

Learning under uncertainty in the young and older human brain:  
Common and distinct mechanisms of different attentional- and  
intentional systems

Inaugural-Dissertation

zur

Erlangung des Doktorgrades  
der Humanwissenschaftlichen Fakultät der Universität zu Köln nach  
der Promotionsordnung vom 10.05.2010  
vorgelegt von

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2019

**Diese Dissertation wurde von der Humanwissenschaftlichen Fakultät der  
Universität zu Köln im Januar 2020 angenommen.**

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„Each of us literally chooses, by his ways of attending to things, what sort of a universe he shall appear to himself to inhabit.“

– William James, 1980



## Acknowledgements

First, I want to express my gratitude to my supervisor Jun. Prof. Dr. Simone Vossel. Thank you for your everlasting support, exceptional expertise and enthusiasm for science. You were an influential scientific role model and I am thankful for the chance to work with, and learn from you. Not less important on my path accomplishing this thesis, were my colleagues Dr. Pascasie Dombert and Dr. Paola Mengotti. Thank you for the great collaboration and for sharing this journey. Great thanks go to Prof. Dr. Gereon Fink for your helpful comments and genuine interest in this work and all former colleagues at the Institute of Neuroscience and Medicine (INM-3) responsible for creating an inspiring working atmosphere. Particularly, Dr. Rouhollah Abdollahi for your insights, Dr. Shivakumar Viswanathan for your endless curiosity, Dr. Charlotte Nettekoven, Okka Risius, Alexander Geiger, Dr. Jonas Bühler and Michael Wiesing for emotional support.

Finally, words are not enough to describe the appreciation and profound gratitude I have for my family and friends. Anna Kraus, Dr. Christian Etzer, Gale Burton, Clara Otto, Johannes Koll, Steffen Schmalstieg and everyone I'm not mentioning but are an integral part of my life, I deeply cherish our friendship. My parents Claudia and Erich, thank you for letting me chose my paths and for supporting me in every way imaginable. Mali, Benny, and Myles you are my strongest backing and simply the best siblings I could have wished for. Always keep swimming, this is for you!



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## Abbreviations

ADHD	attention deficit hyperactivity disorder
AIP	anterior intraparietal area
BOLD	blood oxygen level dependent
%CV	percentage of cue validity
CBV	cerebral blood volume
CRF	cerebral blood flow
CRUNCH	Compensation-Related Utilization of Neural Circuits hypothesis
DCM	dynamic causal modeling
ERP	event-related potential
FEF	frontal eye fields
fMRI	functional magnetic resonance imaging
GLM	general linear model
HAROLD	hemispheric asymmetry reduction in older adults
HRF	hemodynamic response function
IPS	intraparietal sulcus
LIP	lateral intraparietal area
LPFC	lateral prefrontal cortex
MMN	mismatch negativity
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
MVPA	multivariate pattern analysis
PFC	prefrontal cortex
PPC	posterior parietal cortex
RDK	random dot kinematogram
RF	radiofrequency
RL	reinforcement learning
ROI	region of interest
RT	reaction time
rTMS	repetitive transcranial magnetic stimulation
SMG	supramarginal gyrus
SN	selection negativity
SNR	signal to noise ratio
SOA	stimulus onset asynchrony
SPM	statistical parametric mapping
SSVEP	Steady-state visual evoked potential

T	Tesla
TMS	transcranial magnetic stimulation
TPJ	temporo-parietal junction
VFC	ventral frontal cortex

## 0. Summary

The human brain is able to infer the probability of future events by combining information of past observations with current sensory input. Naturally, we are surrounded by more stimuli than we can pay attention to, so selection of relevant input is crucial. The present thesis aimed at identifying common and distinct neural correlates engaged in predictive processing in spatial attention (selection of attended locations) and motor intention (selection of prepared motor responses). Secondly, age-related influences on probabilistic inference in spatial-attention, feature-based attention (selection of attended color) and motor intention, and the impact of task difficulty were considered.

Orienting attention during goal-directed behavior can be supported by visual cues, whereas reorienting to unexpected events following misguiding information is linked to behavioral costs and updating of predictions. These processes can be investigated with a cueing paradigm in which differences in reaction time (RT) between valid and invalidly cued trials increase with higher cue validity (%CV) (Posner, 1980). Bayesian models can describe the experience-dependent learning effects of inferring %CV, following novel events (Vossel et al., 2014c; Vossel, Mathys, Stephan & Friston, 2015).

The principle aim of the first experiment was to identify and compare the neural correlates involved in inferring probabilities in the spatial attentional and motor intentional domain. Cues indicated either the possible location or prepared the motor response associated with the target. Instead of a fixed probability context, participants were exposed to a volatile environment, in which the validity of the cue information changed unpredictably over time. Combining functional magnetic resonance imaging (fMRI) data with behavioral estimates derived from a Bayesian learning model (Mathys, Daunizeau, Friston & Stephan, 2011) unveiled domain-specific predictability-dependent responses within the right temporoparietal junction (TPJ) for spatial attention and the left angular gyrus (ANG) and anterior cingulate (ACC) in the motor intention task. The blood oxygen level dependent (BOLD) amplitude particularly increased in accord with violations of cue predictability in high cue validity contexts (i.e. when invalid trials were least expected). Valid trials however, induced no (TPJ and ANG) or decreased modulation (ACC). A further aim was to examine possible commonalities in the neural signatures of predictability-dependent processing. Connectivity analysis uncovered common coupling of all three seed regions involved in predictability-dependent processing with the right anterior hippocampus.

## SUMMARY

Since cognitive functions undergo substantial changes in healthy ageing, a second behavioral study was conducted to test whether age differentially influences probabilistic inference in different attentional subsystems, and how task difficulty impacts on learning performance. Thus, following up on the first experiment, similar tasks and the same computational model was used to assess updating behavior in healthy aging. Older and younger adults performed two separate experiments with different difficulty levels. Each experiment included three versions of a cueing task, entailing predictive spatial- (i.e. location), feature- (i.e. color of target) and motor intention cues (i.e. prepare response). Results of the easier version demonstrated a preserved ability of older adults to generate predictions and profit from all cue types. Interestingly, increased task demand uncovered a reduced ability to use motor intention cues to update predictions in older compared to younger adults.

In conclusion, the results provide evidence for a segregated functional anatomy of probabilistic inference in spatial attention and motor intention. Nonetheless a common connectivity profile with the hippocampus also points at commonalities. Finally age seems to differentially impact the efficiency of learning behavior in the motor intention system, supporting the notion of independence of the attentional- and intentional subsystems.

## 1. General introduction

### 1.1 Attention in the human brain

As you are reading these lines, you are using it, that marvelous cognitive ability called 'attention'. It can be voluntarily directed to what you want to concentrate on, while you are surrounded by a potpourri of sensory stimuli and perform other cognitive processes: Although cars are passing outside your office, the fan is making a buzzing sound, a distant memory of an old friend pops up, you still manage to somehow 'tune out' the irrelevant and use it to highlight the task at hand.

In cognitive psychology, the term *selective attention* describes the process of selecting what is relevant, while irrelevant sensory information or thoughts are canceled out (Gazzaniga, Ivry & Mangun, 2009). It enables an organism to prioritize specific stimuli either by focusing on e.g. specific objects, stimulus features or regions of space (focused attention) or by dividing attentional resources to multiple stimuli (divided attention) (Corbetta, Miezin, Dobmeyer, Shulmann, & Petersen, 1991). Accordingly, perception is not only made up of physical input reaching our sensory channels, but is also carved by internal factors and processes. Two basal operations are necessary to select relevant information described as *top-down* (i.e. endogenous) and *bottom-up* (i.e. exogenous) attention. Whereas *top-down* processes are goal-driven e.g. attending a stoplight to prepare to accelerate the car, *bottom-up* allocation of attention is driven by sensory input e.g. a siren of a passing ambulance suddenly draws our attention (Shomstein, 2012). Relevant information is assumed to be continuously favored through interplay of bottom-up stimulus features and top-down attention modulation. This multi-stage selection process combining sensory information and attention is proposed to result in an integrated priority map for spatial events (Colby & Goldberg, 1999; Treue, 2003). Originally, a partition of the intraparietal sulcus (IPS) in monkeys, known as lateral intraparietal area (LIP) has been related to visual attention (Colby & Goldberg, 1999) and intention to perform saccades (Anderson & Buneo, 2002). With regard to these results, LIP has been considered a candidate area for a priority map. Therefore, LIP contains a map of the visual world and neural activity towards objects or locations is interpreted to correlate with behavioral relevance. In other words, orienting related activity is higher, with high priority of the given area and vice versa (Bisley & Goldberg, 2010).

Additionally, prior beliefs of relevant upcoming sensory information can improve detection and accelerate response. This entails internal processes that are able to build

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expectancies about future events. Spatial cues have been used to support selective attention in predicting probable target locations on a trial-to-trial basis. Moreover, cueing tasks can induce updating of the probability that a cue will be valid (Posner, 1980). In turn, when the cue carries false information (invalid cue), prior beliefs are violated and RTs increase. The difference in RTs between valid and invalid cues (invalid – valid) is termed validity effect (further information on the Posner task is provided in 1.1.2). Saliency of a stimulus in this case is determined by how much it deviates from previous expectation. Therefore, whenever a violation of expectation takes place, the brain integrates the new information to correct prior probabilities (Summerfield & de Lange, 2014). Trail-by-trial or experience-dependent learning follows Bayesian principles and can be explained by computational models, which will be more thoroughly discussed in 2.1.

Although most studies focus on spatial attention, our surroundings can contain stimuli that have a certain feature such as color or contain information, which trigger preparation of an adequate response (i.e. motor intention). The following example should give an impression of how expectation about an upcoming response is built, based on different visual attributes overlapping in real-life situations: Imagine a stoplight, seeing the red light one would prepare to push the brakes of the car. This simple example contains the red color of the light as the feature cue, the topmost position in the vertically arranged stoplight as spatial information, and knowledge about what action needs to be planned, as motor intention. Expectancies can be formed, not only for perceptual events, but also for motor responses (Rushworth, Ellison & Walsh, 2001a). Interestingly, activity related to motor intention was found exclusively in parietal areas of the left hemisphere, even though participants responded with their left hand. Spatial- and feature based attention was investigated in neuroimaging studies, which hint at a close relationship, but also distinct mechanisms (Egner et al., 2008; Greenberg, Esterman, Wilson, Serences & Yantis, 2010).

It is indisputable that visual attention contributes to distinguishing task-relevant from irrelevant information to support behavioral goals. Prior beliefs about stimulus characteristics aid to speed up perception and response. However, questions remain regarding the neural correlates of updating expectancies in the different attentional and intentional domains. The following sections will provide more detailed information about the various domains as well as discuss attentional functioning in relation to aging.

### 1.1.2 Spatial attention

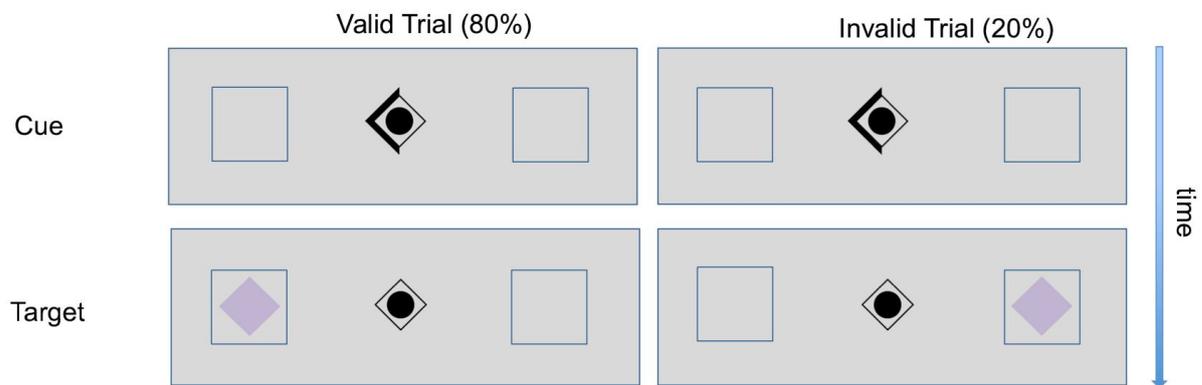
In order to detect what one is looking for, it is helpful to know *where* to look. Spatial attention has been extensively investigated over the past decades and seems to be innately coupled to saccade preparation (Doré-Mazars, Pouget & Beauvillain, 2004). Primate studies using single-cell recordings demonstrated that voluntarily directing attention changes the firing rate of cells in the visual cortex. This effect is even more pronounced when: the receptive fields lie within the focus of attention shift and the stimulus characteristics match the cell's preference (for a review see Treue, 2001). This further supports the notion that attention is not purely stimulus driven, but also modulated by top-down attentional influence. This section will outline current theories on spatial attention, how it can be quantified and which brain regions are involved.

In the domain of visuospatial processing, two metaphors have been used to describe attentional selection. The 'spotlight theory' theory claims that attention resembles a flashlight, which illuminates a clear focal point in which the efficiency of stimulus detection is enhanced and which can operate covertly independent of eye movements (Posner, Snyder & Davidson, 1980). Thus, even if participants are asked to fixate a given location, attentional selection can occur independently towards different locations. An expansion of this model suggests that orienting attention has the ability to increase and decrease the size of the focus, similar to a 'zoom lens' (Eriksen & James, 1986). A larger distribution of attentional focus thus results in slower processing, since attention is a limited resource. Finally, the 'premotor theory' closely links spatial attention to the activation of sensory motor circuits controlling action preparation. Attention shifts are viewed as a precondition of saccade preparation and enhance discrimination performance at the attended location (Deubel, 2008). This allocation of attentional resources is not exclusive for eye movements, but has also been demonstrated for manual responses (Jonikaitis & Deubel, 2011). In fact when motor plans are made for manual as well as eye movements, attention is allocated in parallel but separate processes. According to the theory, RT costs following falsely cued locations are ascribed to readjustment of premotor preparation (Bédard, Massiou, Pillon & Nandrino, 1993; Rizzolatti, Riggio, Dascola & Umiltá, 1987).

