, with all test trials in one block per piece. The order of the blocks and the order of test trials within a block were separately randomized for each of the two coders.

Mean inter-rater reliability was 0.88 (0.87, 0.86, and 0.90 for Pieces A, B, and C, respectively). All discrepancies in coding were resolved between the coders, and the resolved scorings were used for analyses.

3.4.2.5. Subjective whole-piece performance ratings

Six experienced string instrument players (4 violists and 2 violinists) were asked to evaluate all LSJ's test trial performances from audio recordings. All raters were professional musicians or music students (mean number of years played 13.7; range 9-22). All raters were blind to both test trial and to which pieces had been practiced.

The string players evaluated the test trial performances on a scale of 1-5 according to three qualitative dimensions of musical performance chosen based on prior research (Zdzinski & Barnes, 2002): *intonation, rhythm,* and *tone.* In addition, the evaluators were also asked to rate the performances *overall.*

The performances were presented to the evaluators in three blocks, all test trials of one piece comprising one block. The order of blocks and the order or trials within each block were randomized across raters.

3.4.3. Results

Learning was expected to result in a positive linear trend, perhaps both overall (as all pieces, including the control piece, were performed many times throughout the experiment). In addition, it was anticipated that a quadratic trend might also occur, reflecting a plateauing of scores from Test Trial 4 to Test Trial 5, as no additional training took place over the delay. Most importantly, however, more pronounced learning effects were expected for the practiced Pieces A and B than for the unpracticed Piece C.

3.4.3.1. Note-by-note analyses

All three pieces were challenging for LSJ to sight-read at the dictated tempo. The mean percentage of correctly played notes across the three pieces was 29% in her first test trials, showing that the complexity of the material clearly exceeded her sight-reading capacity at the designated (fast) tempo. Qualitatively, all trials included several points of temporal breakdown and violations of the underlying beat, demonstrating that she was unable to maintain the temporal continuity expected in music performance.

To investigate potential learning through practice, we compared three critical trials most comparable across the different pieces: Test Trial 1, administered before no pieces had been practiced, Test Trial 4, administered on the same day after both target pieces had been practiced, and Test Trial 5, administered 14 days after practice. As potential learning effects were expected similarly in both practiced pieces, results were collapsed across Pieces A and B, and compared to the unpracticed control piece C.

As shown in Figure 16, effects of learning can be seen clearly in the critical trials. Mean percentages of correct notes increased across pieces from 29% to 61% in Test Trials 1 and 5, respectively. A repeated-measures ANOVA (2 piece types x 3 test trials) showed a significant main effect of piece type (practiced versus unpracticed; $F(1,246) = 71.23$, $p < 0.001$), a significant main effect of test trial ($F(2,492) = 111.95$, $p < 0.001$), and importantly, a significant interaction ($F(2,492) = 19.58$, $p < 0.001$).

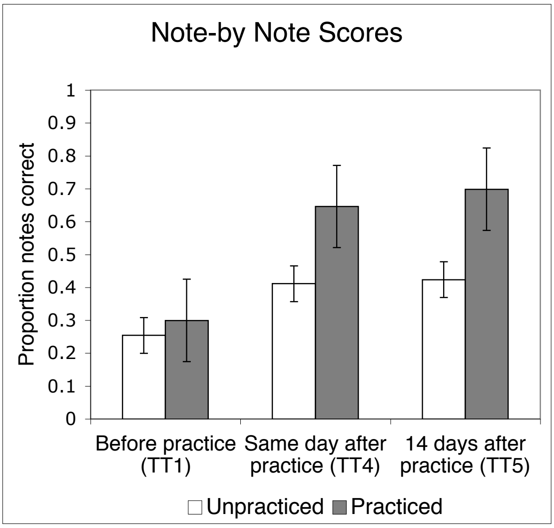

Figure 16. Mean proportion of correctly played notes in LSJ's sight-reading performances on the viola before practice, after practice on the same day, and after a 14-day delay. Results have been collapsed across the two practiced pieces, Piece A and Piece B. Error bars represent standard error of the mean. Adapted from Study III.

For the main effect of test trial, there was a significant linear trend across trials ($F(1,246) = 161.38$, $p < 0.001$), reflecting an overall improvement in note scores for both piece types from Test Trial 1 to 5. The quadratic trend was also significant ($F(1,246) = 44.06$, $p < 0.001$), reflecting the increase in note scores immediately after practice and followed by a plateauing of scores across the 14-day delay.

Critically, the improvement in LSJ's performance was larger in the practiced pieces than in the unpractice piece in both the linear and the quadratic trends, $F(1,246) = 43.66$, $p < 0.001$ and $F(1,246) = 3.95$, $p < 0.05$, respectively. As Figure 15 demonstrates, note scores improved after practice for all pieces, but this improvement was larger for the practiced pieces. The learning was also retained during the 14-day delay: as shown in the figure, the note scores for Test Trial 5 stayed almost exactly at the level of the previous trial for both practiced and unpracticed pieces, but were higher for practiced pieces.

The effect of practice is also apparent when the results are examined for individual pieces in the different test trials. As shown in Table 7, the piece practiced in a given session always showed the largest numerical performance improvement after the practice session. (The only exception to this pattern was a poor score for Piece A on Test Trial 3: On that particular trial, LSJ exceptionally played most of the piece in half tempo either deliberately or by accident, providing a zero-score for all the corresponding notes. After this one trial, however, her subsequent scores for Piece A were again systematically higher than on the first trial.)

Table 7. Mean percentages of correctly played notes according to piece and test trial.

Test Trial	Piece A correct (%)	Piece B correct (%)	Piece C correct (%)
1: Before Practice	39	21	26
2: After Practicing A	66	39	45
3: Before Practicing B	35	34	47
4: After Practicing B	59	70	41
5: After 14-Day Delay	76	64	43

3.4.3.2. Subjective whole-piece performance ratings

Effects of targeted practice were also evident in the performance ratings given by experienced string instrumentalists. Mean ratings increased across all pieces from before to after practice in all four dimensions. As shown in Table 8, the numerically most pronounced improvement in all rating dimensions was observed after each practice session for the piece that had been practiced, and the practiced piece showed better performance also thereafter than the unpracticed piece.

As with note-by-note scores, the results were analysed for the critical three test trials most comparable to each other: Test Trials 1, 4, and 5, with the data collapsed across the two practiced pieces. Separate repeated-measures ANOVAS (2 piece types x 3 test trials) showed a significant main effect of test trial in all rating dimensions, showing that performance ratings improved across test trials: intonation ($F(2,10) = 9.07$, $p < 0.01$), rhythm ($F(2,10) = 6.52$, $p < 0.05$), tone ($F(2,10) = 6.49$, $p < 0.05$), and overall ($F(2,10) = 8.72$, $p < 0.01$). The main effect of piece type (practiced versus unpracticed) was also significant for intonation ($F(1,5) = 17.1$, $p < 0.01$), tone ($F(1,5) = 7.66$, $p < 0.05$) and overall ratings ($F(1,5) = 13.35$, $p < 0.05$).

Critically, practice affected the ratings differently in the practiced pieces relative to the unpracticed control piece in ratings of intonation and tone: the interaction between piece type and test trial was significant in these dimensions ($F(2,10) = 6.150$, $p < 0.05$; $F(2,10) = 10.181$, $p < 0.01$, respectively). The ratings improved for the two practiced pieces after the practice sessions and stayed the same or fell slightly after the 14-day delay, while ratings for the control piece showed less or no improvement and a marked decline over the delay ($F(1,5) = 9.494$, $p < 0.05$; $F(1,5) = 16.304$, $p < 0.01$ for linear trend in practiced versus unpracticed pieces for intonation and tone, respectively). The interaction also approached significance in overall ratings ($F(2,10) = 3.545$, $p = 0.069$), but was insignificant in rhythm ratings ($F(2,10) = 1.746$, $p = 0.224$).

Table 8. Mean performance ratings by string instrumentalists for all evaluated performance dimensions according to piece and test trial.

Performance dimension	Test Trial	Piece A	Piece B	Piece C
Intonation	1: Before Practice	2.83	3.67	2.83
	2: After Practicing A	3.33	3.00	2.50
	3: Before Practicing B	3.33	2.67	2.67
	4: After Practicing B	3.17	4.17	3.00
	5: After 14-Day Delay	3.33	3.00	1.67
Rhythm	1: Before Practice	2.83	2.33	2.50
	2: After Practicing A	4.00	2.83	2.33
	3: Before Practicing B	2.83	2.17	2.67
	4: After Practicing B	3.67	3.83	3.00
	5: After 14-Day Delay	4.33	2.67	2.67
Tone	1: Before Practice	3.17	3.00	3.33
	2: After Practicing A	3.67	2.83	2.50
	3: Before Practicing B	3.50	2.83	2.67
	4: After Practicing B	3.17	4.00	3.17
	5: After 14-Day Delay	3.83	3.17	2.50
Overall	1: Before Practice	2.83	2.83	2.50
	2: After Practicing A	3.83	3.00	2.67
	3: Before Practicing B	3.17	2.17	2.67
	4: After Practicing B	3.17	4.00	3.00
	5: After 14-Day Delay	3.67	3.00	2.00

3.4.4. Discussion

Study III investigated the learning of novel viola pieces from written sheet music in a profoundly amnesic patient with bilateral MTL damage whose hippocampus has been nearly completely destroyed. Despite LSJ's extremely severe anterograde amnesia, two separate analyses of her music performance showed clear and systematic improvement after practice as compared to an unpracticed control piece. Effects of learning were observed both on the day of practice and still 14 days after practice.

The results show that non-hippocampal structures alone can support cognitively complex learning such as learning for music performance through sight-reading. Previous studies have shown simple motor learning to be possible without the hippocampus. However, unlike motor tasks that involve repetition of simple motor movements, music performance through sight-reading is a complex process that poses high cognitive demands and requires the execution of unique motor sequences the performer has never encountered before.

It is important to note that the results do not suggest that LSJ's learning was normal or on a par to that of a neurologically intact musician. Although no data are available that would allow comparisons to her pre-morbid level of performance, it is more than likely that LSJ would have shown superior learning prior to her illness. While the results of Study III show that at least some learning can occur even in the complete absence of the hippocampus, it is important to bear in mind that the MTL- and non-MTL-based memory systems normally function in unison. The integrity of the MTL/hippocampal system would certainly have assisted LSJ in any complex learning tasks, including the one used here.

In the intact brain, both the MTL and some, many or all various non-MTL-based learning mechanisms are likely simultaneously active. There is evidence to suggest that the relative degree of engagement of MTL versus non-MTL-based mechanisms during learning may depend on which aspect of the to-be-learned material is focused on. Furthermore, their relative engagement may change during the time course of learning (Poldrack et al., 2001). Thus, despite important dissociations such as the one demonstrated here, it is important to keep in mind that in the intact brain, the different learning mechanisms are likely to interact dynamically during learning.

So, what might the non-MTL mechanisms be that supported learning in LSJ's case? On the basis of Study III, it is not possible to identify the brain mechanisms that supported LSJ's learning—other than that the learning did not depend on intact hippocampal tissue. However, several interesting possibilities are available for consideration. Various brain mechanisms have been proposed to explain the learning that has been observed in amnesic patients with MTL damage. For example, the basal ganglia, the cerebellum and the neocortex have been implicated (Cave & Squire, 1992; Eichenbaum, 2000; Knowlton et al., 1996; Schacter & Buckner, 1998; Tulving & Schacter, 1990; Woodruff-Pak et al., 1996). In addition, although virtually all of LSJ's hippocampal tissue has been lost, some tissue remains in her parahippocampal, entorhinal, and perirhinal cortices. It seems possible that some or all of these structures may have contributed to LSJ's learning.

In addition to the brain systems mentioned above, other mechanisms may also have contributed to the observed learning. Because of its inherent complexity and sensory multimodal nature, music performance engages brain regions that are likely to encompass nearly the whole brain. For example, auditory, visual, tactile and motor areas of the cortex are all involved during sight-reading (Altenmüller & Schneider, 2009; Peretz & Zatorre, 2005; Zatorre et al., 2007). If learning can generally be supported by inherent plasticity as a property of cerebral cortex in general, as suggested by Reber (2013), these regions could perhaps all be potential candidates for supporting at least some aspects of the observed learning. In addition, specific aspects of music performance such as controlling timing, for example, have been linked to the cerebellum, basal ganglia and the supplementary motor area, and the execution of rhythmic patterns to the dorsal premotor cortex, lateral cerebellar hemispheres and prefrontal cortex (Janata & Grafton, 2003; Levitin & Tirovolas, 2009; Zatorre et al., 2007). Retrieval processes from long-term memory, on the other hand, are thought to depend on inferior frontal regions (Peretz & Zatorre, 2005).

Conceivably, the recruitment of such wide-ranging networks of cortical and subcortical brain mechanisms could help in supporting the observed learning. Future studies will hopefully further elucidate these mechanisms and the ways they interact.

3.5. Study IV

3.5.1. Does new memory acquisition affect sensory cortical processing?

Study III investigated the neural basis of new memory acquisition by examining whether brain structures outside the MTL/hippocampal system can support learning in a cognitively complex task. A second question not fully understood regarding the neural basis of new memory acquisition concerns the extent to which non-MTL-based brain regions, such as the sensory cortices, may contribute to the process of new declarative-memory acquisition. Study IV is concerned with the latter question.

Evidence indicates that the MTL interacts with non-MTL-based structures when new memories are acquired (Poldrack et al., 2001). However, in contrast to the considerable amount of research on the hippocampus and the MTL, relatively few studies have tried to understand how the MTL/hippocampal system interacts with other brain areas when new declarative memories are acquired (e.g., Simons & Spiers, 2003).

One reason for the relative dearth of studies on the interaction between the MTL and sensory processing may be related to traditional views of how these regions function. Traditionally the MTL/hippocampal region has been seen as a system exclusively specialized for declarative memory that has little to do with functions such as perception or attention (e.g., Squire et al., 2004). Similarly, sensory processing areas have been considered (at least relatively) modular. Sensory systems have been viewed as (at least relatively) independent of other sensory modalities and of MTL-driven memory processes (Fodor, 1983). Thus, sensory processing and memory acquisition have mostly been studied separately from each other.

The traditional view that the MTL/hippocampal system functions in isolation from perceptual processing has been recently challenged (Henke, 2010; Nadel & Peterson, 2013; Shohamy & Turk-Browne, 2013). Several authors have argued that the MTL may not function as exclusively in the service of declarative memory as previously thought. In vision, for example, damage to the perirhinal cortex of the MTL impairs several types of perceptual judgment in visual discrimination tasks, which has lead some authors to conclude that MTL areas have important functions in online visual perceptual processing in addition to subserving memory (Barense et al., 2012). Consistent with this view, Nadel and Peterson (2013) argue that the hippocampus integrates sensory information to distinguish between singular episodic events and wholistic patterns. In their view, the hippocampus functions via dynamic feed-forward-feedback connections. Nadel and Peterson (2013) argue that through such connections, hippocampal function also affects sensory processing in a top-down fashion.

If the notion is correct that MTL and hippocampal function affect sensory processing, could evidence of this interaction be seen during new memory formation—a process driven by the MTL/hippocampal memory system? That is, might the MTL-driven memory processes directly affect the brain systems in the sensory cortices? Do sensory cortices interact with the MTL when new memories are encoded, for example, by modulating their responses?

This question has not been investigated directly, but several pieces of evidence suggest that the encoding of new memories might modulate sensory cortical processing. First, sensory processing in auditory cortex is known to be modulated by top-down effects such as attention (Fujiwara, Nagamine, Imai, Tanaka, & Shibasaki, 1998; Näätänen, 1992). Conceivably, perhaps the acquisition of new declarative memories might also affect concurrent auditory processing.

A second source of evidence that sensory cortical areas might be affected by new memory encoding comes from research indicating that auditory cortex is able to support at least some forms of long-term memory representation. Some patients with MTL damage—including patient HM—have shown preserved learning in certain conditioning tasks that involve auditory tones (Woodruff-Pak, 1993). Corkin (2013) argues that this learning is supported by auditory cortex. More generally, learning is known to modify the representation of acoustic information in auditory cortex (Weinberger, 2007a; Weinberger, 2007b). For example, Polley, Steinberg and Merzenich (2006) trained two groups of rats to respond to the same set of auditory stimuli, such that one group was rewarded for responding to changes in frequency and the other for responding to changes in intensity. After training, both primary auditory cortex and the suprarhinal auditory field showed training-induced cortical reorganization that was specific for the auditory feature on which they had been trained[8]. Grosso et al. (2015) also argue that primary auditory cortex plays an important role in many forms of long-term learning (such as conditioning and emotional learning).

