The effects of spatially relevant and irrelevant optic flow: An investigation with fMRI

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Summary

A major part of our brain is devoted to the processing of visual sensory information. Within our visually dominated perception of the world, spatial structures such as edges or corners represent important cues to segregate and structure the incoming visual input into distinct forms or objects. The perception of such spatial information is mainly ruled by phase information that determines the appearance of our environment.

While previous studies have investigated the response of the early visual cortex to manipulation of phase information for static images, the results are divergent regarding how such images activate the visual cortex. Although static images can provide us with a snapshot of how our visual system responds to manipulated phase information, the processing can potentially differ for phase-manipulated images in the temporal domain for which spatial structure is no longer contained. It is so far unknown which brain areas are involved in processing spatiotemporal visual input that is highly structured compared to visual input that no longer contains spatial structure due to phase manipulation. Which brain network is recruited when our brain perceives visual input that neither immediately reveals a clear meaning nor can be categorized as noise? This doctoral thesis attempts to answer this question with functional magnetic resonance imaging (fMRI) analysis and by combining data-driven and model-based connectivity analyses.

To reveal the different brain regions involved in processing spatially structured and spatially unstructured optic flow stimuli, subjects performed different tasks on such stimuli during a fMRI experiment. For this experiment the spatially unstructured stimuli were created through phase-scrambling of structured stimuli, resulting in stimuli with comparable image statistics but without edges or a regular spatial structure. These phase-scrambled stimuli compared with emotionally neutral, spatially structured stimuli evoked an increase in visual cortex activation. The recognizable, spatially structured stimuli resulted in increased lateral occipital and strong bilateral activity foci in the precuneus, implicated in updating of spatial representations. This study demonstrates that spatiotemporal scrambling elicits increased visual cortex activity, although basic image statistics and average local

flow were matched between both stimulus types. This finding can neither be explained by local luminance differences, performance differences nor differences in eye movements. Data-driven independent component analysis was applied to the fMRI data and the independent component with activation in early visual areas revealed also hippocampal activation indicating that activity in the visual cortex and the hippocampus represents a statistically independent process. Moreover, the hippocampal activation in response to phase-scrambled, indistinct stimuli was confirmed by regressional model analysis.

A second fMRI study investigated whether the hippocampal activation is caused by a stimulus or task-dependent effect, such as integrating optic flow motion over time. Within a factorial design, subjects performed an optic flow motion and a detection task while viewing the same visual stimuli. This study found again bilateral posterior hippocampal activation in response to indistinct motion stimuli, that was independent of task. Due to a lack of explicit memory demands for both tasks, the resulting hippocampal activation was an implicit response and helps to elucidate the role of the hippocampus as distinct from the classical view that the hippocampus is associated with explicit learning. In addition, we applied model-based psychophysiological interaction analysis (PPI) to identify brain regions showing connectivity with the hippocampus. In response to phase-scrambled stimuli, PPI analysis revealed a stimulus dependent functional connectivity between the hippocampus and areas within the dorsal and ventral visual stream. In contrast, for spatially structured stimuli connectivity between the hippocampus and early visual cortex was found. Thus, the found cortico-hippocampal connectivity changed according to perceptual demands.

In summary, the results of this thesis contribute to a better understanding of the brain's response to indistinct, phase-scrambled spatio-temporal stimuli by demonstrating that even purely visual tasks on such stimuli recruit the hippocampus, a higher cognitive area. This finding can neither be explained by memory, stimulus or contextual novelty processing, or task effects. In keeping with recent suggestions that vision is more like "recognition-by-analogy" (Bar, 2009), the found cortico-hippocampal connectivity of visuospatial, object recognition areas and the hippocampus speaks for an attempted retrieval of an analogy through the concerted action of these functionally connected areas. The new approach of phase-scrambling over space and time that was applied here could be used in future studies of scene processing to optimally control for visual information.

1 Introduction

The human visual sense represents for us the most dominant source of sensory information about our environment. With the largest part of the human cortex being devoted to visual information processing, it is one of the most highly developed senses we have. How much we rely on our visual system and on highly structured visual input becomes particularly apparent when we find ourselves robbed of visual cues or spatial structure such as in extreme darkness or in thick fog.

Our brain constantly filters and quickly abstracts visual input to reduce processing demands. Once we recognize objects in our environment no further information processing is needed as we can draw on prior knowledge from past experience. Recently, it was proposed that our human brain not only rapidly extracts rudimentary information but also derives analogies which link the visual input to existing memory representations (Bar, 2007). Furthermore, it was suggested that visual perception relies on memory functions within the medial temporal lobe (Bar, 2009).

The human visual system not only processes snapshots of reality but everything we perceive is contained in a continuous spatiotemporal stream of information. In fact motion processing represents an important function and allows us to parse visual input into distinct objects (Ostrovsky et al., 2006). How complex visual tasks can be is demonstrated in the field of computer vision, where recognition is much slower than in humans, more volatile for disruption and often typically specialized for a specific task. The problem of visual classification becomes even harder when no spatial information, in form of discrete forms and shapes, is present. So the question arises how visual information is processed in conjunction with existing memory information and whether a link between the visual system and existing memory structures is established. It is unclear what happens in situations where no quick abstraction is possible because no obvious forms and shapes are recognizable, such as during dense fog or within the middle of a snow storm. To find out how our brain processes its surroundings in such situations where visual input is everything but clear cut boundaries and edges, this thesis investigates which brain networks are involved in processing indistinct motion stimuli that lack a clear spatial structure.

In the following, a synopsis on visual processing systems including a description of the dorsal and ventral visual stream as well as optic flow processing will be given. Furthermore, the hippocampus and its functions, the perceptual effects of manipulation of image structure and the novel approach for creating indistinct stimuli are described. In addition, methodological aspects of this work and the aim of this doctoral thesis are presented.

1.1 The dorsal and ventral visual stream

Visual cortical areas have been proposed to be organized in two distinct anatomical and functional information processing streams: the ventral visual stream and the dorsal visual stream (Mishkin and Ungerleider, 1982) (Figure 1.1).

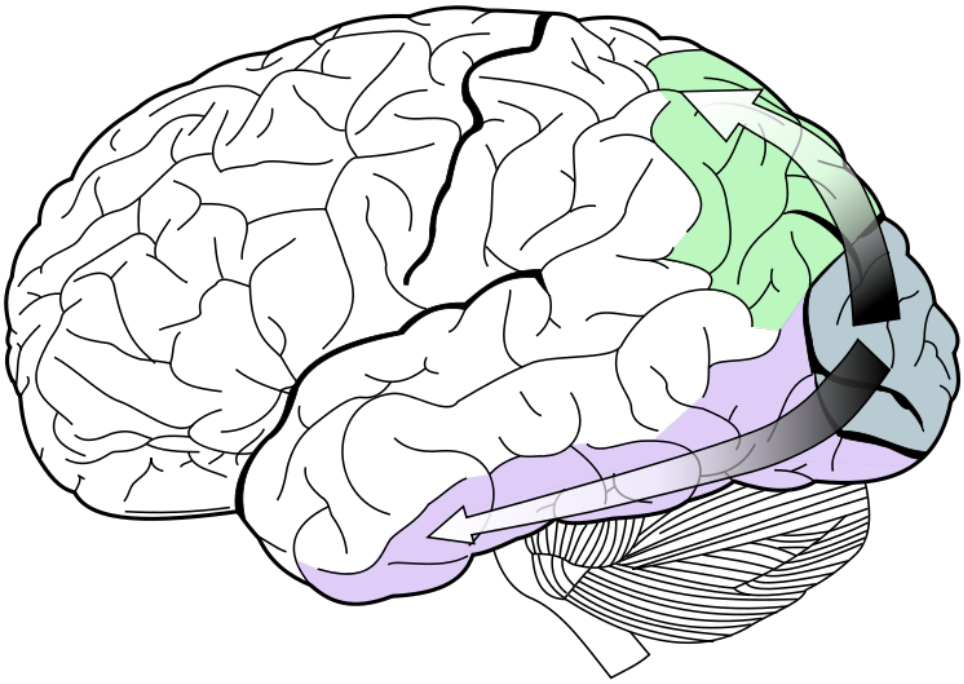

Figure 1.1: The ventral visual (in purple) and dorsal visual stream (in green). From http://www.websters-online-dictionary.org/definitions/Visual Perception.

Based on findings in monkeys, Ungerleider and Mishkin (1982) proposed that the ventral visual stream, named the "what" stream, processes mainly object information and visual features, while the dorsal visual stream processes spatial information and was referred to as "where" stream. The evidence for anatomically separate pathways starts in the primary visual cortex. Magnocellular pathways mainly project to the posterior parietal cortex (being part of the dorsal pathway) while parvocellular layers project mainly to the inferior temporal cortex (which is part of the ventral stream) (Wurtz and Kandel, 2000).

In contrast, the later perception-action model (Milner and Goodale, 1995) proposed that the dorsal stream processes information for action control as it guides the programming and unfolding of our actions, whereas the ventral stream processes visual information for perception. This proposed dissociation of perceptual and motor processes, however, is challenged by recent findings (Schenk and McIntosh, 2010). The following section will focus on brain regions within the dorsal pathway, which is essentially involved in visuospatial and motion processing and comprises many regions specialized for the processing of motion.

1.2 Processing of optic flow information

A pattern of visual motion, called optic flow, can arise through travel in space. Optic flow is defined as the dynamic pattern of retinal image stimulation produced when objects move toward or away from an observer or when an observer moves through a cluttered environment. It provides cues about the organization of the environment as well as information to our posture within it and is critical for determining the direction of observer movement (which is referred to as "heading"). In image processing optic flow is detected by finding corresponding points in a sequence of images, which can be used to derive the motion within this sequence.

As motion represents an important source of information, many brain regions are devoted to its processing. Among those the middle temporal visual area (MT or V5), which in monkeys is located at the edge of the parietal cortex within the posterior middle temporal gyrus, is specialized for processing of optic flow (Born and Bradley, 2005) or moving patterns as the majority of MT neurons are tuned for velocity (Nishimoto and Gallant, 2011). The area possesses a columnar organization in which cells coding for similar directions are organized in vertical cortical columns (Albright, 1984). Area MT has larger receptive fields than primary visual cortex (V1) neurons and thus allows for the integration of motion signals from a larger region of visual space than V1 neurons. It receives major feedforward inputs from early visual areas (V1, V2, V3) and is also known to feed back to V1 (Sekuler et al., 2002). Spontaneous or electrically induced fluctuations of activity in V5 correlate with behavioral performance, as revealed by single cell recordings and microstimulation experiments, and thus suggest a direct role for V5 in the perception of motion direction and speed (Bartels et al., 2008b). Moreover, numerous imaging studies have confirmed the motion sensitivity of area MT (Huk and Heeger, 2002; Heeger et al., 2000; Zeki et al., 1991).

In addition to area MT, other brain regions are known to respond to motion. Adjacent to area MT lies area MST, which also responds to optic flow but additionally processes vestibular input (Gu et al., 2007). In general, both areas are activated in response to optic flow. For different types of coherent and incoherent motion area V5/MT and MST respond equally (Fischer et al., 2011), so that within this thesis these two areas will subsequently not be differentiated. While area MT demonstrates no selectivity for motion-boundaries (Marcar et al., 1995), such responsiveness is ascribed to another motion sensitive region also referred to as the kinetic occipital region, which processes motion as well as shape information (Dupont et al., 1997).

1.3 The hippocampal formation

Optic flow information or self-motion information arising from multiple sensory systems has been shown to be conveyed to the hippocampal formation, located within the medial temporal lobe. Hippocampal neurons use self-motion information to determine the current location within an environment (Terrazas et al., 2005; Jeffery, 2007). The hippocampal formation is the subject of a vast amount of investigations and has mostly been identified to be crucial for memory, although its detailed functioning is still unclear. In general, the hippocampal formation allows us to built up comprehensive representations of our environment by using many different converging sensory inputs. The discovery that resection of the medial temporal lobe including the hippocampal formation had devastating effects on memory in humans (Scoville and Milner, 1957) lead to an increased research focus regarding this brain region and its impact on memory. Research during the following decades elucidated that damage to the hippocampal formation, specifically the hippocampus, is sufficient for a moderately severe memory impairment and thus highlighted its role for memory (Squire and Wixted, 2011; Zola-Morgan et al., 1989). The following section will give an overview on the anatomical structure and the function of the hippocampal formation.

1.3.1 Anatomy of the hippocampal formation

The hippocampal formation consists of the dentate gyrus, the hippocampus proper (fields CA1, CA2, CA3), and the subiculum (all together referred to as hippocampus). It is surrounded by the parahippocampal region, which consists of the entorhinal, perirhinal, and parahippocampal cortices (Burwell and Agster, 2008). In contrast to the parahippocampal region, in which all structures possess six discernible neuronal layers and reciprocal connections, all structures in the hippocampal formation possess a trilaminar structure and they are mostly unilaterally connected

between themselves. Regarding this unidirectional nature, the brain circuit of the hippocampal formation is unique. This hippocampal formation receives major sensory input from higher-order, multimodal cortical regions that converges on the hippocampus through the entorhinal cortex. In the monkey, the majority of neocortical inputs project through the perirhinal and parahippocampal cortices to the entorhinal cortex. Polysensory associational regions in the frontal and temporal lobes as well as the insular and the cingulate cortex project to the entorhinal cortex (Insausti et al., 1987). Distinct from the entorhinal input pathway, anatomical tracer studies in monkeys have further identified direct input from the temporal and parietal cortex to area CA1 of the hippocampus (Rockland and Van Hoesen, 1999). The majority of information that comes from the entorhinal cortex passes through the perforant path to the granule cells of the dentate gyrus, from where information is projected to CA3. The pyramidal cells in CA3 project unidirectionally to CA1, which in turn projects to the subiculum (Figure 1.2). Once information is processed in the hippocampal formation, most of it is returned back through the entorhinal cortex to many of the polysensory cortical regions. In addition, hippocampal neurons have also been shown to project directly back to cortex, as in the case of CA1 neurons projecting to ventromedial temporal areas (Iwai and Yukie, 1988).

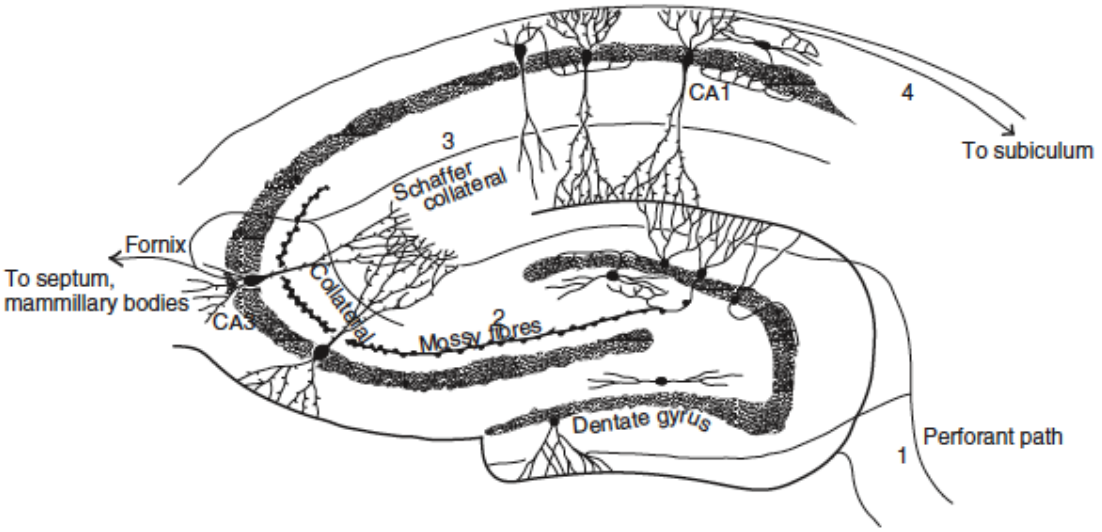

Figure 1.2: Through the perforant path (1), which has synapses with the dendrites of granule cells of the dentate gyrus and the dendrites of pyramidal cells in CA3, sensory inputs reach the hippocampus. Via the mossy fibers (2) dentate granule cells project to the CA3 pyramidal cells, which project to the CA1 pyramidal cells via the Shaffer collaterals (3). Image taken from (Rolls, 2010).

1.3.2 The functional role of the hippocampal formation

The hippocampal formation is a highly unique and interesting structure for which many different ideas and theories of hippocampal function have been proposed. The hippocampus forms lasting memories for events (Zola-Morgan et al., 1989; Scoville and Milner, 1957; O'Keefe and Nadel, 1978) by encoding these events in a spatiotemporal context (Eichenbaum and Fortin, 2003; Squire, 1992; Tulving, 2002). Indeed, numerous fMRI studies have associated activation of the human hippocampus (Figure 1.3) with episodic encoding and retrieval. Not surprisingly, the hippocampal formation is a highly plastic brain structure that can even change in size according to the demands placed by the environment (Maguire et al., 2000). The specific anatomical characteristics of hippocampal regions help a mechanism called pattern completion, by which a stored memory trace can be retrieved. Given the central role of the hippocampus for memory, different hippocampal theories will be discussed in the following.

Pattern completion and attractor dynamics

During encoding of information, activity patterns in neurons become inscribed as memory trace, which can later be restored during recall. The re-establishment of the original activity pattern or the reactivation of a stored neural representation by a cue that is part of that representation is known as 'pattern completion' (e.g. Bird and Burgess, 2008). This pattern completion is believed to occur in the hippocampus because it was discovered that CA3 pyramidal cells possess extensive excitatory and recurrent connections (Amaral et al., 1990) and the CA3 region has been shown to be involved in encoding associative information (Zeineh et al., 2003; Eldridge et al., 2005). When an external retrieval cue is presented, the activation of a small number of CA3 pyramidal cells can trigger the reactivation of previously modified synapses (Carr et al., 2011) that help to retrieve full representations (Bird and Burgess, 2008). Due to its excitatory recurrent collaterals, the CA3 region is assumed to act as attractor network. Attractor dynamics can be characterized by effective energy landscapes in which local minima represent stable points of firing. When the system settles into such a stable firing pattern, this corresponds to the recall state of a memory. Because an external stimulus can change the system's state, continuously changing input or high levels of noise prevent the attractor system from stabilizing and converging onto a stable point (Rolls, 2010).

Standard model of systems consolidation

The standard model of systems consolidation posits that memories are formed by encoding and registering novel information in the medial temporal lobe system, in-

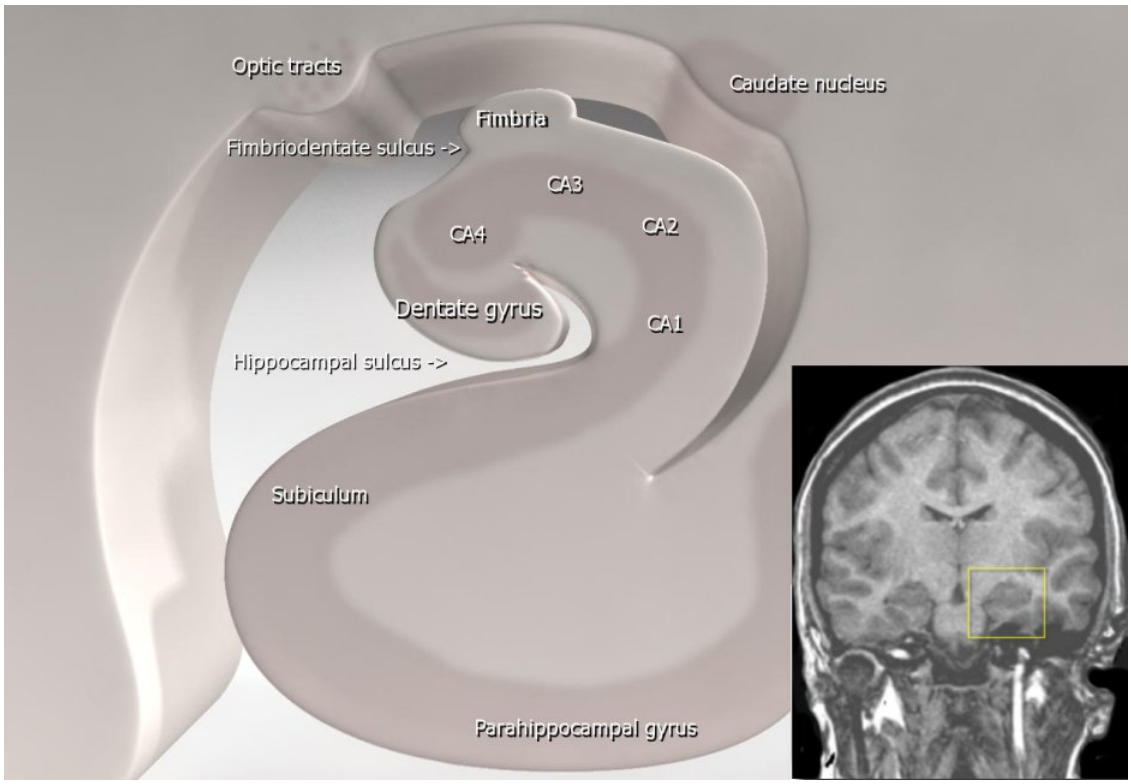

Figure 1.3: Enlarged view depicting the schematic organization of the human hippocampus within one hemisphere. Adapted image under the Wikimedia Commons License.

cluding the hippocampus (Squire and Alvarez, 1995). According to this theory, which is also called declarative memory theory, all declarative memory, both semantic and episodic, is thought to be dependent on the hippocampal formation (Squire et al., 2004). Over time these memories are consolidated by transferring the information to neocortex (Bird and Burgess, 2008). This consolidation process can establish a stable associative network of memory traces through the dynamic interaction between the hippocampus and the cortex, which can later be used for memory retrieval (Wang and Morris, 2010). With each recall of the memories, the cortico-cortical connections are thought to be strengthened, so that the memories eventually become independent of the hippocampus (Frankland and Bontempi, 2005). While recent episodic memories are still dependent on the hippocampus, remote memories or facts that were learned long ago are represented in neocortical networks and no longer require the hippocampus to be retrieved.