Taken together, orienting attention optimizes the sensitivity and encoding of information in a region of interest. Reorienting attention to a different location is necessary when the sensory event unexpectedly occurs outside the current focus of attention. Experiments applying cueing paradigms are especially suited to investigate orienting and

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reorienting processes. Posner (1980), in his seminal work, introduced a simple location-cueing paradigm (see figure 1).



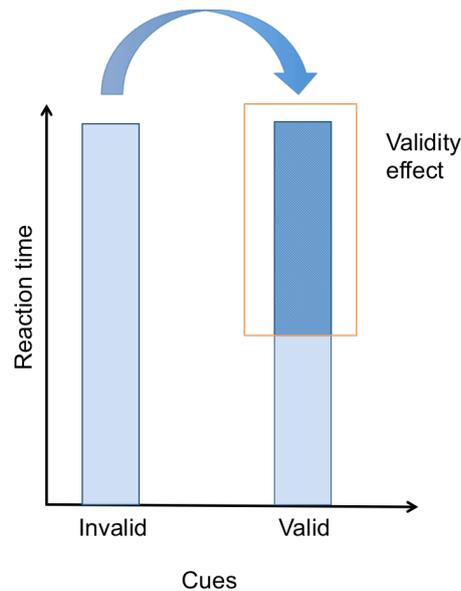
(adapted from Posner, 1980)

**Figure 1. Posner task: schematic representation of the trial organization for valid and invalid cue-target conditions. The cueing conditions contain an arrow pointing towards the position of the upcoming target in 80% of the trials (valid) or towards the opposite position of target occurrence in 20% (invalid).**

In the experiment, spatial cues either correctly guide attention to the actual target location (i.e. valid) or are misinforming (i.e. invalid), which leads to reorientation. Participants were instructed to respond to the targets as fast as possible upon detection by pressing a button. More valid cues (80% of trials) than invalid cues (20% of trials) were presented and results showed a benefit in reaction time (RT) towards targets appearing at the expected location, in relation to invalidly cued targets. This difference in RT is known as 'validity effect' (see figure 2). It is a result of additional behavioral operations following invalid cues namely, disengaging attention, shifting attention to the uncued space of target occurrence and re-engaging attention (Posner, 1980). Also, the magnitude of the validity effect varies depending on the validity context. Hence, highly valid contexts (i.e. a high proportion of valid as compared to invalid trials) result in larger validity effects (Vossel, Thiel & Fink, 2006).

Covert orienting of attention and the facilitating effect of informative cues in RT tasks is not unique to the visual modality. Validity effects have been reported for the auditory domain as well and are believed to be universal across sensory modalities (Bédard, Massioui, Pillon & Nandrino, 1993).

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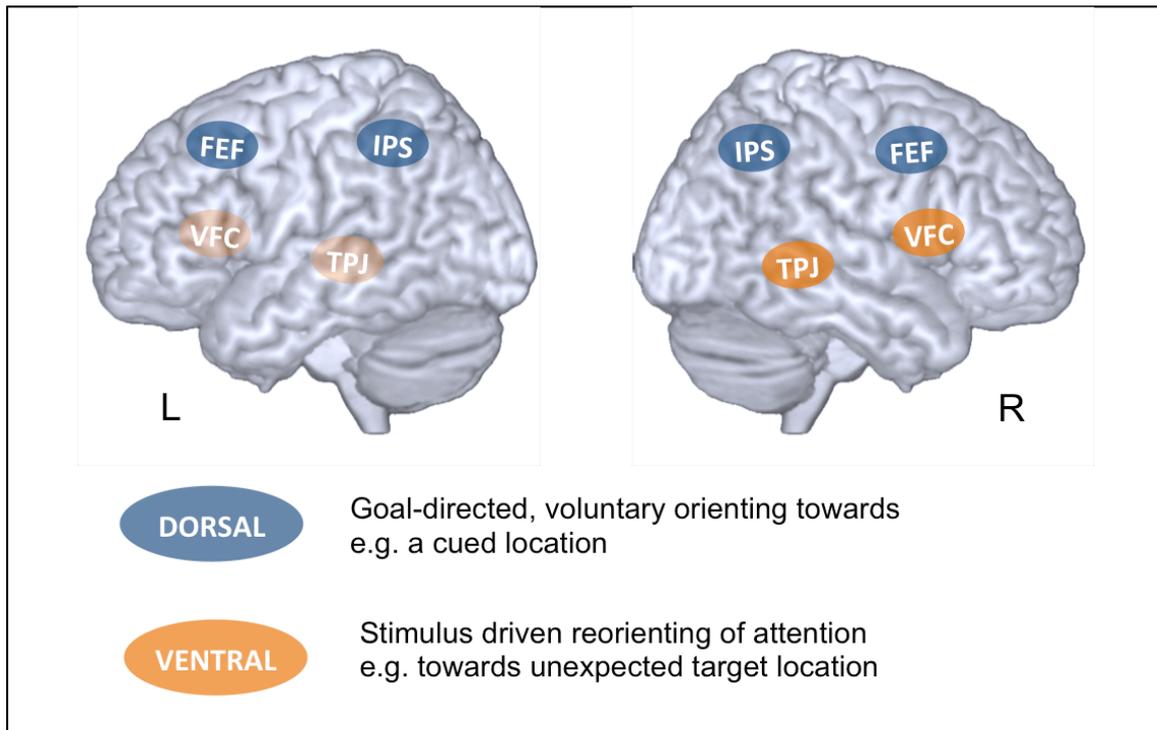
**Figure 2. Illustration of the validity effect (fictitious data). Attention needs to be reoriented after invalid cues, resulting in increased RTs. The difference between RTs following invalidly and validly cued targets is termed 'validity effect'.**

Today, flexible attentional control – orienting to an expected location and reorienting when necessary – is believed to be mediated by an interacting frontoparietal network, defined by Corbetta and Shulman (2002). Neuroimaging revealed a functional anatomical segregation of a 'dorsal' and 'ventral' attention network. The dorsal network engages in goal-directed behavior and is bilaterally distributed within the IPS and frontal eye fields (FEF). It is suggested to govern spatial priority maintenance for covert allocation of attention (e.g. to a cued location). Topographic maps of the visual space have been found within the IPS (Silver, Ress & Heeger, 2005) as well as the FEF (Kastner, et al., 2007). In comparison, the ventral system is more prominent in the right hemisphere and reacts upon unexpected but relevant events (e.g. target appearance at falsely cued location). Associated neural regions are the ventral frontal cortex (VFC) and the temporoparietal junction (TPJ) (see figure 3). It is believed to act as a 'circuit breaker' of continuous selection in the dorsal network.

Although TPJ activity has been reported in both hemispheres following salient changes in sensory environment, right TPJ exerts the strongest activation. This activation of rTPJ was found across multiple modalities in the detection of salient stimuli (Downar, Crawley, Mikulis & Davis, 2000). Extending the results, a neuroimaging study compared BOLD signals following endogenous versus exogenous shifts of spatial attention. rTPJ was only significantly modulated during task-relevant reorienting (i.e. targets at unattended locations), but not after salient (i.e. red color singleton) but irrelevant stimuli

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(Kincade, Astafiev, Shulman & Corbetta, 2005). Taken together, within the context of a task, behavioral relevance seems crucial for TPJ modulation.



(adapted from Corbetta & Shulman, 2002; Vossel, Geng & Fink, 2014b)

**Figure 3. Illustration of functional anatomy of selective attention as proposed by Corbetta and Shulman (2002).**

Valuable information about the neuroanatomy of spatial behavior can also be drawn from lesion models. For instance, patients suffering from hemispatial neglect show severe deficits in attending and responding to stimuli in the contralesional space. This syndrome mostly occurs as a result of a vascular stroke and symptoms are generally more persistent and severe after right hemisphere damage (Halligan, Fink, Marshall & Vallar, 2003; for a review see Danckert & Ferber, 2007). Patients show a bias towards exploring the ipsilesional space, while being unaware of contralesional events. The neglected portions can range from personal- to extrapersonal space. In severe cases patients bump into objects situated to their left or even "forget" to shave one half of their face. Recent evidence correlates neglect with a dysfunction of frontoparietal networks including the PPC, lateralprefrontal cortex (LPFC) and TPJ (Doricchi, de Schotten, Tomaiuolo & Bartolomeo, 2008; for a review see Bartolomeo, de Schotten & Chica, 2012). A traditional explanation for the observed deficits comes from Posner and colleagues (1984), who find comparable RTs for validly cued targets towards either side of space (contra- and ipsilesional) in patients with right parietal damage. On the contrary, RTs were prolonged following invalid cues, when the target was to be found in the contralesional

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side. The deficit was ascribed to difficulties in disengaging attention from the ipsilesional side (i.e. 'disengagement deficit'), as a result of lesions to TPJ (Friedrich, Egly, Rafal & Beck, 1998). Even after recovery, the group with lesions to TPJ showed a disproportionate difficulty to detect targets following cues to the ipsilesional space, as compared to patients with parietal lobe damage (Friedrich et al., 1998). Translated into the attention model (see Figure 3), communication between dorsal and ventral pathways seems disrupted.

Novel means of explaining the neglect syndrome in right brain damaged individuals see possible deficits in detecting statistical regularities in probabilistic environments (Danckert & Ferber, 2007; Shaqiri & Anderson, 2012). Others accordingly, argue for a close communication of rTPJ with top-down signals of the dorsal network in monitoring and responding to mismatches between expectation and sensory information (Kincade, Astafiev, Shulman & Corbetta, 2005). After all, in the healthy human brain, having advance information (e.g. predictive cues) leads to an estimation of reliability of top-down information, which in turn modulates the behavioral- as well as neural activity. With higher cue validity, increased RTs following incorrect cues as well as higher reorienting-related activity in rTPJ and right frontal cortex are found (see 1.1. and Vossel, Thiel & Fink, 2006).

Together, the findings might suggest a more superordinate computational function of TPJ. This notion is supported by electrophysiological and other methods with high temporal resolution, showing that signals in the TPJ occur later than signals in FEF (for a review see Geng & Vossel, 2013). Only recently, Geng and Vossel (2013) challenge previous believes and incorporate novel data by introducing a 'contextual updating hypothesis'. TPJ is regarded to update an internal model of the external world, with integration of new sensory information, in order to construct appropriate expectations and reactions (Vossel & Geng, 2013). It remains to be tapped into defining the role of TPJ in computational operations in the brain and whether they are specific to the spatial domain.

#### 1.1.4 Feature-based attention

Not only is it helpful to know *where* one needs to orient attention, but also *what* to look for. Imagine meeting a friend at a restaurant, she tells you on the phone, that she is wearing a red jacket. Having advance information about the stimulus feature (i.e. friend in a red jacket) will help orient attention to red items and speed-up detection. Nonetheless, goal-directed behavior can be disturbed by irrelevant distractors that share the same feature, such as a red apron on a waitress (Folk, Remington & Johnston, 1992). Where these feature-selective processes are represented in the brain will be introduced in the following.

Brain regions engaged in feature-selective attention have been shown to correspond closely with those found for the spatial attention domain. Neuroimaging studies provide evidence that expectations about locations, but also features activate the dorsal network (see 1.1), biasing top-down attentional control (Hopfinger, Buonocore & Mangun, 2000; Egeter et al., 2008). Increments in activity following increasing cue information were observed in the bilateral dorsal orienting nodes including IPS and FEF, with no difference in modulation between spatial and feature cues. Upon closer analysis of the representation of cue information in these common neural hubs, no interaction between spatial and feature information was found. Authors suggest differential priming of neurons in IPS according to the nature of cue information, possibly resulting in a saliency map. Thus, expectations following spatial cues would enhance responsiveness of IPS neurons whose receptive fields correspond with expected target location. However, feature cues would globally enhance neurons responsive to the expected target feature (Egeter et al., 2008). This is in line with findings of extrastriate neuron populations, explicitly coding for features of interest across the entire visual field in both human and primates (McAdams & Maunsell, 2000; Saenz, Buracas & Boynton, 2002). In humans purely feature-selective experiments demonstrated spatially global modulations in visual cortical neurons. In separate experiments, participants had to attend to motion or to color. Whenever the distractors displayed the same feature (e.g. same colored dots in ignored visual field), fMRI data showed a stronger response across the visual cortex (Saenz et al., 2002).

Real-life situations often provide us with more than one attribute of the to-be-detected target: Consider the initial example with a friend waiting in her red jacket at a restaurant and assuming she also told us she is sitting at a table to the right-hand side. Having spatial (i.e. right side) and feature (i.e. red jacket) information, doubles the response gain in extrastriate visual neurons in macaque monkeys. More precisely, this additive effect was only found in neurons that are selective of the stimulus feature and if

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the locus of attention lies within their receptive field, as compared to neurons only having one piece of information (Treue & Martinez-Trujillo, 1999).

Taken together, supplementary information, whether spatial or carrying the same feature information lead to a complimentary gain in modulation within the visual cortex. More importantly, feature-based attention leads to global modulation throughout the visual field, which is independent from spatial attention as demonstrated by event-related potential (ERP) measures (Zhang & Luck, 2009). Further support for distinct mechanisms come from a studies using transcranial magnetic stimulation (TMS) (Schenkluhn, Ruff, Heinen & Chambers, 2008) or lesion models (Ptak, Valenza & Schnider, 2002; Malhotra, Coulthard, Husain, 2009). Even when spatial selective attention was disrupted by TMS stimulation, feature processing remained untouched (Schenkluhn, et al., 2008). Unlike effects seen in spatial attention, feature-based attention is not completely affected by right brain damage such as neglect. Results indicate a preserved ability to identify features (color and/or shape) and profit from cues, as demonstrated by significant validity effects for contralesional stimuli (Ptak, et al., 2002). Also, vigilance decrements were only reported for sustained attention towards stimulus locations, but not towards features (patterns or letters) (Malhotra et al., 2009).