In sum, previous studies show (1) that the MTL/hippocampal memory system interacts with other memory systems during the acquisition of new memories, (2) that top-down processes such as selective attention modulate sensory processing in auditory cortex, and (3) that auditory cortex can support

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[8] Roughly analogous top-down effects have been reported for primary visual cortex (Li, Piech, & Gilbert, 2004).

at least some forms of memory representation. However, the potential interaction of MTL structures and auditory cortex during the encoding of memories has not been directly investigated. In particular, it is not known how task-irrelevant sounds are processed in the brain during the simultaneous encoding of new memory representations.

The aim of Study IV was to investigate whether a sensory cortical area—the human auditory cortex—modulates its pattern of responding during the encoding of new declarative memories unrelated to the incoming auditory stimuli. To this end, Study IV used a time- and space-sensitive brain-imaging method, magnetoencephalography (MEG), to record brain activity for irrelevant tones during the acquisition of declarative memory representations.

While in Study III the question was whether the required learning would be possible without the hippocampus, the situation is quite different here. Study IV used a declarative memory task that requires memory for serial order and explicit verbal recall, both of which are known to recruit the MTL/hippocampal memory system (Eichenbaum, 2000; Gabrieli, 1998; Henke, 2010; Jonides et al., 2008; Ranganath & D'Esposito, 2001; Squire & Knowlton, 2000; Squire et al., 2004; Squire & Wixted, 2011). Thus, in this context, potential modulation in the activity of the auditory cortex can reasonably be assumed to occur in concert with, or at least simultaneously with the activation of the MTL/hippocampal memory system.

However, many other brain areas in addition to the MTL undoubtedly also contribute to the processing required by a memory task under complicated conditions. For example, executive processes are presumably also needed when one tries to keep distracting auditory stimulation out during the memorization of visually presented material. Therefore, to focus on the effects of memory processes specifically, three different levels of difficulty were used in the memory task. In one condition, the subjects had no memory load; in the second, the subjects were given a low memory load; and in the third, a high memory load was introduced. If MTL/hippocampally-driven memory processes specifically affect auditory cortex function, such effects should be seen, presumably, as a function of increasing memory load.

3.5.1.1. The irrelevant sound effect

Study IV was conducted in the context of a well-established behavioral phenomenon, *the irrelevant sound effect* (ISE, also called *the irrelevant speech effect)*. The ISE refers to the finding that when irrelevant background speech, music or tones are presented during a declarative memory task—typically requiring serial recall—the irrelevant auditory stimuli cause a clear disruption in memory performance relative to a silent control condition (Bell, Dentale, Buchner, & Mayr, 2010; Colle & Welsh, 1976; Elliott & Briganti, 2012; Jones & Macken, 1993; Miles, Jones, & Madden, 1991; Neath, 2000; Salamé & Baddeley, 1982).

From a theoretical perspective, the ISE has been predominantly studied in the contexts of short-term memory and attention. One of the proposed accounts attributes the ISE to the operation of the verbal subcomponent of working memory (Baddeley, 1986; Baddeley & Salamé, 1989; Salamé & Baddeley, 1982), while a competing explanation ascribes it to processes representing serial order in short-term memory (Jones & Macken, 1993; Jones, Beaman, & Macken, 1996). In a third, non-memory based account, Cowan (1995) has argued that the effect is a consequence of capacity limitations in the focus of attention. How the effect should best be explained, however, is still under debate (Bell, Röer, Dentale, & Buchner, 2012; Buchner, Bell, Rothermund, & Wentura, 2008; Campbell, Winkler, Kujala, & Näätänen, 2003; Elliott & Briganti, 2012; Gisselgard, Petersson, Baddeley, & Ingvar, 2003; Gisselgård, Petersson, & Ingvar, 2004; Hanley & Shah, 2012; Lange, 2005; Little, Martin, & Thomson, 2010; Neath, 2000; Page & Norris, 2003; Röer, Bell, & Buchner, 2014; Schlittmeier, Weissgerber, Kerber, Fastl, & Hellbrueck, 2012; Viswanathan, Dorsi, & George, 2014).

While immediate recall is typically used within the ISE paradigm and experimental results have mostly been used to inform theories of short-term memory and attention, the ISE paradigm also lends itself to the investigation of declarative memory encoding processes in general. Although many short-term and long-term memory processes are dissociable (Baddeley, 1986; Cowan, 2008; Warrington, Logue, & Pratt, 1971), initially short- and long-term memory acquisition processes overlap (e.g., Jonides et al., 2008; Moscovitch et al., 2006). That is, during the phase when the stimuli are initially presented—in the ISE paradigm, typically one by one in a relatively fast succession—encoding processes cannot differentiate whether the to-be-remembered material will have to be recalled immediately or after a (short or a long) delay. Important differences between short- and long-term memory processes obviously emerge immediately if recall is delayed after stimulus presentation, leading in turn to the recruitment of (at least partly) divergent neural processes also (Jonides et al., 2008; Ranganath & D'Esposito, 2001). In contrast, however, during the initial stimulus presentation phase when the material is being encoded in memory, the encoding processes are unlikely to depend prospectively on the time of memory retrieval in the future.[9] Arguably, therefore, the cognitive processes that support the acquisition of new declarative-memory representations during the encoding phase will not differ depending on whether retrieval will be delayed after encoding, or on the length of such a retention interval. Thus, a typical ISE task is also suited to the investigation of encoding processes in declarative memory in general.

Consistent with the notion that initial memory-encoding processes do not depend on whether immediate or delayed recall will be required, evidence indicates that memory tasks typically used in the ISE paradigm—such as memorizing series of letters—engage the hippocampus and the MTL even when immediate recall is required (Henke, 2010; Kalm, Davis, & Norris, 2013; Nee & Jonides, 2013; van Vugt et al., 2010). Hippocampal involvement seems especially strong when memory load is high (Axmacher et al., 2007). Several authors have recently argued more generally that the role of the hippocampus does not seem to depend on the length of the retention interval (Henke, 2010; Yee, Hannula, Tranel, & Cohen, 2014), also consistent with the notion that the memory-encoding phase in a typical ISE-paradigm task recruits the MTL/hippocampal memory system regardless of whether recall is delayed. According to the review of the evidence by Jonides et al. (2008), MTL structures

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[9] One can imagine being told to memorize, in serial order, a string of digits presented visually in quick succession. How would you go about memorizing the digits if you knew you would be asked to retrieve them (a) immediately after presentation, or (b) an hour after presentation? Phenomenologically, it would seem that the two tasks would begin to diverge immediately after presentation, but not before the presentation of the stimuli has ended.

are important in both short-term and long-term-memory tasks for supporting the creation of novel memory representations, especially the binding of items to context in novel ways.

In the ISE paradigm, while the participant is memorizing the visually presented material, sounds are simultaneously presented that are irrelevant to the memory task. As any audible stimulation automatically activates the sensory cortical processing mechanisms related to auditory perception, the brain responses for the irrelevant sounds can be used to index sensory processing in auditory cortex during the construction of new declarative-memory representations. Therefore, the ISE paradigm provides an ideal context in which the potential interaction between the MTL/hippocampally-driven declarative-memory acquisition processes and sensory cortical processing can be investigated.

Is sensory auditory processing affected by concurrent declarative-memory encoding known to depend on the MTL and the hippocampus? In Study IV, brain responses were recorded to irrelevant sounds while the participants were engaged in a declarative-memory task unrelated to the presented sounds. The study utilized whole-head magnetoencephalography (MEG) to measure event-related magnetic fields (ERF's) while the subjects memorized visually presented digits.

Conceivably, memory acquisition might have different effects on sensory processing depending on whether the material is easy to memorize or whether the task requires active effort. To take this into consideration, the experiment included a no-task condition, in which the participants had no memory task at all, a low-load condition, in which memory-task demands were low, and a high-load condition, in which the memory task was considerably difficult. In addition, to investigate potential differences between the active encoding phase and the maintenance of the memorized material in mind, brain responses to irrelevant tones were recorded separately for the memory encoding phase during which the to-be-memorized material was presented and a subsequent retention phase, during which the memorized material had to be kept in mind.

3.5.2. Methods

3.5.2.1. Participants

Twenty neurologically normal adult subjects participated in the behavioral part of the experiment (mean age 26; range 18-51; 9 male; 2 left-handed). All subjects reported normal hearing and normal or corrected-to-normal vision. Of all subjects, 15 also participated in MEG measurements.

3.5.2.2. Stimuli

The digits used in the memory task were presented on a computer display in white against a black background. In the MEG measurements, the digits (width ca. 3 cm; height ca. 5.5 cm) were projected onto a screen 210 cm from the subject (visual angle ca. 1.5°). The digits ranged either from 0 to 8 or from 1 to 4, depending on experimental condition (see below). Each digit was shown for 700 ms (offset-to-onset ISI 300 ms).

The irrelevant auditory stimuli were pure tones with frequencies of 1000, 1500, 2000, and 2500 Hz (intensity 80 dB SPL, duration 100 ms). The tones were repeated in a fixed repeated sequence from lowest to highest. The durations and interstimulus intervals of the auditory stimuli were chosen to ensure that the visual and auditory stimuli would overlap as little as possible and to rule out any systematic contaminating effects. The offset-to-onset ISI between two tones was 387 ms. In the MEG part of the experiment, the tones were delivered binaurally through plastic tubes and ear pieces.

3.5.2.3. Procedure

Each trial consisted of (1) an encoding phase, during which digits were presented one at a time and the participant memorized them, and (2) a retention phase of 20 seconds, during which the memorized material had to be kept in mind. Irrelevant tones were presented during both phases, except in the silent control condition, in which no auditory stimulation was presented. After the retention phase, the participant was prompted to report the digits aloud in serial order.

The memory task contained three different conditions: in the difficult task condition (DT), the participant had to memorize nine digits in order (high memory load), and in the easy task condition (ET), there were four digits to memorize (low load). These conditions were compared to a no-task condition

(NT), in which nine digits were presented, and the subject was instructed to fixate on the digits but not to memorize them (no load). The silent control condition was not paired with the low-load or no-load conditions, but only with the difficult task condition for the difficult-task control condition (DTC).

In the DT and NT conditions, there were 18 trials. Because of the low number of magnetic responses during a single trial in the ET condition, the number of trials was increased to 30. Although the number of trials in the different conditions was not large *per se*, the design allowed the recording of a considerable number of ERF's in every condition. Because of the short duration and ISI of the auditory tones, more than a thousand ERF's could optimally be recorded during the encoding and retention phases in only one DT/NT trial.

The presentation order for the different conditions was determined through a latin square design. Six practice trials were presented before data collection was begun.

3.5.2.4. Behavioral data analyses

In the memory tasks, one point was awarded for a correct digit in the correct serial position. The scores were averaged across trials.

3.5.2.5. Magnetoencephalography (MEG)

Brain responses were measured with a 306-channel whole-head magnetometer with a 600-Hz sampling rate, a pre-stimulus baseline correction of 100 ms, and band-pass filtering of 1-30 Hz. Eye movements were measured vertically with electrodes above and below the left eye, and horizontally with electrodes at the outer canthus of each eye. Epochs containing artifacts were discarded. Event-related magnetic fields were recorded from the onset of auditory stimuli and averaged over a period of 500 ms, including a 100-ms pre-stimulus baseline. Epochs were averaged according to task condition (NT, ET, DT) and task phase (encoding, retention). At least 240 epochs were collected from each participant in each experimental condition and averaged separately.

The auditory N1m responses were analysed by selecting 44 gradiometer sensors from both hemispheres and fitting an unrestricted equivalent current dipole (ECD) to the response. Source amplitudes, latencies, locations and goodness-of-fit estimates were calculated separately for each participant, task condition, task phase and the left and right hemisphere. Data from two participants were excluded from analyses because the averaged goodness-of-fit estimates were below 65%. (For further details, see Study IV, materials and methods).

3.5.3. Results

3.5.3.1. Memory task

In the ET condition, participants made extremely few errors (mean score for all serial positions across all participants 99.6%). In the difficult task (conditions DT and DTC), task demands were clearly much higher (see Figure 17). The mean proportion of digits participants recalled correctly in a given serial position was 57.9%.

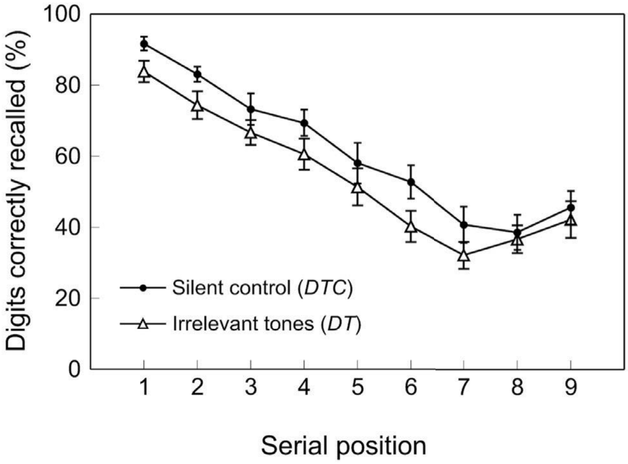

Figure 17. Serial recall for visually presented digits as a function of serial position in the DT (difficult task) and DTC (difficult task, silent control) conditions. Irrelevant tones disrupted memory performance as compared to a silent control condition in which no auditory stimulation was presented. Vertical bars represent standard errors of the means.

A two-way 9 x 2 repeated-measures ANOVA (9 serial positions x 2 auditory stimulation conditions) showed that in the difficult task, a digit's serial position affected memory performance ($F(8,152) = 38.96$, $p < 0.001$). Planned polynomial contrasts showed that as expected (e.g., Jones & Macken, 1993), performance declined from the first positions (linear polynomial trend $F(1,19) =$

102.92, $p < 0.001$) and then plateaued or improved again at final positions (quadratic polynomial trend $F(1,19) = 10.45$, $p < 0.01$).

As shown in Figure 17, an irrelevant sound effect was evident in the results. Memory performance was superior in the silent control (DTC) condition, in which participants remembered 61.5% of the presented digits correctly, relative to the irrelevant sound condition (DT), in which only 54.3% of digits were reported correctly ($F(1,19) = 11.71$, $p < 0.01$). No interaction was observed between auditory stimulation and serial position.

3.5.3.2. Event-related magnetic fields

The presented tones elicited prominent N1m responses. ECD modelling indicated that the responses were generated in the vicinity of auditory cortex in the temporal lobes.

N1m amplitudes. Event-related fields showed that both task condition and task phase had a clear effect on auditory processing. The mean N1m response amplitudes from the left and right hemispheres in the different task conditions and in the two task phases are shown in Figures 18 and 19 and in Table 9.

A 2 x 2 x 3 repeated-measures ANOVA (hemisphere x task phase x memory load) of N1m response amplitudes showed that both task phase (encoding vs. retention) and memory load (NT, ET, DT) affected sensory processing, but hemisphere (right vs. left) did not. As shown in Figure 19, response amplitudes were larger in the encoding than the retention phase ($F(1,12) = 92.18$, $p < 0.001$).

Table 9. The magnitudes of N1m responses to irrelevant auditory tones according to task condition (no task, easy load, high load) and phase (encoding, retention).

Memory load	**N1m response amplitudes (nAm)**			
	Encoding		**Retention**	
	Mean	S.E.	Mean	S.E.
No load (NT)	23.32	2.03	14.07	1.30
Low load (ET)	29.17	3.19	13.74	1.28
High load (DT)	30.11	2.44	16.16	1.69

Interestingly, amplitudes increased with memory load ($F(2,24) = 3.61$, $p < 0.05$). As shown in Figure 18, the N1m amplitude was most prominent in the DT condition and smallest in the NT condition (significant linear trend in planned polynomial contrasts, $F(1,12) = 5.94$, $p < 0.05$). In addition, there was a significant interaction between memory load and task phase ($F(2,24) = 4.64$, $p < 0.05$). This appears to have resulted from a difference in how responses changed from encoding to retention in the no-task condition versus the two memory-load conditions. While mean response amplitudes dropped by nearly or more than 50% during retention in the memory load conditions relative to the encoding phase (52.9% and 46.3% in the ET and DT conditions, respectively), this reduction was only 39.7% in the no-task condition (planned comparisons for encoding vs. retention: NT vs. ET, $F(1,12) = 9.08$, $p < 0.05$; NT vs. DT, $F(1,12) = 6.78$, $p < 0.05$). All other main effects and interactions were statistically nonsignificant.

N1m source locations. Task phase and memory load also affected the locations of N1m sources in the temporal lobe. In general, the source was deeper during encoding, and memory load shifted source locations along the anterior-posterior axis. For details, see Study IV.