Other hippocampal theories

Besides this standard declarative memory theory, there exists a whole range of theories about hippocampal function that differ regarding the type of memory that is hippocampus dependent. Even the role of the human hippocampus for long-term

memory is still under debate (Bird and Burgess, 2008). The multiple memory trace theory for example posits that the hippocampus plays an important role for encoding of episodic and semantic content. While successful recollection of episodic memories is thought to stay crucially dependent on the hippocampus throughout life, semantic memories are thought to become independent of the hippocampus as they are stored in neocortex (Nadel et al., 2000).

Another major theory, named the cognitive map theory, assigned the hippocampus the spatial role of constructing and storing allocentric (i.e. world-centered) representations of locations in the environment (O'Keefe and Nadel, 1978). This theory is based on the discovery of place cells in the rodent hippocampus (O'Keefe and Dostrovsky, 1971), which are hippocampal neurons that fire selectively in different regions or "place fields" of an environment. Their firing is independent of the orientation of the animal and place cells can flexibly participate in the representation of different environments. Place cell firing can be influenced by distal and proximal sensory information (O'Keefe and Conway, 1978; Muller and Kubie, 1987) as well as recent experience in an environment. Furthermore, place field locations are not only controlled by external sensory information but also influenced by idiothetic information (Skaggs and McNaughton, 1998) and can even be maintained in the absence of cues (O'Keefe and Speakman, 1987). In contrast to the declarative memory theory, this theory predicts lasting hippocampal involvement for spatial tasks but it does not explain the hippocampal role in nonspatial memory tasks. As hippocampal place cell firing can be altered by minor changes of the environment (Colgin et al., 2008), one view is that these cells "represent the significant features of a task or event" including spatial features, as an early step in establishing a memory. Recent evidence demonstrates that place cells can also signal future choice, past events, and motivational state (Pastalkova et al., 2008; Kennedy and Shapiro, 2009).

Evidence from rodents demonstrating that hippocampal lesions affect more than spatial tasks indicate that the hippocampus is certainly not solely spatial (Eichenbaum, 1996). Furthermore, hippocampal lesions in humans have not impaired the ability to keep track of a reference location using self-motion cues, called path integration, as long as no long-term memory was required (Shrager et al., 2008). Despite numerous publications on the hippocampus and its central role for memory, an overarching hippocampus theory reconciling these different functions is still aspired. Newest findings indicate that the hippocampus may possess genetically defined parallel subpathways, which would allow for processing of different types of information in relative isolation and could potentially explain the diversity of

hippocampal functioning (Moser, 2011).

1.4 Perception of phase-manipulated visual stimuli

Each image can be seen as a two-dimensional matrix consisting of pixels with a certain intensity. For each greyscale image the pixel values of each row and each column represent a signal over space. Each signal can be composed of different oscillations of which each is characterized by a certain frequency, amplitude and phase. While both the phase and the amplitude spectrum play a role in the perception of images, the phase spectrum dictates the appearance of visual images (Piotrowski and Campbell, 1982). For the perception of spatial structure and edges within an image the phases of different spatial frequency components must be aligned (Wichmann et al., 2006). Accordingly, phase manipulation is a possibility to make images indistinct.

1.4.1 Previous work on the perception of phase-manipulated static images

Previous studies investigated the effect of viewing unrecognizable images on activation of visual areas by manipulating the phase information in static images and found divergent results. One single cell recording study in anesthetized monkeys investigated the effect of phase coherence on activation in occipital visual areas. By using a blend of phases from the original images and random phase spectrum stimuli became increasingly hard to recognize. However, the corresponding brain response showed non-monotonic BOLD signal behavior. Cells in V1 responded most strongly to natural images, most weakly to 50:50 image-noise blends and then recovered for pure noise images (Rainer et al., 2001).

In contrast to this finding, Dakin et al. (2002) proposed a strict monotonic dependence of psychophysical detectability on signal-to-noise ratio. They criticized the phase blending procedure of the previous study as it leads to an over-representation of near 0 degree phase components and to side effects such as altering contrast and kurtosis/sparseness statistics, which are both known to be linked to human perception of structure in images (Dakin et al., 2002).

In another monkey study natural images were made hard to recognize by scrambling them into different numbers of segments. This study observed an increase in activity in primary visual cortex (V1) with scrambling, except that very highly scrambled images (128 x 128 segments) led to a decrease in BOLD activity. Al-

though scrambling into segments does not affect the overall identity of the pixels, this approach leads to many new edges in the image and introduces high frequency components (Rainer et al., 2002).

One study in humans investigated the response of early visual cortex to static natural and phase-manipulated images, which were created by adding random perturbations to the phase spectrum. This study found no difference in activation of V1 between phase-manipulated and normal natural images, suggesting that spatial phase structure does not affect the BOLD fMRI response (Olman et al., 2004). Based on this study, Wichmann et al. (2006) argued that RMS contrast of the stimuli seems to mainly drive the BOLD response in primary visual cortex but not particular phase relationships. However, the presented stimuli were intervened by blank grey patches, so that the results can not be easily transferred to other ways of stimulus presentation.

Another study in humans investigated the effect of global phase manipulations in a psychophysical experiment with a rapid visual categorization task (Wichmann et al., 2006). To create stimuli that are hard to recognize, the Fourier spectra of the presented images were manipulated by adding zero-mean random phase noise at all spatial frequencies to images of natural scenes. The added phase noise was uniformly and symmetrically distributed between 0° and 180°. For such random phase-manipulations, except when phase was completely randomized, the visual system was highly robust and the authors suggested that the visual system does not seem to code global phase per se.

1.4.2 Phase-manipulation of spatiotemporal stimuli

Although analysis of static images can provide useful insights regarding brain functions, everyday life confronts us with spatiotemporally continuous visual input for which the processing demands may differ. In particular, the detection and analysis of motion represent vital and pervasive functions of the visual system. This thesis investigated the brain's response to highly structured spatially relevant motion stimuli and stimuli which contained optic flow but did not provide spatially relevant information. To obtain stimuli that are most similar regarding image statistics to a spatially structured motion stimulus but are indistinct (i.e. lack a clear spatial structure but are also not noise stimuli), neutral films with spatially relevant content were subjected to manipulation of the phase information (Figure 1.4) by help of the Fourier transform.

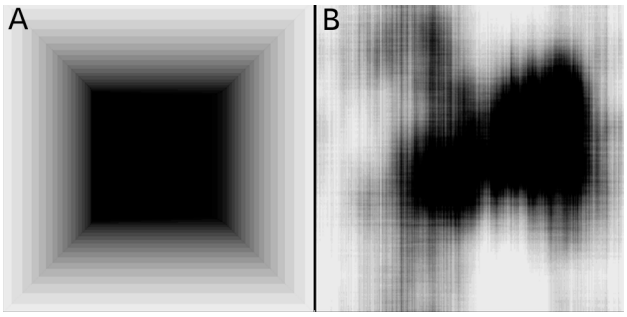

Figure 1.4: The two types of stimuli used in our experiment. Frame from a spatially structured, meaningful tunnel stimulus (A) and a corresponding indistinct version of it that resulted from phase-scrambling (B).

1.4.3 Fourier transform

The Fourier transform, introduced by Jean Baptiste Joseph Fourier (1768-1830), takes advantage of the fact that every signal can be represented by a sum of multiple sinusoidal functions. While originally developed to solve the heat equation by modeling a heat source as a linear combination of simple sine and cosine waves, the Fourier transform can be applied in the domain of image analysis to decompose a periodic signal into such a frequency spectrum (Oppenheim et al., 1991). This spectrum consists of complex numbers representing the frequency components of the original stimulus, which are characterized by amplitude and phase information. The amplitude spectrum represents the contribution of various frequencies to the original image and is obtained by taking the absolute values of the frequency components. The phase of each frequency component, on the other hand, represents the shift of the wave function within the signal and is computed by the inverse tangent of the quotient of the imaginary part and the real part. To again obtain the values of the frequency components the 3D amplitude spectrum is multiplied with $e^{i \cdot \alpha}$, with i being the imaginary unit and α being the phase angle. The resulting frequency spectrum, characterized by phase and amplitude values, can be transformed back into a spatial signal via the inverse Fourier transform. If the frequency spectrum is not manipulated, the result is the original signal.

The Fourier transform can be applied to n-dimensional signals (e.g. two-dimensional in case of an image) and the resulting Fourier spectrum has as many dimensions as the original source signal. In case of a film, each pixel over all frames represents an additional signal over time. Thus, a three-dimensional Fourier transform can be applied to the film stimuli to decompose the signal into its constituent frequency components. Because the signal is digital a discrete Fourier transform (DFT) is used. In this thesis, the DFT was applied to create indistinct film stimuli by manipulating phase information. After the transform the amplitude and phase spectra

are obtained. The computed phase values of all frequency components are then randomly interchanged across all three dimensions, whereas the amplitude spectrum remains unchanged. The phase and amplitude values are then combined to retrieve the manipulated frequency spectrum and the inverse Fourier transform is applied to obtain an indistinct, phase-scrambled signal in space and time. This process of phase-scrambling that destroys the previous alignment of phase information is illustrated in Figure 1.5.

1.4.4 Computation of optical flow

Because phase manipulation could affect the optic flow contained in the stimuli and potentially lead to differential processing, we computed optic flow in the image sequences for both stimulus types in order to examine whether the two different stimuli differ regarding optic flow. There are many different algorithms for the computation of optic flow, which allow to estimate 2D pixel motion in images that change over time. Most of these are based on the assumption of brightness constancy of individual pixels while moving on the image plane. For the computation of optic flow local and global differential methods exist, which compute spatial and temporal image derivatives. Although local methods that compute only local changes of light patterns can offer relatively high robustness under noise, they do not give dense flow fields. Because local methods have serious limitations and can not unambiguously determine a velocity field, a global approach, the classical method of Horn and Schunck was used in the present study to compute optical flow (Horn and Schunck, 1981). Although global methods are more sensitive to noise, their advantage is that they offer 100% density in flow fields.

1.5 Methodological aspects

The following section gives an overview of functional magnetic resonance imaging and describes the different analysis techniques that have been applied in this thesis.

1.5.1 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is a powerful brain imaging technique that allows the measurement of hemodynamic changes over time. fMRI is noninvasive and possesses a relatively high spatiotemporal resolution in comparison to other techniques. During brain activation the energy demands of the local tissue increases. The hemodynamic response to this energy demand is that vasodilation occurs leading to a local increase in blood volume, blood flow and cerebral oxygenation. fMRI is most frequently used to assess brain function with the Blood Oxygen

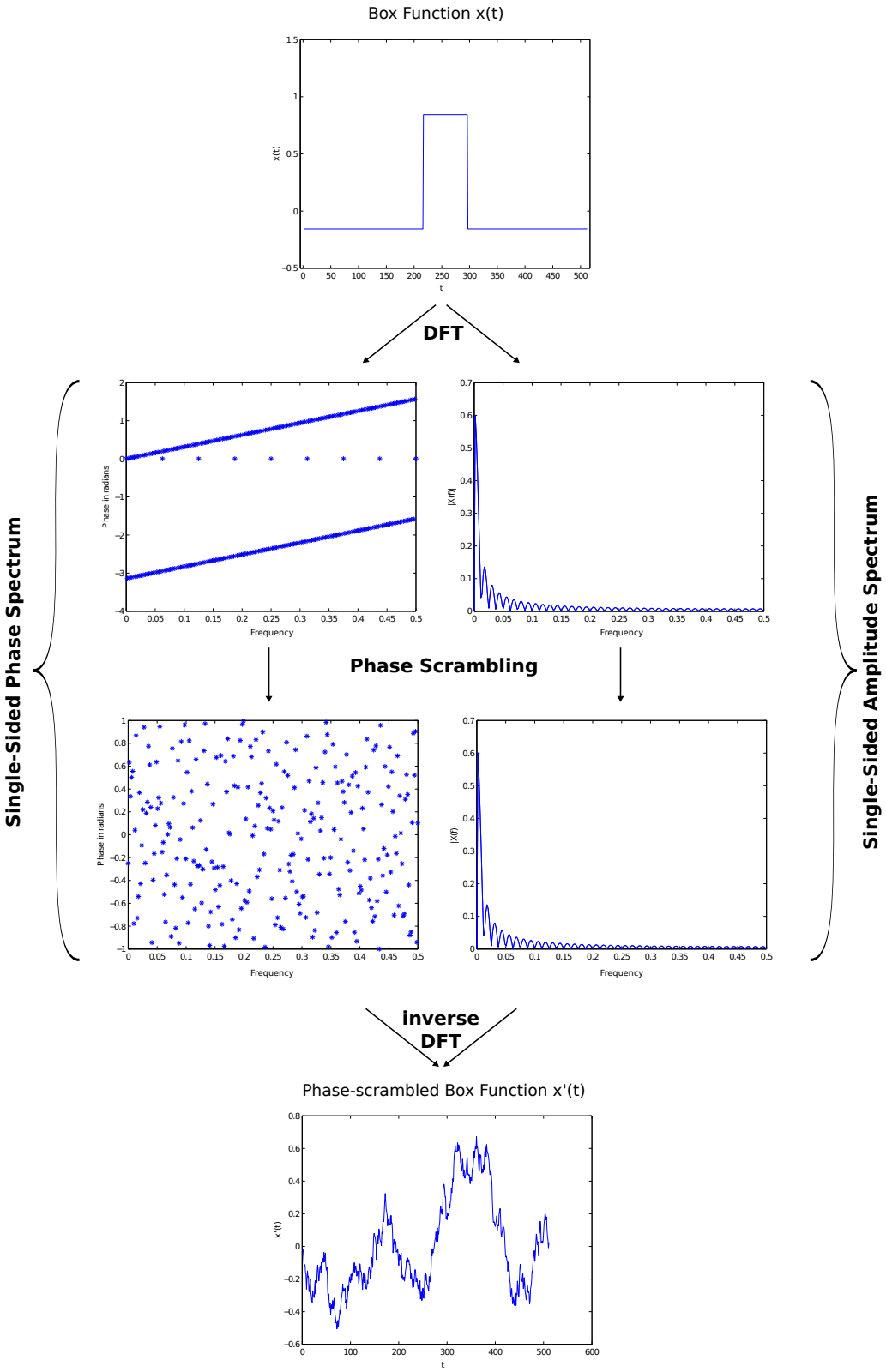

Figure 1.5: Illustration how phase manipulation affects a 1 dimensional box function x(t), which corresponds to two edges in an image. The Fourier Transform is applied to the box function to obtain the signal's phase and amplitude spectrum. Afterwards phase-scrambling is applied by permuting the phases of all frequency components, whereas the amplitude spectrum remains unchanged. The inverse Fourier transform for the new phase spectrum and the amplitude spectrum results into a new phase-scrambled signal, which no longer resembles the original box function.

Level Dependent (BOLD) signal, which capitalizes on the fact that an increased ratio of oxyhemoglobin to deoxyhemoglobin leads to a decreased level of paramagnetically induced dephasing and stronger signal. The neural signal of a single neuron can directly translate into vasodilation or constriction of a blood vessel and can thus influence the microcirculation (Cauli et al., 2004). Figure 1.5 schematically illustrates the innervation of a microvessel.

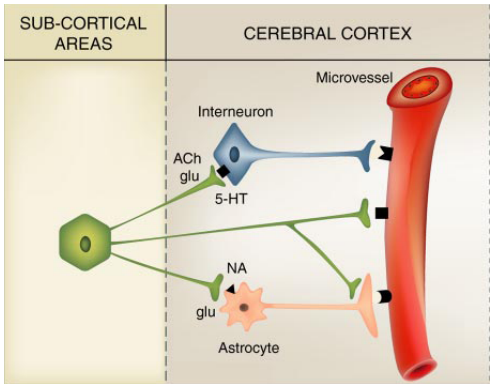

Figure 1.6: The depicted model assumes that even sub-cortical afferents may directly contact and act upon astrocytes or microvessels. Neuron-driven changes in vascular tone arise through different dynamics of neurovascular coupling of interneurons, astrocytes, and pyramidal cells. The signaling of neurons and astrocytes translates neuronal activity into an integrated vascular response, which is highly dependent on which target neurons are activated. Adapted from Hamel (2006).

Simultaneous measurements of neuronal activity and the hemodynamic response have demonstrated that the BOLD signal correlates well with single unit data and local field potentials and that the BOLD response directly reflects an increase in neural activity (Logothetis et al., 2001; Kim et al., 2004). Although fMRI data can reflect an increase in the spiking of neurons (Logothetis, 2008), local field potentials are the most reliable predictor of BOLD responses (Logothetis and Pfeuffer, 2004). There is also evidence for an approximately linear coupling between BOLD and neuronal activity (Kim et al., 2004). In particular, fMRI responses from visual cortex have been shown to be proportional to firing rates (Heeger et al., 2000) and fMRI responses in primary visual cortex have been found to be extremely sensitive to perceptual states (Heeger, 1999; Polonsky et al., 2000). Overall, the BOLD signal is now known to be primarily driven by local dendrosomatic processing and synaptic activity (Lippert et al., 2010) that translates into vascular signals through complex interactions of neurovascular coupling. fMRI also reflects the neuromodulatory feedback from higher areas, which cannot be captured by single unit activity (Logothetis, 2008). Thus, fMRI represents a complementary technique to local electrical

measurements and also allows one to reveal entire networks of brain areas engaged during the performance of a particular task.

1.5.2 Functional connectivity

Our brain represents an incredibly complex system of interconnections on multiple levels ranging from individual synaptic connections to networks connecting neuronal populations in different brain regions. Studying the functional integration of distinct brain regions allows one to gain a more thorough understanding of the brain. The temporal correlations or statistical dependencies between spatially remote neurophysiological events are referred to as functional connectivity. By assessing spontaneous fluctuations in the blood oxygenation level-dependent (BOLD) signal, fMRI can help to delineate "neural functional architecture" (Cole et al., 2010). As for fMRI many repeated scans are acquired in quick succession, fMRI data provide a rich source of information about correlated activity fluctuations (Friston, 1994).

The potential that intrinsic activity correlations (in form of low frequency fluctuations) represent a manifestation of functional connectivity was first demonstrated in the motor cortex (Biswal et al., 1995). Koch et al. (2002) provided initial evidence that BOLD signal correlations are mediated by direct and indirect anatomical projections. According to their results, high functional connectivity should arise for regions that are directly linked by white matter fiber tracts. However, functional connectivity can also arise through indirect mediations from more distant grey matter regions. Recent mathematical models suggest that neural dynamics and propagation properties might build the basis for these intrinsic activity correlations. Although functional connectivity is distinct from anatomical connectivity, there is increasing evidence that intrinsic BOLD fluctuations are constrained by anatomic connectivity (Dijk et al., 2010). However, functional connectivity is not merely a reflection of direct structural connections, as task performance can introduce regional variation in correlation strengths (Sepulcre et al., 2010).

The computational methods applied for assessing functional connectivity can be categorized into data-driven and model-driven methods. While data-driven independent component analysis represents a technique that allows functional connectivity of the whole brain to be assessed, model-based functional connectivity explorations often select a region of interest (ROI) as seed region and examine whether other regions are functionally connected to this area. Based on the idea that functionally connected regions should have correlated BOLD time courses, functional connectivity can be assessed by computing cross correlations between them. The selection of

the seed region is mostly based on prior knowledge, such as that the voxels' time courses within this region mainly follow the time course of the model.

Independent Component Analysis

Independent component analysis (ICA) represents a blind source separation method for multivariate analysis of fMRI data that decomposes the fMRI data set into statistically independent processes or components. While ICA can either maximize independence over time (temporal ICA) by extracting temporal source signals or maximize independence over space (spatial ICA) by extracting spatial source signals, spatial ICA is typically used for extracting features from fMRI images (Stone, 2004). Spatial ICA provides a measure of connectivity because it extracts spatially distributed source signals. As ICA is an exploratory data analysis technique, which does not depend on any prespecified temporal profile of local brain activity, it can be applied to cognitive paradigms for which detailed a priori models of brain activity are not available. ICA is a powerful technique that can separate consistently or transiently task-related fMRI activations as well as nontask-related signals such as high- and low-frequency artifacts or movements from the data (McKeown et al., 1998).