Finally, work on discriminating reorienting-related anatomical areas for feature-based attention is still in its infancy. It seems that a left lateralized network containing precuneus, IPS and precentral gyrus is in charge during shifts between features in task-contexts (Shulman, d'Avossa, Tansy & Corbetta, 2002; Weidner, Krummenacher, Reimann, Müller & Fink, 2009). A recent cueing study by our group was able to disentangle the neural mechanisms underlying feature- from spatial-specific reorienting. The neuroimaging data provided evidence for reorienting related activity (induced by an invalid cue) in the left IPS for feature attention (Dombert, Kuhns, Mengotti, Fink & Vossel, 2016). Current literature certainly points at common, but also distinct neural areas for the different attentional systems. Further comparative data with other domains and in different age contexts is needed to pinpoint distinct mechanisms underlying feature-selective attention.

### 1.1.5 Motor intention

Split seconds can decide whether the goalkeeper reacts correctly and can prevent a goal. Reacting adequately is not only defined by orienting to features and locations, but is closely linked to the selection of a motor response. Having an internal plan of an imminent motor response has been termed *motor intention* and seems to be independent of whether the intention is executed or not (see, Thoenissen, Zilles & Toni, 2002; Desmurget & Sirigu, 2009). Here, intent is defined as higher-order planning and selection of an upcoming movement (Connolly, Kentridge & Cavina-Pratesi, 2016; Hesse, Thiel, Stephan, & Fink, 2006). Interestingly, similar to the processes mentioned for spatial- and feature-based attention, expectancies about an upcoming motor response (e.g. by a cue indicating the most likely responding hand for an upcoming target) accelerate reaction time (Rushworth, et al., 2001a).

Which brain areas are involved in motor intention and readjustment of prepared responses, when necessary? Currently, different conclusions are drawn about the underlying neural mechanisms. A map for motor intention in non-human primates has been proposed to reside in the left posterior parietal cortex (PPC) (Andersen & Buneo, 2002). In the human brain some ascribe the selection of relevant intentional cues to the PPC and movement preparation to frontal premotor areas (Toni, Thoenissen & Zilles, 2001), while others report a closer association of PPC with spatial attention as compared to motor intention (Connolly et al., 2016) or find common neural preparatory signatures for attending, looking and pointing across FEF and IPS (Astafiev et al., 2003). This has led to propositions of a supramodal involvement of PPC in attention and priority maintenance (Astafiev et al., 2003; Bisley & Goldberg, 2010).

Then again, an exclusive role has been ascribed to motor preparatory signals in the PPC of the left hemisphere. Especially prominent selective activation has been reported in left PPC, frontal cortex (Astafiev et al., 2003), supramarginal gyrus (SMG), and anterior intraparietal sulcus (AIP) (Rushworth, Ellison & Walsh, 2001a; Rushworth, Krams, & Passingham, 2001b), irrespective of which hand is prepared for response. This claim is further confirmed by a fMRI study, in which neural involvement following motor, alerting and spatial preparatory cues was compared (Hesse et al., 2006). Their findings argue for a modality specific role of left SMG in motor intention. It should be noted, that this effect was solely cue related and independent of influences from responding hand or target presentation, which was kept identical across conditions.

## INTRODUCTION

Redirecting initially planned covert motor intentions has also been linked to the left SMG. Repetitive transcranial magnetic stimulation (rTMS) stimulation of left SMG led to a disruption of reorienting-related performance in a motor cueing task (Rushworth et al., 2001a). More precisely, changing the plan of the initial movement due to invalid pre-cues was impaired after TMS of anterior parietal cortex, but not after PPC stimulation (Rounis, Yarrow & Rothwell, 2007; Rushworth et al, 2001a). This disruption of motor intention can also be the result of lesions to the left parietal cortex (Rushworth, Nixon, Renowden, Wade & Passingham, 1997). Stroke patients with left hemisphere lesions had disproportionate difficulties redirecting their original motor plan, following invalid pre-cues, compared to right stroke patients and healthy controls. Overall it can be concluded that left-lateralized parietal areas play a predominant role in motor intention and selection (for a review see, Rushworth, Johansen-Berg, Göbel & Devlin, 2003).

Although many aspects of perceptual attention and motor intention seem to converge within the dorsal system, the evaluated literature also suggests distinct mechanisms. The comparative cueing studies reveal a lateralization of control in left PPC for motor intention and right PPC for perceptual attention. Also, they provide evidence for the facilitation of behavioral performance by cues indicating the required response. So far, authors focused on defining neural areas responsible for motor intention formation and adaption of selected responses. It remains to be specified how trial-wise predictions about an imminent motor act are encoded in the human brain. In particular, it is unclear whether these computational processes are domain-specific or whether they share common mechanisms.

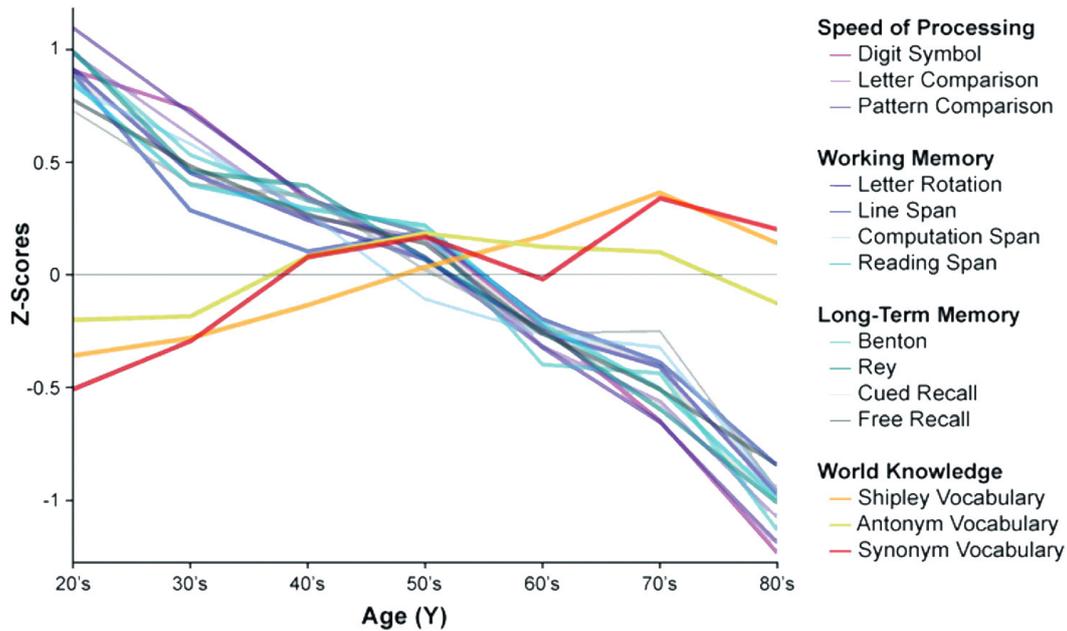
### 1.1.6 Healthy ageing and attention

As the healthy brain ages, some of its' cognitive functions decline, while others are relatively spared. The purpose of the following section is to give a general overview of cognitive and brain ageing processes, as well as their possible explanations. Consecutively, it will be discussed how attention and learning may be affected by aging. Although it is assumed that age-related cognitive decline begins in early adulthood after the brains' maturation, the magnitude seems to accelerate at older ages (Salthouse, 2009). First significant changes in cognitive abilities can be detected as early as age 60. Most abilities are significantly affected by the time an individual reaches its mid-70s and severe decrements are observed at age 80 (Schaie, 2005). Especially, executive control processes such as working memory (Cepeda, Kramer & Gonzalez de Sather, 2001), attention (Cabeza et al., 2004) and task switching are age-sensitive (for a review see Craik & Salthouse, 2011). Longitudinal as well as cross-sectional data also unveil substantial changes in episodic memory, demonstrated by significant difficulties in learning and retrieving actions and lists of words (Rönnlund, Nyberg, Bäckman & Nilsson, 2005). In contrast, emotional regulation (Carstensen et al., 2011), accumulated knowledge about the world (semantic memory) and vocabulary (Laver, 2009) seem unaffected and performance can even increase at least until the age of 60 (Craik & Salthouse, 2011; see figure 4).

Neuroscience today aims at providing answers for cognitive aging by comparing functional and structural brain differences between young and older adults or conduct longitudinal studies with the same cohort. Interpretation of functional results is somewhat delicate since some studies report task-related increases (for a review see: Rajah & D'Esposito, 2005), while others find decreases in brain activity in older adults (Grady, Springer, Hongwanishkul, McIntosh & Winocur, 2006; Rypma & D'Esposito, 2000). Less brain activity is commonly associated with cognitive deficits and lower level of functioning (Rypma & D'Esposito, 2000).

On the other hand, several mechanisms have been proposed to explain the over-recruitment of brain activity. Therefore, it might reflect a compensatory mechanism, a reduction in differentiation of brain response, or inefficiency in the use of neural resources (Rajah & D'Esposito, 2005).

## INTRODUCTION



(adapted from Park & Bischof, 2013)

**Figure 4. Cross-sectional aging data on behavioural performance of tests on: speed of processing, working memory, long-term memory, and world knowledge. Cognitive functions summarized under fluid intelligence decline with age, while world knowledge even shows slight increases with age. (Reprinted from *Dialogues in clinical neuroscience*, 15(1), Park, D.C. & Bischof, G.N., *The aging mind: neuroplasticity in response to cognitive training*, p. 111, Copyright 2013, LLS).**

In the light of the compensatory hypothesis, the aging brain exhibits stronger activity to possibly counteract loss of function and can even aid performance. This phenomenon can be observed when old and young adults display similar task performance, whilst older adults show more brain-activity (Cabeza, Anderson, Locantore & McIntosh, 2002) or when a positive correlation between brain activity and performance is found exclusively in the older group (Davis, Dennis, Daselaar, Fleck & Cabeza, 2007). For instance, an increase in bilateral prefrontal cortex (PFC) activity in older adults is reported in working- and episodic memory tasks (see, Rajah & D'Esposito, 2005), which is believed to account for reduced occipitotemporal activity (Davis, Dennis, Daselaar, Fleck & Cabeza, 2007). Further support for a compensatory account comes from an fMRI study investigating inhibition of prepotent responses in go/nogo tasks (Vallesi, McIntosh & Stuss, 2011). Older adults not only show a stronger recruitment of the dorsal attention network (see 1.1.2), but the result is behaviorally correlated with fewer errors in the old group compared to younger adults (Vallesi, McIntosh & Stuss, 2011). Conversely to the lateralized use of prefrontal cortical regions in young adults, older adults appear to additionally recruit contralateral PFC to retain performance abilities, which has been

## INTRODUCTION

subsumed under the HAROLD (hemispheric asymmetry reduction in older adults) model. Reduction in hemispheric asymmetry might delineate functional dedifferentiation processes and has been demonstrated for perceptual processing, inhibitory control and various memory domains (Cabeza 2002). Yet, enhanced neural recruitment is not always beneficial, but can reflect inefficient use of neural resources and alterations in functional connectivity in prefrontal regions (Colcombe, Kramer, Erickson & Scalf, 2005; Grady et al., 2010).

As mentioned earlier, compensation through over-activation is not always possible and that older adults can also show similar to less activation especially when task load increases. According to the 'Compensation-Related Utilization of Neural Circuits hypothesis' (CRUNCH), study results reporting compensatory activation or a lack thereof are not mutually exclusive (Reuter-Lorenz & Cappell, 2008). Thus, the neural strategies to overcome processing inefficiencies in older age, are to activate involved brain sites sooner or more than younger adults. This is only possible at low task demands and a ceiling effect occurs when cognitive load is increased, resulting in a decline in task performance (Reuter-Lorenz & Cappell, 2008).

How do aging processes affect selective attention? To recapture (1.1) selective attention describes the process of focusing on the relevant, while cancelling-out irrelevant information. In ageing research the 'inhibitory deficit theory' is a longstanding assumption that older adults face increasing difficulty inhibiting irrelevant and distracting information (Hasher & Zacks, 1988; Hasher, Lustig & Zacks, 2007). Diverse experimental set-ups can be utilized to tap into age-related changes in attention. Effects can thus be provoked by the choice of different stimulus onset asynchrony (SOA) (Greenwood, Parasuram & Haxby, 1993), cue characteristics (e.g. large arrow versus small arrow cue) (Folk & Hoyer, 1992) or simple versus choice RT tasks. Evidence for changes in selective visual attention and sensory processing is provided by measures of e.g. overall slower responses in spatial cueing tasks (Hong, Sun, Bengson, Mangun & Tong, 2015; Curran, Hills, Patterson & Strauss, 2001), diminished attention allocation and task-related activity over visual cortex (Gazzaley et al., 2008), or reduced brain oscillatory activity correlated to anticipatory attention (Deiber, Ibanez, Missonier, Rodriguez & Giannakopoulos, 2013). Additionally, task complexity is a crucial determinant of performance in age. With increasing difficulty, older adults demonstrate a decline in inhibiting unwanted responses, are less accurate, and have deficits using cue information (for a review see, Zanto & Gazzaley, 2014). In the following sections ageing effects for the domains of spatial attention, feature attention and motor intention will be discussed. Also, trial-wise learning in age will be highlighted.

## INTRODUCTION

While there is accumulating evidence for retained top-down control of visuospatial attention, early sensory processing (bottom-up) is suggested to decline (Curran et al., 2001). These claims are supported by EEG signatures following spatial cueing, which yielded comparable cue validity effect related ERP amplitudes between young and older adults, but delayed early ERP components related to target stimuli (i.e. P1, N1, Nd1) in the older age group (Curran et al., 2001). Similarly, fMRI results indicate a stronger engagement of the frontoparietal network (top-down) in a cued spatial task, suggesting a compensatory mechanism to counteract decline in bottom-up functioning to preserve performance (Talsma, Kok & Ridderinkhof, 2006). Additionally, age-related increases in behavioral response (RT) towards left as opposed to right targets may be related to the assumption that age more strongly affects right-hemispheric cognitive functions and processing in the left visual field (Lux, Marshall, Thimm & Fink, 2008; Nagamatsu, Carolan, Liu-Ambrose & Handy, 2011). Taken together, spatial attentional control seems largely intact, while over-recruitment of frontal areas aid at compensating deteriorating bottom-up processing and attention towards left visual field.