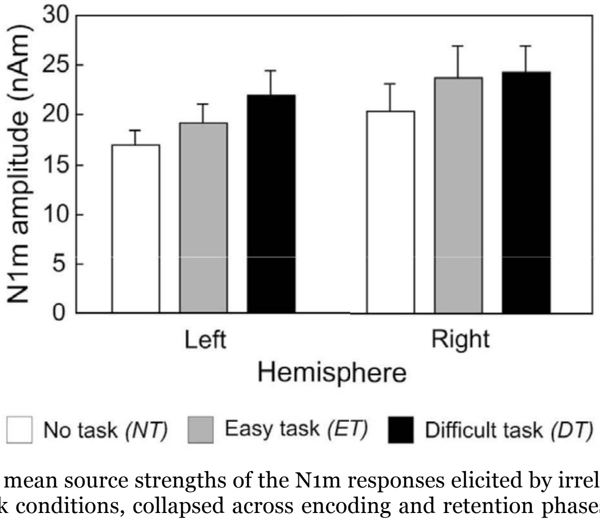

Figure 18. The mean source strengths of the N1m responses elicited by irrelevant tones during the different task conditions, collapsed across encoding and retention phases. As memory load was increased from a no-task to an easy-task and a difficult-task condition, the amplitude of the N1m response increased in both the left and right hemispheres. The vertical bars represent standard errors of the means.

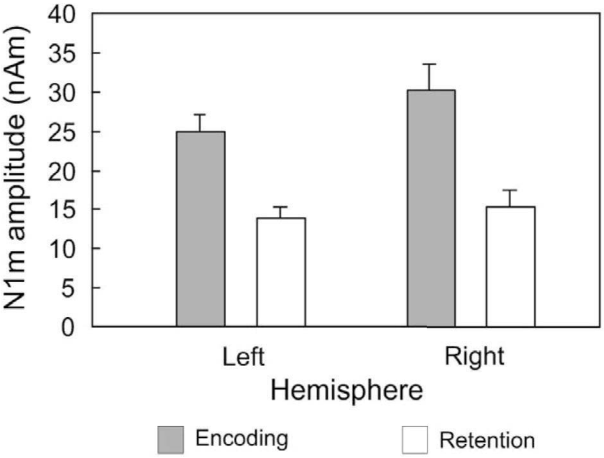

Figure 19. The mean source strengths of the N1m responses elicited by irrelevant tones during different task phases. The responses were larger during encoding than the retention phase of the memory task. The vertical bars represent standard errors of the means.

3.5.4. Discussion

Study IV investigated the sensory processing of irrelevant tones in the human auditory cortex during the acquisition of new declarative-memory representations in neurologically healthy adults. Magnetic recordings of neural activity showed that the encoding of new declarative memories affects cortical auditory processing even when the memory task and the auditory stimulation are completely unrelated. N1m response amplitudes for irrelevant tones increased as a function of memory load, such that amplitudes were larger in the easy-load condition relative to a no-task condition and largest in the high-load condition. Response amplitudes were higher during the phase in which new memory representations were initially encoded than during the retention phase, a 20-second period during which the memorized items had to be kept in mind before recall. These results show that the voluntary acquisition of new declarative memories affects early sensory processing in the human auditory cortex, even when the auditory stimulation is irrelevant for the memory task and presented in a different sensory modality.

That memory acquisition should affect the cortical processing of irrelevant sounds is not easily explained by traditional views of memory systems in the brain. The acquisition of new declarative memories is thought to be driven by the MTL/hippocampal memory system, and these processes have traditionally not been thought to affect sensory processing of unrelated items (e.g., Squire et al., 2004). It is not immediately clear why a sensory cortical region should modulate its responding for irrelevant items when new declarative memories are encoded. Why and how this interaction occurs would seem to warrant further investigation in future studies. However, it is interesting to note that some authors have recently suggested that MTL regions participate in some perceptual processes such as those required in visual discrimination (Barense et al., 2012; Squire & Wixted, 2011). The results of Study IV are consistent with Nadel and Peterson's (2013) view that the MTL/hippocampal system functions via dynamic feed-forward-feedback mechanisms. Similarly, Shohamy and Turk-Browne (2013) have suggested that memory systems and the hippocampus could be seen as nodes in interactive networks that can influence a wide range of cognitive functions, including perception. Conceivably, such feed-forward-feedback mechanisms or interactive networks could also affect auditory sensory processing when new declarative memories are encoded.

That stronger N1m responses were observed for conditions with higher memory load was unexpected. Cortical responses to irrelevant tones were expected to decrease as task demands increased in the memory task. Presumably, a visually presented memory task might be expected to increase processing in non-auditory areas such as those related to attention, working memory and the encoding of the to-be-memorized material, such as the prefrontal cortices and the MTL. Previous studies have shown attention to modulate responses in sensory cortical areas in favor of *relevant*, not irrelevant stimuli (Fujiwara et al., 1998; Näätänen, 1992; Paavilainen, Tiitinen, Alho, & Näätänen, 1993; Woldorff, Hackley, & Hillyard, 1991). Studies using hemodynamic measures, on the other hand, have indicated greater activity in prefrontal areas during memory tasks accompanied by irrelevant speech: Gisselgård et al. (2003) reported that in their PET study, regional blood flow increased in the dorsolateral prefrontal cortex bilaterally, which they interpreted to reflect executive functions recruited during the memory task. Thus, the increased N1m amplitudes for irrelevant auditory stimuli observed in Study IV may seem counterintuitive.

Despite the apparent counterintuitiveness of the results, however, research conducted after Study IV has reported consistent findings. In an EEG study, Bell and colleagues (2010) measured responses to auditory stimuli while participants memorized visually presented digits. Similarly to Study IV, Bell et al. (2010) also recorded event-related responses separately during encoding versus a retention phase before recall. In important ways, the results replicated those reported in Study IV. First, the amplitudes of the N1—the electric counterpart of the N1m—were larger during encoding than during retention, exactly as in Study IV. Second, although the study design did not include a passive no-task condition or an easy-load condition (the NT and ET conditions in Study IV) that would permit comparisons between different levels of memory load, Bell et al. (2010) did have an interesting comparison of relevance to our results: they compared a steady-state auditory stream, in which an identical stimulus is presented repeatedly, to a changing-state stream, consisting of changing stimuli—such as those used in Study IV. A changing-state stream has been shown to cause a larger disruption in memory performance than steady-state stimuli (Jones et al., 1996). Thus, the more distracting changing-state stimuli would logically seem to pose higher demands on the cognitive resources required for successful encoding—perhaps similarly to a higher memory load. In Bell et al.'s (2010) study (and consistently with Campbell et al., 2003), the auditory stimuli elicited larger N1 amplitudes in a changing-state than in a steady-state stream. While this N1-result is not a direct replication of the memory-load effect observed in Study IV with N1m amplitudes, the findings are certainly consistent: the higher the task demands on declarative-memory encoding processes, the higher the N1(m) amplitudes. Thus, these results corroborate those from Study IV, showing that a cognitively taxing memory task enhances, rather than diminishes, the cortical processing of simultaneous irrelevant auditory distractors. Therefore, declarative-memory acquisition seems to affect cortical auditory processing in a manner contrary to selective attention. Conceivably, this difference could result from the interaction between auditory cortex and the medial temporal lobe memory system. Further research will hopefully be able to demonstrate whether this hypothesis is correct.

As an additional note of interest, a qualitative difference would seem to emerge in the auditory processing stream somewhere between the earliest sensory processing stages and the cortical processing that the prominent N1m wave reflects. Auditory-evoked brainstem responses (ABR) are elicited very early, a few milliseconds after the presentation of the stimulus. The ABR response is thought to reflect activity transmitted through the brainstem towards the thalamus and thus to index a very different stage of processing than post-thalamic processing in auditory cortex. Interestingly, ABR recordings for unattended sounds during memory encoding have shown amplitudes to *decrease*, rather than to *increase,* as memory load is increased—i.e., in a pattern opposite to the one observed in Study IV (Sorqvist, Stenfelt, & Ronnberg, 2012). Thus, apparently in these earliest stages of processing, an increased memory load decreases neural responses for unattended sounds, while the opposite effect emerges (roughly) 100 milliseconds later in auditory cortex. It is interesting to speculate whether the involvement of the MTL memory system might account for this difference: conceivably, the ABR response could occur too early for the MTL to be engaged, whereas the N1m is elicited late enough to allow MTL involvement. Future research will hopefully elucidate the neural mechanisms accounting for this difference.

As a concluding remark, a particular limitation of Study IV should be noted. Specific care was taken to design the experiment in a way that would avoid several potential pitfalls. For example, the irrelevant tones and the visual presentation of the digits had to be carefully coordinated to avoid stimuli from one modality contaminating the brain responses to stimuli from another. However, despite successfully controlling for a number of such confounding factors, the experimental design still does leave some important questions unanswered. One of them concerns the differences in neural responses between the encoding and the retention phases of the memory task. To ensure a sufficient signal-to-noise ratio, the recorded brain responses were averaged across the task phase as a uniform block. Unfortunately, these averaged responses do not permit further analyses of possible changes that may have occurred *within* a task phase. As a relevant possibility, sensory processing systems in auditory cortex could habituate to the ongoing auditory stimulation over time. In a recent well-conducted behavioral study, Bell and colleagues (2012) reported that in five separate experiments, the irrelevant sound effect was markedly reduced after passive listening to the distractory auditory material before the memory task. Although there are important differences between Bell et al.'s (2012) materials and the ones used here—for example, the use of speech as a distractor—their results nevertheless suggest that some habituation effects may occur during the task. Amplitudes of N1 responses have also been shown to diminish over time if identical stimuli are presented repeatedly (Näätänen & Picton, 1987; Näätänen, 1992). Conceivably, the amplitude difference seen between the encoding and the retention phases may have resulted partly from habituation effects. Partly alleviating this concern, however, is that the auditory stream used was "changing-state"—i.e., the tone sequence consisted of different-frequency tones. Tones of changing frequencies should be somewhat more resistant to habituation effects than identical stimuli that are repeated monotonously. Future research will hopefully shed more light on this issue as well.

In sum, the results of Study IV showed that the acquisition of new declarative memories affects the processing of auditory stimuli in the auditory cortex, even when the auditory stimuli are irrelevant to the memory task and presented in a different modality. This finding is consistent with the notion that during the construction of new declarative memories, the MTL/hippocampal memory system interacts with brain mechanisms that perform early sensory feature analyses of incoming auditory stimuli. While both MTL/hippocampally-driven memory processes and prefrontally-driven executive processes are considered important for the ability to keep irrelevant distractors at bay during the acquisition of new memories, the results of Study IV suggest that other early sensory processing mechanisms may be relevant as well. The results suggest that modulation of activity in sensory areas in the cortex may also contribute when the influence of irrelevant distractors needs to be suppressed during new memory acquisition.

3.6. The Neural Basis for the Acquisition of Memory Representations

Part Two of this dissertation investigated the neural basis for the acquisition of new memory representations. While prior studies have established that the MTL/hippocampal memory system is crucial for the construction of new declarative memories, the role of non-hippocampal structures and non-MTL-based neural systems and their interaction with the MTL have received far less attention. Two studies in Part Two of this dissertation investigated potential ways in which non-hippocampal and non-MTL-based structures may contribute to the construction of new memories in the intact brain.

Study III studied learning in a rare case of amnesia in a context that involves motor control but is cognitively complex. The study was conducted with LSJ, a profoundly amnesic patient with bilateral MTL damage including the near-complete bilateral destruction of the hippocampus. The results of Study III showed that LSJ performed novel viola pieces consistently better after targeted practice relative to an unpracticed control piece. Learning was observed both in note-by-note analyses and in subjective whole-piece performance ratings conducted by experienced string instrumentalists. To our knowledge, this was the first demonstration that non-hippocampal structures alone can support some learning of new music via sight-reading for music performance, as prior studies have not been able to rule out the potential contribution of remaining hippocampal tissue. Together with previous findings (Altenmüller & Schneider, 2009; Palmer & Meyer, 2000; Palmer, 2006; Reber, 2013; Robertson, 2007; Schendan et al., 2003; Stark et al., 2002; Watanabe et al., 2008; Wilson & Saling, 2008), the results suggest that both the MTL/hippocampal memory system and non-hippocampal structures cooperate in the intact brain in the construction of new memory representations when new music is learned for performance.

Study IV used magnetoencephalography to investigate sensory processing of irrelevant sounds in the human auditory cortex in neurologically intact adults when new declarative memories were encoded. The results showed that the acquisition of declarative-memory representations enhanced sensory processing in the auditory cortex. Together with prior studies that have shown memory load to modulate neural activity in the hippocampus (van Vugt et al., 2010) and in other MTL regions (Axmacher et al., 2007), the results of Study IV suggest that when new declarative memories are acquired, the MTL/hippocampal memory system works in concert with other neural networks already at a level as early as the feature-analysis systems devoted to sensory cortical processing. The results challenge traditional views that have assumed sensory systems to operate independently of each other (e.g., Fodor, 1983) and of the MTL/hippocampal memory system (e.g., Squire et al., 2004).

The results of Part Two show that several brain regions are actively involved when new memory representations are initially acquired. On the one hand, the learning required in both of the experimental tasks used in Part Two depends on the hippocampus. Although the learning of new music for performance and the learning of serial order in a declarative-memory task are inherently very different, in both tasks the required learning depends in part on the ability to acquire memories for single items and on the ability to form novel associations between previously unrelated items. Prior studies have established that the hippocampus is essential for these abilities (Gold, Hopkins, & Squire, 2006; Henke, Buck, Weber, & Wieser, 1997; Henke et al., 1999; Stark & Squire, 2003). Both of the tasks used in Studies III and IV also required the material to be learned in a temporally sequential pattern, one that unfolds over time. Functional neuroimaging studies have shown the hippocampus to be engaged in neurologically intact humans when temporal sequences are learned (Robertson, 2007; Schendan et al., 2003). In addition, studies with non-human animals have also demonstrated performance impairments in temporal sequence completion tasks when the hippocampus is lesioned in laboratory animals (Hoang & Kesner, 2008), suggesting that the hippocampus is necessary for learning that requires temporal order. The results of Part Two extend these results by showing that in addition to MTL-based and hippocampal structures known to be critical for learning, non-MTL-based and non-hippocampal structures also subserve memory-acquisition processes in the intact brain.

4. General Discussion: Levels of Analysis, Converging Evidence and Methods in Cognitive Neuroscience

According to Marr's (1982) influential proposal, understanding any complex information-processing system requires three levels of analysis: A complete explanation needs to account for the system's behavior at the *computational,* the *algorithmic/representational,* and the *implementation* levels. Although the details of Marr's proposal have been debated, the requirement of multiple levels of analysis remains a central principle in the study of cognition (e.g., Peebles & Cooper, 2015). In cognitive neuroscience, the levels are typically regarded as semi-independent, with each level seen as providing constraints on the others (e.g., Ochsner & Kosslyn, 2014).

How can different methodological approaches inform multiple levels of analysis in understanding how the brain enables the mind? Through four empirical studies, this dissertation attempts to elucidate some aspects of this question. More precisely, an attempt is made to demonstrate four methodological points: (1) that an important source of evidence for formulating hypotheses at the cognitive level comes from the study of cognitive deficits, (2) that a detailed, empirically-driven cognitive framework is particularly valuable for guiding future research both at the levels of cognitive function and neural implementation, (3) that studies of brain-damaged individuals can provide important complementary evidence to functional neuroimaging about how cognitive processes are neurally implemented, and (4) that magnetic recordings of brain activity can be informative of multi-regional interaction at the neural level. Each of these points is discussed in turn, with a particular emphasis on the relative advantages and limitations of single-patient studies of cognitive deficits. Finally, recommendations and methodological notes are made concerning future research.

4.1. Levels of analysis and the investigation of cognitive deficits

Experimental studies of cognitive deficits are often seen as particularly informative when used for collecting fine-grained evidence at the cognitive level. This is also one of the suggestions of this thesis: that a particularly useful source of evidence for formulating and testing cognitive theories comes from the study of cognitive deficits.

4.1.1. Advantages of the single-patient method for studies of cognition

One of the advantages of studying cognitive deficits is that they can provide a unique window into cognitive functions that is not easily available through other means (Caramazza, 1992; Caramazza & Coltheart, 2006; Coltheart, 2001; Frith, 1998; Humphreys & Price, 2001; Martin & Hull, 2007; McCloskey, 2001; 2003). The normal cognitive system is assumed to consist of several subcomponents that are functionally (at least relatively) distinct and devoted to processing disparate kinds of information. Often the role of these subcomponents can be seen more clearly when some of them have been selectively impaired and others spared.