Among the different classes of algorithms, which can be used for spatial ICA, the information maximization (Infomax) algorithm (Bell and Sejnowski, 1995; McKeown et al., 1998) was applied in this thesis. Being an iterative unsupervised learning algorithm and one of the most commonly used ones, the Infomax algorithm estimates maximally statistically independent components by maximizing the kurtosis of the components and minimizing mutual information between components. Under the assumption that the measured fMRI time series data X (with time points as signals and voxels as samples) results from linear combinations of independent components, called sources M, and an unknown mixing matrix A, the goal of the ICA is to find these independent components Y (Figure 1.6). Because the sources are unknown, ICA recovers the source activities of the original recordings by finding the inverse of A, the unmixing matrix W. The estimated source activation matrix M that consists of independent component maps is computed by the following equation:

$$M = W*X$$

The Infomax algorithm has been shown to always converge to a stable solution, to be extremely stable for repeated ICA decompositions, and to result in reproducible results (Duann et al., 2005). Furthermore, comparative work between different algorithms attested the Infomax approach superior global estimation and noise reduction

capabilities (Esposito et al., 2002).

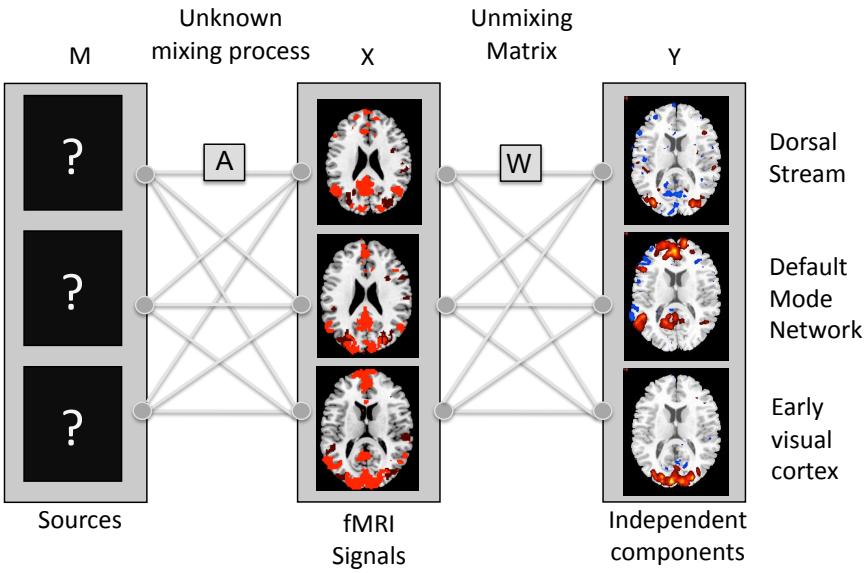

Figure 1.7: Illustration of the ICA mixing and unmixing model that is relevant for extracting independent components from the measured fMRI signals by the learned weights of the unmixing matrix W. Each seperated output in Y represents a component map which consists of voxel values at fixed 3D locations and a unique associated time course of activation.

Once the algorithm has computed the independent components, ICA components can be ordered according to the amount of variance explained. The sum of the component variances approximately equals the total signal variance. To ensure that the interesting sources can be found, which are most likely weak in comparison to other artifactual sources, it is important to choose a relatively large number of independent components. A too excessive dimensionality reduction can be problematic as it could force two separate sources into one component. In contrast, too many components could lead to the problem that one source will be split into separate components. Thus, this method requires experience and validation of decomposition results by comparison to known functional networks.

Psychophysiological interaction analysis

Psychophysiological interaction (PPI) analysis can identify functional integration between regions and allows for the detection of interactions between brain regions in relation to an experimental paradigm. PPI can explain a physiological and regionally specific response by an interaction between another brain region's activity and an experimental task or stimulus factor. Psychophysiological interaction can be understood as a "change in contribution of one area to another" that is context

or functionally specific (Friston et al., 1997). The contribution one area makes to a second corresponds to the degree by which activity in the second area can be predicted by the first.

PPI examines coactivations with a seed region and detects in which brain region this coactivation differs significantly between two psychological or stimulus conditions. Thus, in response to a cognitive or sensory process, PPI allows to capture the modulation of activity in one brain region by activity in another brain region in relation to a cognitive state or stimulus.

To test for psychophysiological interactions a regression model is used which includes a non-linear interaction term between a psychological or input variable and a physiological variable. This interaction term allows for the assessment of connectivity changes and to model contextual input effects. While the input variable is determined by the stimulation protocol, the physiological variable for each subject is obtained by extracting the first scaled eigenvariate (or eigenvector) of the physiological activity in the seed region by singular value decomposition (SVD). The first eigenvariate represents the temporal pattern which accounts for the greatest amount of the variance-covariance structure, i.e. represents the time course that explains most of the variance of the signal pattern within that region. Because interactions occur at a neural level, the physiological signal first has to be deconvolved in order to transform the BOLD signal into a neural signal. One advantage of prior deconvolution before interaction calculation is that signal noise has less effect on the computed neural interaction (Gitelman et al., 2003). Under the constraint that the neural signal should have a uniform spectral density the neural signal is approximated by a discrete cosine set. Then the interaction between the recovered neural signal and the psychological variable can be computed and the resulting vector is reconvolved with the hemodynamic response function. The convolved interaction term is then entered into a first level fMRI model. The individual contrast images of the interaction term are then entered into a random effects analysis on the second level. The significantly activated brain regions for the interaction contrast represent a functional network that differentially covaries for the different stimulus conditions.

1.5.3 Eye movement recordings and analysis

Eye movements in response to moving visual stimuli have been shown to be able to modulate responses of MT neurons (Nadler et al., 2009), as well as MST (Newsome et al., 1988). Saccades are characterized by a quick velocity phase through very high initial acceleration and deceleration, and peak velocity, whereas slow eye movements

to any direction are characterized by slow phase velocity.

To control for the effect of eye movements on the found fMRI activation, we recorded eye movements. The resultant data was later analyzed off-line using Matlab (The MathWorks). Eye movements were recorded with an eye tracker that tracked eye position with a camera by infrared illumination of the pupil. This in-house custom-built hardware system, with software based on "EyeSeeCam" (Schneider et al., 2009), stored horizontal and vertical eye positions, eye velocities, and video recordings. The right eye of the subjects was monitored with an analogue video camera at 60 frames per second. Resolution of this video-oculography(VOG) device was < 0.1 deg. In all subjects a 2D-calibration was performed for which subjects had to fixate five target positions.

In the experiment, two viewing conditions were used. One group of subjects could look freely at the presented stimuli whereas the remaining subjects had to fixate on a red cross positioned in the middle of the screen. For the subjects of the fixation group eye movements were controlled by computing the median slow phase velocity, which did not significantly differ between the tunnel and the indistinct, phase-scrambled stimuli. The functional brain data acquired from fixation versus the natural viewing condition were statistically compared by computing two-sample t-tests for both contrasts of interest (tunnel vs. phase-scrambled stimuli and phase-scrambled vs. tunnel stimuli). The result of this test was not significant, indicating that the found brain activations can not be explained by differential eye movements.

1.6 Aim of this thesis

During recent years functional magnetic resonance imaging has become a well-established approach for analysis of brain function at a global level. Previous fMRI studies investigating the effect of phase manipulation have only investigated static stimuli and reported distinct activations in early visual areas. One aim of this thesis was to investigate the visual system's response to dynamic phase-manipulated visual motion stimuli. Because the cognitive processing demands may differ significantly for spatiotemporal stimuli compared to static visual input, we examined how our brain processes indistinct dynamic phase-scrambled stimuli that neither immediately reveal a clear meaning nor can be categorized as noise. To create indistinct visual motion stimuli, which by definition are structured such that no obvious objects and forms are contained and that constantly change their appearance, we chose to phase-scramble virtual tunnels that represent self-motion in space. Phase-scrambling was preferred to simple scrambling of image segments as the latter introduces additional

edges at the borders between the segments and the segment size imposes additional variation in frequencies. Furthermore, phase-scrambling allows for the creation of an indistinct stimulus which has the exact same amplitude spectrum and optic flow properties as the stimulus from which it was created.

In a first step towards understanding the mechanisms underlying the processing of this type of dynamic visual input, we investigated with functional MRI which brain areas are differentially activated in response to such dynamic visual stimulation. One central question guiding our investigation is whether higher cognitive structures, in particular the hippocampus, is recruited in response to dynamic visual motion processing. Besides examining the activated brain regions in response to such stimuli, we applied independent component analysis to analyze functional connectivity of visual brain areas. In addition, we performed psychophysiological interaction analysis to understand the interactions between the involved brain regions as it allows for the identification of brain regions whose connectivity with a seed region changes according to a psychological context. Choosing the hippocampus as seed region, this analysis allows to reveal hippocampal networks in the human brain under different perceptual conditions.

2 Cumulative Thesis

This cumulative thesis consists of two journal articles. In the following the abstracts of these publications are presented and the contributions of the author to the respective publications is indicated. The publications can be found in the enclosure of this thesis. Furthermore, a behavioral experiment that was conducted as part of this thesis will be described. The complete list of publications, including work that is not part of this thesis, can be found on page 49.

2.1 Spatiotemporal phase-scrambling increases visual cortex activity

Fraedrich EM, Glasauer S, Flanagin VL (2010) Spatiotemporal phase-scrambling increases visual cortex activity. Neuroreport 21: 596-600.

The hemodynamic response of the visual cortex to continuously moving spatial stimuli of virtual tunnels and phase-scrambled versions thereof was examined using functional magnetic resonance imaging. Earlier functional magnetic resonance imaging studies found either no difference or less early visual cortex (VC) activation when presenting normal versus phase-manipulated static natural images. Here we describe an increase in VC activation while viewing phase-scrambled films compared with normal films, although basic image statistics and average local flow were the same. The normal films, in contrast, resulted in an increased lateral occipital and precuneus activity sparing VC. In summary, our results show that earlier findings for scrambling of static images no longer hold for spatiotemporal stimuli.

The author of this doctoral thesis contributed to Fraedrich et al. (2010) with planning and performing the experiment, analyzing the data, and by writing major parts of the manuscript.

2.2 Hippocampal involvement in processing of indistinct visual motion stimuli

Fraedrich EM, Flanagin VL, Duann JR, Brandt T, Glasauer S (2012) Hippocampal involvement in processing of indistinct visual motion stimuli. Journal of Cognitive Neuroscience, in press.

Perception of known patterns results from the interaction of current sensory input with existing internal representations. It is unclear how perceptual and mnemonic processes interact when visual input is dynamic and structured such that it does not allow immediate recognition of obvious objects and forms. In a functional MRI (fMRI) experiment meaningful visual motion stimuli depicting movement through a virtual tunnel and indistinct, meaningless visual motion stimuli, achieved through phase-scrambling of the same stimuli, were presented while subjects performed an optic flow task. We found that our indistinct visual motion stimuli evoked hippocampal activation whereas the corresponding meaningful stimuli did not. Using independent component analysis (ICA) we were able to demonstrate a functional connectivity between the hippocampus and early visual areas, with increased activity for indistinct stimuli. In a second experiment we used the same stimuli to test whether our results depended on the subjects' task. We found task-independent bilateral hippocampal activation in response to indistinct motion stimuli. For both experiments, psycho-physiological interaction (PPI) analysis revealed a coupling from the posterior hippocampus to dorsal visuospatial and ventral visual object processing areas when viewing indistinct stimuli. These results indicate a close functional link between stimulus-dependent perceptual and mnemonic processes. The observed pattern of hippocampal functional connectivity, in the absence of an explicit memory task, suggests that cortical-hippocampal networks are recruited when visual stimuli are temporally uncertain and do not immediately reveal a clear meaning.

The author of this doctoral thesis contributed to this work by performing all fMRI recordings and data analysis, which included regressional model analysis as well as independent component, and psychophysiological analysis. The author further contributed by writing major parts of the manuscript.

2.3 Behavioral experiment

2.3.1 Verbal responses to phase-scrambled stimuli

As phase-scrambled, indistinct stimuli are not noise stimuli but still contain naturalistic motion and structure to some extent, an open question was whether subjects have some type of associations in response to these stimuli. To examine this question subjects, who had previously participated in one of the fMRI experiments, were asked to report any associations they had in response to viewing phase-scrambled stimuli. During this behavioral experiment subjects saw different indistinct, phase-scrambled stimuli sampled from both experiments. During the first part of the behavioral experiment subjects were presented 8 different 6 seconds long phase-scrambled stimuli and were asked to report their spontaneous associations to each film stimulus in form of verbal responses. Initially participants were instructed to press a button in order to start the first film. Each film had a duration of six seconds. During the film and after film presentation subjects were able to say what came to their mind and these answers were recorded by help of a digital voice recorder. After each film presentation participants could start the next film by pressing a button if they had no more association coming to their mind.

Verbal responses were rated according to their originality by 3 independent raters on a scale of 1 to 2 in steps of 0.25. A score of 1 was given when the subject gave an answer that was an obvious description of the stimulus (such as left/right movement), a score of 1.25 was given when the subject made an obvious association (clouds), 1.5 was given for an answer that was more than a simple observation and a creative answer (e.g. figures or indistinct picture of a person), 1.75 was given when the level of abstraction was even higher and the highest score of 2 was given for exceptionally creative answers such as for example trumpet player or lung. The individual answers given by subjects and the corresponding originality ratings from three independent raters as well as their average originality rating are in the appendix.

To further investigate whether the made associations are related to the creativity of the subject, each participant subsequently completed the Test of Creative Imagination. Since it is known that the hippocampus is involved in memory retrieval, it was further examined whether the originality of verbal responses is correlated with the found hippocampal activation.

2.3.2 Test of creative imagination

The Test of Creative Imagination (TCI) is a relatively new test that was created (by Kujawski) in the beginning of the 1990s and allows a nonverbal assessment of cre-

ativity. It consists of a single sheet of paper with 16 shapes, including four straight lines, four dots, four curvy lines and four semicircles (Figure 2.1). Participants are instructed to use these elements to draw as many schematic drawings as possible of something that does not exist but should exist in their opinion. They are told that they can either draw new appliances, medicines or inventions, or schematically expressed ideas. Because there is no limitation regarding the subject matter of the drawings, subjects are instructed that they can draw whatever they like, provided that it does not exist. All 16 elements or less can be used for the drawings, however, for each drawing not more than 16 elements can be used. Participants are instructed to draw as many original pictures as they can. They are further reminded that their artistic abilities will not be rated and that the drawings do not have to be nice, but that it is the idea that counts. Subjects have 30 minutes to complete the task and are instructed to sign each picture and to give a short description what the depicted thing could work for.

Figure 2.1: TCI Stimulus material.

The test comprises three scales: the fluency scale (A), the elaboration, transformativeness and visualization scale (B) as well as an originality scale (C). The first scale fluency is assessed through the number of created drawings which conform to the test criteria (has not used more than the given 16 elements and has given an explanation or description for the drawing). The second scale elaboration etc. "measures transformative capabilities as well as elaboration and an extent of drawing visualization" (Karwowski, 2008). It is computed by:

$$\frac{\sum(l_{\mathrm{st}}+l_{\mathrm{el}})}{N}$$

l_{st}= Number of different sign categories within one drawing

l_{el}= Number of elements within one drawing

N = Number of valid drawings

The third scale originality is a subjective measure that assesses the "originality of the creative drawings" (Karwowski, 2008).

TCI results

In general, the diverse range as well as the large number of different verbal responses in response to the phase-manipulated stimuli elucidate that the stimuli do not allow to settle on one definite percept. This is in keeping with the constantly changing nature of the stimuli. Furthermore, the diverse answers demonstrate that the made associations for each film can differ quite substantially between subjects.

For all subjects who participated in the behavioral experiment, all three TCI scales as well as the number of their verbal responses to the stimuli and the average originality ratings were entered as covariates for the contrast indistinct, phase-scrambled versus tunnel stimuli. Neither of these covariates could explain the hippocampal activation. The reason is probably that the hippocampal activation is related to an automatic, implicit process that is not directly linked to conscious tasks such as verbal associations and creative imagination. However, as subjects were tested at a later time point from the original experiment, it can not be excluded that the verbal responses were different to the subjects' associations during the experiment.

Furthermore, it was investigated whether the three TCI scales correlate with the verbal associations, but no significant correlation was found. This is probably due to the fact that creativity is a very complex construct that encompasses many different neuropsychological functional concepts. Whereas the TCI captures a process of creative imagination, where novel concepts or objects have to be generated, the source of verbal responses to the association task is driven by the perception of the visual input.

3 Discussion

This thesis investigated how the human early visual cortex as well as higher cognitive brain areas process stimuli that are indistinct and lack a clear structure compared to clearly structured spatially relevant stimuli. While previous studies in monkeys and humans have investigated the response of the visual cortex to static phase-manipulated images, the findings differ regarding the effect of phase structure on visual cortex activity. Furthermore, it is still unclear how findings in anesthetized monkeys relate to findings in awake humans. One common aspect of these studies is that the used stimuli were static. However, neuronal behavior can differ markedly in response to dynamic visual input. Naturally, all sensory information is contained within a continuous stream of information from the environment. Thus, we presented spatiotemporal stimuli that are spatially structured or unstructured in form of tunnel stimuli and their phase-scrambled versions. Phase-scrambling the stimuli makes them indistinct and ensures that the new stimulus no longer contains any recognizable pieces of the previous film. This contrasts to another method used in an fMRI study that presented temporal stimuli in which segments of the film were piecewise-scrambled at different time scales so that visible objects and forms were still contained within each scrambled film (Hasson et al., 2008). Our approach on the other hand allowed to retain comparable image statistics and to retain optical flow.

This chapter discusses the fMRI activation results of both studies in response to indistinct and spatially structured motion stimuli, the functional connectivity, and the psychophysiological interaction analysis findings in response to these stimuli.

3.1 Early visual cortex response to phase-scrambled stimuli

One main finding of this thesis is that dynamic phase-scrambled stimuli that lack a clear spatial structure evoke increased early visual cortex activity in contrast to the stimuli with high spatial structure. This result demonstrates that previous findings for static phase-manipulated images no longer hold for dynamic stimuli. In our

study neither task performance nor eye movements can explain the found increase in visual cortex activity. Furthermore, image statistics were controlled for both stimulus types and did not differ regarding skewness (equivalent to the 3rd central moment), kurtosis (equivalent to the 4th central moment), and mean RMS contrast. In addition, the amplitude spectrum was equal for the stimuli. Accordingly, none of these properties can explain the activation difference.

The early visual cortex activation in response to indistinct stimuli that we found despite equal RMS contrast for both stimulus types is in contrast with a previous fMRI study for stationary images, which found no measurable effect of spatial phase structure on BOLD fMRI response in early visual cortex (Olman et al., 2004). Wichmann et al. (2006) concluded from this study that the activity in primary visual cortex is independent of phase relationships. Since RMS contrast was equal for phase-manipulated and non-manipulated stimuli, they proposed that V1 activity is mostly driven by RMS contrast. However, the found early visual cortex activity in our study can not be explained by this proposal but suggests that phase structure does have an effect for spatiotemporal stimuli.

One difference between both stimulus types was that the average local luminance changes over frames were significantly larger for the phase-scrambled stimuli in the first experiment. Since stimuli with a high luminance contrast have been shown to elicit more activity in the visual cortex than stimuli with a low contrast (Pooresmaeili et al., 2010), the second experiment controlled for this aspect by decreasing the overall contrast for phase-scrambled stimuli, which removed the difference in frame-wise local luminance changes between stimulus types. Despite this modification the phase-scrambled stimuli still elicited more pronounced early visual cortex activation. Thus, local luminance differences cannot explain the increased activity in early visual cortex for indistinct stimuli.

As the first experiment already demonstrated that task performance does not explain the found activation, the second experiment further showed that neither the optic flow nor the detection task can explain this activation difference in early visual cortex. For the detection task subjects had to constantly fixate the red cross in the middle of the screen and to detect a target that occurred rarely and unpredictably at different peripheral locations over a prolonged time period. This task required sustained and covert attention, which can also lead to signal increases in early visual cortex (Lauritzen et al., 2009). However, since the detection task elicited early visual cortex activation for phase-scrambled stimuli and the task was equally difficult for both stimulus types, as indicated by the matched performance between them,

differential covert attention can not hold as explanation.