Feature selective attention supports the search for certain characteristics of a stimulus such as color or size. The current literature hints at a decline in feature selectivity in older adults (Quigley, Andersen, Schulze, Grunwald & Müller, 2010; Zanto, Toy & Gazzaley, 2010). An EEG study used a delayed-recognition task to assess working memory performance for color and motion features in young and old adults. Even when accounting for age-related slowing in perceptual processing and response, elderly were still slower to respond. ERP measures of early perceptual processing (bottom-up) remained comparable (P1), but in the older group a delay during working memory encoding for measures of attention allocation (selection negativity (SN) and alpha band activity) for both feature types was reported. Apart from these generalized feature-based effects, feature-specific delay in N1 latency for color encoding was apparent (Zanto, Toy & Gazzaley, 2010). Further electrophysiological support for decreased feature-attention selection in age comes from a study in which two random dot kinematograms (RDKs) of different colors were superimposed. Young and old participants were instructed by a color cue to attend to the motion of the according RDK. Steady-state visual evoked potential (SSVEP) before and after cue onset were compared. While young adults clearly responded to attended cues after presentation, as measured by enhancement of SSVEP post-cue, older adults showed no distinction between attended and ignored stimuli. These results were later replicated in a task in which motion of horizontal and vertical bars needed to be attended (Quigley & Müller, 2014). Based on these findings it seems that older adults lack modulation of feature selective (top-down) attention and exhibit

## INTRODUCTION

processing speed delays, which can not be attributed to changes in bottom-up processing (Quigley, Andersen, Schulze, Grunwald & Müller, 2010; Quigley & Müller, 2014).

On the contrary, Madden and colleagues (2004) conducted a visual search task supported by color cues in which top-down attentional guidance was age-invariant. More specific, in a condition guided by highly informative color singletons, significant decreases in RT were found in both age groups (Madden, Whiting, Cabeza & Huettel, 2004). This difference in results is possibly due to the informative value of the cue. Since the cue color did not facilitate feature detection, but prepared the upcoming location of the target, thus incorporating spatial information. Also, differently from the studies using RDKs, this study did not contain motion perception, which might be a critical variable in the observed decline.

Processing motor information (i.e. cues indicating the responding hand) and preparing an upcoming response, seems to substantially change with age (Sterr & Dean, 2008), whereas simple motor actions are not affected (Skoura, Papaxanthis, Vinter, & Pozzo, 2005). The formation of simple motor intentions, regardless whether executed or simulated (motor imagery), remained comparable between age groups. Interestingly, when introducing spatiotemporal constraints, internally simulated motor actions were more strongly altered by age as opposed to executed movements. The authors ascribe the observed behavioral dissimilarities to task complexity and the lacking peripheral sensory feedback (Skoura, Papaxanthis, Vinter, & Pozzo, 2005). In a more challenging experiment using a motor priming paradigm, Sterr and Dean (2008) investigated performance and ERP-data to unveil changes in the anticipation and preparation of motor information between young and old adults. Participants could rely on preparatory cue (arrows pointing left or right) corresponding with left or right button press 80% of the time. Contrary to younger participants, older adults lacked validity effects and showed diminished activation of higher-order motor areas during anticipation, as indicated by reduced foreperiod amplitudes. Preparation of motor response was also changed, since lateralized activity was absent. This suggests that older adults do not profit from motor preparatory signals (Sterr & Dean, 2008). A possible explanation to understand motor-related changes might be brain atrophy in the dorsolateral prefrontal cortex (Lemaître et al., 2005) associated with motor preparation and cognitive control (Simon et al., 2002).

Finally, this brings us to the question, whether older adults show performance decrements in learning? Naturally we are confronted with a dynamically changing environment, which makes adapting our expectation a crucial necessity. In this case, learning describes the processes of integrating novel observations and adapting or

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maintaining behavior depending on the respective goal. Reward-based paradigms give insights into describing the ability to learn future outcomes (for a review see Eppinger, Haemmerer & Li, 2011). A study combining a three-stage Markov decision task with fMRI, suggests that older adults have difficulties predicting future reward and functionally exhibit decreased PFC activity compared to younger adults (Eppinger, Heekeren & Li, 2015). Also, an age comparative study using a predictive inference task revealed a reduction in using uncertainty to learn novel outcome contingencies in older participants (Nassar et al., 2016). A possible source for changes in learning is ascribed to dopaminergic neurons in the ventral striatum, which seem less sensitive towards prediction error. Diffusion tensor imaging during a probabilistic reward task, revealed that frontostriatal white matter integrity was an important determinant of performance in age. In other words, age-related connectivity deficits between frontal and striatal regions, lead to changes in prediction error signaling (Samanez-Larkin, Levens, Perry, Dougherty & Knutson, 2012). Thus, to study developmental alterations in learning under uncertainty, probabilistic choice tasks in combination with computational models are particularly useful. This approach can offer insights into mechanisms (e.g. learning rate) that stay hidden when relying on descriptive statistics alone. More detailed description and application of computational models will be provided in 2.1.

To conclude, mixed evidence is provided regarding how attention and learning processes are affected by age and which variables are responsible for the observed differences. Despite some support for age-related decline in attention, it does not seem absolute. Spatial attention is suggested to have retained top-down control, but needs to overcome the deterioration of bottom-up processing through over-recruitment of frontal areas (Talsma, Kok & Ridderinkhof, 2006). A mixed picture is provided for feature attention. While some report age-invariant bottom-up functioning, but declined top-down selection especially for color encoding (Quigley & Müller, 2014), others find retained bottom-up functioning (Madden, Whiting, Cabeza & Huettel, 2004). Motor intention seems to be altered when older adults face more complex or time restrained tasks. Under these conditions, they fail to use motor preparatory information (Sterr & Dean, 2008). The variance in effects reported for the different attentional systems suggests the importance of distinguishing between these domains, while carefully considering experimental set-up and information provided by the cue. No prior work has been done to examine age-related differences in generating predictions, while considering the impact of task complexity and differentiating between spatial- and feature-based attention and motor intention.

## 2. Experimental techniques

### 2.1 Mathematical models for learning under uncertainty

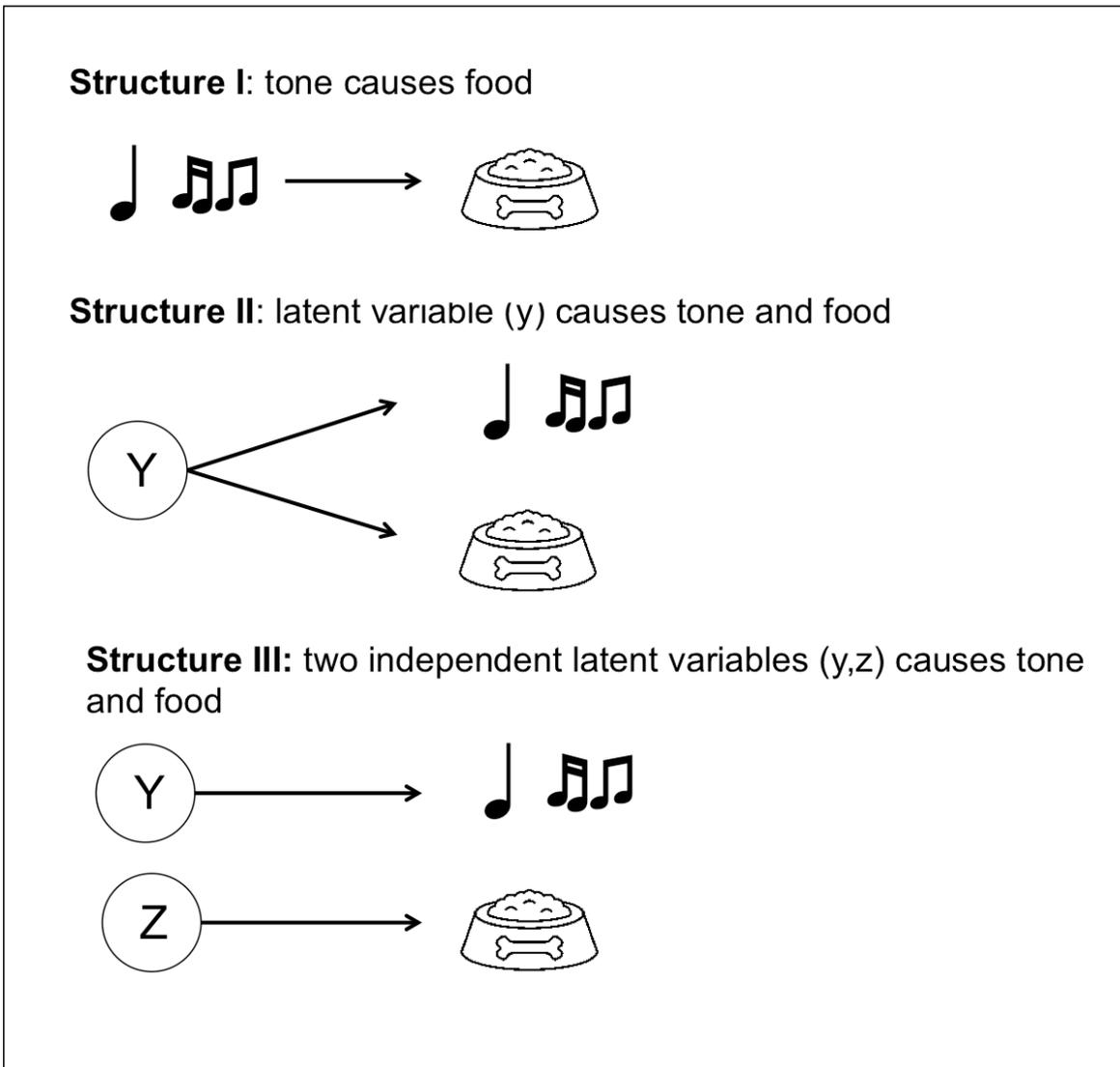
Navigating through an uncertain world and reacting upon events, the human brain not only relies on the current sensory information, but also incorporates previous observations and internal states. Building expectancies about incoming sensory input is believed to reflect the brain's faculty to resemble a prediction machine. Computational neuroscience ascribes the adaptive success of the brain to predictive coding, which includes minimization of prediction error as core faculty (Clark, 2013). *Prediction error* describes the difference between an expected and actual signal. Predictions are derived from generative models, carrying information about environmental states, calculated from prior observations and new events and are proposed to emerge in a Bayes-optimal scheme (Friston & Kiebel, 2009). The next sections will focus on the advantages of using computational learning models for RT analyses, as well as describe their key elements.

In this work, attentional processes are deduced from RTs. Analyzing RT data in general is a delicate endeavor, since the distribution is typically skewed to the right and can contain spurious RTs. These are caused by e.g. inattentiveness or guesses, and can lead to reduced statistical power and even misinterpretation (Whelan, 2008; Wilcox, 1998). Vossel et al. (2006) elegantly demonstrates how ex-Gaussian distribution can be applied to individual RT data to counteract the issue of outlying variables. Nonetheless, the use of central tendency measures can carry valuable information to explain differences in task conditions. Posner (1980) for instance, illustrated the accelerating effect on RTs on valid trials, compared to unexpectedly cued locations (compare section 1.1.1 above).

Using computational learning models expands the possibility over and above what traditional RT analyses can offer and aim to uncover underlying mechanisms necessary for predicting future outcomes. More precisely, instead of seeing RTs as *random variables*, they can be treated as the product of perceptual inference (den Ouden, Daunizeau, Roiser, Friston & Stephan, 2010). Single-trial RTs can be used to track the inference process and quantify the subject's trial-wise beliefs about environmental statistics.

## EXPERIMENTAL TECHNIQUES

Two prominent frameworks for trial-by-trial learning are reinforcement learning (RL) and Bayesian learning models. The Rescorla-Wagner model is a popular model for RL due to its conceptual simplicity and computational efficiency (Rescorla & Wagner, 1972). The estimated probability after the observation of a particular trial is determined by a fixed learning rate and a *prediction error*. *Prediction error* is the difference between actual- and predicted signals (Gershman & Niv, 2010). Unfortunately, this model follows a heuristic approach and performs poorly when applied to real-world situations, since it has no knowledge about the environment. Consequently, having to infer the multitude of naturally occurring unknown situations (states) and actions from observations, slows down learning. Also, it does not follow assumptions of probability theory. Gershman and Niv (2010) suggest applying Bayesian theory to overcome the limitations and be able to describe the influence of latent variables. Here *structure* stands for possible causal relationships between latent and observed variables. Classical conditioning experiments demonstrate how unobserved information can be learned. For example, a dog is exposed to food and tones (see Figure 5). Instead of associating one to the other it is proposed, that animals try to learn the hidden causes. In this case, the hidden cause is the manipulation of the experimenter who changes the relationship between perceived stimuli by the animal (e.g., acquisition, extinction). After several trial runs, expectations are built about the occurrence of tones and/or food. In spatial cueing tasks the latent cause would translate into the manipulated change in probability level of the cue being valid. Thus, participants build an internal model of how much they can trust the cue to make predictions.



(adapted from Gershman & Niv, 2010)

**Figure 5. Depiction of three possible causal relationships (structures) between observed and latent variables in a classical conditioning experiment. Latent variables are circled, while observed variables are not. Probabilistic dependencies are shown by arrows. For example, in Structure II, the latent variable defines the value of the model parameter (e.g. acquisition: tone predicts food vs. extinction: tone does not predict food).**

Hence, before observing any novel data, *prior distribution*  $P(S)$  over possible structures encodes the agents belief about the hidden structure  $S$ . This mirrors your belief about how likely each structure accurately describes the environment *a priori*. In terms of Bayes' rule belief-updating, after observing new events  $D$  is described as follows:

$$P(S|D) = \frac{P(D|S)P(S)}{P(D)}$$

$P(S|D)$  is the *posterior distribution* over structures given the observed data and represents an estimate of the probability that each structure describes the environment *a posteriori*. *Likelihood* is denoted by  $P(D|S)$  and explains the likeliness that sensory data  $D$  was generated by structure  $S$  (for example see, Gershman & Niv, 2010). Bayesian learning models offer a more naturalistic account of how beliefs are updated, since they overcome the issue of a fixed learning rate. In comparison to model-free RL models, the Bayesian learner considers environmental volatility and uncertainty to estimate future outcomes. Here, learning rate is driven by detected volatility of reward-likelihood that leads to uncertainty and drives adaption of the initial estimate. For instance, the initial belief is violated if suddenly an invalid trial occurs after observing 50 valid trials. Thus, individual adaptive behavior entails the constant update of probabilities (e.g. that the next target will be validly cued). These are built from prior beliefs and new observations to decrease prediction error (Knill & Pouget, 2004; Friston, 2010). The update period can be seen in higher BOLD responses of the ACC whenever the subjects' estimate of the volatility does not match the observed trial outcome (Behrens, Woolrich, Walton & Rushworth, 2007).