Studies I and II used detailed analyses of patterns of impaired performance to shed light on the cognitive representations and cognitive processes that support the ability to appreciate the spatial orientation of perceived objects. The results suggested that spatial orientation representations are compositional in nature. This hypothesis might not have suggested itself as easily on the basis of evidence from healthy participants only, as the compositional nature of these representations (if this suggestion is correct) is not as readily apparent in the performance of neurologically intact adults (Gregory & McCloskey, 2010; Gregory et al., 2011).

The workings of different subcomponents in the cognitive system can, of course, be studied in the healthy population. In the intact system, however, when all relevant subcomponents and processes are simultaneously active, the possibilities of investigating their relative roles independently are more limited. For example, in Study IV, a modulation of N1m responses was seen as a function of memory load. There are several different memory systems, however. Was the observed modulation caused by the engagement of short-term memory processes, declarative long-term memory encoding processes, or both? The answer is unclear, as presumably both of these were activated during the same task. Disentangling these processes experimentally in intact participants is challenging, because all memory-related processes are (or at least can be) active simultaneously.

Thus, studies of cognitive deficits offer a rare possibility to investigate cognition in a way that can bypass some of the limitations in studying intact human participants. This dissertation extends the substantial body of literature showing that single-patient studies of individuals with cognitive impairments are a powerful source of evidence for understanding the human visual system, spatial representation and normal cognitive function (e.g., Behrmann, Winocur, & Moscovitch, 1992; Bisiach & Luzzatti, 1978; Buxbaum, 2006; Caramazza & Hillis, 1990a; 1990b; Cooper & Humphreys, 2000; Davidoff & Warrington, 1999; Dilks, Serences, Rosenau, Yantis, & McCloskey, 2007; Farah, 1990; Fendrich, Wessinger, & Gazzaniga, 1992; Friedman-Hill, Robertson, & Treisman, 1995; Goodale, Milner, Jakobson, & Carey, 1991; Humphreys, 1999; Humphreys & Riddoch, 2006; Leek, 2001; Milner & Goodale, 2006; Moscovitch, Winocur, & Behrmann, 1997; Pflugshaupt et al., 2007; Priftis et al., 2003; Rapp, 2001; Sahraie, Hibbard, Trevethan, Ritchie, & Weiskrantz, 2010; Silvanto, Cowey, Lavie, & Walsh, 2007; Turnbull & McCarthy, 1996)

4.1.2. Cognitive theories as a guide for functional neuroimaging

In addition to having inherent value, an understanding of cognitive processes is also critical for investigating how cognitive functions are implemented in the brain. Neural activation patterns, such as those studied using functional neuroimaging, are informative of how the brain enables the mind only if one understands the psychological phenomena to which the patterns of neural activation are related (Wager & Lindquist, 2011). Simply collecting functional neuroimaging data from participants without an understanding of the cognitive function under investigation leads to a disorganized picture uninformative of the processes involved (Cooper & Peebles, 2015), because the value of functional neuroimaging methods is limited if the mental functions under investigation are poorly specified (Love, 2015). In the words of Cooper and Peebles (2015 p. 248), “the *neurophysiological/implementation* level appears to be the wrong level to begin”.

Therefore, a critical understanding of processes and representations at the cognitive level is crucial for guiding investigation and the interpretation of data at the level of neural processing. The level of *representation and algorithm* can be described as an essential bridge between what an information-processing system is trying to do and how this is physically instantiated (Peebles & Cooper, 2015). Coltheart (2010b) has suggested that functional neuroimaging studies could be vastly more productive if they made better use of the best existing contemporary cognitive models of the processes they investigate. In practice, neuroimaging work is not always conducted this way. In Poldrack's words (2010, p. 149), "Whereas formal theories from cognitive psychology could often provide substantial guidance as to the design of such tasks, it is uncommon for neuroimaging studies to take meaningful guidance from such theories".

The COR framework proposed in Study II provides an example of how a detailed, empirically driven cognitive-level hypothesis can guide functional neuroimaging. COR has already been used for investigating orientation representations in intact adults (Gregory & McCloskey, 2010) and in normally developing children (Gregory et al., 2011), and it is currently being applied to the investigation of spatial orientation processing in the brain using functional neuroimaging (Hatfield et al., 2014; Hatfield et al., under review). Thus, the development of the COR hypothesis and the on-going process of inquiry in subsequent studies demonstrate one possible way in which a detailed hypothesis at the cognitive level can inform research at other levels of analysis, including neuroimaging.

4.1.3. Brain-damaged patients and theories of brain function

In addition to informing cognitive theories, experimental data from brain-damaged patients can also be valuable for investigating how cognitive functions are implemented in the brain. In Study III, the single-patient approach was used to investigate whether particular brain structures can support specific cognitive abilities.

4.1.3.1. Advantages of patient studies for investigating brain function

In the investigation of brain function, the single-patient method complements evidence provided by functional neuroimaging and electromagnetic measurements in healthy participants. Through the use of carefully designed experiments, studies of brain-damaged patients can be particularly informative for establishing whether a given neural structure is necessary for a given cognitive function.

In investigating the role a given brain structure plays in cognition, the single-patient method has certain advantages over functional neuroimaging methods (McCloskey, 2001). First, the level of inference is weaker in evidence based on functional neuroimaging than on brain damage. For example, one cannot infer that the activation in a given brain region is necessary for a cognitive function on the basis of functional neuroimaging data alone (e.g., Rorden & Karnath, 2004). In addition, increased activation in a brain region to a given set of stimuli or in a particular task does not mean that the region is unresponsive to other kinds of stimuli or during other tasks. Empirical evidence shows that the same brain regions are often activated in functional neuroimaging studies even when the assumed cognitive processes are different (Cabeza & Nyberg, 2000). Further, brain activity is a function of both excitation and inhibition, and increased inhibition can lead to increased metabolism, affecting the BOLD signal (Bechtel & Richardson, 2010; Wager et al., 2007).

For these reasons, studies of brain-damaged patients can provide important converging evidence for neuroimaging findings. Recently, a single-patient study of LSJ—the same patient as in Study III—provided evidence that the MTL is necessary for statistical learning, the ability to detect statistical regularities in sensory input over repeated exposure to patterns containing co-occurring items (Schapiro et al., 2014). Previous fMRI studies had implicated the MTL and the hippocampus (see Schapiro et al., 2014), but these findings had left open the possibility that these structures could be merely epiphenomenally involved but not necessary. The study by Schapiro et al. (2014) importantly complements these findings by providing converging evidence that the MTL plays a critical role in statistical learning.

A second advantage is that patient studies are more easily applicable to certain questions than other techniques in cognitive neuroscience. For example, neuroimaging healthy participants cannot be used for investigating whether a cognitive function can be performed without a particular neural structure.[10] The

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[10] A method that can be used to ask questions of this type is transcranial magnetic stimulation (TMS). TMS can be used to interfere with normal neural processing in a brain area to investigate whether it is necessary for a particular cognitive function. A detailed discussion of this method is beyond the scope of this thesis, but for introductions to TMS, see Walsh & Pascual-Leone (2003) and Stewart & Walsh (2006).

absence of activation in a neuroimaging study does not necessarily mean that the area has no functional role (Bechtel & Richardson, 2010). Functional MRI cannot detect the possible contribution of an area that is constantly active in all task conditions, if a change does not occur in blood flow. Neuroimaging methods can sometimes fail to detect functionally necessary regions because the BOLD signal may increase only marginally in some regions because of their generally high blood flow, or simply because the resolution is inadequate. (For further reasons, see Bechtel & Richardson, 2010; Wager et al., 2007).

In contrast, the single-patient approach is well suited for investigating questions of this type, as Study III shows. Prior neuroimaging studies had indirectly suggested that the hippocampus is engaged when new music is learned for performance (see Study III). Even if this evidence were direct, it would not allow any conclusions about whether some learning of new music is possible without the hippocampus. Study III provided evidence for this possibility, complementing previous neuroimaging findings.

As a third advantage, the single-patient approach can also be used for studying functions involving complex motor behavior. An example of this is Study III, which investigated how the learning of new material for music performance is supported neurally. Neuroimaging participants playing real instruments (such as the viola in Study III) is technically difficult, which partly explains the relative dearth of cognitive neuroscience studies investigating music performance as compared to music recognition (Levitin & Tirovolas, 2009; Peretz & Zatorre, 2005).

As a fourth advantage, the logic of inference is more direct in studies of brain-damaged patients. The inferences based on fMRI activation patterns rely on numerous methodological assumptions about how the signal is derived, complicating the interpretation of data. This complexity in combination with numerous possibilities for data analysis can lead to spurious findings or misleading interpretations (Bennett, Wolford, & Miller, 2009; Mole & Klein, 2010; Poline, Thirion, Roche, & Meriaux, 2010; Simmons, Nelson, & Simonsohn, 2011; Vul & Kanwisher, 2010). Because of these issues, several authors have pointed out the need for increased methodological rigor in future neuroimaging studies (Poldrack, 2012). Thus, despite fMRI's prominence and widespread use, many unresolved questions remain about its optimal use, caveats and about the interpretation of results. (The details are beyond the scope of this thesis, but for an edited volume discussing current challenges and possibilities of functional neuroimaging, see Hanson & Bunzl, 2010.) In contrast to these complications, results from experiments such as Study III are relatively straightforward to interpret.

This discussion is not intended to imply that functional neuroimaging techniques are not useful for understanding brain function—clearly they are. However, it is important to note that the evidence from neuroimaging is correlative in nature, and that the logic of drawing inferences is relatively indirect and complex by necessity as compared to patient studies aiming to localize function.

4.1.4. Limitations of the single-patient approach

One of the main disadvantages of single-patient studies is related to the unique pattern of deficits these studies investigate. Obviously, questions of interest can only be asked if a suitable patient is found. This difficulty is certainly easy to appreciate from the perspective of Study III: it would be incredibly difficult, perhaps impossible, to find another musically proficient patient with virtually no remaining hippocampal tissue and whose musical performance and sight-reading skills have been spared to the same extent as in LSJ.

A second, partly related disadvantage is that replicating a study with another patient can be impossible in the same sense as with intact human participants. The requirement that results can be replicated is central to all empirical science; however, in patient studies it is possible that an identical case of brain damage may never be reported. This is clearly an important limitation of the approach. What partially alleviates this is that all results can be replicated in other experiments with the same patient (Caramazza, 1986; Coltheart, 2001; McCloskey, 1993). The same patient is typically tested extensively with a wide range of stimuli and in multiple tasks. In Study I, patient BC's spatial orientation processing was tested in four different experiments, and the interpretation of results was based on systematic patterns that were identified across tasks.

An additional remedy to the problem of replicability is the possibility of converging evidence from other studies. If the universality assumption is correct, and if the results from the studied patient are reliable, converging evidence from other studies should be able to corroborate the findings (Caramazza, 1992). Importantly for Study I, the proposal that orientation representations are compositional did receive corroborating evidence from studies with other patients (Study II, McCloskey, 2009) and normal participants (Gregory & McCloskey, 2010; Gregory et al., 2011).

A third potential disadvantage of single-patient studies is the possibility that the cognitive mechanisms presumed to be universal could function in a qualitatively different way in some people within the general population (McCloskey, 1993). Conceivably, in this hypothetical scenario, investigating the cognitive performance of a brain-damaged patient with a premorbidly aberrant cognitive architecture could lead to misleading conclusions that cannot be generalized to be true of the general population. This is a potential concern, and it cannot be completely eliminated. In practice, however, several considerations alleviate this concern.

First, one can, for example, be careful about only selecting patients with no evidence of a history of cognitive developmental deficits. Second, as noted previously, one should always expect to find converging evidence for reliable results from other studies. In Study I, the possibility cannot be ruled out with absolute certainty that the pattern of orientation errors in BC's performance could have resulted from a premorbidly abnormal organization of cognitive function. However, similar patterns of performance identified in other patient studies (Study II, McCloskey, 2009) suggest that this concern is probably not very significant in practice. In contrast, one should always be careful about drawing strong conclusions from an isolated study unsupported by any other empirical data, regardless of method.

A third factor mitigating the concern about qualitatively atypical individuals is the logical fact that if such aberrant cases exist but are rare in the whole population, then the probability of sampling one as an experimental subject among all brain-damaged individuals should also be small. In contrast, if the individual variation among the healthy population were extensive, this would constitute a major methodological problem not only for single-patient studies but for virtually all studies of cognition. Extensive individual variation would lead to serious issues in the logic of nearly all experimental research in cognitive psychology and cognitive neuroscience, including experiments conducted with intact participants (McCloskey & Caramazza, 1988; McCloskey, 1993; Rapp, 2011). Extensive heterogeneity in the healthy population would call into question the logic of reducing noise by aggregating data across groups of participants (in the form of group averages, for example) in samples from the healthy population, as the results could not be generalized to be true of the population.

4.2. Converging evidence from neuroimaging and studies of brain damage

Because of their relative advantages and limitations, functional neuroimaging methods and studies of brain-damaged patients are widely seen as complementary. For this reason, several authors have spoken for the importance of complementing neuroimaging findings with evidence from patient studies (Chatterjee, 2005; Cooper & Peebles, 2015; D'Esposito, 2010; Rorden & Karnath, 2004).

In practice, however, neuroimaging studies are currently far more frequently conducted than patient studies, particularly in basic research. In a systematic review of the literature, Fellows et al. (2005) found that functional neuroimaging studies were not only overwhelmingly more popular in number of publications as compared to studies of brain-damaged patients, but they were also cited three times more often and published much more frequently in high-impact journals, despite the weaker and less direct nature of the inferences that can be drawn from the data. Fellows et al. (2005) suggest that the novelty of the method and the allure of “seeing into” the normally functioning brain, rather than careful considerations about drawing inferences, are driving the prominence of functional neuroimaging. Chatterjee (2005) argues that the predominance of functional neuroimaging at the expense of patient studies may stem from practical and sociological factors, as opposed to scientific considerations: for example, it is often easier to find access to an fMRI scanner than to suitable patients.

As one potential solution to the imbalance between studies of brain-damaged patients and neuroimaging, some authors have argued that academic journals and funding agencies should prioritize research using multiple methods (D'Esposito, 2010). Perhaps a first, slightly more easily attainable step in this direction might be an attempt by different researchers to become more aware of the work of their peers using different methodologies. Citation patterns show that there is much room for improvement in this regard. In Fellows et al.'s (2005) study, the authors of both patient and neuroimaging studies were disproportionately likely to cite work that used the same methodology, and the bias was especially prominent in neuroimaging. According to Fellows et al. (2005, p. 854), this within-method bias shows that "there is no ongoing, intensive use of converging methods, at least as indexed by citation patterns", despite repeated arguments from several prominent authors advocating the use of complementary methods.

A similar concern has been voiced about the relation between studies conducted with healthy participants in cognitive psychology and studies of cognitive processing conducted with individuals with cognitive impairments: McCloskey (2001) argues that many opportunities and relevant evidence is missed because studies of impaired and normal cognitive performance are typically published in different journals and presented in different conferences, although the aims and theoretical questions are the same.

As a relevant example related to this thesis, a substantial body of literature exists attributing the disruption that irrelevant sounds cause for memory performance to short-term memory processes (see Study IV). However, as noted previously, serial recall tasks arguably recruit both short- and long-term-memory encoding mechanisms in intact participants. These processes are conflated in typical ISE-paradigm studies with healthy participants, such as Study IV. It seems clear that disentangling these processes could have potentially significant implications for the competing accounts. So far, the irrelevant sound effect has drawn the interest of researchers working with normal participants only. Again, converging evidence from patient studies might be particularly helpful for elucidating these issues.

At the same time, however, methodological advances in cognitive neuroscience may make across-method approaches increasingly challenging. Many recent innovations in methodology promise improved precision and sophisticated solutions to previous limitations of fMRI signal processing, and some of these can also be applied to EEG and MEG (e.g., Haxby, Connolly, & Guntupalli, 2014; Lewis-Peacock & Norman, 2014). While these methodological advances hold much promise, it may be increasingly challenging to prevent further segregation of the field as different methods become technically increasingly complicated.

4.3. Levels of analysis and evidence from MEG

In addition to single-patient studies of cognitive deficits, this dissertation also utilized MEG. In terms of different methodological approaches in informing theories at different levels of analysis, Study IV demonstrates a potential role for magnetic measurements at a level that seems distinct from purely cognitive theories or strict localization of function. However, their usefulness depends importantly on the researcher's ability to decompose the psychological tasks used and on how well the brain responses in question are understood.