Instead, the finding of decreased visual cortex activation in response to the tunnel stimuli might be a result of the much more predictable nature of its direction of motion, as indicated by high mutual information between frames (Fraedrich et al., 2012). This is in accordance with a previous study demonstrating that V1 responses are lowest when the direction of motion can be predicted by the direction of apparent motion (Alink et al., 2010) and fits with a wide range of other studies which demonstrated that V1 responds less to coherent than to incoherent motion (McKeefry et al., 1997; Bartels et al., 2008a). Striate cortex activations for coherent relative to incoherent motion have been found to be suppressed by backward connections when predictions from higher levels match the incoming data from lower levels (Harrison et al., 2007). This phenomenon where global percepts at higher levels influence local processing at lower levels is called predictive coding. The found relative decrease in early visual cortex activation in response to recognizable tunnel stimuli speaks for a possible predictive coding mechanism. Their clearly recognizable spatial structure and their high mutual information between frames allows higher cortical levels to make predictions that match the incoming sensory input. Thus, activity in early visual cortex can be explained away by higher cortical structures.

3.2 Hippocampal involvement for indistinct (phase-scrambled) stimuli

Besides the early visual areas that were activated more strongly in response to indistinct visual motion stimuli, the two fMRI studies presented in this thesis revealed that indistinct visual motion stimuli also recruit higher cognitive areas, in particular the hippocampus. In both studies posterior bilateral hippocampal activation was consistently observed. This is in contrast to prior studies investigating static phase-manipulated images for which no hippocampal activation has been reported (Olman et al., 2004; Wichmann et al., 2006). Reanalyzing the data of the first experiment with a large sample size of 29 subjects revealed for the optic flow task strong hippocampal activation in response to the indistinct stimuli. Because the optic flow motion in these stimuli was less coherent than in tunnel stimuli, the hippocampal activation could have theoretically been caused by integrating optic flow motion over the length of the stimulus, which was not necessary for the tunnel stimuli. The second experiment controlled for this aspect by giving subjects the additional task of detecting a target within the motion stimuli, since target detection was not reported to recruit the hippocampus (Linden et al., 1999;

Novitskiy et al., 2011). In this experiment, the contrast phase-scrambled, indistinct stimuli compared to meaningful tunnel stimuli revealed hippocampal activation for both the optic flow and the detection task, demonstrating that this hippocampal activation is independent of task. Although the hippocampus has been proposed to act as novelty detector (Tulving et al., 1994; Kumaran and Maguire, 2007), stimulus novelty per se can not explain our hippocampal findings, since subjects were previously exposed to the same stimulus material during training and had equal exposure to both stimulus types. Furthermore, neither first time task performance (i.e. context novelty) nor associative novelty can explain the findings. Since these classic definitions of novelty do not account for these findings, our results indicate that the hippocampus responds to a further type of novelty whose feature is that the current state of stimulation does not explain much about the next state, as revealed by less mutual information for indistinct stimuli.

As indistinct visual motion stimuli had less mutual information between frames, one frame contains less information about the next one compared to recognizable stimuli. The future visual input is therefore less predictable given the current sensory input. This discrepancy between the actual and predicted stimulus presentation for indistinct stimuli is likely to have caused a mismatch. Given the hippocampal role as mismatch detector this can lead to continuous updating of the mental representation. Since the hippocampus was especially active in response to dynamically and unpredictably changing visual input that mismatches prior expectations, the updating of the representation may comprise the integration of uncertainty for these stimuli. The hippocampal activation for indistinct spatiotemporal stimuli furthermore extends previous findings that linked hippocampal activation to higher unpredictability of static visual stimuli (Strange et al., 2005). Thus, the hippocampus seems to act not only as integrator of new information through updating of mental representations (McKenzie and Eichenbaum, 2011), but seems to particularly respond to the temporally uncertain nature of the stimuli.

From a systems dynamics perspective the hippocampal activation results from the combination of continuous structural change with the naturalistic motion still contained in the indistinct stimuli. This keeps the hippocampal activation in a reverberating state for which no quick convergence onto a stable point within the hippocampal attractor network can be achieved. Because the phase-scrambled stimulus is unlike visual noise, subjects could not simply classify the stimulus as such. As demonstrated in the behavioral experiment, the diverse range of made associations in response to phase-scrambled stimuli shows that subjects did not associate one single thing within the visual motion stimuli. A covariate analysis for the conscious

associations made in the behavioral experiment revealed that they can not explain the hippocampal activation. However, the fact that conscious associations can not explain the found activation does not exclude the possibility that our brain attempts to establish such associations unconsciously by trying to make sense of the indistinct stimuli.

3.3 Functional connectivity revealed by indistinct visual motion stimuli

The ICA over 18 subjects revealed common independent components including regions of activations (ROAs) for visual areas, higher visual areas, the default mode network, precuneus, left somatosensory/motor region, secondary somatosensory cortex, left inferior and right inferior frontal cortex. While the independent component analysis expresses the original fMRI data as statistically independent components and takes into account multiple voxels, the found connectivity in the components is not necessarily condition dependent. For all subjects an independent component with activity in early visual cortex was found to be stimulus locked and thus a common group analysis over the spatially normalized ROAs of this independent component was computed. This analysis revealed significant activation not only in visual areas such as the right cuneus, left middle occipital area and fusiform, but also bilaterally in the hippocampus.

Congruent with our functional connectivity finding between the hippocampus and the visual cortex, indicating one statistically independent process, recent electrophysiological work in rats established a close link between the early visual cortex and the hippocampus, suggesting that visual information processing represents a dynamic mechanism, which underlies the formation of visually driven memories (Tsanov and Manahan-Vaughan, 2008). Furthermore, coordinated activity replay of multicellular firing sequences has been found in the rat hippocampus and the early visual cortex (Ji and Wilson, 2007), demonstrating a close dialogue between both structures.

Whether the hippocampus contributes to visual perception is currently debated in the literature. Patients with developmental amnesia have demonstrated a stimulus specific impairment for virtual scene perception. The debate indicates that stimulus type may be a critical performance predictor on memory tasks (declarative and nondeclarative) (Graham et al., 2006). Furthermore, previous findings from patients with medial temporal lobe lesions demonstrated deficits in object discrim-

ination that were related to the degree of feature ambiguity, thus indicating that this region might be implicated in perception of ambiguous properties (Barense et al., 2005). This could reflect a selective inability to remember complex stimuli with ambiguous features, but it might equally reflect a selective inability to perceive or create a representation of such stimuli at the time of encoding.

3.4 Stimulus dependent psychophysiological interaction analysis results

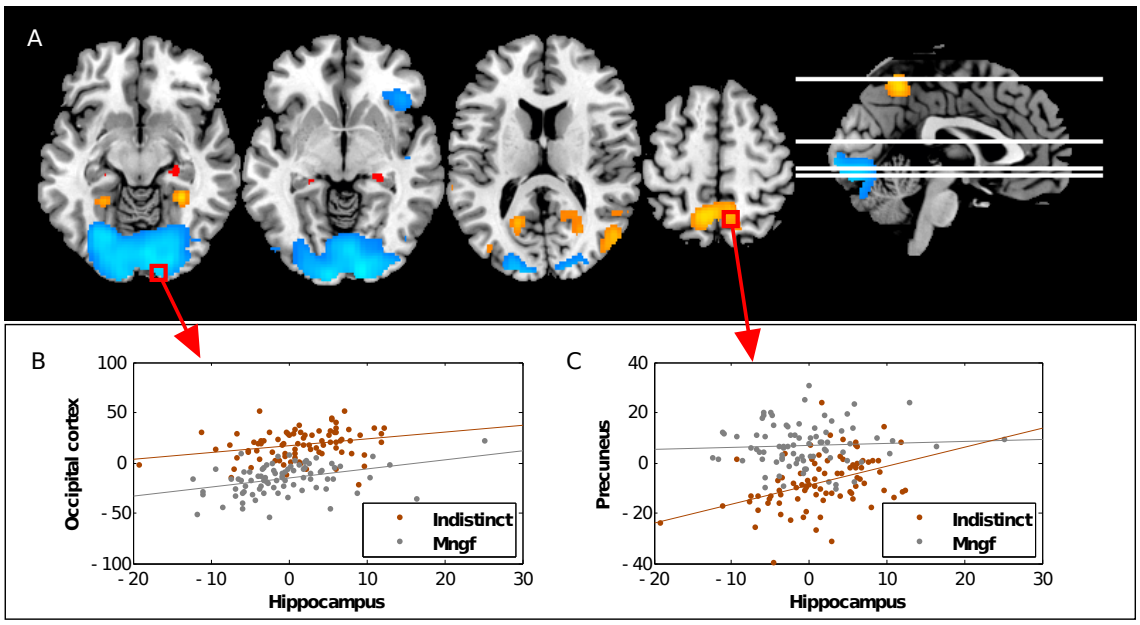

Figure 3.1: Cortico-hippocampal connectivity. (A) When subjects viewed indistinct stimuli, the posterior hippocampus was connected to areas along the dorsal and ventral visual stream in both experiments (yellow), whereas for meaningful motion stimuli the hippocampus was mainly correlated with activity in early visual areas (blue). The red color within the hippocampus indicates the location of the seed region. Significantly correlated regions with the hippocampus are depicted on axial (z = -10, -5, 14, 58) slices to show the exact location of activity. (B & C) Activity correlations between the hippocampus and the occipital cortex as well as the precuneus for two exemplary, preprocessed voxels from one subject (voxel location indicated by red arrows).

The psychophysiological interaction analysis in response to phase-scrambled stimuli consistently revealed a stimulus-dependent change in coupling between the hippocampus and areas within the dorsal and the ventral visual stream. Within the ventral visual stream, activity in the temporal occipital fusiform gyrus correlated with the hippocampus. This ventral region is known to be involved in visual object

recognition processes (Ishai et al., 2000). The task independence of the hippocampal activation together with the cortical coupling to visuospatial and object recognition areas may represent the neuronal substrate for the attempt to recognize these indistinct stimuli. Given that vision is thought of as "recognition-by-analogy" by which the visual input is linked to existing information stored in analogous memory representations (Bar, 2009; Bar, 2007), the found connectivity of object processing areas and the hippocampus may represent such a link. However, since the indistinct stimuli are neither noise nor do they reveal any obvious recognizable form it is not possible to retrieve a clear pattern.

In contrast to a resting state functional connectivity study that suggested that interactions with the medial temporal lobe might be generally dominated by extrasensory areas (Kahn et al., 2008), our connectivity findings clearly demonstrate that for visual stimulation interactions with the hippocampus can be dominated by sensory areas. In general, as no explicit memory demands were placed by the optic flow and the detection task, these results extend previous hippocampal findings for navigational or memory processing and point towards a more general role of the hippocampus that interacts with perceptual processes. Given that visual motion has been found to induce a forward prediction of spatial pattern in behavioral experiments (Roach et al., 2011) and the hippocampus has been centrally implicated for forward models of prediction (Schacter and Addis, 2009), this stimulus-dependent connectivity between the hippocampus and visual processing areas could bridge the gap between these two separate findings.

Intriguingly, the connectivity results are congruent with electrophysiological and histological findings in rats that demonstrate that the hippocampus receives crucial sensory input from the visual cortex and that the dorsal visual cortex projects multisynaptically via occipital connections and the ventral visual pathway via temporal connections to the hippocampus (Tsanov and Manahan-Vaughan, 2008). The findings corroborate distinct intrinsic functional connectivity in humans between the posterior hippocampus and the parietal cortex (Kahn et al., 2008). Anatomical tracer studies in monkeys have previously identified the existence of a pathway that provides direct monosynaptic input from temporal and parietal levels to the hippocampus. This pathway is distinct from the known entorhinal input pathways to the hippocampus (Rockland and Van Hoesen, 1999). Furthermore, in monkeys hippocampal CA1 neurons have been found to possess bilateral projections with ventromedial temporal areas (Iwai and Yukie, 1988). Since our hippocampal connectivity findings include the parietal as well as the ventromedial temporal areas, the findings point towards the existence of corresponding pathways in humans.

For meaningful tunnel stimuli, the PPI analysis revealed connectivity to early visual areas including the occipital pole, the lingual gyrus, and V5 bilaterally, as well as activation in left precentral gyrus, left precuneus cortex, and minor activations in bilateral paracingulate gyrus, bilateral anterior insular cortex, and right inferior frontal gyrus (Figure 3.1 A - blue). This finding is illustrated by the found change in correlation in the occipital cortex, where meaningful stimuli showed a slightly stronger correlation with the hippocampus (Figure 3.1 B). Nevertheless, indistinct stimuli had a generally higher activation level and confirmed the functional connectivity results of the ICA, which demonstrated also increased activity in response to them.

The constantly changing nature of the indistinct stimuli might also have lead to more attention for these stimuli, which might have modulated connectivity in visual pathways (Büchel and Friston, 1997). However, attention can not hold as explanation for the differential connectivity found, as the second experiment demonstrated equal task performance to both stimulus types for the detection task. Rather, the consistent connectivity between the hippocampus and early visual areas might represent a basic connectivity between the early visual cortex and the hippocampus.

The PPI and ICA methods have different approaches for assessing functional connectivity so that functional connectivity results of both methods do not have to match exactly. While PPI analysis reveals brain areas for which the correlation with the seed region changes in response to stimulus type, ICA analysis reveals also functional connectivity networks which are stimulus independent. However, in contrast to the PPI approach that inherently limits the to be found connectivity by the selection of the seed location, ICA assesses functional connectivity in the whole brain. ICA has the plausible constraint of assuming statistically independent spatial activation patterns given a certain dimensionality and, in contrast to PPI analysis, does not assume a certain temporal form for the hemodynamic response function.

Despite these differences the two complementary analyses consistently associated the posterior hippocampus with other visual processing systems and thus confirm the cytological and molecular boundaries of the hippocampus (Fanselow and Dong, 2010) as well as the proposed posterior hippocampal role in visual-spatial processing (Hüfner et al., 2011; Maguire et al., 2000).

Through changing functional connectivity between distributed cortical regions and the hippocampus our brain can flexibly respond to different perceptual demands. This ability to flexibly integrate different cortical areas makes the hippocampus a powerful structure that can access vast amounts of stored memory representations.

As the hippocampus has also been associated with successful recognition (Bernard et al., 2004), the hippocampus may be a necessary component of human perception. In contrast to systems for computer vision, humans can rely on rich contextual and prior knowledge from experience, stored in neocortex, that help in recognizing our environment. Thus, the present hippocampal-neocortical network speaks for an inherent attempt to relate previous knowledge to current sensory input.

3.5 Activation in response to spatially recognizable stimuli and task specific activation

The clearly structured tunnel stimuli, which presented radial optic flow motion, elicited activation in fusiform gyrus that extended far anteriorly into inferior temporal gyrus, as well as in posterior parietal cortex, including the precuneus. The posterior parietal cortex has been implicated in many different functions regarding temporal and perceptual space, such as three dimensional object recognition (Yamazaki et al., 2009). The fact that tunnel stimuli revealed no significant activation of early visual cortex is further in keeping with an earlier finding that this region was not active for translation or expanding versions of coherent motion (de Jong et al., 1994). Fittingly, the independent component for early visual areas showed decreased activity in response to tunnel stimuli. The hippocampus was not significantly activated in response to the tunnel stimuli.

As revealed by the second experiment, the arrow detection task versus optic flow task revealed no significant activation per se. Anticipatory activations in spatiotopic occipital cortex were avoided (Ruff and Driver, 2006) because subjects did not know when or where an arrow would appear, and how prominent the target stimulus (arrow) would be. The task of detecting the presence of a slightly red arrow was made difficult by making the arrow transparent, by only having a brief processing time, by presenting the target at locations far from the fixation, and by increased target position uncertainty. As under one of these conditions improvement on a detection task is slower (Ahissar and Hochstein, 2004), subjects were initially trained on the target detection task to ensure a relatively high performance level. Furthermore, the detection task required subjects to 'divide' their attention, which is a skill that can be acquired through training (Jans et al., 2010).

For the second experiment task specific activation was found. The contrast optic flow direction compared with the detection task revealed significant activation

in bilateral frontal inferior gyrus (including Broca's area), inferior orbitofrontal, supramarginal gyrus (including Wernicke's region), inferior temporal gyrus, inferior parietal, superior frontal, precentral gyrus, optic radiation and inferior occipital cortex. The activation of language processing areas demonstrated a left hemispheric dominance and was most likely caused by the linguistic nature of the response ('left' or 'right'). As the optic flow direction task focused attention on the flow motion, this task also recruited the motion sensitive area V5.

3.6 Conclusion

This thesis demonstrates that phase-manipulated spatiotemporal stimuli activate early visual cortex to a higher extent than spatially structured optic flow stimuli, despite controlled spatial image statistics. Neither local luminance differences nor performance differences or eye movements can account for this differential activation. Overall, the findings in early visual cortex demonstrate that previous findings in response to static phase-manipulated stimuli can not be generalized to dynamic stimuli. Furthermore, the relative decrease in activation for the meaningful tunnel stimuli points towards predictive coding for which activity in lower visual areas is reduced as higher level visual areas can explain the visual input. In addition, our findings demonstrate that purely visual tasks on dynamically changing visual motion stimuli, achieved through phase-scrambling of recognizable visual motion input, recruit the hippocampus. Traditionally, the hippocampus has been associated with explicit (declarative) forms of learning (Squire, 2009) and spatial navigation, but the findings of the current thesis are in line with an important notion that the traditional view of the hippocampus proves insufficient. Our experiments demonstrate here that hippocampal activation can also be found for non-spatial stimuli which require no explicit memory processing. Since no explicit memory demands were placed on subjects and phase-scrambled stimuli evoked task-independent bilateral hippocampal activation in both experiments, the hippocampal activation is related to implicit processing of the stimulus.

The temporally uncertain nature of the stimuli, in particular the unpredictable dynamic structural changes that are introduced through phase manipulation of our spatiotemporal stimuli and quantified by mutual information, appear to be the determining factor for hippocampal recruitment in response to indistinct stimuli. The hippocampal sensitivity to these motion stimuli supports the view that the hippocampus responds especially to unpredictable sensory information. This expands the previous finding that the hippocampus is recruited in response to higher unpre-

dictability of static visual stimuli (Strange et al., 2005).

The differential connectivity findings between the hippocampus and different cortical areas for both stimulus types demonstrate that the hippocampus is flexibly involved in different cortical networks depending on perceptual demands. The findings are especially remarkable as demonstrations of functional connectivity between the hippocampus and other cortical representations in humans can be linked to electrophysiological and anatomical work in animals. Our connectivity findings in response to indistinct visual motion stimuli demonstrate an interaction between perceptual and mnemonic processes for which the hippocampus was functionally coupled to higher visual cortical areas along the dorsal and ventral visual processing streams. The found connectivity extends to occipito-temporal areas, which are involved in perceptual closure processes. Based on the proposal that visual perception requires to link current visual input with analogous representations stored in memory (Bar, 2007), these findings implicate the hippocampus as a potential candidate that allows to compare visual sensory input to known features stored in memory by functionally and flexibly linking perceptual areas with itself. Thus, the task-independent hippocampal activation with the found hippocampal-cortical interaction gives evidence for the idea that information from both streams are combined to match current visual input to a corresponding memory representation to recognize these indistinct stimuli.

Having established which brain areas are involved in processing spatially relevant and spatially irrelevant optic flow stimuli, further avenues of inquiry with regard to the functional integration of brain networks could now investigate the directionality of their interactions with structural equation models or dynamic causal modeling. Furthermore, investigating the temporal dynamics among these brain structures could help to reveal the exact processing mechanisms that underlie the perception of recognizable compared to indistinct visual motion stimuli. In addition, this work demonstrates that processing demands for spatiotemporal stimuli differ quite remarkably from static ones. Given that spatiotemporal stimuli recently also lead to the discovery of novel receptive field properties, which were not discovered with conventional static stimuli (Nishimoto and Gallant, 2011), this speaks for a more frequent use of spatiotemporal stimuli in neuroscience.

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List of Publications

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Enclosure

1 Spatiotemporal phase-scrambling increases visual cortex activity

Spatiotemporal phase-scrambling increases visual cortex activity

Eva M. Fraedrich[a], Stefan Glasauer[a,b] and Virginia L. Flanagin[a,b]

The hemodynamic response of the visual cortex to continuously moving spatial stimuli of virtual tunnels and phase-scrambled versions thereof was examined using functional magnetic resonance imaging. Earlier functional magnetic resonance imaging studies found either no difference or less early visual cortex (VC) activation when presenting normal versus phase-manipulated static natural images. Here we describe an increase in VC activation while viewing phase-scrambled films compared with normal films, although basic image statistics and average local flow were the same. The normal films, in contrast, resulted in an increased lateral occipital and precuneus activity sparing VC. In summary, our results show that earlier findings for scrambling of static images no longer hold for spatiotemporal stimuli. ***NeuroReport*** **21:596–600**

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Introduction

The response of the visual system to the statistical properties of an image, such as contrast, luminance, or frequency spectrum, has been examined earlier using both electrophysiological and imaging techniques. However, the neural response to spatial phase characteristics is still largely unknown. Essential shape information in images like edges is conveyed through the phase alignment of different frequency components [1]. By changing the phase spectrum across frequencies the amplitude spectrum can be preserved while the resulting image is rendered unrecognizable.