A Bayesian learning model, considerate of a generic hierarchical architecture, was proposed by Mathys and colleagues (2011). What is striking, is that it allows to quantify inter-individual learning under uncertainty, whether perceptual or caused by a volatile environment. It encompasses a generative model with hidden states arranged in a hierarchical manner which all, but the first level, evolve in time as Gaussian random walks. The hierarchical depth of the generative model can be arbitrarily expanded. The step size of these walks (i.e. volatility) is determined by the next higher level. Trial-by-trial update equations of posterior expectations of the hidden states can be derived by an approximate Bayesian approach. These equations combine the best of both worlds, since they are inspired by RL models and minimize free energy (for a review on free-energy see, Friston, 2010). Additionally, parameters are introduced which can have different values for each agent and control the coupling across the different levels. This differentiation between dynamic hidden states, varying in time, and the fixed parameters, able to characterize subject-specific learning patterns, are the pivotal components (Mathys et al., 2011).

The scope of the model's application is manifold as has been demonstrated in studies of visuospatial attention (Vossel et al., 2014c), under effects of pharmacological manipulation (Vossel et al., 2014a), in combination with fMRI and connectivity analysis (Vossel, Mathys, Stephan & Friston, 2015). Recently, in the field of computational neuropsychology it aids to characterize disease mechanisms in a wide range of pathologies including visual neglect (Parr, Rees & Friston, 2018) or Autism Spectrum

Disorder (Haker, Schneebeli & Stephan, 2016). To investigate how computational states translate into observable behavior in volatile environments, location-cueing paradigms with different levels of %CV (cue validity) can be used (see 1.1.1). Model comparison in the first study, clearly favored a Bayesian model with three hierarchical states, combined with a precision-based response model to explain trial-by-trial estimates of belief (subject's probabilistic representation of sensory input) and individual learning (Vossel et al., 2014). The winner model was subsequently used and the stable learning parameters lend to reveal within-subject enhancement of updating expectancies in visuospatial attention, following a pharmacological modulation using galantamine (Vossel et al., 2014b). Finally, neural correlates and dynamics of probabilistic inference processes in the deployment of spatial attention were studied with fMRI. Results revealed increased neural activity in a bilateral frontoparietal network, following invalidly as compared to validly cued targets and a modulation of reorienting-related activity in right TPJ, FEF and putamen by precision-dependent attention (Vossel et al., 2015). In sum, this Bayesian hierarchical model represents a promising tool to elucidate inter-individual belief-updating under uncertainty.

## 2.2 Functional magnetic resonance imaging (fMRI)

Magnetic resonance imaging (MRI) is a non-invasive tool, using the magnetic properties of organic tissue to create structural images (Lauterbur, 1973). More specifically, the method exploits the fact that atoms contain different amounts of protons and neutrons, making them more or less susceptible to changes in the magnetic field.

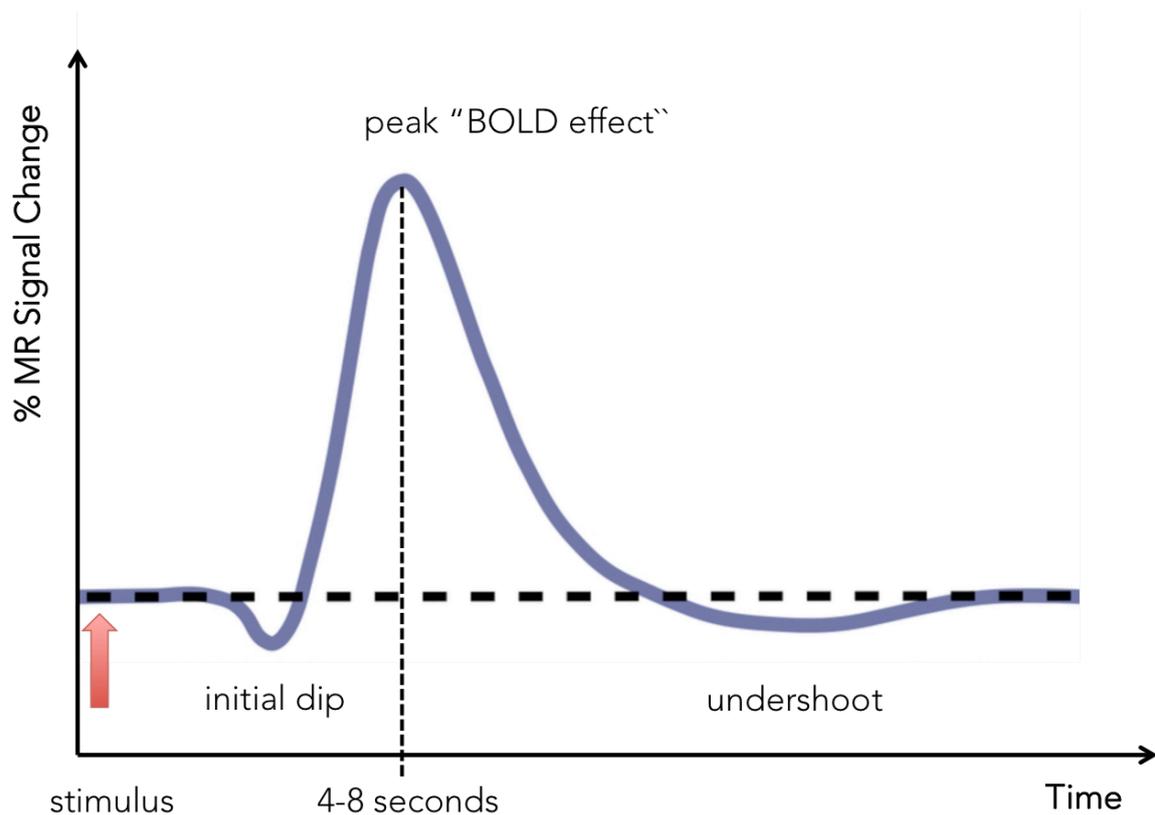
In MRI research, mostly hydrogen atoms are relevant, which are found throughout the brain. Their nuclei are made from a single positively charged proton, spinning around its principal axis ("spin"), thereby creating a magnetic field. By manipulating the external magnetic field in the scanner, the previous random orientations of the protons become aligned parallel to the force of the magnet. Consecutive, radiofrequency (RF) pulses are introduced, perturbing the protons once more in a predictable direction. When the RF-pulse is turned off, a synchronized rebound into the original orientation along the magnetic field occurs, which produces energy signals. These signals are picked-up by a sensitive receiving coil, placed around the subject's head (McRobbie, Moore, Graves & Prince, 2006). Sharp images of structures such as sulci and gyri can be obtained, as they have different relaxation properties, due to variations in proton count. Grey matter for example has higher densities than white matter or cerebrospinal fluid (Gazzaniga, Ivry, & Mangun, 2009).

### 2.2.1 Physical and physiological principles of fMRI

Functional magnetic resonance imaging (fMRI) allows cognitive neuroscientists to map functionally induced changes in blood oxygenation and blood flow, coupled to neuronal activity (D'Esposito, Zarahn, & Aguirre, 1999). A crucial cornerstone for the evolution of this technique was set by Pauling in 1935, who described alterations in magnetic properties of hemoglobin in dependence on the amount of oxygen it carries. Whereas oxygenated hemoglobin is diamagnetic, deoxyhemoglobin is paramagnetic and influences the surrounding hydrogen proton signal, causing a reduction in fMRI signal intensity. Physiologically, more oxygen is made available by increased blood flow, when a brain area is active and in need of energy. The difference in magnetic susceptibility of oxygen-rich versus deoxygenated hemoglobin serves as a natural contrast agent, known as blood oxygenation level dependent (BOLD) signal (Ogawa, Lee, Kay, & Tank, 1990). Higher signals (high concentration of oxyhemoglobin) result in brighter voxels, as opposed to areas with low concentration (Amaro & Barker, 2006).

The hemodynamic response function (HRF) (see **figure 6**) is a mathematical model for describing the time-course of the BOLD signal. After an initial dip in BOLD

signal (use of local oxygen by active neurons), cerebral blood flow (CRF), and –volume (CBV) are enhanced. Over time, an oversupply of oxygen and glucose takes place, reflected by an augmentation of the BOLD signal (increased hemodynamic response). The rise peaks around 4-8 seconds after the actual firing of neurons. Before reaching steady baseline levels, an "undershoot" of the decaying signal is observed (D'Esposito, Zarahn, & Aguirre, 1999; Vazquez and Noll, 1997).



(adapted from Kornak, Hall & Haggard, 2011)

**Figure 6. Model of a hemodynamic response function (HRF) following a hypothetical stimulus. After stimulus onset, deoxygenated hemoglobin increases indicated by the initial dip. This is followed by an increase of oxy/deoxygenated ratio, resulting in a higher MR signal.**

In sum, this advancement in imaging methodology is widely applied to track hemodynamic changes in participants engaged in cognitive tasks. It allows researchers to test hypotheses about functional anatomy and has a high spatial resolution. Combining imaging and behavioral measures is a powerful tool to aid our understanding of the relationship between mind and brain (Raichle, 1994). It is important to interpret the fMRI data in the light of correlation, not causation.

### 2.2.2 fMRI data analysis

The primary aim of fMRI experiments is to create a brain activation map, based on the modulation of the brain's response (BOLD effect) following a certain cognitive event (e.g. orienting to a cued location). Analyzing acquired fMRI data comprises two steps: preprocessing and statistical analysis of the effects of interest (Friston, Holmes, Price, Büchel & Worsley, 1999).

Lying inside a tight bore and not moving for a long period of time can be very challenging for participants. Therefore, the first preprocessing steps entail spatial realignment and coregistration of all functional images, to account for movement. To be able to perform group statistics, anatomical intersubject differences need to be resolved, by spatially normalizing the scans to a standard brain space provided, for example by the Montreal Neurological Institute (MNI template) or the atlas by Talairach and Tournoux (1998). Finally, the data is smoothed using a Gaussian kernel to improve the signal to noise ratio (SNR) and statistical power (Friston, 1997; McRobbie et al., 2006).

Next, a general linear model (GLM) is applied for each voxel, to model explanatory variables (experimental conditions and regressors of no interest) and residual errors ( $\varepsilon$ ) in a linear fashion. In the following notation,  $Y$  represents the BOLD signal (dependent variable) and  $X$  contains the design matrix (explanatory regressors). The estimated beta values ( $\beta$ ) for each column in the design matrix describe the relative contribution of the respective regressor to the data.

$$Y = X \cdot \beta + \varepsilon$$

In event-related designs, the evoked hemodynamic responses are time-locked to the stimuli in the experimental task, separately for different experimental conditions, which are presented in a randomized or pseudo-randomized order. The resulting parameter estimates are consequently tested for statistical significance by F- or T-contrasts. This statistical image (or *Statistical Parametric Map*) shows the location of significantly activated voxels. One can either test the effects relative to baseline activity or compare different conditions with one another. fMRI data analysis can be applied on a single-subject level (1<sup>st</sup>-level analysis) as well as on a group level (2<sup>nd</sup>-level analysis), for population-based inferences. When conducting inter-subject analyses, one must be aware to correct for multiple comparisons. Apart from the overly conservative Bonferroni correction, one can apply a false discovery rate correction, a region of interest analysis (Genovese, Lazar & Nichols, 2002) or cluster size exclusion (Andrade et al., 2001).

Depending on the fMRI study, the experimental design can make use of subtractive, factorial or parametric strategies (Friston et al., 1999; Kiebel & Holmes, 2003). The first method rests on the principle of pure insertion (i.e. assuming that separate conditions can be added and do not interact with one another). Each newly added cognitive component results in additional physiological activation, so subtracting one condition from the other allows to characterize cognitive neuroanatomy (Amaro & Barker, 2006; Friston et al., 1996). Factorial designs in turn are valuable to test interaction effects, simply said to detect a difference in a difference between conditions (e.g. invalid > valid: motor intention > spatial attention). Finally, different levels of cognitive demand in a given task can be investigated using parametric modulation. This is particularly useful if a parameter of interest is continuous or has multiple dimensions, changing over time. For instance in a model-based approach, subjects' trialwise belief estimates about cue predictability can be correlated with changes in BOLD amplitude to describe the neural basis of learning behavior (see, e.g. Vossel, Mathys, Stephan & Friston, 2015).