4.3.1. Goals of brain measures and Study IV

Coltheart (2010b) has proposed functional neuroimaging to have three possible goals: (1) to localize cognitive processes neuroanatomically; (2) to inform theories of cognition at the psychological level; or (3) to test purely neural models. By extension, these levels can also be applied to studies using MEG and EEG.

However, a consideration of Study IV suggests that this classification may be somewhat restrictive. In Study IV, a modulation of responses generated in auditory cortex was seen as a function of memory load and task phase. The N1m responses for irrelevant tones were the strongest when memory load was the highest. The manipulation of memory load in this study is an example of what can be referred to as a parametric variation design (e.g., Wager & Lindquist, 2011), in which a brain measure is used to investigate whether brain activity in a given region changes as the involvement of a cognitive process is incrementally varied. Although the obtained evidence is correlative in nature, the design can provide more convincing evidence for inferences than experiments that fail to show a relation between different levels of the psychological variable and the brain measure(s).

In Study IV, the results are informative of how neurons in a sensory cortical area respond in a particular context during a specific cognitive activity. However, what is potentially interesting about the finding is not *where* the processing of auditory stimuli took place (Coltheart's goal 1). While the role of functional neuroimaging and other brain measures is sometimes equated with neuroanatomical localization of function (Coltheart, 2010b; Tressoldi, Sella, Coltheart, & Umiltà, 2012), it is not clear that this is the best description of studies such as Study IV, because the aim was not to investigate *where* irrelevant sounds are processed during a serial memory task but rather, how. The study arguably did not aim to localize cognitive functions, but the results are also not directly informative at the level of cognitive functions (goal 2) either, as it is not at all clear what the results mean for the relevant cognitive theories (partly because we currently do not understand the underlying cognitive processes fully, see Study IV). However, it would also seem incorrect to say that the results are only relevant for purely neural models (goal 3), as the point was to investigate neural responses in a very particular context related to memory acquisition. Thus, Coltheart's (2010b) categorization may be missing something important about the practical aims of at least some studies using functional neuroimaging and/or electromagnetic tools.

According to Bechtel and Richardson (2010), the point of identifying brain structures with cognitive functions should be understood more widely than simply finding out where given processes are instantiated. Bechtel and Richardson (2010) argue that the process of inquiry in cognitive neuroscience progresses through stages of reiteration involving different levels of analysis. According to Bechtel and Richardson (2010), functional neuroimaging (and by extension, other brain measures) can be useful for understanding how the brain enables the mind even if they currently cannot be used to test precise predictions about cognitive theories or their instantiation in the brain. Study IV can be seen as one example of what this can mean in practice. Although we are far from fully understanding why increased memory load should enhance responses for unrelated sounds in auditory cortex during memory acquisition, the results seem like a potentially interesting piece in a larger puzzle. Future research will hopefully be able to shed more light on the precise nature of this interaction and where it will fit in a more complete picture of memory acquisition and auditory processing.

As Marr (1982) noted, the *algorithmic/representational* and *implementational* levels are not completely independent of each other, and a complete understanding of how the brain enables the mind also requires an account of how the levels relate to each other. Conceivably, in a reiterative process such as the one described by Bechtel and Richardson (2010), advances at any level of analysis could potentially aid progress on the others. There is another side to the same coin, however: in the investigation of the relation between psychological phenomena and neural processes, the interpretation of experimental data depends on our knowledge of both sides of the relation. That is, the implications of the findings such as those from Study IV can only be interpreted in relation to what is known about the cognitive processes recruited by the behavioral task(s) used, about the patterns of responding in the relevant sensory cortical areas in other contexts, about the neural processes underlying the measured brain responses, and so on. As our knowledge of all these areas is incomplete, any and all of our conclusions can be subject to future revision.

For example, many aspects regarding the N1m wave and the neural processes it reflects are well understood, but not all. The N1m has been shown to be generated within the Sylvian fissure in the auditory cortices and to reflect physical stimulus properties (Näätänen & Picton, 1987; Näätänen, 1992; Pantev et al., 1990; Papanicolaou et al., 1990). Evidence shows its latency to be extremely closely tied to the detection of auditory stimuli in terms of behavioral reaction times (Mäkinen, May, & Tiitinen, 2004). However, the exact details about the relation of the neural processes underlying the N1m wave and those related to cortical dynamics of auditory perception more generally are not entirely clear. For example, while one view holds that the N1m reflects stimulus detection and feature analysis on a very basic level without involving memory or other higher-order processing (e.g., Näätänen et al., 2005), another view suggests that the N1m is a holistic reflection of the functioning of auditory cortex, including memory, perceptual learning, and top-down influences (May & Tiitinen, 2010).

To quote Kappenman and Luck (2012, p. 16): “It is more difficult than one might think to demonstrate that a given ERP component (or any other physiological measure) reflects a specific neural or psychological process. The challenge arises from the fact that we are looking for a neural measure of a given process because we do not fully understand the process and wish to use the neural measure to study the process. Because we do not fully understand the process, it is difficult to design unambiguous tests of the hypothesis that a given component reflects this process.”

Electromagnetic recordings of brain activity are and will continue to be important in the investigation of how the brain enables the mind. However, the point of this discussion is that inferences from all data in cognitive neuroscience have to be made relying both on the strength of each individual piece of evidence and the amount of converging evidence altogether—even in the case of event-related EEG and MEG responses, arguably the most direct non-invasively measurable indexes of human brain activity.

4.3.2. Advantages of MEG

One of the relative advantages of electrophysiological methods, especially MEG, can be seen in Study IV. In the context of the study, the processes of interest regarding individual stimulus items occurred in the range of hundreds of milliseconds. Within a period of seconds, several visual and auditory stimuli were presented, and in the low-load condition, the whole encoding phase was over in four seconds. Investigating how auditory stimuli are cortically processed would be fairly difficult in this context using hemodynamic tools with a temporal resolution in the range of seconds, such as PET of fMRI. In contrast, MEG was well suited for the task. Despite other temporally overlapping sensory processes (i.e., those related to the processing of visual stimuli), it was possible to pinpoint the modulation that occurred in auditory processing with MEG because the event-related fields could be recorded without systematic overlap with the visual stimuli, and the encoding and retention phases could be sharply delineated in the categorization of the recorded ERF’s. Future studies investigating brain function in multimodal settings might benefit from a more frequent use of electromagnetic methods in combination to hemodynamic tools.

As a final MEG-related note, recent methodological advances may now also provide a means for sharpening the spatial resolution of MEG through the use of multivariate analysis methods (Cichy et al., 2015). This has already been seen as having a potentially important impact on the field (Stokes et al., 2015), and may hold much promise for future studies.

4.4. Further methodological observations

Finally, the studies in this dissertation motivate two further notes regarding methodological issues. First, the questions relating to universality and potential heterogeneity within the healthy population would seem to warrant further discussion in future work. Second, the studies in this dissertation provide several reminders of the importance of a careful, critical analysis of the cognitive processes recruited in a given task.

4.4.1. Universality, individual variability and cognitive neuroscience

The prevailing approach is to assume that both the human cognitive architecture and the organization of brain function are fundamentally universal (Caramazza, 1986; 1992; Caramazza & Coltheart, 2006; McCloskey & Caramazza, 1988). However, it is not clear how individual functional and anatomic variability should be taken into consideration. The extent and nature of individual variation in cognitive mechanisms is understood relatively poorly, as surprisingly little work has been dedicated to it. There is a potential concern that the range of individual variation could be such that it would affect a researcher's ability to discriminate between relevant scientific hypotheses (Rapp, 2011). For this reason, some authors go as far as explicitly rejecting the universality assumption (Bub, 2011). However, it is not clear what the implications of this solution are in practice, as currently nearly all experimental cognitive psychology and cognitive neuroscience relies on it, even if the assumption is seldom explicated.

According to Rapp (2011), an understanding of individual variation is critical for all disciplines concerned with cognition, but before an understanding is achieved of what the nature and extent of this variability might be, attractive alternatives to the universality assumption may be hard to find. For example, in explaining patterns of performance in brain-damaged patients, it is problematic to invoke notions of premorbid variability without a clear understanding of the nature of this variation independent of the experimental data. Without such independent understanding, individual differences between patients prior to brain damage cannot be distinguished from the variability resulting from the damage itself.

While the nature and extent of individual variance are currently not understood at the level of cognitive processing, individual brains are also anatomically different. Such differences might constitute additional problems especially for studies aiming to localize cognitive functions in the brain. Empirical reviews of functional neuroimaging studies of cognition find both consistencies and variability both at the individual and group levels (Cabeza & Nyberg, 2000). Some authors have argued that variability among neurologically intact experimental subjects may be one of the main causes for why many fMRI studies have failed to replicate reliably (Poline et al., 2010). Others seem to have at least some fundamental reservations about the universality assumption with respect to how cognitive processes are instantiated in the brain (Humphreys & Price, 2001). Others have explicitly argued that individual variability constitutes a major challenge for cognitive neuroscience in general (Uttal, 2013) and even suggested that the possibilities of localizing cognitive functions reliably with neuroimaging tools are limited because of such issues (Brett, Johnsrude, & Owen, 2002).

Although these potential problems are generally acknowledged (Rapp, 2011; Rorden & Karnath, 2004) and some methods exist for taking differences into account in functional neuroimaging (Poline et al., 2010; Wager & Lindquist, 2011), no consensus exists on what the extent of the problem or the best solutions might be. The nature and extent of individual variation therefore seems to warrant more detailed work. A thorough theoretical discussion of individual functional and neuroanatomical variability in light of the universality assumption and different methods in cognitive neuroscience would be useful for clarifying these issues.

4.4.2. Task analysis and cognitive processes

As a final note, it should be kept in mind that a crucial component of all studies of brain and behavior is a careful analysis of the cognitive functions that given behavioral tasks recruit. That this is a critical step is both self-evident and easy to overlook in practice.

In this dissertation, a key step towards a better understanding of orientation representations was the realization that the use of symmetrical, non-obliquely oriented stimuli conflated several potential forms of reflection error. This called previous interpretations of these empirical phenomena into question. The stimulus materials used in many previous studies, including those used in Study I, were inadequate for disentangling the underlying cognitive processes (see Study II).

A second example of the importance of careful task analysis comes from the context of Study III: an important aspect of the motivation for the study was the observation that some of the experimental evidence from Milner and colleagues' (Corkin, 1968; 2002; Milner, 1962) seminal studies with patient HM had probably not been interpreted correctly (Stanley & Krakauer, 2013). As Stanley and Krakauer (2013) contend, the evidence from tasks such as mirror drawing with HM, as immensely important as it has been for cognitive neuroscience, does not apply to complex motor skill but only one component of motor skill, unlike most authors have previously assumed (see Study III).

As a third example, the interpretation of the data from Study IV depends crucially on our knowledge of the cognitive processes involved. As noted before, parametric designs, such as the one used in Study IV, can often provide more compelling evidence of brain-behavior correlations than mere activation differences between two conditions. However, as in any experiments investigating the neural basis of cognitive processes, the usefulness of the data hinges on our ability to decompose the psychological task to understand which cognitive processes are parametrically manipulated and how (Poldrack, 2010). This is far from a trivial task, and in practice often limits the usefulness of collected data in cognitive neuroscience (e.g., Coltheart, 2010b; Cooper & Peebles, 2015; Kappenman & Luck, 2012; Love, 2015; Peebles & Cooper, 2015; Poldrack, 2010; 2012).

The best of methods can only provide us with answers as sophisticated as our questions. Making use of the best cognitive models available and selecting the behavioral tasks as carefully as possible is therefore critical, regardless of which methods are used.

5. References

Albouy, G., Sterpenich, V., Balteau, E., Vandewalle, G., Desseilles, M., Dang-Vu, T., et al. (2008). Both the hippocampus and striatum are involved in consolidation of motor sequence memory. *Neuron, 58*, 261-272.

Altenmüller, E., & Schneider, S. (2009). Planning and performance. In S. Hallam, I. Cross & M. Thaut (Eds.), *The Oxford handbook of music psychology* (pp. 332-343). Oxford: Oxford University Press.

Appelle, S. (1972). Perception and discrimination as a function of stimulus orientation: The "oblique effect" in man and animals. *Psychological Bulletin, 78*, 266-278.

Axmacher, N., Mormann, F., Fernandez, G., Cohen, M. X., Elger, C. E., & Fell, J. (2007). Sustained neural activity patterns during working memory in the human medial temporal lobe. *Journal of Neuroscience, 27*, 7807-7816.

Baddeley, A. D. (1986). *Working memory*. New York, NY: Clarendon Press.

Baddeley, A. D., & Salamé, P. (1989). Effects of background music on phonological short-term memory. *Quarterly Journal of Experimental Psychology, 41*A, 107-122.

Baillet, S. (2011). Electromagnetic brain mapping using MEG and EEG. In J. Decety, & J. T. Cacioppo (Eds.), *The Oxford handbook of social neuroscience* (pp. 97-133). New York, NY: Oxford University Press.

Barense, M. D., Ngo, J. K. W., Hung, L. H. T., & Peterson, M. A. (2012). Interactions of memory and perception in amnesia: The figure-ground perspective. *Cerebral Cortex, 22*, 2680-2691.

Barredo, J., Oztekin, I., & Badre, D. (2015). Ventral fronto-temporal pathway supporting cognitive control of episodic memory retrieval. *Cerebral Cortex, 25*, 1004-1019.

Beatty, W. W., Rogers, C. L., Rogers, R. L., English, S., Testa, J. A., Orbelo, D. M., et al. (1999). Piano playing in alzheimer's disease: Longitudinal study of a single case. *Neurocase,* 5, 459-469.

Bechtel, W., & Richardson, R. C. (2010). Neuroimaging as a tool for functionally decomposing cognitive processes. In S. J. Hanson, & M. Bunzl (Eds.), *Foundational issues in human brain mapping* (pp. 241-261). Cambridge, MA: MIT Press.

Beery, K. E., & Buktenica, N. A. (1997). *The Beery-Buktenica developmental test of visual-motor integration (VMI)*. Fourth (revised) ed. Parsippany, NJ: Modern Curriculum Press.

Behrmann, M., Winocur, G., & Moscovitch, M. (1992). Dissociation between mental imagery and object recognition in a brain-damaged patient. *Nature, 359*, 636-637.

Bell, R., Dentale, S., Buchner, A., & Mayr, S. (2010). ERP correlates of the irrelevant sound effect. *Psychophysiology, 47*, 1182-1191.

Bell, R., Röer, J. P., Dentale, S., & Buchner, A. (2012). Habituation of the irrelevant sound effect: Evidence for an attentional theory of short-term memory disruption. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 38*, 1542-1557.

Bennett, C. M., Wolford, G. L., & Miller, M. B. (2009). The principled control of false positives in neuroimaging. *Social Cognitive and Affective Neuroscience,* 4, 417-422.

Bisiach, E., & Luzzatti, C. (1978). Unilateral neglect of representational space. *Cortex, 14*, 129-133.

Bornstein, M. H. (1982). Perceptual anisotropies in infancy: Ontogenetic origins and implications of inequalities in spatial vision. *Advances in Child Development and Behavior, 16*, 77-123.

Braine, L. G. (1978). A new slant on orientation perception. *American Psychologist, 33*, 10-22.

Brett, M., Johnsrude, I., & Owen, A. (2002). The problem of functional localization in the human brain. *Nature Reviews Neuroscience,* 3, 243-249.

Broca, P. (1861). Remarques sur le siège de la faculté du langage articulé suivies d'une observation d'amphémie (perte de al parole). [Remarks on the seat of the faculty of articulate language, followed by an observation of aphemia] *Bulletin Et Memoires De La Societé Anatomique De Paris, 36*, 330-357.

Bub, D. (2011). Facing the challenge of variation in neuropsychological populations: Lessons from biology. *Cognitive Neuropsychology, 28*, 445-450.

Bub, J., & Bub, D. (1988). On the methodology of single-case studies in cognitive neuropsychology. *Cognitive Neuropsychology,* 5, 565-582.

Buchner, A., Bell, R., Rothermund, K., & Wentura, D. (2008). Sound source location modulates the irrelevant sound effect. *Memory & Cognition, 36*, 617-628.

Buckner, R., & Wheeler, M. (2001). The cognitive neuroscience of remembering. *Nature Reviews Neuroscience,* 2, 624-634.

Buxbaum, L. J. (2006). On the right (and left) track: Twenty years of progress in studying hemispatial neglect. *Cognitive Neuropsychology, 23*, 184-201.

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience, 12*, 1-47.

Campbell, T., Winkler, I., Kujala, T., & Näätänen, R. (2003). The N1 hypothesis and irrelevant sound: Evidence from token set size effects. *Cognitive Brain Research, 18*, 39-47.

Caplan, D., & Chen, E. (2006). Using fMRI to discover cognitive operations. *Cortex, 42*, 393-395.