Studies on the effect of phase manipulation have so far mostly used static natural images. A functional magnetic resonance imaging (fMRI) study comparing static natural images with and without added phase noise found that spatial phase structure had no measurable effect on the perceived contrast or on the blood oxygen level dependent (BOLD) response in primary visual cortex (V1) [2]. In contrast, for anesthetized monkeys, BOLD signal responses in V1, extrastriate cortex, and superior temporal sulcus were found to be consistently smaller for phase-scrambled stimuli than for natural images [3]. Another study investigating BOLD activity found stronger activity for nonscrambled artificial edge and line stimuli versus random phase stimuli in many visual areas, including primary visual cortex [4].

In a study investigating temporal scrambling of natural films activity in early visual areas such as V1 and in the motion-sensitive area, MT+ did not change [5]. As scrambling was achieved by exchanging segments of a minimum duration of approximately 4 s, the phase structure of the films was left largely intact. Early visual areas have been found to respond to nonpredictable temporal differences such as contrast and luminance changes, but lacked responses to predictable motion-induced changes [6].

In virtual reality research, the spatiotemporal structure of the visual stimulus is crucial for the illusion of self-motion (vection) and for spatial presence in virtual environments. Virtual reality stimuli have the advantage to be free of noise and to possess controllable statistical image properties. This study applied spatiotemporal phase scrambling of continuously changing virtual spatial scenes to examine the response of human visual areas to spatiotemporal image structure independent of the spatial image statistics.

Methods

Participants

Twenty-nine right-handed healthy volunteers (17 males, mean age = 25.0 years) participated in the fMRI experiment. All participants had normal or corrected-to-normal vision and no history of medical, psychiatric, or neurological disorder. The local ethics committee of the medical faculty at the Ludwig-Maximilians University approved the study. Informed written consent was obtained from all participants in accordance with the Declaration of Helsinki.

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Stimuli

The participants were presented with two kinds of stimuli: tunnel films and phase-scrambled films [see Fig. 1 and Video, supplemental digital content 1, (Supplemental digital content 1, *http://links.lww.com/WNR/A51*) showing both types of videos]. The tunnel films, which were earlier used in a virtual reality experiment [7], show a tunnel consisting of a straight section, a curved section, and a final straight section. Twelve different tunnel films (resolution: 550×549) with turn angles of 30, 40, 70, 80, 110, or 120° for left and right turns were used.

Phase-scrambled tunnel films were obtained by applying a three-dimensional Fourier transform to each of the 12 tunnel films, randomly changing the position of the phase component over all three dimensions (x, y, and time) in Fourier space and then transforming them back into the time domain to leave the frequency spectrum intact. The luminance of each scrambled movie frame was then matched to the original one. This phase-scrambling method led to movies containing the same amount of local flow motion, average contrast, and luminance, but lacked consistent edges or sharp features.

Procedure

Main experiment

Alternating pairs of tunnel and phase-scrambled tunnel movies were presented to 18 participants. The participants were visually primed to indicate either the direction of the tunnel trajectory or the main direction of visual motion (left or right) with a left or right button press after viewing the full movie. The task types were separated across sessions. For the phase-scrambled films, participants always indicated the direction of the optic flow motion. Each participant completed two sessions, with task order and starting tunnel type being randomized across participants.

To ensure that all participants were equally familiar with detecting the continuous flow motion during the experiment, a training session was conducted before scanning. During training participants viewed films with similar angles to those used in the experiment, and were given feedback on the direction of correct motion.

In total, the 12 different tunnel films and the corresponding 12 phase-scrambled films were presented in a pseudorandomized order in a standard block design. To account for the length of the hemodynamic response function, two films of the same type were presented sequentially for a total block length of 18 s. Visual stimuli were presented within a black frame at a distance of 60 cm (60 frames/s, screen resolution: 800×600). The films were viewed over a front surface mirror to a back-projected screen with a field of view of 24° (horizontal) and 19° (vertical). Participants were instructed to fixate the middle of the screen and were given a fixation cross between films.

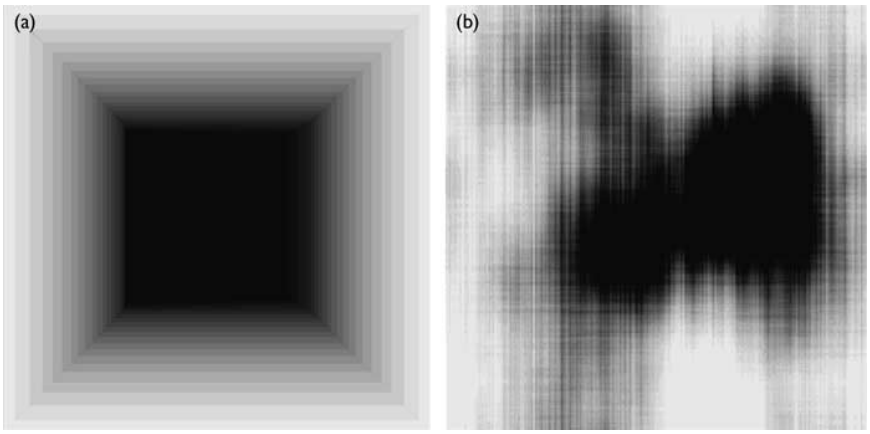
Control experiment

To control for the effect of eye movements, we conducted a second experiment in which 11 participants performed the same experiment except that they had to focus on a permanently visible fixation cross. The eye movement traces were continuously monitored with an MRI-compatible camera with EyeSeeCam software [8]. At all times, participants fixated the fixation cross.

MRI acquisition

The participant's head was positioned in an eight-channel head coil of a 3T whole-body scanner (Signa HDx, GE Healthcare, Milwaukee, Wisconsin, USA). A T2*-weighted EPI sequence (TR 2250 ms, FOV 220 mm, matrix 64×64, slice thickness 3.5 mm) was used to acquire 36 slices covering the whole brain, including the cerebellum.

Fig. 1



Example stimuli: (a) single frame from a straight section of the virtual reality film. (b) Phase-scrambled version of the same frame as in (a).

Each scanning session comprised a successive time series of 192 scans. A T1-weighted anatomical image with a voxel size of $0.86 \times 0.86 \times 0.7\,mm^3$ was acquired using a fast spoiled gradient echo recalled sequence.

Statistical analysis

The fMRI data were analyzed using SPM5 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK). The first five images of each time series were discarded because of spin saturation effects. All remaining volumes were corrected for subject motion and normalized to the standard MNI space [9]. Functional images were smoothed with an 8-mm full-width at half-maximum isotropic Gaussian kernel. A high-pass filter (128 s) was included in the filtering matrix to remove low-frequency noise and slow drifts in the signal. Single subject statistical parametric maps were generated on a voxel-wise basis using the general linear model. The general linear model on the single-subject level consisted of regressors for the tunnel films, the phase-scrambled films, and motor responses as well as motion correction parameters (as effects of no interest).

The resulting contrast images for the differences between the two film types were then used for a between-subject random effects analysis. The results were thresholded at P value less than 0.05 and corrected for family-wise error for multiple comparisons across the brain and projected onto a skull-stripped single-subject MNI template brain.

For the behavioural data, the percentage of correct responses was computed for the tunnel films (task types pooled) and their phase-scrambled counterparts. A paired t-test was used to test whether participants differed significantly in their performance between both conditions.

Two behavioural covariates were included into the fMRI second level analysis to identify brain activations that are related to performance differences and to control for attentional effects. The first covariate was the participants' average response performance across the two film types and the second was the difference of the percentage of correct responses between the two conditions. Thus, BOLD activity could then be tested independently of the subject's performance and of the difference in performance between the two film types.

To test for a possible effect of eye movements, the data from the main experiment (free eye movements) was compared with the control data (fixation) by computing two-sample t-tests for both contrasts (tunnel vs. phase-scrambled films and phase-scrambled vs. tunnel films).

Results

The result of the two-sample t-test for both contrasts revealed no statistically significant difference between the main experiment and the fixating control group (corrected for both family-wise error and false discovery rate). Therefore, in the following we report only the results of the main experiment.

Periods in which participants viewed tunnel films exhibited activation in the right superior middle occipital gyrus bordering the parietal cortex and strong bilateral foci in the precuneus compared with periods when phase-scrambled films were viewed. The reverse contrast resulted in strong activation including the left inferior middle occipital cortex as well as primary visual areas extending ventrally into the superior lateral cerebellum. Both contrasts failed to show significant activity in human correlates of medial temporal/medial superior temporal cortex. Stereotactic coordinates and statistical magnitudes are reported in Table 1 and illustrated in Fig. 2.

The mean ratio of correct performance was significantly [$t(16) = 3.69$, $P < 0.01$] larger for tunnel films (98.5%) compared with phase-scrambled films (87.5%). Neither of the performance measures was significantly correlated with BOLD activity. At an uncorrected t-threshold, activations did not overlap with those found in the original model. Furthermore, the regions found for the film contrasts after partialing out the performance were not different from the original model, and the t-values for the cluster centroids were comparable (data not shown).

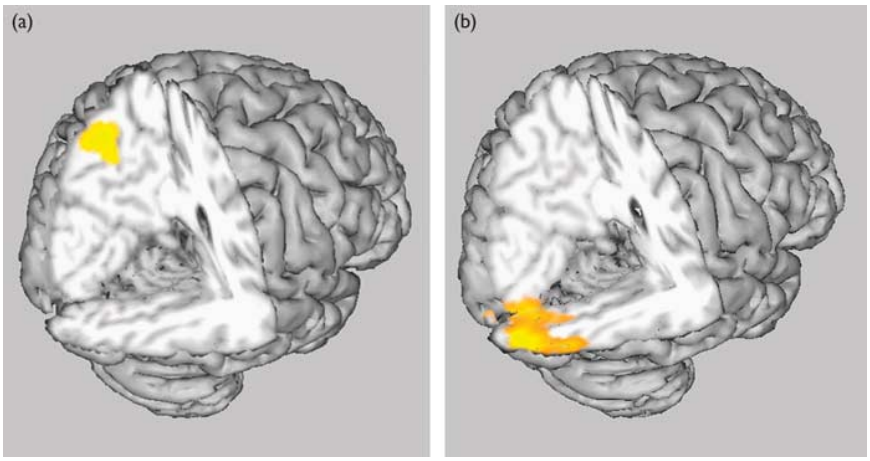
We analysed spatial image statistics by calculating the third and fourth central moment (skewness and kurtosis) as well as the mean RMS contrast [10] for both tunnel and phase-scrambled films. None of these parameters differed significantly between the two film types (see Table 2). To assess spatiotemporal characteristics, we computed the norm of differences of all pixels for each pair of consecutive frames to compute the average local luminance change. The mean pixelwise norm of luminance differences between consecutive frames was significantly [$t(11) = 9.22$, $P < 0.001$] smaller for tunnel films than for phase-scrambled films. To evaluate whether the

Table 1 fMRI contrasts for both film stimuli

	t-value	*x*	*y*	*z* (mm)
Tunnel-scrambled				
Right superior middle occipital	10.16	38	−78	34
Right superior middle occipital	9.26	46	−82	22
Left precuneus	10.07	−12	−56	48
Left precuneus	8.73	−8	−58	62
Right precuneus	8.48	10	−48	52
Right precuneus	8.12	10	−64	60
Scrambled-tunnel				
Right lingual	13.72	16	−98	−6
Left Inferior middle occipital	13.59	−20	−98	−2
Left Inferior middle occipital	12.68	−16	−102	26
Superior lateral cerebellum	8.88	36	−64	−26

Localization of regions differentially activated by the contrasts: tunnel film – phase-scrambled film (top) and phase-scrambled film – tunnel film (bottom). Region label, *t*-values and MNI coordinates are given for the most significant voxel in a given cluster. Positive *x, y, z* coordinates indicate locations right, anterior, and superior to the middle of the anterior commissure.

Fig. 2



Cortical activations mapped on the skull-stripped single-subject template brain. Significantly activated voxels ($P<0.05$ family-wise error corrected) shown in yellow for the contrast (a) tunnel – phase-scrambled film (precuneus, lateral occipital cortex) and (b) phase-scrambled – tunnel film (early visual cortex).

Table 2 Image statistics for both film types

Film stimuli	Skewness	Kurtosis	RMS contrast	Luminance difference[a]	Local optic flow (pixels/frame)
Tunnel	−0.48 ± 0.05	1.88 ± 0.14	0.34 ± 0.01	0.012 ± 0.001	2.33 ± 0.32
Phase-scrambled	−0.47 ± 0.05	1.86 ± 0.12	0.34 ± 0.01	0.025 ± 0.005	2.35 ± 0.27

Spatial and spatiotemporal image statistics for an average over all frames across all tunnel and phase-scrambled films (mean ± SD).
[a]Denotes significant difference.

difference in local luminance changes resulted from local motion, we further calculated the local optic flow for the two film types [11]. The mean local flow did not differ significantly between film types, showing that the phase-scrambled films contained more changes in local luminance across frames than the tunnel films (Table 2).

Discussion

In contrast to earlier work investigating static natural images [1,3], the virtual tunnel films did not elicit more activation in early visual areas compared with the phase-scrambled films, which had comparable spatial image statistics. Instead, significant activation was found in right superior middle occipital areas and in the precuneus bilaterally (Fig. 2a), an area implicated in updating of spatial representations [12]. The reverse comparison of the phase-scrambled film with the tunnel film revealed a strong activation increase in early visual areas and the inferior left middle occipital area, which corresponds to kinetic occipital region (Fig. 2b). Kinetic occipital region has been shown to process shape and motion information that is present in kinetic contours and was activated when uniform motion was subtracted from kinetic gratings [13]. As revealed by the covariate analyses, performance differences cannot account for the changes in BOLD activity. Likewise, differences in eye movements cannot explain the activation patterns, as shown by our control experiment.

Although an earlier study [5] presenting temporally scrambled films on a long time scale (> 4 s) found no differences in V1 activity, phase-scrambling in this study affected the whole frequency range. Overall, there were no significant differences in the amount of local motion between the tunnel and phase-scrambled films. Correspondingly, there was no significant difference in BOLD activity in the human correlates of medial temporal/medial superior temporal cortex, which have been shown to be tuned to local motion [14]. The analysis of both film types revealed that the phase-scrambled films contained more local luminance changes than the tunnel films. V1 cells are 'tuned to variation in luminance at a particular orientation at a particular scale (i.e. spatial frequency)' [15], which could explain the higher activation in early visual areas for the phase-scrambled tunnel films. This is in keeping with other work showing that V1 is correlated with residual temporal luminance changes that are not due to local motion [6].

Predictive coding models of vision could also explain the found differences in early visual cortex activation by assuming that activity in lower visual areas is reduced through feedback processes from high-level visual areas [16,17]. The phase-scrambled films in this study obviously possess a much more recognizable, spatially and temporally coherent, and therefore predictive structure

(Fig. 1). Earlier findings show a reduction of primary visual cortex activity when elements formed coherent shapes and recognizable objects compared with scrambled low-level feature-matched counterparts [18]. Motion studies that examined early visual cortex activation also report higher responses to incoherent motion than to coherent motion [19,20]. However, answering whether luminance changes or predictive coding contribute more to the observed differences in early visual cortex activity is beyond this study.

In summary, our results show that earlier findings for phase scrambling of static images (natural or artificial) no longer hold for spatiotemporal stimuli.

Conclusion

This study examined the effects of spatiotemporal image structure in films on visual cortex activation. The results clearly indicate that BOLD fMRI responses differ in early visual cortex between continuous virtual films and phase-scrambled films, although spatial image statistics, task performance and eye movements cannot account for these differences. The three-dimensional spatiotemporal phase manipulation applied to these films leads to a stronger activation of early visual cortex, which is caused by larger local luminance changes and a less coherent and therefore less predictive spatial and temporal structure.

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2 Hippocampal involvement in processing of indistinct visual motion stimuli

Hippocampal Involvement in Processing of Indistinct Visual Motion Stimuli

Eva M. Fraedrich[1,2], Virginia L. Flanagin[3], Jeng-Ren Duann[4,5], Thomas Brandt[1,3], and Stefan Glasauer[1,3]

Abstract

■ Perception of known patterns results from the interaction of current sensory input with existing internal representations. It is unclear how perceptual and mnemonic processes interact when visual input is dynamic and structured such that it does not allow immediate recognition of obvious objects and forms. In an fMRI experiment, meaningful visual motion stimuli depicting movement through a virtual tunnel and indistinct, meaningless visual motion stimuli, achieved through phase scrambling of the same stimuli, were presented while participants performed an optic flow task. We found that our indistinct visual motion stimuli evoked hippocampal activation, whereas the corresponding meaningful stimuli did not. Using independent component analysis, we were able to demonstrate a functional connectivity between the hippocampus and early visual areas, with increased activity for indistinct stimuli. In a second experiment, we used the same stimuli to test whether our results depended on the participants' task. We found task-independent bilateral hippocampal activation in response to indistinct motion stimuli. For both experiments, psychophysiological interaction analysis revealed a coupling from posterior hippocampus to dorsal visuospatial and ventral visual object processing areas when viewing indistinct stimuli. These results indicate a close functional link between stimulus-dependent perceptual and mnemonic processes. The observed pattern of hippocampal functional connectivity, in the absence of an explicit memory task, suggests that cortical–hippocampal networks are recruited when visual stimuli are temporally uncertain and do not immediately reveal a clear meaning. ■

INTRODUCTION

When exploring our environment, we are confronted with dynamic visual input that is recognized by reference to existing memories and concepts. Although recognition and categorization of images occurs quickly and without conscious effort, it is an open question how indistinct dynamic visual stimuli are processed, for which a meaning is not immediately apparent and which cannot be easily categorized. One brain area of major importance for the creation, retrieval, and manipulation of explicit memories and concepts is the hippocampus and the medial-temporal lobe (Carr, Rissman, & Wagner, 2010; Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Eichenbaum, 2004). The hippocampus represents a convergence zone for multiple sensory inputs, receiving highly integrated information from the association cortices of the respective sensory regions (Buckner, 2010; Burwell & Agster, 2008; Lavenex & Amaral, 2000; Amaral & Witter, 1989), and would thus be a candidate area involved in processing indistinct visual stimuli.

For static images, several studies have addressed which brain regions are active for meaningful and recognizable stimuli versus meaningless stimuli. One report found that the hippocampus was active as participants viewed meaningful scenes when compared with meaningless, scrambled scenes (Binder, Bellgowan, Hammeke, Possing, & Frost, 2005). Visual discriminations between meaningful (known) everyday objects relative to unknown novel objects have also been found to activate the posterior hippocampus bilaterally (Barense, Henson, & Graham, 2011). Furthermore, visual noise stimuli do not evoke hippocampal activation (Martin, 1999), and studies investigating static phase-manipulated images have not reported hippocampal activation (Wichmann, Braun, & Gegenfurtner, 2006; Olman, Ugurbil, Schrater, & Kersten, 2004). Thus, based on these studies using static visual input, one would not expect to find hippocampal activation in response to meaningless visual input.

Despite the evidence accumulated with static images, the cognitive processing demands may differ significantly for dynamic visual input that neither immediately reveals a clear meaning nor can be categorized as noise. Object and scene recognition occurs naturally in a dynamic environment, and it appears that the temporal dimension is critical for our ability to recognize objects independent of size, location, and viewing angle (Li & DiCarlo, 2010). In a

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first step toward understanding the mechanisms underlying the processing of this type of dynamic visual input, we wanted to clarify which brain areas are involved in such situations and investigate their functional connectivity.

A recent perspective on human perception suggests that visual recognition requires linking current visual input to a corresponding memory representation (Bar, 2009). Retrieval of incomplete or degraded sensory cues can be accomplished through pattern completion, a mechanism by which a stored memory trace can be retrieved through hippocampal recurrent connections (Bird & Burgess, 2008; Norman & O'Reilly, 2003; Rudy & O'Reilly, 2001, Levy, 1996). Thus, perception of visual input that is difficult to recognize may elicit retrieval processes of stored memory representations.

The hippocampus has also been associated with imagination (Buckner, 2010) and implicated in a network for making predictions (Bar, 2009; Schacter & Addis, 2009). Computational models have suggested that predictions are automatically compared with sensory input to detect if the environmental input represents a mismatch to the expectation (Lisman & Grace, 2005; Hasselmo, Schnell, & Barkai, 1995).

By definition, indistinct visual motion input is structured such that no obvious objects and forms are contained and that constantly changes its appearance; therefore, correct predictions should be harder to make for indistinct visual motion stimuli than for clearly structured visual motion. The comparison between indistinct visual input and the expectation should evoke a continuous mismatch. In human imaging studies, mismatch has shown hippocampal activity that scales with the number of changes in the environment (Duncan, Ketz, Inati, & Davachi, 2012). The mismatch signal may be essential for encoding to ensure the accuracy of subsequent predictions. Similarly, one study that investigated a context-specific form of novelty processing found entropy or expected uncertainty of events, in particular, contextual uncertainty for visual stimuli, to be associated with hippocampal activation (Strange, Duggins, Penny, Dolan, & Friston, 2005).