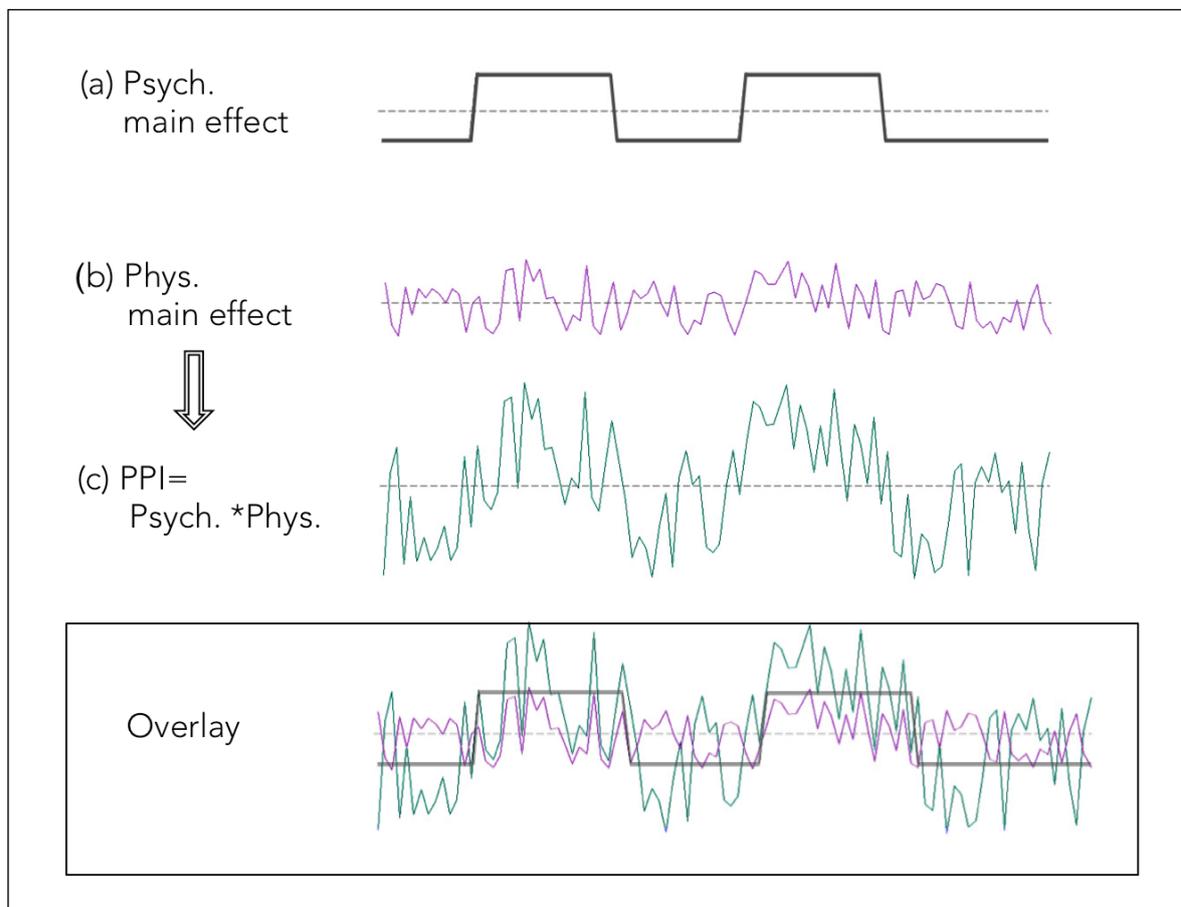
### 2.2.3 Psychophysiological interaction (PPI) analysis

The application of a psychophysiological interaction (PPI) analysis to fMRI data adheres the possibility to investigate cortical responses in one area, in terms of an interaction between another area (physiological factor) and a psychological context (sensory or task-related). Differently put, it detects task-related changes in the statistical relationship between brain regions referred to as functional connectivity (Friston et al., 1997). In what follows, the basis of PPI analysis will be outlined (for SPM), and possibilities of interpreting the data.

A basic idea of a PPI analysis is that if two brain regions demonstrate synchronous behavior of increasing and decreasing activity, they must be interacting (O'Reilly, Woolrich, Behrens, Smith & Johansen-Berg, 2012). To identify interacting areas, a 'seed' region of interest (ROI) is defined. Generally, the chosen mask is based on the voxels showing a task-related effect in the 2nd-level fMRI analysis. Then a representative time course of activity in the predefined mask is extracted which yields a vector containing values for each time point in the data set. This seed ROI time course is then entered as a regressor in a GLM.

In a PPI analysis, *task- or context-specific* changes in functional connectivity between different areas are analyzed by generating an 'interaction regressor'. A well-chosen PPI regressor ideally illustrates a stronger relationship during one experimental condition, as opposed to another condition or rest (see **figure 7**). Statistically, a PPI is a change in slope of a regression, using data collected in different sensory or psychological

contexts. If one regresses the activity of one region over the activity of another, the slope would describe the influence the latter could have on the first (Friston et al. 1997). PPI is not restricted to a single interaction effect, but one can choose to create several PPI regressors, to look at multiple seed regions in relation to a task, or vice versa. In order to rule out possible false positives and only get the connectivity effects, the task and physiological time courses are included as nuisance co-variates in the final PPI model. This ensures that variance is solely explained by the interaction term and is additional to the main effects. The interactions can be interpreted in the light of context-sensitive changes in how the remote area contributes to the known seed, but it could also mean that the remote area mediates the context-dependent increases in response in the reference area (Friston et al., 1997).



(adapted from O'Reilly et al., 2012)

**Figure 7. Generating a PPI regressor. (a) The first row depicts the main effect of the psychological variable in a block design (black line) (b) Then a seed region time-course is selected, representing the physiological main effect (purple line). (c) A PPI regressor (green line) is created as an element-by-element product of task (black line) and seed ROI (purple line).**

## EXPERIMENTAL TECHNIQUES

## 2.3 Thesis aims

The purpose of the present thesis is to characterize common and distinct neural and behavioral mechanisms for predicting upcoming events, following different perceptual-attentional and motor intentional cues in the healthy human brain. Two Experiments will be elucidated in the subsequent section, to answer the following questions:

- 1) What are the neural correlates of dynamic experience-dependent updating of spatial-attentional and motor-intentional predictions? (Experiment 1)
- 2) Does age influence experience-dependent updating of spatial and feature-based attentional and motor intentional predictions? (Experiment 2)
- 3) Does task difficulty impact the performance of predicting upcoming events in older-compared to younger adults? (Experiment 2)

In Experiment 1 computational modeling of response times was combined with fMRI to identify neural correlates of dynamic experience-dependent updating of spatial-attentional and motor-intentional expectancies (Kuhns, Dombert, Mengotti, Fink & Vossel, 2017). Participants conducted an adapted version of the classical cueing paradigm by Posner (1980) (see 1.1.2). In order to disentangle the cortical networks, cues either guided spatial attention (arrow pointing towards left or right hemifield) or were preparatory for a motor response (prepare response of right index- or middle finger). Different %CV levels (~50%, 70%, and 90%) changed unpredictably over time, creating a volatile environment. Reaction time data was used to predict trial-wise updating of the probabilistic context using the generic hierarchical model based on Bayesian principles (see 2.1, Mathys, Daunizeau, Friston & Stephan, 2011). The trial-wise probabilistic beliefs from the computational model were then included as parametric regressors in the design matrix for analyzing the BOLD time series and compared between the spatial attention and motor intention condition. Moreover, PPI analysis (see 2.2.3) lend to explore common predictability-dependent coupling patterns of the two domains.

Although functional anatomy of preparatory spatial attention and motor intention seem to share common systems, they also display distinctions (Rushworth et al., 2001a). Left posterior parietal cortex seems to be critical for motor intention, whereas spatial attentional control is complementary lateralized in the right cortex. Therefore, it was hypothesized that domain-specific, as well as common neural correlates of experience-dependent updating would be identified.

Since the healthy human brain undergoes age-related changes (like, e.g., atrophy and dedifferentiation; see 1.1.6) it was of primary interest in Experiment 2 whether experience-dependent updating would be affected. Given the fMRI evidence for overlapping but also differential neural systems (Dombert et al., 2016; Kuhns et al., 2017) for spatial attention, feature-based attention and motor intention, older and young adults had to complete three distinct cueing versions. It has been shown, that task complexity can largely affect performance in older adults (Zanto & Gazzaley, 2014). Therefore, two task difficulty levels of the three cueing versions were introduced. It was hypothesized that older adults would show reduced updating-speed of trial-by-trial estimates of the probabilistic environment compared to the young group. The reduction however could vary for the different attentional- and intentional domains.

### **3. Spatial attention, motor intention, and probabilistic inference in the human brain**

Abbreviated title: Attention, intention and probabilistic inference

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The Journal of Neuroscience, May 24, 2017; 37(21):5334-5344

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## **Abstract**

Predictions about upcoming events influence how we perceive and respond to our environment. There is increasing evidence that predictions may be generated based upon previous observations following Bayesian principles, but little is known about the underlying cortical mechanisms and their specificity for different cognitive subsystems. The present study aimed at identifying common and distinct neural signatures of predictive processing in the spatial attentional and motor intentional systems. Twenty-three female and male healthy human volunteers performed two probabilistic cueing tasks with either spatial or motor cues while lying in the fMRI scanner. In these tasks, the percentage of cue validity changed unpredictably over time. Trial-wise estimates of cue predictability were derived from a Bayesian observer model of behavioral responses. These estimates were included as parametric regressors for analyzing the BOLD time series. Parametric effects of cue predictability in valid and invalid trials were considered to reflect belief updating by precision-weighted prediction errors. The brain areas exhibiting predictability-dependent effects dissociated between the spatial attention and motor intention task, with the right temporoparietal cortex being involved during spatial attention and the left angular gyrus and anterior cingulate cortex during motor intention. Connectivity analyses revealed that all three areas showed predictability-dependent coupling with the right hippocampus. These results suggest that precision-weighted prediction errors of stimulus locations and motor responses are encoded in distinct brain regions, but that crosstalk with the hippocampus may be necessary to integrate new trial-wise outcomes in both cognitive systems.

## **Significance Statement**

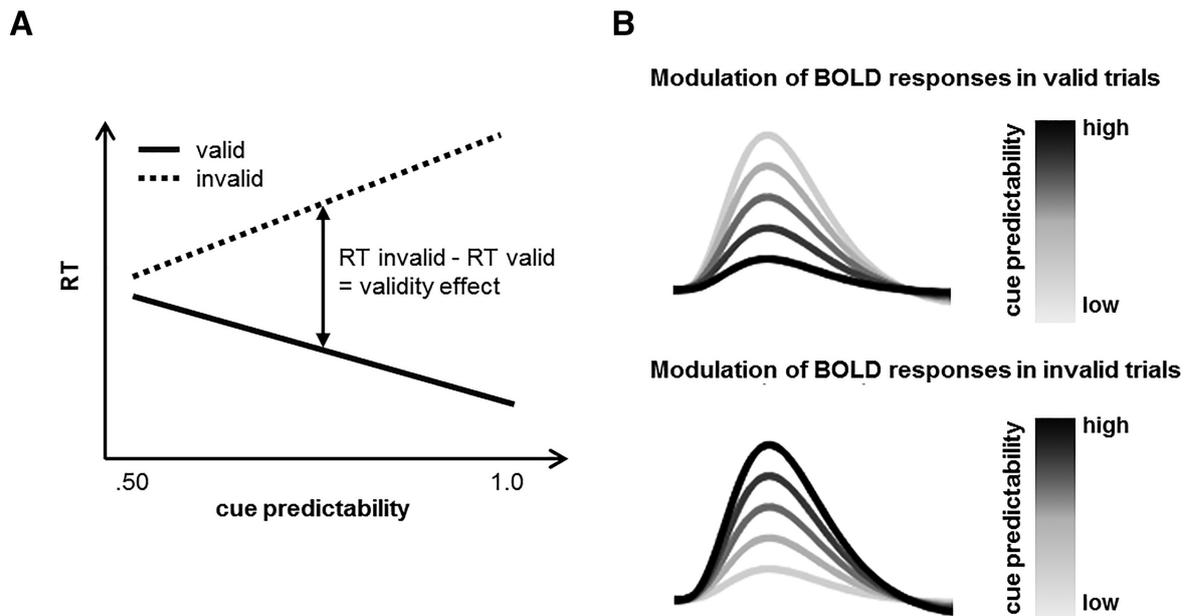
The brain is able to infer the environments' statistical structure and strongly responds to expectancy violations. In the spatial attentional domain, it has been shown that parts of the attentional networks are sensitive to the predictability of stimuli. It remains unknown, however, if these effects are ubiquitous or if they are specific for different cognitive systems. The present study compared the influence of model-derived cue predictability on brain activity in the spatial attentional and motor intentional system. We identified areas with distinct predictability-dependent activation for spatial attention and motor intention, but also common connectivity changes of these regions with the hippocampus. These findings provide novel insights into the generality and specificity of predictive processing signatures in the human brain.

### 3.1 Introduction

How we perceive and respond to our environment does not depend solely on the sensory input we receive, but also on predictions that we make about upcoming events or motor acts. Paradigms in which cues predict the location of a stimulus (Posner et al., 1980) or the motor response to a target (Rushworth et al., 1997) are used to study these effects. Response times (RTs) are accelerated if the cue is valid, whereas slower RTs are observed in invalid trials when the prediction is violated and reorienting of attention or reprogramming of the motor response become necessary. A ventral frontoparietal network including the right temporoparietal junction (TPJ) exhibits enhanced neural activity for spatially invalid (compared with valid) targets (Corbetta et al., 2008). Repetitive transcranial magnetic stimulation applied over the left supramarginal gyrus disrupts the performance in invalidly cued motor (but not spatial) trials (Rushworth et al., 2001a) regardless of the subjects' responding hand or verbal strategies (Rushworth et al., 2001b).

Spatial reorienting is not an all-or-none phenomenon because RTs in valid and invalid trials are affected differentially by the predictability of the cue (i.e., the probability with which the cue correctly predicts the target location in a given trial determined by the proportion of valid and invalid trials in a trial sequence). While RTs in valid trials decrease, RTs in invalid trials increase with higher cue predictability, resulting in bigger validity effects (Fig. 1A).

Moreover, there is evidence that subjects infer the trialwise cue predictability on the basis of past trials and that this estimation can be described by a hierarchical Gaussian filter (a special case of generalized predictive coding or Bayesian filtering) (Mathys et al., 2011; Vossel et al., 2014a). This model estimates hidden states (in our specific case: beliefs about cue predictability and its stability over time) and this estimation can be framed in terms of propagating precision-weighted prediction errors from one hierarchical level to the next. Here, beliefs about cue predictability are represented on the lower level of the model and are influenced by beliefs about the stability (volatility) of cue predictability represented on a higher level and also by subject-specific parameters. Although the higher-level volatility is of major relevance for the flexibility of the model (Behrens et al., 2007; den Ouden et al., 2010), the focus of this study concerned the effects of (lower-level) cue predictability on behavior and BOLD responses. Here, as for RTs, we expected differential effects in valid and invalid trials; that is, increased BOLD responses with higher cue predictability in invalid trials, but decreased BOLD responses with higher predictability in valid trials (Fig. 1B).