Caramazza, A. (1986). On drawing inferences about the structure of normal cognitive systems from the analysis of patterns of impaired performance: The case for single-patient studies. *Brain and Cognition,* 5, 41-66.

Caramazza, A. (1992). Is cognitive neuropsychology possible? *Journal of Cognitive Neuroscience, 4*, 80-95.

Caramazza, A., & Badecker, W. (1991). Clinical syndromes: Are not god's gift to cognitive neuropsychology: A reply to a rebuttal to an answer to a response to the case against syndrome-based research. *Brain and Cognition, 16*, 211-227.

Caramazza, A., & Coltheart, M. (2006). Cognitive neuropsychology twenty years on. *Cognitive Neuropsychology, 23*, 3-12.

Caramazza, A., & Hillis, A. E. (1990a). Levels of representation, co-ordinate frames, and unilateral neglect. *Cognitive Neuropsychology, 7*, 391-445.

Caramazza, A., & Hillis, A. E. (1990b). Spatial representation of words in the brain implied by studies of a unilateral neglect patient. *Nature, 346*, 267-269.

Caramazza, A., & McCloskey, M. (1988). The case for single-patient studies. *Cognitive Neuropsychology, 5*, 517-527.

Cavaco, S., Feinstein, J. S., van Twillert, H., & Tranel, D. (2012). Musical memory in a patient with severe anterograde amnesia. *Journal of Clinical and Experimental Neuropsychology, 34*, 1089-1100.

Cave, C. B., & Squire, L. R. (1992). Intact and long-lasting repetition priming in amnesia. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 18*, 509-520.

Chatterjee, A. (2005). A madness to the methods in cognitive neuroscience? *Journal of Cognitive Neuroscience, 17*, 847-849.

Cichy, R. M., Ramirez, F. M., & Pantazis, D. (2015). Can visual information encoded in cortical columns be decoded from magnetoencephalography data in humans? *Neuroimage, 121*, 193-204.

Cohen, D. (1968). Magnetoencephalography: Evidence of magnetic fields produced by alpha-rhythm currents. *Science, 161*, 784-786.

Colle, H. A., & Welsh, A. (1976). Acoustic masking in primary memory. *Journal of Verbal Learning & Verbal Behavior, 15*, 17-31.

Coltheart, M. (2001). Assumptions and methods in cognitive neuropsychology. In B. Rapp (Ed.), *The handbook of cognitive neuropsychology: What deficits reveal about the human mind* (pp. 3-21). New York, NY: Psychology Press.

Coltheart, M. (2006a). Perhaps functional neuroimaging has not told us anything about the mind (so far). *Cortex, 42*, 422-427.

Coltheart, M. (2006b). What has functional neuroimaging told us about the mind (so far)? *Cortex, 42*, 323-331.

Coltheart, M. (2010a). Lessons from cognitive neuropsychology for cognitive science: A reply to Patterson and Plaut (2009). *Topics in Cognitive Science, 2*, 3-11.

Coltheart, M. (2010b). What is functional neuroimaging for? In S. J. Hanson, & M. Bunzl (Eds.), *Foundational issues in human brain mappin*g (pp. 263-272). Cambridge, MA: MIT Press.

Cooper, A. C. G., & Humphreys, G. W. (2000). Task-specific effects of orientation information: Neuropsychological evidence. *Neuropsychologia, 38*, 1607-1615.

Cooper, R. P., & Peebles, D. (2015). Beyond single - level accounts: The role of cognitive architectures in cognitive scientific explanation. *Topics in Cognitive Science,* 7, 243-258.

Corballis, M. C., & Beale, I. L. (1976). *The psychology of left and righ*t. Oxford, UK: Lawrence Erlbaum.

Corkin, S. (1968). Acquisition of motor skill after bilateral medial temporal-lobe excision. *Neuropsychologia, 6*, 255-265.

Corkin, S. (2002). What's new with the amnesic patient H.M.*? Nature Reviews Neuroscience, 3,* 153-160.

Corkin, S. (2013). *Permanent present tense: The unforgettable life of the amnesic patient, H.* M. New York, NY: Basic Books.

Cowan, N. (1995). *Attention and memory: An integrated framewor*k. New York, NY: Oxford University Press.

Cowan, N. (2008). What are the differences between long-term, short-term, and working memory*? Progress in Brain Research, 170*, 323-338.

Cowles, A., Beatty, W. W., Nixon, S. J., Lutz, L. J., Paulk, J., Paulk, K., et al. (2003). Musical skill in dementia: A violinist presumed to have Alzheimer's disease learns to play a new song. *Neurocase, 9,* 493-503.

Crystal, H. A., Grober, E., & Masur, D. (1989). Preservation of musical memory in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 52*, 1415-1416.

Danker, J. F., & Anderson, J. R. (2010). The ghosts of brain states past: Remembering reactivates the brain regions engaged during encoding. *Psychological Bulletin, 136*, 87-102.

Davidoff, J., & Warrington, E. K. (1999). The bare bones of object recognition: Implications from a case of object recognition impairment. *Neuropsychologia, 3*7, 279-292.

Davidoff, J., & Warrington, E. K. (2001). A particular difficulty in discriminating between mirror images. *Neuropsychologia, 39*, 1022-1036.

Deregowski, J. B., McGeorge, P., & Wynn, V. (2000). The role of left-right symmetry in the encodement of spatial orientations. *British Journal of Psychology, 91*, 241-257.

D'Esposito, M. (2010). Why methods matter in the study of the biological basis of the mind: A behavioral neurologist's perspective. In P. A. Reuter-Lorenz, K. Baynes, G. R. Mangun & E. A. Phelps (Eds.), *The cognitive neuroscience of mind: A tribute to Michael S. Gazzaniga* (pp. 203-221). Cambridge, MA: MIT Press.

Dilks, D. D., Reiss, J. E., Landau, B., & Hoffman, J. E. (2004). Representation of orientation in Williams syndrome. *Poster presented at the meeting of the Psychonomic Society, Minneapolis, MN.*

Dilks, D. D., Serences, J. T., Rosenau, B. J., Yantis, S., & McCloskey, M. (2007). Human adult cortical reorganization and consequent visual distortion. *The Journal of Neuroscience, 27*, 9585-9594.

Driver, J., Baylis, G. C., & Rafal, R. D. (1992). Preserved figure ground segregation and symmetry perception in visual neglect. *Nature, 360*, 73-75.

Duhamel, J. R., Colby, C. L., & Goldberg, M. E. (1992). The updating of the representation of visual space in parietal cortex by intended eye-movements. *Science, 255*, 90-92.

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nature Reviews Neuroscience, 1,* 41-50.

Eichenbaum, H. (2013). What H.M. taught us. *Journal of Cognitive Neuroscience, 25*, 14-21.

Elliot, C. D. (1990). *Differential ability scale*s. San Diego, CA: Harcourt, Brace, Jovanovich.

Elliott, E. M., & Briganti, A. M. (2012). Investigating the role of attentional resources in the irrelevant speech effect. *Acta Psychologica, 140*, 64-74.

Ellis, A. W. (1987). Intimations of modularity, or, the modelarity of mind: Doing cognitive neuropsychology without syndromes. In M. Coltheart, G. Sartori & R. Job (Eds.), *The cognitive neuropsychology of languag*e (pp. 397-408). Hillsdale, NJ: Lawrence Erlbaum.

Enquist, M., & Arak, A. (1994). Symmetry, beauty and evolution. *Nature, 372*, 169-172.

Faillenot, I., Sunaert, S., Van Hecke, P., & Orban, G. A. (2001). Orientation discrimination of objects and gratings compared: An fMRI study. *European Journal of Neuroscience, 1*3, 585-596.

Farah, M. J. (1990). *Visual agnosia: Disorders of object recognition and what they tell us about normal visio*n. Cambridge, MA: MIT Press.

Fellows, L. K., Heberlein, A. S., Morales, D. A., Shivde, G., Waller, S., & Wu, D. H. (2005). Method matters: An empirical study of impact in cognitive neuroscience. *Journal of Cognitive Neuroscience, 17*, 850-858.

Fendrich, R., Wessinger, C. M., & Gazzaniga, M. S. (1992). Residual vision in a scotoma: Implications for blindsight. *Science, 258*, 1489-1491.

Ferber, S., & Karnath, H.-O. (2003). Friedrich Best's case Z with misidentification of object orientation. In C. Code, C. Wallesch, Y. Joanette & A. R. Lecours (Eds.), *Classic cases in neuropsychology, vol. II* (pp. 191-198). Hove: Psychology Press.

Ferster, D. (2003). Assembly of receptive fields in primary visual cortex. In L. M. Chalupa, & J. S. Werner (Eds.), *The visual neuroscience*s (pp. 695-703). Cambridge, MA: Bradford.

Ferster, D., & Miller, K. D. (2000). Neural mechanisms of orientation selectivity in the visual cortex. *Annual Review of Neuroscience, 2*3, 441-471.

Fodor, J. A. (1983). *The modularity of mind*. Cambridge, MA: MIT Press.

Friedman-Hill, S. R., Robertson, L. C., & Treisman, A. (1995). Parietal contributions to visual feature binding: Evidence from a patient with bilateral lesions. *Science, 269*, 853-855.

Frith, C. D. (1998). Deficits and pathologies. In W. Bechtel, & G. Graham (Eds.), *A companion to cognitive scienc*e (pp. 380-390). Malden, MA: Blackwell.

Fujinaga, N., Muramatsu, T., Ogano, M., & Kato, M. (2005). A 3-year follow-up study of 'orientation agnosia'. *Neuropsychologia, 43*, 1222-1226.

Fujiwara, N., Nagamine, T., Imai, M., Tanaka, T., & Shibasaki, H. (1998). Role of the primary auditory cortex in auditory selective attention studied by whole-head neuromagnetometer. *Cognitive Brain Research,* 7, 99-109.

Furmanski, C. S., & Engel, S. A. (2000). An oblique effect in human primary visual cortex. *Nature Neuroscience,* 3, 535-536.

Furneaux, S., & Land, M. F. (1999). The effects of skill on the eye-hand span during musical sight-reading. *Proceedings of the Royal Society of London B-Biological Sciences, 266*, 2435-2440.

Gabrieli, J. D. E. (1998). Cognitive neuroscience of human memory. *Annual Review of Psychology, 49*, 87-115.

Gaffan, D., Harrison, S., & Gaffan, E. A. (1986). Visual identification following inferotemporal ablation in the monkey. *Quarterly Journal of Experimental Psychology Section B-Comparative and Physiological Psychology, 38*, 5-30.

Gazzaniga, M. S., Ivry, R. B., & Mangun, G. R. (2002). *Cognitive neuroscience: The biology of the mind*. (2nd ed.). New York, NY: W.W. Norton.

Gazzaniga, M. S., & Mangun, G. R. (Eds.). (2014). *The cognitive neuroscience*s (5th ed.). Cambridge, MA: MIT Press.

Gisselgard, J., Petersson, K. M., Baddeley, A. D., & Ingvar, M. (2003). The irrelevant speech effect: A PET study. *Neuropsychologia, 41*, 1899-1911.

Gisselgård, J., Petersson, K. M., & Ingvar, M. (2004). The irrelevant speech effect and working memory load. *NeuroImage, 22*, 1107-1116.

Gold, J. J., Hopkins, R. O., & Squire, L. R. (2006). Single-item memory, associative memory, and the human hippocampus. *Learning & Memory, 13*, 644-649.

Goodale, M. A., Milner, A. D., Jakobson, L. S., & Carey, D. P. (1991). A neurological dissociation between perceiving objects and grasping them. *Nature, 349*, 154-156.

Goodglass, H., & Kaplan, E. (1983). *Boston naming tes*t. Philadelphia, PA: Lea and Febiger.

Gregory, E., Landau, B., & McCloskey, M. (2011). Representation of object orientation in children: Evidence from mirror-image confusions. *Visual Cognition, 19*, 1035-1062.

Gregory, E., & McCloskey, M. (2010). Mirror-image confusions: Implications for representation and processing of object orientation. *Cognition, 116*, 110-129.

Gregory, E., McCloskey, M., & Landau, B. (2014). Profound loss of general knowledge in retrograde amnesia: Evidence from an amnesic artist. *Frontiers in Human Neuroscience, 8,* 287.

Gross, C. G., Rocha-Miranda, C. E., & Bender, D. B. (1972). Visual properties of neurons in inferotemporal cortex of the macaque. *Journal of Neurophysiology, 35*, 96-111.

Grosso, A., Cambiaghi, M., Concina, G., Sacco, T., & Sacchetti, B. (2015). Auditory cortex involvement in emotional learning and memory. *Neuroscience, 299*, 45-55.

Hämäläinen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J., & Lounasmaa, O. V. (1993). Magnetoencephalography – theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics, 65*, 413-497.

Hamann, S. B., & Squire, L. R. (1995). On the acquisition of new declarative knowledge in amnesia. *Behavioral Neuroscience, 109*, 1027-1044.

Hammill, D. D., Pearson, N. A., & Voress, J. K. (1993). *Developmental test of visual perception, 2nd edition (DTVP-2*). Austin, Texas: Pro-Ed.

Hanley, J., & Shah, N. (2012). The irrelevant sound effect under articulatory suppression is a suffix effect even with five-item lists. *Memory, 20*, 415-419.

Hanson, S. J., & Bunzl, M. (Eds.). (2010). *Foundational issues in human brain mappin*g. Cambridge, MA: MIT Press.

Harris, I. M., Harris, J. A., & Caine, D. (2001). Object orientation agnosia: A failure to find the axis*? Journal of Cognitive Neuroscience, 13,* 800-812.

Hatfield, M., Gregory, E., & McCloskey, M. (2015). The canonical upright in the representation of object orientation. *Journal of Vision, 15*, 238-238.

Hatfield, M., McCloskey, M., & Park, S. (2014). Mirror-image confusion in object-selective cortex: Are all reflections alike*? Journal of Vision, 14*, 1366-1366.

Hatfield, M., McCloskey, M., & Park, S. (under review). Neural representation of object orientation: A dissociation between MVPA and repetition suppression.

Haxby, J. V., Connolly, A. C., & Guntupalli, J. S. (2014). Decoding neural representational spaces using multivariate pattern analysis. *Annual Review of Neuroscience, 37*, 435-456.

Heeley, D. W., Buchanan-Smith, H. M., Cromwell, J. A., & Wright, J. S. (1997). The oblique effect in orientation acuity. *Vision Research, 37*, 235-242.

Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nature Reviews Neuroscience, 11*, 523-532.

Henke, K., Buck, A., Weber, B., & Wieser, H. G. (1997). Human hippocampus establishes associations in memory. *Hippocampus, 7,* 249-256.

Henke, K., Weber, B., Kneifel, S., Wieser, H. G., & Buck, A. (1999). Human hippocampus associates information in memory. *Proceedings of the National Academy of Sciences USA, 96*, 5884-5889.

Henson, R. (2005). What can functional neuroimaging tell the experimental psychologist*? The Quarterly Journal of Experimental Psychology A: Human Experimental Psychology, 58A,* 193-233.

Herbert, A. M., & Humphrey, G. K. (1996). Bilateral symmetry detection: Testing a 'callosal' hypothesis. *Perception, 25,* 463-480.

Hoang, L. T., & Kesner, R. P. (2008). Dorsal hippocampus, CA3, and CA1 lesions disrupt temporal sequence completion. *Behavioral Neuroscience, 122*, 9-15.

Holdstock, J. S., Mayes, A. R., Isaac, C. L., Gong, Q., & Roberts, N. (2002). Differential involvement of the hippocampus and temporal lobe cortices in rapid and slow learning of new semantic information. *Neuropsychologia, 40*, 748-768.

Holmes, E. J., & Gross, C. G. (1984). Effects of inferior temporal lesions on discrimination of stimuli differing in orientation. *Journal of Neuroscience, 4,* 3063-3068.

Hubel, D. H., & Wiesel, T. N. (1962). Receptive fields, binocular interaction and functional architecture in cats visual cortex. *Journal of Physiology, 160*, 106-154.

Hubel, D. H., & Wiesel, T. N. (1968). Receptive fields and functional architecture of monkey striate cortex. *Journal of Physiology, 195,* 215-243.

Humphreys, G. W. (Ed.). (1999). *Case studies in the neuropsychology of visio*n. Hove, UK: Psychology Press.

Humphreys, G. W., & Price, C. J. (2001). Cognitive neuropsychology and functional brain imaging: Implications for functional and anatomical models of cognition. *Acta Psychologica, 107*, 119-153.