We thus investigated brain activity in response to meaningful moving stimuli, which can be easily categorized, compared with indistinct moving stimuli, for which a category is hard to find. Meaningful stimuli were emotionally neutral virtual tunnels that represent self-motion in space, whereas indistinct visual input was constructed by phase scrambling the meaningful visual stimuli as it renders the stimuli that are hard to categorize although distinct from visual noise. Because the alignment of phase information is essential for recognizing edges and spatial structure in images (e.g., Wichmann et al., 2006), phase scrambling of the tunnel films created new stimuli, which are comparable in terms of image statistics but do not contain recognizable features such as edges or structural information. Previously, we had shown that these stimuli evoked strong activation in early visual areas (Fraedrich, Glasauer, & Flanagin, 2010). For the current study, we investigated in a first step the functional connectivity of the previously found visual areas using independent component analysis (ICA) to determine how the network responds when participants cannot predict upcoming visual scenes. In an additional task paradigm, we tested whether stimulus- or task-dependent hippocampal activation exists. This study seeks to clarify whether the hippocampus is recruited in response to dynamic indistinct stimuli. If the hippocampus is involved in processing such stimuli, then not only the activity of the hippocampus but also its functional coupling is expected to be stimulus-dependent. This was tested in a final step using psychophysiological interaction (PPI) analysis (Friston et al., 1997).

METHODS

Experiment 1

Participants

Twenty-nine right-handed healthy young volunteers (17 men, mean age = 25.0 years, *SD* = 2.05 years) with normal or corrected-to-normal vision and no documented history of neurological or psychiatric history gave their informed consent to participate in the study. The experiment was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the medical faculty at the Ludwig–Maximilians University, Munich.

Stimuli and Experimental Procedure

The original visual motion stimuli comprised 12 different 6-sec virtual tunnels (created with Open GL) consisting of a straight, a curved, and another straight segment (resolution = 550 × 549) with varying turn angles of 30°, 40°, 70°, 80°, 110°, and 120° to the left or right. These stimuli were Fourier-transformed using the discrete 3-D Fourier transform implemented in Matlab (MathWorks, Natick, MA). The phase components of all frequencies were then randomly exchanged, and the signal was back-transformed into the time domain, resulting in the phase-scrambled stimuli. Corresponding stimuli had the same amount of local flow, average contrast, and luminance, but phase-scrambled stimuli had larger frame-wise local luminance changes. As such phase scrambling maintained the spatial and temporal visual motion statistics relevant for low-level visual processing and eliminated the presence of any obvious form, edge, or structure. We therefore refer to phase-scrambled stimuli as indistinct stimuli and tunnel stimuli as meaningful. Stimulus presentation was followed by a 3-sec response interval in which participants were instructed to indicate, with a button press, the main direction of optic flow motion (left or right, Figure 1A). The duration between onset of response interval and button press is referred to as response time. The optic flow motion task will from now on be termed as direction task. Stimuli were presented in pairs of the same stimulus type such that one stimulus block was 18 sec, and the blocks

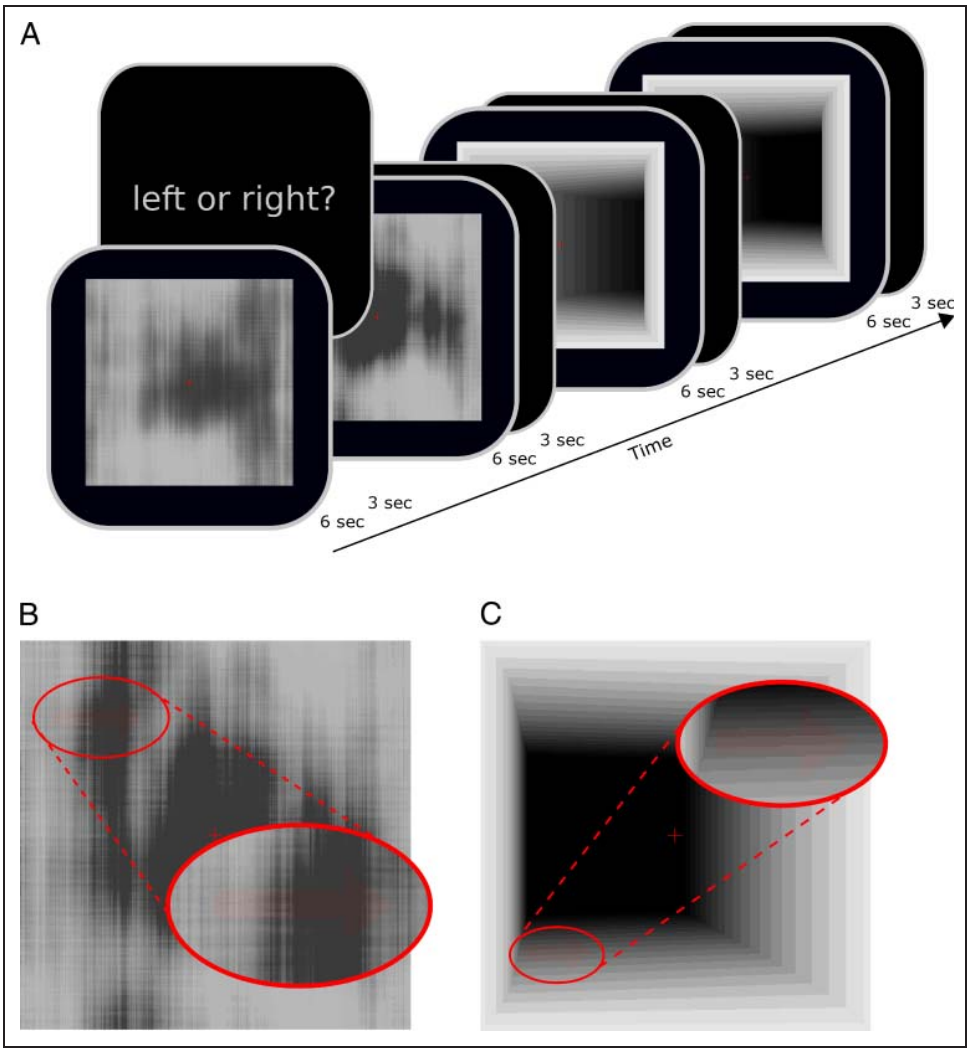

Figure 1. Experimental design and stimuli. (A) The alternating sequence of two indistinct (phase-scrambled) and two meaningful (tunnel) stimuli, repeated over the length of the experiment. Each film was presented for 6 sec and followed by a 3-sec response period, here exemplified with the response choice of the direction task, translated from German. In Experiment 2, each task was presented in a single block preceded by a six-scan fixation cross and a three-scan instruction screen to prevent task switching effects. (B, C) Example frames from the detection task containing the to-be-detected arrows for phase-scrambled stimuli with the arrow in the top left quadrant (B) and for tunnel stimuli with an arrow in the bottom left quadrant (C). The arrows in the insets have been enhanced in their red color to make the arrow more visible to the reader (original saturation in whole frame). Also, note the red fixation cross in both frames.

alternated between stimulus type. Forty-eight stimuli (24 for each film type) were presented in each run, for a total of 12 blocks per stimulus per run (192 scans). Two runs were acquired per participant.

The data collected in the first experiment were also used to examine the visual response to phase manipulation in the spatial and temporal domain and have been published as such elsewhere (Fraedrich et al., 2010). These data were reanalyzed here for functional connectivity and activity in the hippocampus. We will describe these additional analyses here, only summarizing the relevant methodological details. The experiment is described in detail in Fraedrich et al. (2010). The MR data acquisition parameters and visual projection of the stimuli are the same as in Experiment 2 and can be found there.

Mutual Information for Both Stimulus Types

For each stimulus type (meaningful and indistinct stimuli), the mutual information was computed to assess the degree to which one frame contains information about the next one. The mutual information I_i between the current frame X_i and the previous frame X_{i-1} was computed from the entropy $H(X)$ of a frame according to the formula

$$I_i(X_i, X_{i-1}) = H(X_i) + H(X_{i-1}) - H(X_i, X_{i-1}),$$

with $H(X_i,X_{i-1})$ being the joint entropy of the two adjacent frames. Computations were performed using Matlab (MathWorks). This was done for all frames of each film, and the resulting mutual information was then averaged separately over all meaningful ($n = 12$) and indistinct films ($n = 12$). The average mutual information was significantly higher (t test, $p < .0001$) for all meaningful stimuli (mean = 3.25 bits, $SD = 0.05$ bits) than for indistinct stimuli (mean = 2.27 bits, $SD = 0.18$ bits).

Functional Connectivity Using ICA

ICA models functional MRI data as linear mixtures of spatially independent processes, each contributing to

the data set with an unknown time profile and as such provides a measure of functional connectivity between discrete brain regions (Greicius & Menon, 2004; Van de Ven, Formisano, Prvulovic, Roeder, & Linden, 2004). We performed ICA on the 18 participants from the main experiment in Fraedrich et al. (2010) using FMRLAB 4.0 (Duann et al., 2002) for Matlab (MathWorks). We used only the participants who did not see the fixation cross because we wanted to look at the network connectivity under the most natural viewing conditions. Each image was slice-time corrected, minimizing the differences in light intensity because of acquisition timing. Non-brain image voxels were removed from further analysis by masking the fMRI time series images with the intensity-thresholded structural images. The image time series was quadratically normalized, the temporal and voxel means were removed, and then the runs were concatenated for the analysis. The Infomax algorithm (McKeown et al., 1998; Bell & Sejnowski, 1995) was used to separate components by maximizing the kurtosis of the components. The ICA unmixing matrix was computed using the runica routine (Matlab version; Makeig, Bell, Jung, & Sejnowski, 1996). After convergence, 160 spatially independent component maps were derived for each participant, normalized by subtracting the component map's mean from each voxel and dividing by the standard deviation of the map weights. Because of the mostly super-Gaussian nature of independent components, each component map or region of activity (ROA) comprised all voxels with z values above 1.5. Structural images and component maps were normalized to the standard Talairach space using SPM2 (Wellcome Trust, London, United Kingdom).

To select equivalent independent components across participants, two independent observers labeled the artifact-free ICs based on visual inspection of their spatial ROAs, their consistency of brain activation, and the computed overlap ratio between components (overlap ratio = same voxels highlighted as ROA voxels across participants). ROA of each selected component was visualized within a high-resolution structural image (MRIcron anatomic template ch2bet) for comparison across participants. The independent component for early visual areas from each participant was solely selected based on their ROAs in early visual areas. We tested for participation of all brain areas in the visual component on the group level by applying a one-sample t test over the normalized ROAs, thresholding at $p < .05$, false discovery rate (FDR) corrected for multiple comparisons. To investigate whether this component is related to stimulus presentation, the back-projected event-related BOLD responses were computed from the visual independent component for all participants. First, a more specific time course of each component was computed from the highly participating voxels (z threshold of 4.0) in the component ROA. The component time course was then epoched from 4.5 sec before to 18 sec after the stimulus presentation, resulting in 48 22.5-sec epochs. The event-related BOLD response and its standard deviation were computed across epochs of the same event types. Because no explicit baseline measure was acquired, the component time course was compared against a baseline measure obtained from using a bootstrapping approach. This baseline was computed from 100 epochs of equal length that were randomly picked from the entire back-projected component time course and averaged.

Univariate Analysis

All participants were reanalyzed for hippocampal activity using a hierarchical general linear model. fMRI preprocessing and statistical analyses were conducted using SPM5 (Wellcome Trust, London, United Kingdom). EPI data were realigned using a six-parameter rigid body transformation, spatially normalized to Montreal Neurological Institute space, and smoothed with an isotropic 8-mm FWHM Gaussian filter. To remove low-frequency noise and slow drifts in the signal, a high-pass filter (cutoff = 128 sec corresponding to 0.0078 Hz) was included in the filtering matrix. On the single-subject level, regressors for both types of stimuli and the participant responses as well as six motion correction parameters (as effects of no interest) were used to model the data. Contrasts of interest were then entered into a group-level model. Activated brain regions from this analysis are reported at $p < .05$, FDR corrected for multiple comparisons.

Experiment 2

Participants

Twenty right-handed healthy young participants with no red–green color blindness participated in this study (12 women, mean age = 25.5 years, SD = 4.85 years). All participants were naive with respect to the experimental hypothesis and were only informed of the required experimental task. The local ethics committee of the medical faculty at the Ludwig–Maximilian University approved the study. Informed written consent was obtained from all participants in accordance with the Declaration of Helsinki. One participant was excluded because of an anatomical abnormality for a final cohort of 19.

Stimuli and Design

In the second experiment, 8 of the 12 turning angles were used because no effect of turning angle was found. The difference in frame-wise local luminance changes from the first experiment was removed by reducing the overall contrast in indistinct stimuli. Therefore, if the same activity is found in response to these stimuli, then it is not related to differences in local high-frequency light intensity changes in the stimulus. With these stimuli, participants performed a detection task, which, in contrast to the first task, did not require participants to process the original

content of the stimuli. Subjects indicated the presence of a barely visible red arrow, which appeared for 10 frames (0.166 sec) within both types of stimuli. The red component of each pixel was increased by 10/255, and the green and blue component was decreased such that the luminance of each pixel remained constant (Figure 1B and C). The arrows had one of four different lengths, could point either to the left or to the right, and were positioned in the middle of one of the four corner quadrants of an imaginary 3 × 3 grid (nine equal squares). Fifty percent of the stimuli contained an arrow, with an equal distribution of arrows appearing in tunnel and phase-scrambled stimuli distributed over 0.5–5.5 sec of the film. In addition, participants also performed the direction task from the first experiment to ensure that task-specific effects were not because of the new participant cohort.

Experimental Procedure

Participants were initially trained on both tasks to indicate via button press depending on task either (a) the presence of an arrow within the presented film or (b) the direction of optic flow motion (left or right). Subjects were preexposed to a single frame containing an arrow for both types of stimuli for 5 sec before training to increase the accuracy with which participants could perform the task. Detection performance was trained until 80% correct was reached. Subsequently, participants were trained on the direction task as they were trained in Experiment 1. Subjects were instructed to fixate a red fixation cross in the middle of the screen throughout training and during the experiment, and eye movements were monitored with an MRI-compatible camera with EyeSee-Cam software (Schneider et al., 2009).

During the experiment, tasks were presented in a single block, with randomized task order across runs. Each run started with a six-scan (13.6 sec) fixation cross, followed by a three-scan (6.75 sec) task-specific instruction and then the task. The next task was separated by another six-scan fixation period and subsequent three-scan instruction period. Twenty-four stimuli (12 from each stimulus type, six blocks per stimulus) were presented for the direction task, and 48 stimuli (12 blocks per stimulus), for the arrow detection task. Within-task stimulus presentation rates were equalized across both runs, and each presented stimulus and arrow combination was unique. Visual stimuli were presented within a black frame with a projection system (60 Hz, screen resolution = 800 × 600, Christie LX40) and were viewed over a front surface mirror (field of view = 24° × 19°).

Data Acquisition

fMRI images were acquired using an eight-channel head coil on a 3-T whole-body MR scanner (Signa HDx) with a T2*-weighted gradient-echo, echo-planar sequence (repetition time = 2.25 sec, field of view = 220 mm, matrix = 64 × 64). Each volume consisted of 36 axial slices, each with a slice thickness of 3.5 mm with no interslice gap. Padding and adjustable head restraints were used to minimize head motion. A high-resolution T1-weighted anatomical image (0.8 × 0.8 × 0.8 mm isotropic voxels) was also acquired from each participant.

Data Analysis

Data were analyzed using SPM5 (Wellcome Trust, London, United Kingdom) for Matlab (MathWorks, Natick, MA). Data were preprocessed in the same way as in Experiment 1. A high-pass filter (cutoff = 128 sec) was applied to remove low-frequency noise and slow signal drifts. Separate regressors for each stimulus and task combination as well as the behavioral responses modeled the BOLD time courses at the single-subject level. Six additional regressors modeled participant movement. A 2 × 2 factorial design including the interaction between both stimuli and task was used to model group-level effects. Subjects' and task-wise performance as a covariate were also entered into the model. Contrasts for main effects and interactions were analyzed using t test, thresholded at $p < .05$, FDR corrected for multiple comparisons. Behavioral performance was assessed with a 2 × 2 repeated-measures ANOVA with the factors Task (direction vs. detection) and Stimulus (tunnel vs. phase-scrambled) and was computed for percentage of correct responses.

PPI Analysis for Both Experiments

PPI analysis tests whether the neuronal responses in each voxel can be explained by the interaction between the neuronal activity in a given seed region (in this case, the hippocampus) and experiment-related cognitive processes, which, in this case, is viewing meaningful or indistinct stimuli (Friston et al., 1997). As PPI analysis typically involves a common seed region across participants, we created a bilateral ROI based on the hippocampal activation that was identified in the group analysis for indistinct stimuli of both experiments masked with an anatomical image of the posterior hippocampus (see Figure 4). The mean BOLD signal time course was extracted from this ROI for each participant and convolved with the canonical hemodynamic response function for the stimuli resulting in the interaction term. The mean BOLD signal, together with the regressor for each stimulus, and the interaction term were entered into a general linear model. Pearson's product–moment correlation coefficient was computed between the time course of every voxel in the brain and the interaction term. These correlation values were then converted to z values using Fisher's r-to-z transformation. To assess statistical significance across participants for each experiment, whole-brain voxelwise z maps were then entered into a group-level analysis where contrasts of interest were assessed with t tests thresholded at $p < .05$, FDR corrected for multiple comparisons.

RESULTS

Behavioral Analyses

The behavioral results of the first experiment were already published in Fraedrich et al. (2010) and showed a higher percentage of correct responses for meaningful tunnel stimuli. Both the difference in correct responses between stimulus types and the average performance from each individual, irrespective of stimulus, did not correlate with BOLD signal changes in the current analyses. In the second experiment, we tested for differences in performance between stimuli (meaningful vs. indistinct) and task (direction vs. detection). The 2 × 2 repeated-measures ANOVA revealed a main effect for Task, $F(1, 18) = 14.1, p = .001$, a main effect of Stimulus $F(1, 18) = 8.8, p = .008$, and a significant interaction of Task × Stimulus, $F(1, 18) = 5.8, p = .027$. Response accuracy for the detection task did not significantly differ for the meaningful and indistinct films (meaningful: 81.0% vs. indistinct: 80.1%). Performance during the detection task was worse than in the direction task, indicating that the detection task was more demanding. For the direction task, participants were more likely to recognize the correct optic flow direction for the meaningful stimuli (97.9%) than for the indistinct stimuli (84.5%), same as in Experiment 1. The behavioral measures were used to model hemodynamic effects in the group-level general linear model. Testing for the effect of performance did not reveal any significant correlations with brain activation.

For the direction task in the first experiment, the mean response times did not significantly differ [$t(28) = 0.436$, $p = .667$] for indistinct stimuli (mean = 638 msec, SD = 175 msec) and meaningful stimuli (mean = 630 msec, SD = 132 msec). For the second experiment, a repeated-measures ANOVA over response times (factors Stimulus and Task) revealed a significant main effect of Stimulus, $F(1, 18) = 4.7, p = .043$, a significant main effect for Task, $F(1, 18) = 118.2, p < .001$, and a significant interaction, $F(1, 18) = 80.7, p < .001$. The mean response time was lower in the direction task (indistinct: mean = 555 msec, SD = 40 msec; meaningful: mean = 527 msec, SD = 25 msec) compared with the detection task (indistinct: mean = 599 msec, SD = 57 msec; meaningful: mean = 619 msec, SD = 58 msec). The interaction is caused by shorter response times for meaningful stimuli than indistinct stimuli in the direction task, whereas in the detection task, response times were longer for meaningful stimuli.

Eye tracking data revealed that participants constantly fixated the target, and there were no differences between stimuli or conditions.

fMRI Analyses

Functional Connectivity of Early Visual Areas

Because early visual areas were active during presentation of indistinct stimuli, we only analyzed the functional connectivity of the early visual component extracted using ICA. The group analysis over the spatially normalized ROAs of early visual ICs showed significant activation not only in visual areas such as the right cuneus, left middle occipital area, and fusiform but also bilaterally in the hippocampus (Figure 2A), although the selection criteria for labeling this independent component was solely based on the activation in early visual areas. This implies a functional connectivity of early visual areas and the hippocampus that forms one independent BOLD process with highly correlated BOLD time courses. Thus, the viewing of the experimental stimuli evoked temporal dynamics found in the visual areas that can also be found in the posterior hippocampus.

The event-related BOLD responses computed for the independent component of early visual areas were found to be stimulus-locked to meaningful and indistinct visual motion stimuli. For indistinct stimuli, the back-projected component time course for early visual areas (corresponding to BOLD signal) showed an increase in BOLD signal, whereas the back-projected component time course in response to meaningful stimuli showed a relative decrease in signal strength (Figure 2B and C). This pattern of activation corresponds to the visual activation that has previously been found for these stimuli (Fraedrich et al., 2010). Therefore, the functional connectivity between the early visual areas and the posterior hippocampus was related to the stimuli.