**Figure 1. Schematical illustration of the hypothesized effects of cue predictability. A)** Illustration of the expected differential effects of cue predictability on response times (RTs) in valid and invalid trials. **B)** Computational anatomy that can be inferred from the fMRI results. In predictive coding formulations of hierarchical neuronal processing, precision-weighted prediction errors may be encoded neurally. Belief updating in the hierarchical Gaussian filter model rests on prediction errors in the different levels which are weighted by (level-specific) precision terms. In the present study, we focused on this process at the lower level of the model, i.e., on the observation of valid and invalid trials in relation to the expected cue predictability. Here, BOLD amplitudes should be attenuated with higher cue predictability in valid trials, but increase with higher cue predictability in invalid trials (when the prediction is violated). Such effects were identified by including model-derived cue predictability as a parametric modulator for valid and invalid trials in the fMRI analysis and by subsequently contrasting the parametric effects between the two trial types with a planned invalid>valid contrast.

Using a spatial cueing paradigm with saccadic responses, activity patterns as shown in Figure 1B have been observed in the right frontal eye field, TPJ, and putamen (Vossel et al., 2015). However, because saccade preparation is inherently linked to covert shifts of spatial attention (Deubel, 2008), this previous work cannot differentiate between attentional and motor-intentional effects.

In this study, we used two novel cueing tasks to compare directly the effects of cue predictability in the spatial attentional and motor intentional system. The cues either guided spatial attention or signaled the upcoming motor response to the target. The proportion of valid and invalid trials changed unpredictably over time and the subjects' trialwise beliefs about cue predictability were derived from a hierarchical Gaussian filter and were included as parametric regressors for analyzing the BOLD time series. This

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allowed us to test whether the neural signatures of predictive coding share common mechanisms or if there are different physiological implementations for spatial attention and motor intention. We expected a greater predictability-dependent involvement of left parietal areas in the motor intention task. For spatial attention, we expected a modulation of right TPJ activity (Vossel et al., 2015; Dombert et al., 2016a). In addition, we performed explorative connectivity analyses to test for convergent predictability-dependent coupling patterns in the two functional domains.

## **3.2 Materials and Methods**

### **3.2.1 Participants**

Initially, 34 healthy participants gave written informed consent to take part in the present study. Eleven subjects had to be excluded due to head movement >3mm (n=4) or technical problems during scanning (n=7). Therefore, data from 23 subjects (13 males, 10 females; age range 18-36; mean age 26 years) were analyzed. All subjects were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), had normal or corrected-to-normal vision and no history of neurological or psychiatric disorders. The study had been approved by the ethics committee of the German Psychological Society and was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

### **3.2.2 Stimuli and experimental paradigm**

The tasks were presented on a screen (spatial resolution 1024 x 768, 60 Hz sampling rate) mounted at the back of the magnet bore. A mirror system attached to the head-coil enabled the subjects to see the display at a viewing distance of 240 cm. Participants performed two versions of an adapted cueing paradigm (Egner et al., 2008). They were asked to detect a target stimulus (the diamond with one corner missing) in a visual search display and to indicate by button press whether the upper or lower corner of the target was missing. For their motor response, subjects were provided with a button box with two neighboring response buttons which they pressed with their right index finger or their right middle finger (see Figure 2).

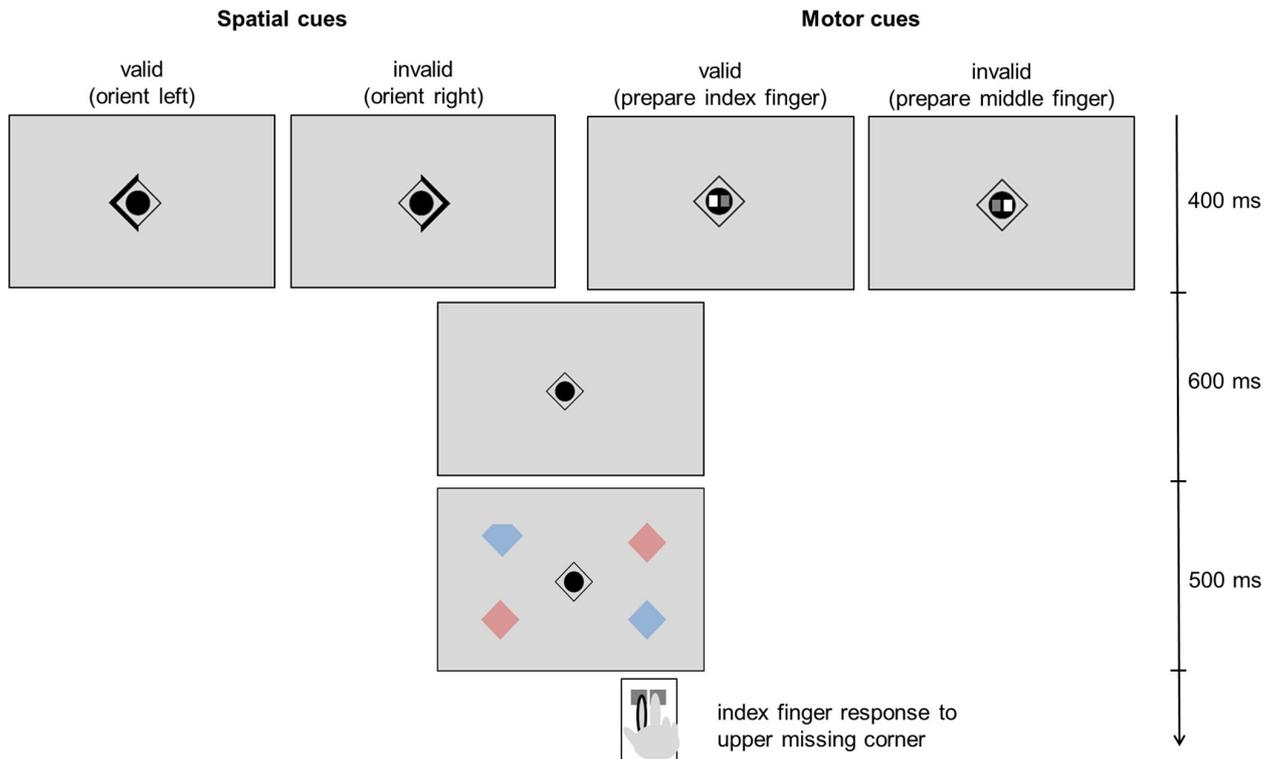
The search display consisted of four diamonds that were positioned in the corners of an imaginary rectangle centered on the fixation diamond (4.8° eccentric in each visual field, see Figure 2). The different colors of the stimuli in the search display were irrelevant for the present task, but were introduced for reasons of comparability with previous research (Dombert et al., 2016a).

The search display was always preceded by a cue stimulus that was shown for 400 ms. In the spatial attention task, the cue was an arrowhead appearing at the central fixation diamond, indicating the most likely hemifield in which the target would appear (Fig. 2). In the motor intention task, the cue stimulus contained an illustration of the two response buttons for the right index and middle finger (Fig. 2). The white button indicated the most likely button press response required by the target. Therefore, in the example depicted in Figure 2, the subjects prepared a button press with the index finger (valid

condition) or a button press with the middle finger (invalid condition). In other words, the target always determined the motor response, but the cue biased the motor preparation toward one or the other response. The response mapping (upper/lower corner missing → index/middle finger) was counterbalanced across subjects. Subjects needed to respond to the target within a period of 1500 ms from target onset. The tasks with motor or spatial cues were presented in two different runs, with counterbalanced order between subjects.

Throughout the experiment, participants were asked to maintain central fixation and to respond as quickly as possible to the target. Moreover, they were instructed to use the cues according to how much they “trusted” them to speed up RTs to the target. The percentage of cue validity (%CV) changed between levels of ~50%, 70%, and 90% valid trials (cf. Fig. 4B). Participants were not aware of the different levels of %CV or when they would change; they were only informed that variations in %CV would occur over the course of the experiment. In the fMRI experiment, 284 trials were shown in each cueing version. In accordance with standard procedures in computational studies of trialwise inference, target stimuli and trial sequence were identical between the two cueing versions. Each %CV block consisted of 22 or 32 trials. This block length was chosen to provide participants with sufficient trials to learn the hidden statistical context. Each block contained an equal number of left and right upper and lower targets counterbalanced across valid and invalid cues. Furthermore, 84 null events (only displaying the fixation diamond) were randomly intermixed to jitter trial onsets. Halfway through each version, a 1 min break was introduced by displaying the word “Pause”. The total duration of the fMRI experiment (both runs) amounted to 34 min. To familiarize the subjects with the task, fixation, and manual responses, we included a prior practice session in the experiment. This practice took place on the same day or the previous day of the fMRI session and consisted of one run with constant %CV of 80% and one run with changes in %CV.

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**Figure 2.** Illustration of the different experimental conditions for the two different tasks. The behaviorally relevant target stimulus was a diamond with a missing corner, which was embedded in a visual search display. The subjects were asked to indicate by button press of one of two adjacent response buttons (for the right index or middle finger) if the upper or lower corner of the target diamond was missing. The allocation of upper/lower corner to index/middle finger was counterbalanced across subjects. This example shows a configuration in which the subjects should respond with the index finger for diamonds where the upper corner is missing. The target search display was always preceded by a cue stimulus. In the spatial attention task, this cue indicated the most likely hemifield in which the target would be located (with variable levels of cue predictability). In the motor intention task, the cue indicated the most likely button press response required by the target. This cue consisted of two squares representing the two response buttons. The white button signaled the most likely button press response (with variable levels of cue predictability). Note that the spatial attention task and the motor intention task were presented in different runs.

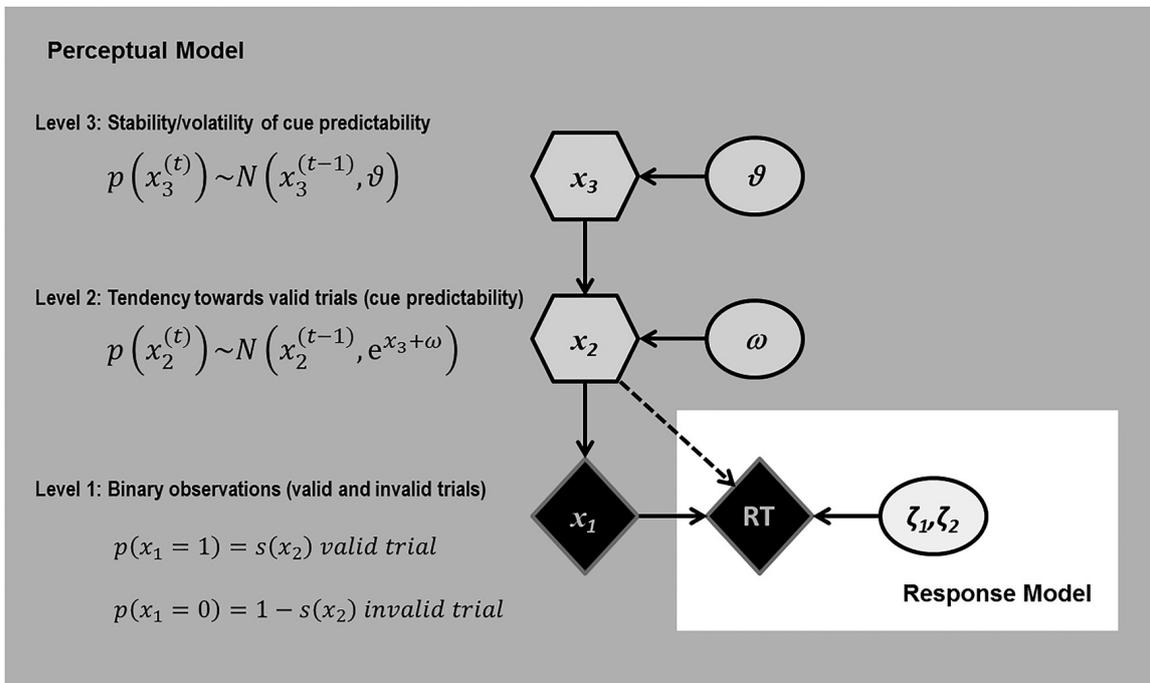
### 3.2.3 Statistical analysis of behavioral data

Classical inference was first performed to investigate whether the different levels of experimentally manipulated cue predictability (%CV) significantly affected RTs and whether these effects differed for spatial attention and motor intention. Incorrect trials, misses, anticipations, and responses deviating  $>2$  SDs from the individual subject's mean RT were excluded from the analysis. Mean RTs from valid and invalid trials for each subject, %CV condition, and task entered a  $2$  (*validity*: valid/invalid)  $\times$   $3$  (%CV: 50/70/90%)  $\times$   $2$  (*task*: spatial attention/motor intention) within-subject ANOVA. Results of this analysis are reported after a Greenhouse-Geisser correction at a significance level of  $p < .05$ . Based on evidence for a linear relationship between validity effects (RT invalid minus RT valid) and %CV (e.g., Dombert et al., 2016a; Dombert et al., 2016b; Egner et al., 2008; Vossel et al., 2014a), we report linear contrasts for the effects of %CV. We expected to find a significant interaction between *validity* and %CV, with decreasing RTs in valid and increasing RTs in invalid trials (i.e., bigger validity effects) with higher %CV. The same within-subjects ANOVA was performed on accuracy (as the percentage of correct responses).

In a second step, a Bayesian observer model (hierarchical Gaussian filter) was used to estimate trial-by-trial beliefs about cue predictability (i.e., the probability that the cue will be valid) based on the single-trial RTs for each participant (Mathys et al., 2011; Vossel et al., 2014a). The parameters that can be derived from this model also allow for a quantification of individual differences in the trialwise estimation of cue predictability. The model incorporates a perceptual and a response model (Fig. 3). While the perceptual model describes updating of beliefs based on the cue–target outcomes (i.e., observations), the response model is used to derive responses (i.e., RTs) based on these beliefs. Details about the derivation of the equations of the perceptual model are provided in Mathys et al. (2011). In what follows, we describe the model parameters as relevant for the present study.