Humphreys, G. W., & Riddoch, M. J. (2006). Features, objects, action: The cognitive neuropsychology of visual object processing, 1984-2004. *Cognitive Neuropsychology, 23,* 156-183.

Insausti, R., Annese, J., Amaral, D. G., & Squire, L. R. (2013). Human amnesia and the medial temporal lobe illuminated by neuropsychological and neurohistological findings for patient E.P. *Proceedings of the National Academy of Sciences USA, 110*, E1953-E1962.

Janata, P., & Grafton, S. T. (2003). Swinging in the brain: Shared neural substrates for behaviors related to sequencing and music. *Nature Neuroscience, 6*, 682-687.

Jones, D. M., Beaman, P., & Macken, W. J. (1996). The object-oriented episodic record model. In S. E. Gathercole (Ed.), *Models of short-term memor*y (pp. 209-237). Hove, UK: Psychology Press.

Jones, D. M., & Macken, W. J. (1993). Irrelevant tones produce an irrelevant speech effect: Implications for phonological coding in working memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 19*, 369-381.

Jonides, J., Lewis, R. L., Nee, D. E., Lustig, C. A., Berman, M. G., & Moore, K. S. (2008). The mind and brain of short-term memory. *Annual Review of Psychology, 59*, 193-224.

Jonides, J., Nee, D. E., & Berman, M. G. (2006). What has functional neuroimaging told us about the mind? So many examples, so little space. *Cortex, 42*, 414-417.

Kalm, K., Davis, M. H., & Norris, D. (2013). Individual sequence representations in the medial temporal lobe. *Journal of Cognitive Neuroscience, 25*, 1111-1121.

Kappenman, E. S., & Luck, S. J. (2012). ERP components: The ups and downs of brainwave recordings. In E. S. Kappenman, & S. J. Luck (Eds.), *The Oxford handbook of event-related potential component*s (pp. 3-30). New York, NY: Oxford University Press.

Karnath, H.-O., Ferber, S., & Bülthoff, H. H. (2000). Neuronal representation of object recognition. *Neuropsychologia, 38*, 1235-1241.

Kinsler, V., & Carpenter, R. H. S. (1995). Saccadic eye-movements while reading music. *Vision Research, 35*, 1447-1458.

Kitchener, E. G., Hodges, J. R., & McCarthy, R. (1998). Acquisition of post-morbid vocabulary and semantic facts in the absence of episodic memory. *Brain, 121*, 1313-1327.

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science, 273*, 1399-1402.

Kosslyn, S. M., & Intriligator, J. M. (1992). Is cognitive neuropsychology plausible? The perils of sitting on a one-legged stool. *Journal of Cognitive Neuroscience, 4*, 96-106.

Kravitz, D. J., Saleem, K. S., Baker, C. I., & Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nature Reviews Neuroscience, 12*, 217-230.

Lange, E. B. (2005). Disruption of attention by irrelevant stimuli in serial recall. *Journal of Memory and Language, 53*, 513-531.

Leahy, R. M., Mosher, J. C., Spencer, M. E., Huang, M. X., & Lewine, J. D. (1998). A study of dipole localization accuracy for MEG and EEG using a human skull phantom. *Electroencephalography and Clinical Neurophysiology, 107*(2), 159-173.

Leek, E. C. (2001). Single case studies of neurological disorders: Their contribution to the cognitive neuroscience of vision. *Visual Cognition, 8*, 263-272.

Lehmann, A. C., & Kopiez, R. (2009). Sight-reading. In S. Hallam, I. Cross and M. Thaut (Eds.), *The Oxford handbook of music psychology* (pp. 344-351).

Levitin, D. J., & Tirovolas, A. K. (2009). Current advances in the cognitive neuroscience of music. *Annals of the New York Academy of Sciences, 1156*, 211-231.

Lewis-Peacock, J. A., & Norman, K. A. (2014). Multivoxel pattern analysis of functional MRI data. *The cognitive neurosciences (5th ed.)* (pp. 911-919). Cambridge, MA, US: MIT Press.

Li, B. W., Peterson, M. R., & Freeman, R. D. (2003). Oblique effect: A neural basis in the visual cortex. *Journal of Neurophysiology, 90*, 204-217.

Li, W., Piech, V., & Gilbert, C. D. (2004). Perceptual learning and top-down influences in primary visual cortex. *Nature Neuroscience, 7*, 651-657.

Li, W., & Westheimer, G. (1997). Human discrimination of the implicit orientation of simple symmetrical patterns. *Vision Research, 37*, 565-572.

Ling, S., Pearson, J., & Blake, R. (2009). Dissociation of neural mechanisms underlying orientation processing in humans. *Current Biology, 1*9(17), 1458-1462.

Little, J. S., Martin, F. H., & Thomson, R. H. S. (2010). Speech versus non-speech as irrelevant sound: Controlling acoustic variation. *Biological Psychology, 85*, 62-70.

Loosemore, R., & Harley, T. (2010). Brains and minds: On the usefulness of localization data to cognitive psychology. In S. J. Hanson, & M. Bunzl (Eds.), *Foundational issues in human brain mappin*g (pp. 217-240). Cambridge, MA: MIT Press.

Love, B. C. (2015). The algorithmic level is the bridge between computation and brain. *Topics in Cognitive Science, 7*, 230-242.

Luck, S. J. (2014). *An introduction to the event-related potential techniqu*e (2nd ed.). Cambridge, MA: MIT Press.

Makinen, V., May, P., & Tiitinen, H. (2004). Transient brain responses predict the temporal dynamics of sound detection in humans. *NeuroImage, 21*, 701-706.

Mansfield, R. J. (1974). Neural basis of orientation perception in primate vision. *Science, 186*, 1133-1135.

Marr, D. (1982). *Visio*n. New York, NY: W.H. Freeman.

Martin, R., & Hull, R. (2007). The case study perspective on psychological research. In R. J. Sternberg, H. L. Roediger & D. F. Halpern (Eds.), *Critical thinking in psycholog*y (pp. 90-109). New York, NY: Cambridge University Press.

Martinaud, O., Mirlink, N., Bioux, S., Bliaux, E., Champmartin, C., Pouliquen, D., et al. (2016). Mirrored and rotated stimuli are not the same: A neuropsychological and lesion mapping study. *Cortex, 78*, 100-114.

May, P. J. C., & Tiitinen, H. (2010). Mismatch negativity (MMN), the deviance-elicited auditory deflection, explained. *Psychophysiology, 47*, 66-122.

McCloskey, M. (1993). Theory and evidence in cognitive neuropsychology: A "radical" response to Robertson, Knight, Rafal, and Shimamura (1993). *Journal of Experimental Psychology: Learning, Memory, and Cognition, 1*9(3), 718-734.

McCloskey, M. (2001). The future of cognitive neuropsychology. In B. Rapp (Ed.), *The handbook of cognitive neuropsychology: What deficits reveal about the human min*d (pp. 593-610). New York, NY: Psychology Press.

McCloskey, M. (2003). Beyond task dissociation logic: A richer conception of cognitive neuropsychology. *Cortex, 39*, 196-202.

McCloskey, M. (2004). Spatial representations and multiple-visual-systems hypotheses: Evidence from a developmental deficit in visual location and orientation processing. *Cortex, 40,* 677-694.

McCloskey, M. (2009). *Visual reflections: A perceptual deficit and its implication*s. New York, NY: Oxford University Press.

McCloskey, M., & Caramazza, A. (1988). Theory and methodology in cognitive neuropsychology: A response to our critics. *Cognitive Neuropsychology, 5*, 583-623.

McCloskey, M., Rapp, B., Yantis, S., Rubin, G., Bacon, W. F., Dagnelie, G., et al. (1995). A developmental deficit in localizing objects from vision. *Psychological Science, 6*, 112-117.

Michel, C. M., Murray, M. M., Lantz, G., Gonzalez, S., Spinelli, L., & de Peralta, R. G. (2004). EEG source imaging. *Clinical Neurophysiology, 115*, 2195-2222.

Miles, C., Jones, D. M., & Madden, C. A. (1991). Locus of the irrelevant speech effect in short-term memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 17*, 578-584.

Milner, A. D., & Goodale, M. A. (2006). *The visual brain in actio*n. Oxford, UK: Oxford University Press.

Milner, B. (1962). Les troubles de la mémoire accompagnant des lésions hippocampiques bilatérales. In P. Passouant (Ed.), *Physiologie de l'hippocamp*e (pp. 257-272). Paris: Centre National de la Recherche Scientifique.

Milner, B. (1971). Interhemispheric differences in localization of psychological processes in man. *British Medical Bulletin, 27*, 272-277.

Mishkin, M. (1978). Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. *Nature, 273*, 297-298.

Mole, C., & Klein, C. (2010). Confirmation, refutation, and the evidence of fMRI. In S. J. Hanson, & M. Bunzl (Eds.), *Foundational issues in human brain mappin*g (pp. 99-111). Cambridge, MA: MIT Press.

Moscovitch, M., Nadel, L., Winocur, G., Gilboa, A., & Rosenbaum, R. (2006). The cognitive neuroscience of remote episodic, semantic and spatial memory. *Current Opinion in Neurobiology, 16*, 179-190.

Moscovitch, M., Winocur, G., & Behrmann, M. (1997). What is special about face recognition? nineteen experiments on a person with visual object agnosia and dyslexia but normal face recognition. *Journal of Cognitive Neuroscience, 9*, 555-604.

Näätänen, R., Jacobsen, T. & Winkler, I. (2005). Memory-based or afferent processes in mismatch negativity (MMN): A review of the evidence. *Psychophysiology, 42*, 25-32.

Näätänen, R. (1992). *Attention and brain functio*n. Hillsdale, NJ: Lawrence Erlbaum.

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

Nadel, L., & Peterson, M. A. (2013). The hippocampus: Part of an interactive posterior representational system spanning perceptual and memorial systems. *Journal of Experimental Psychology: General, 142*, 1242-1254.

Neath, I. (2000). Modeling the effects of irrelevant speech on memory. *Psychonomic Bulletin & Review, 7*, 403-423.

Nee, D. E., & Jonides, J. (2013). Trisecting representational states in short-term memory. *Frontiers in Human Neuroscience, 7*, 796.

Ochsner, K. N., & Kosslyn, S. M. (2014). Introduction to the Oxford handbook of cognitive neuroscience: Cognitive neuroscience: Where are we now? In K. N. Ochsner, & S. M. Kosslyn (Eds.), *The Oxford handbook of cognitive neuroscience* (pp. 1-7). New York, NY: Oxford University Press.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic-resonance-imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences USA, 87*, 9868-9872.

O'Kane, G., Kensinger, E. A., & Corkin, S. (2004). Evidence for semantic learning in profound amnesia: An investigation with patient HM. *Hippocampus, 14*, 417-425.

Olson, D. R., & Hildyard, A. (1977). On the mental representation of oblique orientation. *Canadian Journal of Psychology, 31*, 3-13.

Paavilainen, P., Tiitinen, H., Alho, K., & Näätänen, R. (1993). Mismatch negativity to slight pitch changes outside strong attentional focus. *Biological Psychology, 37*, 23-41.

Page, M. P. A., & Norris, D. G. (2003). The irrelevant sound effect: What needs modelling, and a tentative model. *The Quarterly Journal of Experimental Psychology A: Human Experimental Psychology, 56A*, 1289-1300.

Page, M. P. A. (2006). What can't functional neuroimaging tell the cognitive psychologist*?* *Cortex, 42*, 428-443.

Palmer, C. (1997). Music performance. *Annual Review of Psychology, 48*, 115-138.

Palmer, C. (2006). The nature of memory for music performance skills. In E. Altenmüller, M. Wiesendanger & J. Kesselring (Eds.), *Music, motor control and the brai*n (pp. 39-53). New York, NY: Oxford University Press.

Palmer, C., & Meyer, R. K. (2000). Conceptual and motor learning in music performance. *Psychological Science, 11*, 63-68.

Pantev, C., Hoke, M., Lehnertz, K., Lutkenhoner, B., Fahrendorf, G., & Stober, U. (1990). Identification of sources of brain neuronal-activity with high spatiotemporal resolution through combination of neuromagnetic source localization (nmsl) and magnetic-resonance-imaging (mri). *Electroencephalography and Clinical Neurophysiology, 75*, 173-184.

Papadelis, C., Leonardelli, E., Staudt, M., & Braun, C. (2012). Can magnetoencephalography track the afferent information flow along white matter thalamo-cortical fibers*? Neuroimage, 60*, 1092-1105.

Papanicolaou, A. C., Baumann, S., Rogers, R. L., Saydjari, C., Amparo, E. G., & Eisenberg, H. M. (1990). Localization of auditory response sources using magnetoencephalography and magnetic-resonance imaging. *Archives of Neurology, 47*, 33-37.

Patterson, K., & Plaut, D. C. (2009). "Shallow draughts intoxicate the brain": Lessons from cognitive science for cognitive neuropsychology. *Topics in Cognitive Science, 1,* 39-58.

Peebles, D., & Cooper, R. P. (2015). Thirty years after Marr's Vision: Levels of analysis in cognitive science. *Topics in Cognitive Science, 7*, 187-190.

Peretz, I., & Zatorre, R. J. (2005). Brain organization for music processing. *Annual Review of Psychology, 56*, 89-114.

Pflugshaupt, T., Nyffeler, T., von Wartburg, R., Wurtz, P., Lüthi, M., Hubl, D., et al. (2007). When left becomes right and vice versa: Mirrored vision after cerebral hypoxia. *Neuropsychologia, 45*, 2078-2091.

Poldrack, R. A., Clark, J., Pare-Blagoev, E. J., Shohamy, D., Moyano, J. C., Myers, C., et al. (2001). Interactive memory systems in the human brain. *Nature, 414*, 546-550.

Poldrack, R. A. (2010). Subtraction and beyond: The logic of experimental designs for neuroimaging. In S. J. Hanson, & M. Bunzl (Eds.), *Foundational issues in human brain mappin*g (pp. 147-159). Cambridge, MA: MIT Press.

Poldrack, R. A. (2012). The future of fMRI in cognitive neuroscience. *NeuroImage, 62*, 1216-1220.

Poline, J., Thirion, B., Roche, A., & Meriaux, S. (2010). Intersubject variability in fMRI data: Causes, consequences, and related analysis strategies. In S. J. Hanson, & M. Bunzl (Eds.), *Foundational issues in human brain mappin*g (pp. 173-191). Cambridge, MA: MIT Press.

Polley, D. B., Steinberg, E. E., & Merzenich, M. M. (2006). Perceptual learning directs auditory cortical map reorganization through top-down influences. *The Journal of Neuroscience, 26*, 4970-4982.

Posner, M. I., & Raichle, M. E. (1994). *Images of mind.* New York, NY: Scientific American Library.

Preston, A. R., & Wagner, A. D. (2007). The medial temporal lobe and memory. In R. P. Kesner, & J. L. Martinez (Eds.), *Neurobiology of learning and memor*y (2nd ed., pp. 305-337). Burlington, MA: Academic Press.

Price, C. J., Noppeney, U., & Friston, K. J. (2006). Functional neuroimaging of neuropsychologically impaired patients. *Handbook of functional neuroimaging of cognition (2nd ed.)* (pp. 455-480). Cambridge, MA: MIT Press.

Priftis, K., Rusconi, E., Umiltà, C., & Zorzi, M. (2003). Pure agnosia for mirror stimuli after right inferior parietal lesion. *Brain, 126*, 908-919.

Raichle, M. E. (2006). Functional neuroimaging: A historical and physiological perspective. In R. Cabeza, & A. Kingstone (Eds.), *Handbook of functional neuroimaging of cognitio*n (2nd ed., pp. 3-20). Cambridge, MA: MIT Press.

Ranganath, C., & D'Esposito, M. (2001). Medial temporal lobe activity associated with active maintenance of novel information. *Neuron, 31*, 865-873.

Rapp, B. (Ed.). (2001). *The handbook of cognitive neuropsychology: What deficits reveal about the human mind.* New York, NY: Psychology Press.

Rapp, B. (2011). Case series in cognitive neuropsychology: Promise, perils, and proper perspective. *Cognitive Neuropsychology, 28*, 435-444.

Reber, P. J. (2013). The neural basis of implicit learning and memory: A review of neuropsychological and neuroimaging research. *Neuropsychologia, 51*, 2026-2042.

Rempel-Clower, N. L., Zola, S. M., Squire, L. R., & Amaral, D. G. (1996). Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *Journal of Neuroscience, 16*, 5233-5255.

Riddoch, M. J., & Humphreys, G. W. (1988). Description of a left/right coding deficit in a case of constructional apraxia. *Cognitive Neuropsychology, 5*, 289-315.

Riddoch, M. J., & Humphreys, G. W. (1993). *BORB: The Birmingham object recognition batter*y. Hove, UK: Erlbaum.