Overall Stimulus-related Activity

For indistinct versus meaningful stimuli, the univariate analysis in the first experiment revealed significant activation in the occipital pole extending down to the lingual gyrus, the occipital fusiform gyrus, the hippocampus bilaterally, and the precentral and postcentral gyrus (Figure 3A). The differential hippocampal activation is also reflected in the percent signal change (Figure 3C). Consistent with previous findings that coherent shapes and meaningful objects lead to a reduction of primary visual cortex activity compared with scrambled low-level feature-matched counterparts (Murray, Kersten, Olshausen, Schrater, & Woods, 2002), our indistinct phase-scrambled stimuli lead to a strong increase in early visual cortex activation in comparison with the coherent and meaningful tunnel stimuli. Additionally, active regions were found in the insular cortex bilaterally, paracingulate gyrus, right frontal pole, superior frontal gyrus bilaterally, frontal orbital cortex bilaterally, left frontal pole, left inferior frontal gyrus, primary somatosensory cortex, and middle temporal cortex (see Figure 3A).

The hippocampus is known to be involved in classical conditioning that requires temporal integration over a delay period (Eichenbaum, Otto, & Cohen, 1994; Berger & Thompson, 1978). To correctly perform the direction task for the indistinct stimuli in the first experiment, participants had to integrate the direction of optic flow motion over time. Therefore, the direction task could have

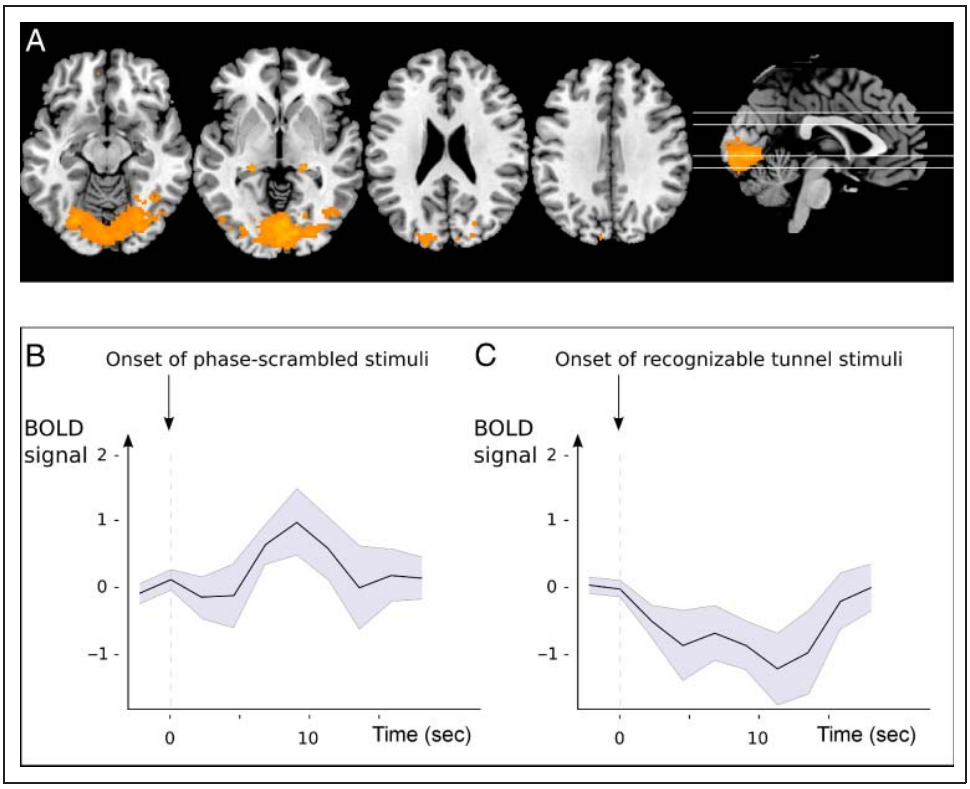

Figure 2. Functional connectivity between the visual system and the hippocampus. (A) Axial brain slices ($z = -12, -2, 24, 34$; MRIcron anatomical template ch2bet) of the resulting thresholded group-level t statistic ($p < .05$, FDR corrected) from the individual early visual cortex independent component ($n = 18$). The test reveals regions that belong to this component in all participants that included visual areas and the hippocampus bilaterally, indicating a statistically independent process between these regions. (B, C) The average BOLD signal (i.e., back-projected component time course) for the component seen in A averaged over 18 participants, locked to the onset of indistinct (B) and meaningful (C) stimuli. The dotted vertical line indicates stimulus onset, and the shaded area represents standard deviation across participants. The time course shows consistently higher values during indistinct stimulus presentation and lower values for meaningful stimuli across all participants.

recruited memory processes, thus evoking hippocampal activation. For the meaningful stimuli, in contrast, it is not necessary to integrate information over the length of the stimulus, as the direction of the tunnel can be determined by processing the optic flow from a very short period of the stimulus. Another possible explanation for the differential hippocampal activity is the higher local luminance changes for indistinct stimuli, which could stimulate the hippocampus, similar to optic flow (Watrous, Fried, & Ekstrom, 2011).

The second experiment was used to control for these two possible effects. In addition to having participants respond to the direction of optic flow, participants were also asked to perform a detection task using the same stimuli because detection tasks do not require temporal integration and should not elicit hippocampal activation (Novitskiy et al., 2011; Hahn et al., 2009; Linden et al., 1999). The phase-scrambled stimuli were modified such that the local luminance changes were equal to their respective tunnel stimuli. In the second experiment, the detection task for indistinct versus meaningful stimuli led to activation in the occipital pole, precentral and postcentral gyrus, primary motor cortex, bilaterally inferior LOC (most likely corresponding to V5), and the hippocampus (Figure 3B; for hippocampal percent signal change, see Figure 3D).

No significant interaction between task and stimulus effects was found in the hemodynamic response. Therefore, we looked at the main effect of stimulus over both tasks, as well as the main effect of task. The main effect of stimulus type revealed activity for indistinct stimuli (Table 1) in the same areas found in the previous analysis. Despite matched local luminance changes between both film types and a globally reduced contrast for indistinct stimuli in the second experiment, the visual activation was still more pronounced for the indistinct stimuli in both task conditions. This corresponds to findings that V1 responses are increased to incoherent than to coherent motion and for less well-predictable motion (e.g., Bartels, Zeki, & Logothetis, 2008; Braddick et al., 2001; McKeefry, Watson, Frackowiak, Fong, & Zeki, 1997). The reduced activity in early visual areas during meaningful stimulus presentation might be based on predictive coding mechanisms (Rao & Ballard, 1999). Although participants were not required to perform temporal integration over time nor a detailed analysis of the spatio-temporal stimulus in the detection task, hippocampal activation was still found in response to indistinct stimuli. Task difficulty was matched between

stimulus types for the detection task, and no significant correlations between BOLD signal change and behavioral response times or performance accuracy were found, suggesting that performance effects cannot explain the hippocampal activation found.

Task-specific Activity

We also tested for task-specific effects in the second experiment, independent of stimulus type. The contrast detection versus direction revealed no significant activation, whereas the opposite contrast yielded significant activation in bilateral frontal inferior gyrus (including Broca's area), inferior orbito-frontal, supramarginal gyrus (including Wernicke's region), inferior temporal gyrus, inferior parietal, superior frontal, precentral gyrus, optic radiation, and inferior occipital cortex ($p < .05$, FDR corrected). The language processing areas showed a left-hemispheric dominance and were most likely related to the linguistic nature of the response ("left" or "right"). The motion-sensitive area V5 was more active for the direction task, likely because of the relevance of visual motion for the task. Eye movements cannot account for the relative differences found in V5 because participants did not differ in their eye movements between tasks.

Connectivity Assessed with PPI Analysis

The PPI analysis disambiguates correlations of a spurious sort from those mediated by direct or indirect neuronal interactions. If the hippocampus is involved in processing indistinct stimuli, then not only the activity of the hippocampus but also its coupling is expected to be stimulus-dependent. We chose to assess this connectivity with a PPI analysis instead of ICA because PPI analyses inherently look at stimulus-related effects, and finding a hippocampal visual connectivity using PPI would suggest that the connectivity between these two regions is dependent on the stimulus. Both experiments were analyzed separately by calculating the within-subject correlation between the activity in the posterior hippocampus and activity in the rest of the brain. The two experiments did not differ in the connectivity patterns found, so we combined the PPI analysis over both experiments ($n = 48$). The posterior hippocampus showed stimulus-dependent correlations with the inferior temporal gyrus (specifically the temporal occipital fusiform gyrus), superior LOC (including 7a), inferior LOC or V5, and in inferior and superior parietal cortex, including the left supramarginal gyrus, for indistinct stimuli (Figure 4A, yellow). These cortical regions lie within the dorsal and ventral visual stream, associated with visuospatial or motion processing and object recognition,

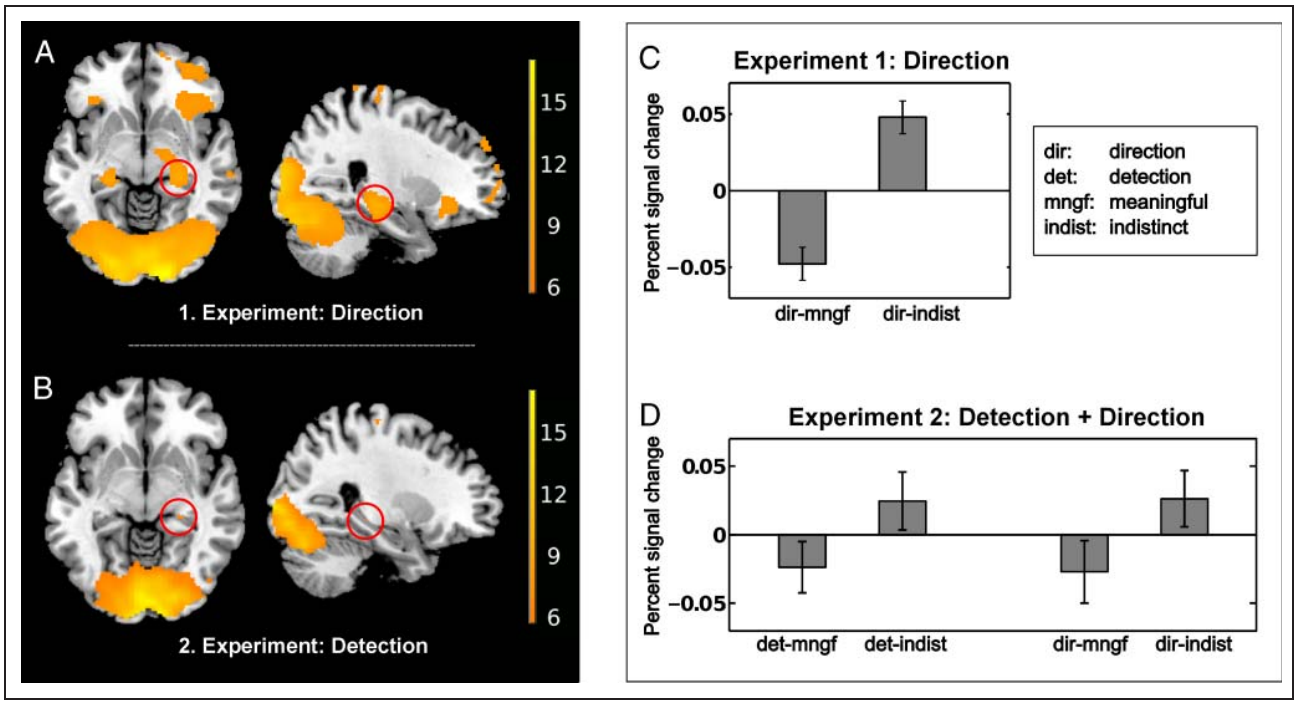

Figure 3. Hippocampal activity when viewing indistinct motion stimuli. (A) Activation map for indistinct stimuli from Experiment 1, the optic flow direction task ($n = 29$; $p < .05$, FDR corrected). (B) Activation map for indistinct stimuli from Experiment 2, the detection task ($n = 19$; $p < .05$, FDR corrected). Both tasks show mainly visual and right-dominant hippocampal activity, suggesting that the activity is stimulus-driven. Maps are superimposed on the MRIcron anatomic template ch2bet. (C, D) Percent signal change computed for Experiments 1 and 2 using the hippocampal group result of indistinct versus meaningful stimuli as ROI. After correction for the individual participant mean, percent signal change in response to both experimental tasks shows a positively increased signal change in the hippocampus in response to indistinct stimuli compared with meaningful ones. The difference in percent signal change for the direction task in Experiment 1 (C) and Experiment 2 (D, right) was not significant (ANOVA, Experiment × Stimulus, $F(1, 46) = 1.93$, $p > .17$).

Table 1. Regions of Activity for Both Tasks from Experiment 2

Region	*Hemisphere*	*Cluster Size (voxels)*	*Max. t*	*x, y, z (mm)*
Indistinct > Meaningful (p < .05, FDR Corrected)				
Calcerine	L	10,008	15.91	0, −92, −10
	R		14.54	10, −98, −2
	R		13.98	26, −92, 2
Postcentral	R	750	5.24	44, −28, 58
	R		4.87	52, −18, 48
Precentral	R		4.76	42, −16, 58
Postcentral	L	315	4.67	−54, −6, 44
	L		4.27	−58, −10, 38
	L		4.13	−50, −16, 52
Frontal inf. operculum	R	398	4.04	38, 18, 18
Frontal inf. tri	R		3.69	44, 14, 26
Frontal inferior orbital	R	201	3.95	42, 32, −2
	R		2.98	30, 32, −6
Mid frontal	R	245	3.54	36, 36, 18
	R		3.45	40, 44, 22
	R		2.93	38, 56, 16
Hippocampus	R	32	3.49	24, −30, −6
Primary motor cortex	L	165	3.23	−24, −24, 52
Paracentral	L		3.21	−6, −30, 56
Precentral	L		3.17	−28, −22, 66
Superior temporal	R	35	3.15	58, −22, −2
	L	13	3.13	−58, −12, −2
Insula	L	16	3.08	−30, −24, 8
	L	8	2.93	32, −24, 4
Hippocampus	L	6	2.89	−24, −32, −6
SMA	R	7	2.87	0, 6, 60
Meaningful > Indistinct (p < .05, FDR Corrected)				
Temp. occ. fusiform	R	9,567	9.89	26, −44, −16
Precuneus	R		9.49	14, −46, 46
Fusiform	L		8.81	−26, −48, −10
Middle occipital	L	666	5.98	−40, −80, 18
Supramarginal	R	79	3.60	60, −30, 26
Superior temporal	R	16	3.50	66, −42, 16
Superior frontal	R	28	3.24	22, −2, 48
Posterior cingulate	L	8	2.98	16, −38, 14

Complete list of regions resulting from the second experiment. Montreal Neurological Institute coordinates of the peak voxel, *t* values, and cluster sizes (in number of voxels). L = left hemisphere; R = right hemisphere; inf = inferior; Temp. occ. = temporal occipital.

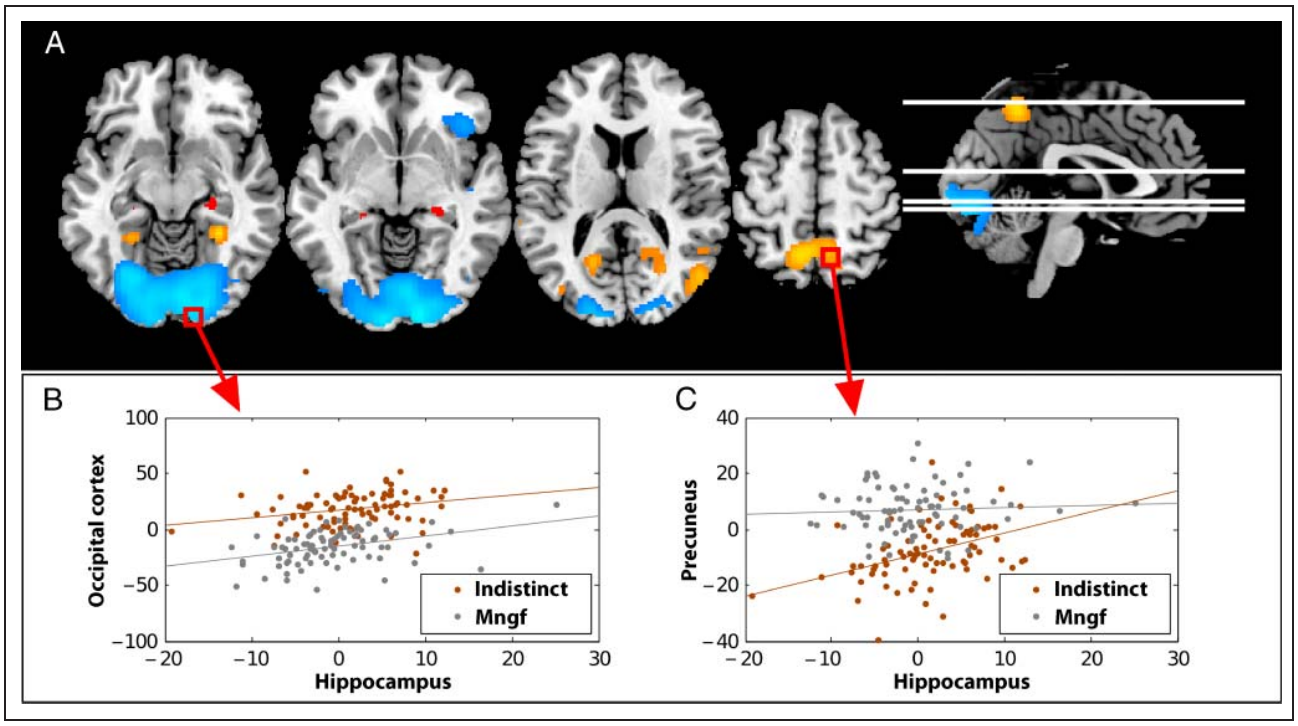

Figure 4. Stimulus-dependent functional connectivity of the posterior hippocampus with other cortical areas for indistinct and meaningful (Mngf) stimuli. (A) The posterior hippocampus showed an increased connectivity to areas along the dorsal and ventral visual stream in both experiments, when participants viewed indistinct stimuli (yellow). While viewing meaningful motion stimuli, the hippocampus showed an increased correlation with activity in early visual areas (blue). The seed region that was identical for both experiments is shown in red. Significantly correlated regions with the hippocampus are depicted on axial ($z = -10, -5, 14, 58$) slices to show the exact location of activity. The statistical threshold for both experiments was $p < .05$ (FDR corrected), and the anatomical template was the same as in Figure 2. (B, C) Correlations between hippocampal activity ($x = 22, y = -30, z = -6$) and activity from an exemplary preprocessed (detrended, high-pass filtered) voxel for one participant within the right occipital cortex (B; $x = 16, y = -88, z = -16$) or the right precuneus (C; $x = 14, y = -54, z = 50$) illustrate the found PPI for both stimulus types. The values on the x and y axes have arbitrary units.

respectively. Thus, the hippocampus shows stimulus-specific connectivity to ventral and dorsal visual stream areas for these stimuli. In addition to these areas, the connectivity result also revealed activity in the bilateral posterior cingulate gyrus, an area that shows strong connectivity with the caudal inferior parietal lobe (Kravitz, Saleem, Baker, & Mishkin, 2011). For meaningful stimuli, the posterior hippocampus showed a stronger correlation with the occipital fusiform gyrus, including activity in early visual areas, in V5 bilaterally, in anterior insular cortex bilaterally, and in left precentral gyrus, as well as minor activation in paracentral gyrus bilaterally and right inferior frontal gyrus (Figure 4A, blue).

Some of the visual regions found in the PPI analysis overlapped with the areas that showed stimulus-dependent activity in the univariate analysis. To shed light on the connectivity patterns, we looked at the correlations in activity in an example voxel from the occipital cortex, the precuneus, and the hippocampus in a single participant. The voxel in the occipital cortex showed higher activation for the indistinct stimuli in accordance to the univariate results described above. It also showed correlated activity with the hippocampus for both stimulus types, with a slightly higher correlation for meaningful stimuli (Figure 4B). The precuneus showed a strong positive correlation to hippocampal activity for indistinct stimuli but not for meaningful tunnel stimuli despite higher overall activation of the precuneus for meaningful stimuli (Figure 4C). These differential effects suggest a hippocampal coupling with the precuneus dependent on perceptual inconsistency or constancy of the stimulus and a stable connectivity between early visual areas and the hippocampus (consistent with the ICA results).

DISCUSSION

Using complementary analysis techniques in two fMRI experiments, we examined the hippocampal recruitment to meaningful visual motion stimuli and the corresponding phase-scrambled indistinct stimuli as well as the functional connectivity between visual and hippocampal areas. Without an explicit memory task, we consistently observed visual and posterior bilateral hippocampal activation in response to indistinct visual motion stimuli. The results of our two experiments showed that hippocampal activation was independent of image statistics and task. The activation was also found for indistinct stimuli in the detection task, for which an explicit processing of the stimulus

content was not required. This indicates that the hippocampal activation is related to implicit processing of the stimulus. Furthermore, the ICA revealed a stimulus-related functional connectivity between the visual cortex and the hippocampus, reflecting mnemonic information processing based on visual sensory input. In addition, the coupling revealed by PPI analysis between the posterior hippocampus and areas within ventral and dorsal visual stream, encompassing the inferior LOC (most likely V5) and the superior parietal cortex bilaterally, was also independent of experiment.