Riddoch, M. J., Humphreys, G. W., Jacobson, S., Pluck, G., Bateman, A., & Edwards, M. (2004). Impaired orientation discrimination and localisation following parietal damage: On the interplay between dorsal and ventral processes in visual perception. *Cognitive Neuropsychology, 21*, 597-623.

Robertson, E. M. (2007). The serial reaction time task: Implicit motor skill learning*? The Journal of Neuroscience, 27*, 10073-10075.

Robertson, L. C., Knight, R. T., Rafal, R., & Shimamura, A. P. (1993). Cognitive neuropsychology is more than single-case studies. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 19*, 710-717.

Röer, J. P., Bell, R., & Buchner, A. (2014). Evidence for habituation of the irrelevant-sound effect on serial recall. *Memory & Cognition, 42*, 609-621.

Rollenhagen, J. E., & Olson, C. R. (2000). Mirror-image confusion in single neurons of the macaque inferotemporal cortex. *Science, 287*, 1506-1508.

Rorden, C., & Karnath, H. (2004). Using human brain lesions to infer function: A relic from a past era in the fMRI age? *Nature Reviews Neuroscience, 5*(10), 813-819.

Rudel, R. G. (1982). The oblique mystique: A slant on the development of spatial coordinates. In M. Potegal (Ed.), *Spatial abilities. development and physiological foundations.* (pp. 129-146). New York, NY: Academic Press.

Rudel, R. G., & Teuber, H. L. (1963). Discrimination of direction of line in children. *Journal of Comparative and Physiological Psychology, 56*, 892-898.

Saarinen, J., & Levi, D. M. (1995). Orientation anisotropy in vernier acuity. *Vision Research, 35,* 2449-2461.

Sahraie, A., Hibbard, P. B., Trevethan, C. T., Ritchie, K. L., & Weiskrantz, L. (2010). Consciousness of the first order in blindsight. *Proceedings of the National Academy of Sciences USA, 107*, 21217-21222.

Sakata, H., Taira, M., Kusunoki, M., Murata, A., Tanaka, Y., & Tsutsui, K. (1998). Neural coding of 3D features of objects for hand action in the parietal cortex of the monkey. *Philosophical Transactions of the Royal Society of London B-Biological Sciences, 353*, 1363-1373.

Salamé, P., & Baddeley, A. D. (1982). Disruption of short-term memory by unattended speech: Implications for the structure of working memory. *Journal of Verbal Learning & Verbal Behavior, 21*, 150-164.

Schacter, D., & Buckner, R. (1998). Priming and the brain. *Neuron, 20*, 185-195.

Schapiro, A. C., Gregory, E., Landau, B., McCloskey, M., & Turk-Browne, N. B. (2014). The necessity of the medial temporal lobe for statistical learning. *Journal of Cognitive Neuroscience, 26*, 1736-1747.

Schendan, H., Searl, M. M., Melrose, R. J., & Stern, C. (2003). An fMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. *Neuron, 37*, 1013-1025.

Schlittmeier, S. J., Weissgerber, T., Kerber, S., Fastl, H., & Hellbrueck, J. (2012). Algorithmic modeling of the irrelevant sound effect (ISE) by the hearing sensation fluctuation strength. *Attention Perception & Psychophysics, 74*, 194-203.

Scoville, W. B., & Milner, B. (1957/2000). Loss of recent memory after bilateral hippocampal lesions. *The Journal of Neurology, Neurosurgery and Psychiatry* (1957), *20,* 11-21. Reprinted in *The Journal of Neuropsychiatry and Clinical Neurosciences* (2000), *12*, 103-113.

Selnes, O. A. (2001). A historical overview of contributions from the study of deficits. In B. Rapp (Ed.), *The handbook of cognitive neuropsychology: What deficits reveal about the human min*d (pp. 23-41). New York, NY: Psychology Press.

Shallice, T. (1988). *From neuropsychology to mental structur*e. New York, NY: Cambridge University Press.

Shapley, R., Hawken, M., & Ringach, D. L. (2003). Dynamic's of orientation selectivity in the primary visual cortex and the importance of cortical inhibition. *Neuron, 38*, 689-699.

Shapley, R., & Ringach, D. (2000). Dynamics of responses in visual cortex. In M. S. Gazzaniga (Ed.), *The new cognitive neuroscience*s (2nd ed., pp. 253-261). Cambridge, MA: MIT Press.

Shen, G., Tao, X., Zhang, B., Smith, E. L.,III, & Chino, Y. M. (2014). Oblique effect in visual area 2 of macaque monkeys. *Journal of Vision, 14,* 3.

Shikata, E., Hamzei, F., Glauche, V., Koch, M., Weiller, C., Binkofski, F., et al. (2003). Functional properties and interaction of the anterior and posterior intraparietal areas in humans. *European Journal of Neuroscience, 17*, 1105-1110.

Shohamy, D., & Turk-Browne, N. B. (2013). Mechanisms for widespread hippocampal involvement in cognition. *Journal of Experimental Psychology-General, 142*, 1159-1170.

Silvanto, J., Cowey, A., Lavie, N., & Walsh, V. (2007). Making the blindsighted see. *Neuropsychologia, 45,* 3346-3350.

Simmons, A. L. (2012). Distributed practice and procedural memory consolidation in musicians' skill learning. *Journal of Research in Music Education, 59,* 357-368.

Simmons, J. P., Nelson, L. D., & Simonsohn, U. (2011). False-positive psychology: Undisclosed flexibility in data collection and analysis allows presenting anything as significant. *Psychological Science, 22*, 1359-1366.

Simons, J. S., & Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nature Reviews Neuroscience, 4*, 637-648.

Sloboda, J. A. (1984). Experimental studies of music reading: A review. *Music Perception, 2*, 222-236.

Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning and Memory, 6*, 174-215.

Sokol, S. M., McCloskey, M., Cohen, N. J., & Aliminosa, D. (1991). Cognitive representations and processes in arithmetic: Inferences from the performance of brain-damaged subjects. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 17,* 355-376.

Somers, D. C., Nelson, S. B., & Sur, M. (1995). An emergent model of orientation selectivity in cat visual cortical simple cells. *Journal of Neuroscience, 15,* 5448-5465.

Song, A. W., Huettel, S. A., & McCarthy, G. (2006). Functional neuroimaging: Basic principles of functional MRI. In R. Cabeza, & A. Kingstone (Eds.), *Handbook of functional neuroimaging of cognitio*n (2nd ed., pp. 21-52). Cambridge, MA: MIT Press.

Sorqvist, P., Stenfelt, S., & Ronnberg, J. (2012). Working memory capacity and visual-verbal cognitive load modulate auditory-sensory gating in the brainstem: Toward a unified view of attention. *Journal of Cognitive Neuroscience, 24*, 2147-2154.

Squire, L. R., & Knowlton, B. J. (2000). The medial temporal lobe, the hippocampus, and the memory systems of the brain. In M. S. Gazzaniga (Ed.), *The new cognitive neuroscience*s (2nd ed., pp. 765-779). Cambridge, MA: MIT Press.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal-lobe memory system. *Science, 253*, 1380-1386.

Squire, L. R. (2009). The legacy of patient HM for neuroscience. *Neuron, 61*, 6-9.

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience, 27*, 279-306.

Squire, L. R., & Wixted, J. T. (2011). The cognitive neuroscience of human memory since HM. *Annual Review of Neuroscience, 34,* 259-288.

Stanley, J., & Krakauer, J. W. (2013). Motor skill depends on knowledge of facts. *Frontiers in Human Neuroscience, 7*, 503.

Stark, C. E. L., Bayley, P. J., & Squire, L. R. (2002). Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. *Learning & Memory, 9*, 238-242.

Stark, C. E. L., & Squire, L. R. (2003). Hippocampal damage equally impairs memory for single items and memory for conjunctions. *Hippocampus, 13*, 281-292.

Stefanacci, L., Buffalo, E. A., Schmolck, H., & Squire, L. R. (2000). Profound amnesia after damage to the medial temporal lobe: A neuroanatomical and neuropsychological profile of patient E.P. *The Journal of Neuroscience, 20*, 7024-7036.

Stewart, L., & Walsh, V. (2006). Transcranial magnetic stimulation in human cognition. In C. Senior, T. Russell & M. S. Gazzaniga (Eds.), *Methods in mind* (pp. 1-26). Cambridge, MA: MIT Press.

Stokes, M. G., Wolff, M. J., & Spaak, E. (2015). Decoding rich spatial information with high temporal resolution. *Trends in Cognitive Sciences, 19*, 636-638.

Suzuki, W., & Amaral, D. (2004). Functional neuroanatomy of the medial temporal lobe memory system. *Cortex, 40*, 220-222.

Treder, M. S. (2010). Behind the looking-glass: A review on human symmetry perception. *Symmetry, 2*, 1510-1543.

Tressoldi, P. E., Sella, F., Coltheart, M., & Umiltà, C. (2012). Using functional neuroimaging to test theories of cognition: A selective survey of studies from 2007 to 2011 as a contribution to the decade of the mind initiative. *Cortex, 48*, 1247-1250.

Tulving, E., Hayman, C. A., & Macdonald, C. A. (1991). Long-lasting perceptual priming and semantic learning in amnesia: A case experiment. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 17*, 595-617.

Tulving, E., & Schacter, D. L. (1990). Priming and human-memory systems. *Science, 247*, 301-306.

Turnbull, O. H. (1997). A double dissociation between knowledge of object identity and object orientation. *Neuropsychologia, 35*, 567-570.

Turnbull, O. H., Beschin, N., & Della Sala, S. (1997). Agnosia for object orientation: Implications for theories of object recognition. *Neuropsychologia, 35*, 153-163.

Turnbull, O. H., Driver, J., & McCarthy, R. A. (2004). 2D but not 3D: Pictorial-depth deficits in a case of visual agnosia. *Cortex, 40*, 723-738.

Turnbull, O. H., Laws, K. R., & McCarthy, R. A. (1995). Object recognition without knowledge of object orientation. *Cortex, 31*, 387-395.

Turnbull, O. H., & McCarthy, R. A. (1996). Failure to discriminate between mirror-image objects: A case of viewpoint-independent object recognition*? Neurocase, 2*, 63-72.

Umiltà, C. (2006). Localization of cognitive functions in the brain does allow one to distinguish between psychological theories. *Cortex, 42*, 399-401.

Ungerleider, L. G., & Pasternak, T. (2003). Ventral and dorsal cortical processing streams. In L. M. Chalupa, & J. S. Werner (Eds.), *The visual neuroscience*s (pp. 541-562). Cambridge, MA: Bradford.

Uttal, W. R. (2013). *Reliability in cognitive neuroscienc*e. Cambridge, MA: MIT Press.

van der Zwan, R., Leo, E., Joung, W., Latimer, C., & Wenderoth, P. (1998). Evidence that both area V1 and extrastriate visual cortex contribute to symmetry perception. *Current Biology, 8,* 889-892.

van Vugt, M. K., Schulze-Bonhage, A., Litt, B., Brandt, A., & Kahana, M. J. (2010). Hippocampal gamma oscillations increase with memory load. *Journal of Neuroscience, 30*, 2694-2699.

Verfaellie, M., LaRocque, K. F., & Keane, M. M. (2012). Intact implicit verbal relational memory in medial temporal lobe amnesia. *Neuropsychologia, 50*, 2100-2106.

Viswanathan, N., Dorsi, J., & George, S. (2014). The role of speech-specific properties of the background in the irrelevant sound effect. *The Quarterly Journal of Experimental Psychology, 67*, 581-589.

Vogels, R., & Orban, G. A. (1994). Activity of inferior temporal neurons during orientation discrimination with successively presented gratings. *Journal of Neurophysiology, 71*, 1428-1451.

Vul, E., & Kanwisher, N. (2010). Begging the question: The nonindependence error in fMRI data analysis. In S. J. Hanson, & M. Bunzl (Eds.), *Foundational issues in human brain mappin*g (pp. 71-91). Cambridge, MA: MIT Press.

Wager, T. D., Hernandez, L., Jonides, J., & Lindquist, M. (2007). Elements of functional neuroimaging. In J. T. Cacioppo, L. G. Tassinary & G. G. Berntson (Eds.), *Handbook of psychophysiolog*y (4th ed ed., pp. 19-55). Cambridge, UK: Cambridge University Press.

Wager, T. D., & Lindquist, M. A. (2011). Essentials of functional magnetic resonance imaging. In J. Decety, & J. T. Cacioppo (Eds.), *The Oxford handbook of social neuroscienc*e (pp. 69-96). New York, NY: Oxford University Press.

Walsh, V. (1996). Neuropsychology: Reflections on mirror images. *Current Biology, 6*, 1079-1081.

Walsh, V., & Butler, S. R. (1996). The effects of visual cortex lesions on the perception of rotated shapes. *Behavioural Brain Research, 76*, 127-142.

Walsh, V., & Pascual-Leone, A. (2003). *Transcranial magnetic stimulation: A neurochronometrics of mind*. Cambridge, MA: MIT Press.

Warrington, E. K., & Davidoff, J. (2000). Failure at object identification improves mirror image matching. *Neuropsychologia, 38*, 1229-1234.

Warrington, E. K., Logue, V., & Pratt, R. T. (1971). The anatomical localisation of selective impairment of auditory verbal short-term memory. *Neuropsychologia, 9*, 377-387.

Watanabe, T., Yagishita, S., & Kikyo, H. (2008). Memory of music: Roles of right hippocampus and left inferior frontal gyrus. *NeuroImage, 39*, 483-491.

Weinberger, N. M. (2007a). Associative representational plasticity in the auditory cortex: A synthesis of two disciplines. *Learning & Memory, 14*, 1-16.

Weinberger, N. M. (2007b). Auditory associative memory and representational plasticity in the primary auditory cortex. *Hearing Research, 229*, 54-68.

Weiss, C., & Disterhoft, J. F. (2015). The impact of hippocampal lesions on trace-eyeblink conditioning and forebrain–cerebellar interactions. *Behavioral Neuroscience, 129*, 512-522.

Westheimer, G. (2003). Meridional anisotropy in visual processing: Implications for the neural site of the oblique effect. *Vision Research, 43*, 2281-2289.

Wilson, H. R., & Wilkinson, F. (2003). Spatial channels in vision and spatial pooling. In L. M. Chalupa, & J. S. Werner (Eds.), *The visual neuroscience*s (pp. 1060-1068). Cambridge, MA: Bradford.

Wilson, S. J., & Saling, M. M. (2008). Contributions of the right and left mesial temporal lobes to music memory: Evidence from melodic learning difficulties. *Music Perception, 25*, 303-314.

Wixted, J. T., & Mickes, L. (2013). On the relationship between fMRI and theories of cognition: The arrow points in both directions. *Perspectives on Psychological Science, 8*, 104-107.

Woldorff, M. G., Hackley, S. A., & Hillyard, S. A. (1991). The effects of channel-selective attention on the mismatch negativity wave elicited by deviant tones. *Psychophysiology, 28*, 30-42.

Woodruff-Pak, D. S. (1993). Eyeblink classical conditioning in H.M.: Delay and trace paradigms. *Behavioral Neuroscience, 107*, 911-925.

Woodruff-Pak, D. S., Papka, M., & Ivry, R. B. (1996). Cerebellar involvement in eyeblink classical conditioning in humans. *Neuropsychology, 10*, 443-458.

Wurtz, R. H. (2009). Recounting the impact of Hubel and Wiesel. *The Journal of Physiology, 587*, 2817-2823.

Yee, L. T. S., Hannula, D. E., Tranel, D., & Cohen, N. J. (2014). Short-term retention of relational memory in amnesia revisited: Accurate performance depends on hippocampal integrity. *Frontiers in Human Neuroscience, 8,* 16.

Zatorre, R. J., Chen, J. L., & Penhune, V. B. (2007). When the brain plays music: Auditory-motor interactions in music perception and production. *Nature Reviews Neuroscience, 8,* 547-558.

Zdzinski, S., & Barnes, G. (2002). Development and validation of a string performance rating scale. *Journal of Research in Music Education, 50*, 245-255.

Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1986). Human amnesia and the medial temporal region – enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *Journal of Neuroscience, 6*, 2950-2967.

Zola-Morgan, S., Squire, L. R., & Ramus, S. J. (1994). Severity of memory impairment in monkeys as a function of locus and extent of damage within the medial temporal-lobe memory system. *Hippocampus, 4*, 483-495.

Zurif, E., Swinney, D., & Fodor, J. A. (1991). An evaluation of assumptions underlying the single-patient-only position in neuropsychological research: A reply. *Brain and Cognition, 16*, 198-210.