Hippocampal Recruitment for Indistinct Visual Motion Stimuli

Participants acquired a mental representation for both stimulus types because they were exposed to both stimuli during training and could give a general description of their appearance when asked. Therefore, although novelty has been associated with hippocampal activation (Kumaran & Maguire, 2007; Nyberg, 2005), stimulus novelty in the sense that a stimulus has not been experienced before cannot explain our hippocampal results as participants had equal exposure to both stimulus types. Other aspects of novelty such as associative and contextual novelty also cannot explain our present findings (cf. Kumaran & Maguire, 2006). Our stimuli did not allow participants to develop an association that could have then been violated, and the context did not change during the experiment. Instead, we believe that the temporally uncertain nature of the stimuli, which can also be seen as a form of novelty, was critical for hippocampal recruitment.

Although the phase manipulation did not change the spatio-temporal amplitude spectrum between both stimulus types, the phase manipulation in the temporal dimension introduced structural changes over time. Previous studies presenting static images with manipulated phase information have not reported hippocampal activation (Wichmann et al., 2006; Olman et al., 2004), suggesting that the structural changes introduced through phase manipulation in the temporal dimension of our stimuli are the determining factor for hippocampal recruitment. Because both stimulus types were matched for image statistics and optic flow and, in the second experiment, also matched for local luminance changes, these factors cannot account for the differential hippocampal activation. The causal difference seems to lie in the differential structural information over time between both stimulus types.

The meaningful stimuli possess a clear and temporally very consistent structure with only minor structural changes over time, which is represented by the significantly higher mutual information between frames. The decreased visual activation in response to meaningful stimuli might speak for predictive coding mechanisms taking place. In contrast, the indistinct stimuli have a continuously changing structure and thus lead to a continuous change in current sensory input. Indistinct stimuli contained less mutual information between frames. Thus, for meaningful stimuli, uncertainty about the following frame is reduced by knowing the present one, whereas indistinct stimuli still defy expectation and thus could drive memory encoding processes to a greater degree. The hippocampal activity was found irrespective of the task participants performed, and the detection task did not explicitly require the processing of the stimulus, suggesting that the hippocampus implicitly processes unpredictable dynamic stimuli.

Stimulus-dependent Hippocampal Connectivity

In both experiments, the same coupling between the hippocampus and areas in the ventral and dorsal visual stream was found for indistinct stimuli. With regard to the roles of these visual streams, this suggests a functional relationship between the hippocampus and object and place recognition centers for these particular stimuli. The connectivity was consistent despite different task demands. The ventral visual stream, in particular, the lateral–occipital complex, is a hub for object recognition (Malach et al., 1995), and activation in this region correlates highly with recognition performance (Grill-Spector, Kushnir, Hendler, & Malach, 2000). Furthermore, activation in bilateral occipito-temporal areas (corresponding to region LO) has been found in response to perceptual closure processes that enable recognition despite only partial visual information (Doniger et al., 2000).

The connections to the dorsal visual stream encompassed regions from the general occipito-parietal system that is known for visuospatial and motion processing (Kravitz et al., 2011; Born & Bradley, 2005). Furthermore, we found a projection from the hippocampus to the inferior parietal cortex that has previously been described as part of the parieto-medial pathway in monkeys (Kravitz et al., 2011). This pathway is implicated in optic flow processing (Phinney & Siegel, 2000); however, this alone cannot explain our results because optic flow and local luminance changes were identical for both stimulus types. Despite the task difference for both experiments and the inclusion of a colored stimulus in the detection task, it is intriguing that the same hippocampal–cortical connectivity pattern was observed across experiments.

Our functional connectivity results are in agreement with electrophysiological and histological findings in rats that the hippocampus receives crucial sensory input from the visual cortex and that the dorsal visual cortex projects multisynaptically via occipital connections and the ventral visual pathway, via temporal connections to the hippocampus (Tsanov & Manahan-Vaughan, 2008). Also, in primates, a direct connection between parietal (area 7a and b) and temporal regions to the hippocampus has been found (Rockland & Van Hoesen, 1999). Furthermore, we confirm earlier observations of distinct intrinsic functional connectivity in humans between the posterior hippocampus and the parietal cortex (Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008). The fact that

the two complementary analyses, independent component and univariate analysis, associated the posterior hippocampus with other visual processing systems corresponds to the cytological and molecular boundaries of the hippocampus (Fanselow & Dong, 2010) and to the proposed role of the posterior hippocampus in visual–spatial processing (Hüfner, Strupp, Brandt, Smith, & Jahn, 2011; Maguire et al., 2000).

In response to meaningful stimuli, the connectivity analysis mainly revealed a coupling of the posterior hippocampus to early visual areas as well as minor activations to other cortical areas such as bilateral paracingulate gyrus and anterior insular cortex. It is important to note that the hippocampus was not active in response to the meaningful stimuli, thus the connectivity pattern found represents a fundamental connectivity between the hippocampus and visual cortex that is independent of experiment.

Unpredictability as Determining Factor for Hippocampal Involvement?

Indistinct stimuli have less mutual information between frames (see Methods). Thus, based on current sensory input, the future visual input is less predictable and possibly causes a mismatch between the actual and predicted stimulus presentation leading to either a continual updating of the mental representation or learning to expect uncertainty, both reliant on the hippocampus. This concept would be akin to evidence linking hippocampal activation to higher unpredictability of visual stimuli (Strange et al., 2005) and, as such, complements the broad literature on the role of the hippocampus in novelty detection. Furthermore, the finding that the hippocampus seems to be especially active when visual input changes dynamically and unpredictably and thus mismatches prior expectations expands the view of the hippocampus as a continuous integrator of new information through updating of mental representations (McKenzie & Eichenbaum, 2011).

Given that forward models of prediction have been suggested for the hippocampus (Schacter & Addis, 2009) as well as for motion pattern analysis of the visual system through behavioral work (Roach, McGraw, & Johnston, 2011), the stimulus-dependent connectivity result between the hippocampus and visual processing areas could bridge the gap between these two separate findings.

From a system dynamics perspective that views the hippocampus as an attractor network (Rolls, 2007), the hippocampal activation could be explained by the combination of continuous structural change with the naturalistic motion still contained in the indistinct stimuli that keep the activation in the hippocampus in a reverberating state, which does not easily converge onto a stable point within the hippocampal attractor network. According to the proposal that vision can be thought of as "recognition-by-analogy" by which the visual input is linked to existing information stored in analogous memory representations (Bar, 2007, 2009), the task independence of the hippocampal activation while viewing indistinct visual motion stimuli with the cortical coupling to visuospatial and object recognition areas may represent the neuronal substrate for the attempt to combine information from both streams to recognize these indistinct stimuli.

Conclusion

Taken together, these functional data demonstrate that the hippocampus is recruited in response to indistinct visual motion stimuli with a temporally unpredictable nature through an interaction between perceptual and mnemonic processes. The pattern of cortico-hippocampal connectivity, in the absence of an explicit memory task, provides evidence for the hippocampus in binding neocortical visual processing areas. Overall, our present findings demonstrate that higher cognitive areas are recruited in response to purely visual tasks and that functional cortico-hippocampal connectivity is flexible and changes depending on perceptual demands.

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3 Behavioral experiment

The following tables show the verbal associations that have been made in response to phase-scrambled stimuli.

Subject 1	Wind, Wellen	Flüssigkeit	Flüssigkeit die sich verteilt	schneller Wind der Wasseroberfläche berührt	schwarze Flüssigkeit nach links bewegend	Flüssigkeit die größer und kleiner wird	Flüssigkeit die größer und kleiner wird	hohle Flüssigkeit	
	1,00	1,00	1,25	1,25	1,00	1,00	1,00	1,00	**1,06**
	1,25	1,25	1,25	1,50	1,25	1,25	1,25	1,25	**1,28**
	1,25	1,25	1,00	1,25	1,00	1,00	1,00	1,25	**1,13**
	1,17	**1,17**	**1,17**	**1,33**	**1,08**	**1,08**	**1,08**	**1,17**	**1,16**

Subject 2	Schneegestöber	Flummerball, Hin und Her	Ball	Schneegestöber	Schneegestöber mit Menschen im Hintergrund	Schneegestöber mit festen Punkten	Fenster im Zug auf Schneegestöber	Zu langer Blick in die Sonne	
	1,00	1,00	1,25	1,00	1,25	1,00	1,00	1,50	**1,13**
	1,25	1,50	1,50	1,25	1,50	1,50	1,50	1,75	**1,47**
	1,25	1,25	1,00	1,00	1,25	1,25	1,50	1,75	**1,28**
	1,17	**1,25**	**1,25**	**1,08**	**1,33**	**1,25**	**1,33**	**1,67**	**1,29**

Subject 3	Ultraschallbilder	aus Herr der Ringe Nasgul	Fußgängerzone mit vielen Leuten	Wüste, Wüstensand der über Dünen weht	Wasser mit Nebel drauf	*(keine Angaben)*	*(keine Angaben)*	Fließband, "sah fast genauso aus wie 2 davor"	
	1,25	2,00	1,50	1,25	1,00	0,00	0,00	1,00	**1,00**
	1,75	2,00	1,75	1,50	1,50	0,00	0,00	1,50	**1,25**
	2,00	2,00	2,00	2,00	1,50	0,00	0,00	1,50	**1,38**
	1,67	**2,00**	**1,75**	**1,58**	**1,33**	**0,00**	**0,00**	**1,33**	**1,21**

Subject 4	Tier: Hund,Pferd	Fluidsimulation	Fluidsimulation, Wabbern	Farbwechsel schwarz zu weiß	*(keine Angaben)*	*(keine Angaben)*	*(keine Angaben)*	*(keine Angaben)*	
	1,75	1,25	1,00	1,00	0,00	0,00	0,00	0,00	**0,63**
	1,75	1,75	1,50	1,25	0,00	0,00	0,00	0,00	**0,78**
	2,00	1,50	1,00	1,00	0,00	0,00	0,00	0,00	**0,69**
	1,83	**1,50**	**1,17**	**1,08**	**0,00**	**0,00**	**0,00**	**0,00**	**0,70**

Subject 5	(keine Angaben)	(keine Angaben)	(keine Angaben)	Zugfahren	*(keine Angaben)*	Bewegung	Bewegung	*(keine Angaben)*	
	0,00	0,00	0,00	1,75	0,00	1,00	1,00	0,00	**0,47**
	0,00	0,00	0,00	1,25	0,00	1,25	1,25	0,00	**0,47**
	0,00	0,00	0,00	1,25	0,00	1,00	1,00	0,00	**0,41**
	0,00	**0,00**	**0,00**	**1,42**	**0,00**	**1,08**	**1,08**	**0,00**	**0,45**

Subject 6	nach rechts und links; Referenztest; verschwommenes Bild	"wieder das gleiche nur diesmal dunkler"; hat an Apfelmännchen gedacht	viele Striche nach oben und unten; wie Lavalampe; Kugeln zusammen gehen und auseinander	dolle Rechtsbewegung zu sehen wie Sandsturm	'ruhigere Bewegung, bissl gedreht"	ein großer Punkt	war leere Stellen; absolut leere Stellen; Ränder geriffelt, sah aus wie Feuer	*(keine Angaben)*	
	1,00	1,25	1,00	1,25	1,00	1,00	1,75	0,00	**1,03**
	1,50	1,75	2,00	1,75	1,25	1,25	1,50	0,00	**1,38**
	1,00	1,25	1,75	1,75	1,00	1,25	1,50	0,00	**1,19**
	1,17	**1,42**	**1,58**	**1,58**	**1,08**	**1,17**	**1,58**	**0,00**	**1,20**

Subject 7	grau, nix	'nee" (kopfschütteln weil ihr nichts einfällt)	'wabbelt einfach nur rum"	'war verteilter als anderen"	'das war ruhiger"	'Das erste sah aus wie Kopf aber dann verschwand es"	0,00	alles grau	
	1,00	1,00	1,00	1,00	1,00	1,25	0,00	1,00	**0,91**
	1,25	0,00	1,25	1,25	1,25	1,50	0,00	1,25	**0,97**
	1,00	0,00	1,00	1,00	1,00	1,50	0,00	1,00	**0,81**
	1,08	**0,33**	**1,08**	**1,08**	**1,08**	**1,42**	**0,00**	**1,08**	**0,90**

Subject 8	Wellenmuster, Sachen die auseinander der und zusammen laufen; Augen zu; müde; Wolken; hin und her tanzen; Gummiband; Rauschen das so eigenen Dynamik hat; Vogelschwarm	Wurm, Wurmding das sich nach rechts und links bewegt; von Dynamik her das gleiche wie vorher; ein Loch, schwarzes Loch das nach links und rechts geht	so ähnlich wie eben, im Nebel verschwindet und wieder auftaucht	fließen nach rechts; erst auch Objekt gesehen, dann fliessen nach rechts	fließen nach links	sonst alles gleich	'auch wieder nichts besonderes", fließen nach links	wie oben, aber alles bisschen grauer	
	1,25	1,00	1,00	1,00	1,00	1,00	1,00	1,00	**1,03**
	1,75	2,00	1,50	1,75	1,25	1,25	1,25	1,25	**1,50**
	2,00	1,25	1,25	1,25	1,00	1,00	1,00	1,00	**1,22**
	1,67	**1,42**	**1,25**	**1,33**	**1,08**	**1,08**	**1,08**	**1,08**	**1,25**

Subject 9	Regen	Wolken und Regen	Wolken und Regen	Sturm	Wolken	Eclipse, Sonnen-finsternis	Fluss	tiefes Loch	
	1,00	1,00	1,00	1,00	1,00	1,50	1,00	1,25	**1,09**
	1,25	1,25	1,25	1,25	1,25	1,50	1,25	1,50	**1,31**
	1,25	1,25	1,00	1,75	1,00	2,00	1,25	1,50	**1,38**
	1,17	**1,17**	**1,08**	**1,33**	**1,08**	**1,67**	**1,17**	**1,42**	**1,26**

Subject 10	*(keine Angaben)*	*(keine Angaben)*	Fragezeichen	Straße, Grauzone	*(keine Angaben)*	*(keine Angaben)*	Fahne die so im Wind weht	*(keine Angaben)*	
	0,00	0,00	1,00	1,25	0,00	0,00	1,50	0,00	**0,47**
	0,00	0,00	1,50	1,50	0,00	0,00	1,50	0,00	**0,56**
	0,00	0,00	1,75	1,50	0,00	0,00	1,75	0,00	**0,63**
	0,00	**0,00**	**1,42**	**1,42**	**0,00**	**0,00**	**1,58**	**0,00**	**0,55**

	Film 1	Film 2	Film 3	Film 4	Film 5	Film 6	Film 7	Film 8	Average
Subject 11	Wolken, ne Gestalt, sonst nichts	*(keine Angaben)*	Reden	Verschwimmen, Wind, Fluss	*(keine Angaben)*	Baum, ruhig, statisch	oben, unten, Strömung, geteilt	starke Strömung, links massiv	
	1,25	0,00	1,25	1,00	0,00	1,50	1,00	1,00	**0,88**
	1,50	0,00	1,25	1,50	0,00	1,50	1,25	1,25	**1,03**
	1,25	0,00	1,50	1,50	0,00	1,75	1,25	1,00	**1,03**
	1,33	**0,00**	**1,33**	**1,33**	**0,00**	**1,58**	**1,17**	**1,08**	**0,98**
Subject 12	Regentropfen, 2 Leute die sich durch die Regentropfen bewegen, 2 Leute die tanzen	Amybia die einen Teich erkundet, Regen	Amybia die sich teilt, in 2	Fluss,im Fluss treiben, Horizont	Landschaft mit Bäumen und Vögeln gesehen aus einem fahrenden Zug	Alien der sich auf mich zu bewegt	Blume, die horizontal nicht vertikal wächst	Kaninchen, dann hat es sich verwandelt in Raum	
	1,50	1,50	1,25	1,00	1,75	1,75	1,75	1,75	**1,53**
	2,00	1,75	1,75	2,00	2,00	2,00	2,00	2,00	**1,94**
	2,00	2,00	1,50	1,50	2,00	2,00	2,00	1,75	**1,84**
	1,83	**1,75**	**1,50**	**1,50**	**1,92**	**1,92**	**1,92**	**1,83**	**1,77**
Subject 13	Schatten, graues Flimmern	Wurm, Kreis	vertikale Striche	nach rechts Flimmern	Helligketi, Chaos	Chaos, Unangenehmes Gefühl	Auseinander Driften	nach links Flimmern	
	1,00	1,50	1,00	1,00	1,00	1,25	1,00	1,00	**1,09**
	1,50	1,75	1,25	1,25	1,25	1,50	1,25	1,25	**1,38**
	1,00	1,50	1,00	1,00	1,25	1,50	1,25	1,00	**1,19**
	1,17	**1,58**	**1,08**	**1,08**	**1,17**	**1,42**	**1,17**	**1,08**	**1,22**
Subject 14	Schwindel, Unwohlsein, Krise	Schwindelgefühl	Figuren	*(keine Angaben)*	*(keine Angaben)*	Wasserfall	(keine Angaben)	*(keine Angaben)*	
	1,50	1,25	1,50	0,00	0,00	1,25	0,00	0,00	**0,69**
	1,50	1,50	1,50	0,00	0,00	1,25	0,00	0,00	**0,72**
	2,00	1,00	1,50	0,00	0,00	1,50	0,00	0,00	**0,75**
	1,67	**1,25**	**1,50**	**0,00**	**0,00**	**1,33**	**0,00**	**0,00**	**0,72**
Subject 15	schlechter Vorspann von Akte X	Ultraschall	Empfangsstörung TV	Wellen, Schatten	(keine Angaben)	Horrorfilm	*(keine Angaben)*	*(keine Angaben)*	
	1,25	1,25	1,00	1,00	0,00	1,50	0,00	0,00	**0,75**
	2,00	1,75	1,50	1,25	0,00	1,75	0,00	0,00	**1,03**
	2,00	2,00	1,25	1,25	0,00	2,00	0,00	0,00	**1,06**
	1,75	**1,67**	**1,25**	**1,17**	**0,00**	**1,75**	**0,00**	**0,00**	**0,95**
Subject 16	Seerosen bilder-Monet	UFO im Wald	Regen, Nebelschwaden	Loch Ness Monster	Wolken	unscharfes Bild von einer Person	Gestalt im Nebel	verschwommenes Tier, Hase	
	2,00	1,75	1,25	2,00	1,00	1,50	1,50	1,50	**1,56**
	2,00	1,75	1,25	1,75	1,25	1,50	1,50	1,75	**1,59**
	1,50	2,00	1,25	1,75	1,25	1,50	1,25	1,75	**1,53**
	1,83	**1,83**	**1,25**	**1,83**	**1,17**	**1,50**	**1,42**	**1,67**	**1,56**
Subject 17	Wasser	Tier	Ultraschall	Fluss	Viehherde, bewegende Tiere	Baum	Berge	*(keine Angaben)*	
	1,00	1,25	1,50	1,00	1,50	1,50	1,50	0,00	**1,16**
	1,25	1,50	1,75	1,50	2,00	1,75	1,75	0,00	**1,44**
	1,25	1,50	1,50	1,25	1,50	1,75	1,75	0,00	**1,31**
	1,17	**1,42**	**1,58**	**1,25**	**1,67**	**1,67**	**1,67**	**0,00**	**1,30**
Subject 18	Amoeba moving upscreen	group of people on top, and somebody left the group	like inverted Y and then it was shifting but not much	this one was moving towards right like a train	now the black figure was moving to the left and the whole thing was moving to the right	background was moving	big object and water	background figure pulsating; looks like growing into river and black things are leaves and they get lumped together	
	1,50	2,00	2,00	1,25	1,00	1,00	1,25	1,75	**1,47**
	1,75	2,00	1,50	1,75	1,75	1,50	1,50	1,75	**1,69**
	2,00	2,00	1,75	1,25	1,00	1,00	1,25	1,75	**1,50**
	1,75	**2,00**	**1,75**	**1,42**	**1,25**	**1,17**	**1,33**	**1,75**	**1,55**
Subject 19	Giraffe	Wald	Zähne, Maul	Afrika, Quadrate	Sonnenuntergang	Gesicht	Kühe	Trompetenspieler Lunge	
	1,75	1,50	1,50	1,75	1,75	1,75	1,75	2,00	**1,72**
	2,00	1,75	2,00	2,00	1,75	2,00	2,00	2,00	**1,94**
	2,00	2,00	2,00	2,00	1,50	2,00	2,00	2,00	**1,94**
	1,92	**1,75**	**1,83**	**1,92**	**1,67**	**1,92**	**1,92**	**2,00**	**1,86**