The perceptual model consists of hierarchically coupled Gaussian random walks which enable a flexible control of updating of the beliefs about cue predictability in each trial, in relation to beliefs about volatility and subject-specific parameters. It comprises three states denoted by  $x$  (Figure 3). The state  $x_1^{(t)}$  represents the environmental state in each trial, which, in the present paradigm, consisted of either a validly or invalidly cued target (with  $x_1^{(t)} = 1$  for valid and  $x_1^{(t)} = 0$  for invalid trials). The probability distribution of the trial being valid (i.e., of  $x_1^{(t)} = 1$ ) is a Bernoulli distribution governed by the next higher

state  $x_2^{(t)}$ . Hence,  $x_2^{(t)}$  is a single real number, which determines the probability of  $x_1^{(t)}$  being 1 (valid) or 0 (invalid) through a sigmoid (softmax) transformation.  $x_2^{(t)}$  changes from trial to trial as a Gaussian random walk. Its value depends on the value from the previous trial  $t-1$  and the magnitude of its change (i.e., how fast  $x_2^{(t)}$  changes after new observations) is determined by two quantities:  $x_3^{(t)}$  (the state of the next upper level of the hierarchy) and a fixed, subject-specific updating parameter  $\omega$ . The third state  $x_3^{(t)}$  represents the belief about the stability of cue predictability and also changes as a Gaussian random walk, with the step size being determined by a second subject-specific parameter  $\vartheta$ . The values of the subject-specific parameters  $\omega$  and  $\vartheta$  are estimated from the individual RT data (see below).



**Figure 3. Depiction of the hierarchical Bayesian model (Gaussian filter) for belief updating about cue predictability.** The perceptual model (shown on grey background) illustrates the three states ( $x_1$ ,  $x_2$ ,  $x_3$ ). The higher levels are influenced by constant parameters  $\omega$  and  $\vartheta$ , which affect trial-wise changes on the respective level. Circles represent constants, while diamonds represent quantities that change over time (trials). Hexagons, like diamonds, represent quantities that change in time but that additionally depend on their previous state in time in a Markovian fashion. The response model parameters  $\zeta_1$  and  $\zeta_2$  quantify the intercept and the slope of the linear function of RT and cue predictability  $\hat{\mu}_1^{(t)}$ .

This allowed us to estimate subject-specific beliefs about trial-by-trial variations in probabilistic contingencies. To infer these subject-specific beliefs from the reaction times, the perceptual model needs to be inverted; this yields the posterior densities over the three hidden states  $x^{(t)}$ . In the following, the mean of the subject's posterior belief will be

denoted by  $\mu^{(t)}$ . We use the hat symbol (^) to denote predictions before the observation of  $x_1^{(t)}$  on a given trial  $t$ . Thus, the relevant trial-wise quantity for the present study was  $\hat{\mu}_1^{(t)}$ , i.e., the posterior belief that the cue will be valid before observation of the outcome of trial  $t$  (or, in other words, the estimated probability that the target will appear at the cued location or will require the cued motor response in the upcoming trial).  $\hat{\mu}_1^{(t)}$  is derived from a sigmoid transformation of  $\mu_2^{(t-1)}$  as follows:

$$\hat{\mu}_1^{(t)} = s\left(\mu_2^{(t-1)}\right)$$

As described in detail in Mathys et al. (2011), variational model inversion under a mean field approximation yields simple analytical update equations – where belief updating rests on precision-weighted prediction errors. These update equations provide approximately Bayes-optimal rules for the trial-by-trial updating of the beliefs about  $\mu_2^{(t)}$  and  $\mu_3^{(t)}$ . Note that this is an individualized approximate Bayes-optimality, in reference to the subject-specific values for the updating parameters  $\omega$  and  $\vartheta$ .

A response model was used to map the derived posterior beliefs to the observed RTs. In previous work using a saccadic response task with spatial cueing, RTs could most plausibly be explained by the trial-wise precision of the prediction at the first level of the perceptual model (Vossel et al., 2014a; Vossel et al., 2014b). However, since we employed a novel paradigm with manual responses in this study, we again compared the three alternative response models considered in this previous work. Variational Bayesian estimation was used to derive the model parameters based on RTs, as implemented in the HGF toolbox (<http://www.translationalneuromodeling.org/tapas/>) running on MATLAB® (2012b, The MathWorks, Inc., Natick, Massachusetts, United States). The relative plausibility of the previous response models was compared using a random effects Bayesian model selection (Stephan et al., 2009). This analysis revealed that the model in which RTs were directly governed by the estimated cue predictability  $\hat{\mu}_1^{(t)}$  described the data most plausibly  $\alpha^{(t)} = \hat{\mu}_1^{(t)}$ . More specifically, this response model describes trial-wise RTs as a linear function of the estimated cue predictability  $\hat{\mu}_1^{(t)}$ . The two response model parameters  $\zeta_1$  and  $\zeta_2$  parameterize the intercept and the slope of the linear function:

$$RT^{(t)} = \begin{cases} \zeta_{1v} - \zeta_{2v}\hat{\mu}_1^{(t)} & \text{for } x_1^{(t)}=1 \text{ (i.e., valid trial)} \\ \zeta_{1i} + \zeta_{2i}\hat{\mu}_1^{(t)} & \text{for } x_1^{(t)}=0 \text{ (i.e., invalid trial)} \end{cases}$$

Again, like the subject-specific parameters  $\omega$  and  $\vartheta$  of the perceptual model, these response model parameters were estimated for each subject from the individual RT data.

### 3.2.4 Eye movement recording and analysis

Eye movement data were acquired using an EyeLink® 1000 MR-compatible eye-tracker system (SR Research Ltd.) at a sampling rate of 500 Hz. Prior to the task, a 9-or 5 point calibration was performed, followed by a validation to ensure that errors were  $<1^\circ$ . Data were processed using the ILAB toolbox (Gitelman, 2002) in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States). The amount of time spent within a fixation zone of  $1.5^\circ$  from the central fixation point was analyzed for the time between cue and target appearance as well as for the time period between target and response. Percentage of fixation time within the central ROI in the cue-target period was compared between spatial and motor cues with a paired t-test. Fixation between target appearance and response was analyzed with a 2 (*task*: spatial attention/motor intention) x 2 (*validity*: valid/invalid) within-subject ANOVA.

### 3.2.5 MRI data acquisition

Using a 3T MRI System (Trio; Siemens), T2\* weighted EPI images with BOLD contrast were acquired with a repetition time of 2.2 sec and an echo time of 30 ms. Two functional runs were acquired consisting of 462 EPI volumes for each run (i.e., for each task). Each volume consisted of 36 axial slices with interleaved slice acquisition. The field of view was 200 mm, using a  $64 \times 64$  image matrix, which resulted in a voxel size of  $3.1 \times 3.1 \times 3.0 \text{ mm}^3$ . The first five volumes were discarded from the analysis to allow for T1 equilibration effects. The remaining  $2 \times 457$  volumes were analyzed using the Statistical Parametric Mapping software SPM12 (Wellcome Department of Imaging Neuroscience, London; Friston et al., 1995; <http://www.fil.ion.ucl.ac.uk/spm>). Images were bias-corrected. Slice acquisition time differences were corrected using sinc interpolation to the middle slice. During spatial realignment, a mean EPI image was computed for each subject and spatially normalized to the MNI template using the segmentation function. Subsequently, the resulting transformation was applied to the individual EPI volumes to translate the images into standard MNI space and resample them into  $2 \times 2 \times 2 \text{ mm}^3$  voxels. Finally, the normalized images were spatially smoothed using an 8 mm full-width half-maximum Gaussian kernel.

### 3.2.6 Statistical analysis of imaging data

At the single-subject level, the spatial attention and motor intention tasks were included as separate sessions in a general linear model (GLM) of the BOLD responses. For each session, regressors of interest for left and right valid and invalid trials were defined. The resulting stimulus functions were convolved with a canonical hemodynamic

response function (HRF) and its first (temporal) derivative. For each task regressor, cue predictability  $\hat{\mu}_1^{(t)}$  as derived from the single-subject computational modeling was included as a parametric modulator. Note that parametric modulations in SPM are used to test whether the trial-wise amplitude of the BOLD response in an experimental condition varies with a continuous variable of interest. RTs were added as a second (orthogonalized) parametric regressor to capture residual variability that was not explained by cue predictability  $\hat{\mu}_1^{(t)}$ . Error trials (anticipations, misses and incorrect responses) and outliers (RTs above or below 2 standard deviations from the subject's mean) were discarded from the effects of interest and modelled separately. In addition, the rest period and 12 movement parameters of the (rigid body) realignment (six motion parameters and their power of two; Friston et al., 1996) were included in the design matrices as nuisance regressors. Data were high-pass filtered at 1/128 Hz.

As shown in Figure 1, the aim of the current study was to identify and compare brain areas in which BOLD responses are differentially modulated by cue predictability in valid and invalid trials, with potentially negative parametric effects for valid trials (i.e., smaller BOLD responses with higher predictability) and positive parametric effects for invalid trials (i.e., higher BOLD responses with higher cue predictability). For this reason, we focused on planned comparisons of the parametric regressors of invalid and valid trials (t-contrasts of invalid>valid) in each task and compared these between the two different tasks using interaction contrasts. These interaction contrasts between *validity* (valid/invalid) and *task* (spatial attention/motor intention) thus isolate domain-specific correlates of predictive processing in one or the other task.

Because no significant interaction with hemifield was observed in the analysis of probability-independent effects (contrast of invalid>valid trials for the HRF regressors) (data not shown) - and to increase the trial numbers for the parametric modulation effects - the analysis of cue predictability was based on a first-level design matrix with only two regressors for all valid and all invalid trials in each task, respectively. At the group-level, the first-level contrast images for variations of BOLD amplitudes with cue predictability  $\hat{\mu}_1^{(t)}$  were analysed with a 2 (*task*: spatial attention/motor intention)  $\times$  2 (*validity*: valid/invalid) within-subject random-effects ANOVA. As explained above, differential predictability-dependent effects for spatial attention and motor intention were investigated with interaction contrasts (spatial attention invalid>valid > motor intention invalid>valid; motor intention invalid>valid > spatial attention invalid>valid). To ensure that the interaction effects were indeed due to significantly higher effects in invalid as in valid trials in the respective task version (and not only due to a reversed effect in the other task), the

interaction contrasts were inclusively masked by the invalid>valid contrast of one task with a mask threshold of  $p < .01$  (uncorrected). We also tested for a common predictability-dependent effects in the two cueing tasks using a conjunction analysis of the two invalid>valid contrasts for the two tasks (SPM conjunction null hypothesis: spatial attention invalid>valid  $\cap$  motor intention invalid>valid). All reported activations were significant at  $p < .05$  family-wise error (FWE), corrected at the cluster-level with a voxel-level cutoff of  $p < .001$ . Since we had a strong a-priori hypothesis that the right TPJ would exhibit predictability-dependent (Dombert et al., 2016a; Vossel et al., 2015), we employed small volume correction in the spatial attention invalid>valid > motor intention invalid>valid contrast using a 12mm sphere centered upon the coordinates from Vossel et al. (2015) (MNI-coordinates [46 -46 6]). Results from this ROI analysis are reported at a significance level of  $p < .05$  FWE, corrected for the search volume. Brain regions were defined anatomically using the SPM Anatomy Toolbox (Eickhoff et al., 2005) for those regions that have been cytoarchitecturally mapped, and the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) for the remaining regions.

### 3.2.7 Psychophysiological interaction (PPI) analyses

Because no common activation patterns were revealed by the conjunction analysis of probability-dependent effects in the two domains (i.e., spatial attention and motor intention), we used PPI analyses (Friston et al., 1997) to test for potentially converging cue-predictability-dependent connectivity patterns of the different seed regions derived from the former analysis [right TPJ for spatial attention; left angular gyrus (ANG) and anterior cingulate cortex (ACC) for motor intention]. PPIs explain the responses in cortical areas in terms of an interaction between the influence of another area and an experimental manipulation. This allows for a whole-brain analysis of context-dependent coupling with one predefined seed region.

For each seed region, time series were extracted from the nearest local maximum within a radius of 8 mm from the group maxima. The first eigenvariate was then computed across all suprathreshold voxels within 4 mm of the subject-specific maxima. The resulting BOLD time series were adjusted for effects of no interest (e.g., rest periods, error trials, and movement parameters) and deconvolved to generate time series of the neuronal signal. These time series were used to construct the first-level design matrices for the PPIs.

Our PPI analysis was, necessarily, more complicated than a standard PPI analysis. This is because a standard PPI analysis tests for a single interaction between a

physiological variable and a psychological variable. However, in our case, the psychological variable of interest is itself an interaction: an interaction between validity and predictability. This means that we were effectively testing for a three-way interaction between a physiological and two psychological variables. In turn, this required us to model, not only the main effects of the psychological and physiological variables, but also two-way interactions between the physiological variable and the psychological variables validity (valid/invalid) and model-derived cue predictability. The resulting explanatory variables therefore contain multiple PPI terms, rendering it a generalized PPI. Analyses were performed with the Generalized PPI (gPPI) Toolbox (McLaren et al., 2012).

In detail, the design matrices for the three separate PPI analyses at the single-subject level contained nine experimental regressors: four regressors for valid and invalid trials and their parametric modulation by predictability; four PPI regressors for the interactions between the physiological variable (i.e., the time series of the seed region) and valid trials, invalid trials, and their parametric modulation by predictability; and one regressor for the physiological variable. Model estimation was performed and first-level contrast images were created for the PPI regressor of the parametric modulator (cue predictability  $\hat{\mu}_1^{(t)}$ ) in valid and invalid trials.

At the second (i.e., group) level, the first-level contrast images entered a conjunction analysis of the invalid>valid contrast of each of the three seed regions (right TPJ for spatial attention, left ANG and ACC for motor intention). The “intermediate null hypothesis” in SPM was chosen to test for a common effect in two or more contrasts. Again, reported activations were significant  $p < .05$  family-wise error (FWE), corrected at the cluster-level with a voxel-level cutoff of  $p < .001$ . This analysis identified areas where the connectivity with two or more regions decreased with higher estimated cue predictability in valid trials and in which connectivity increased with higher estimated cue predictability in invalid trials.

### 3.3 Results

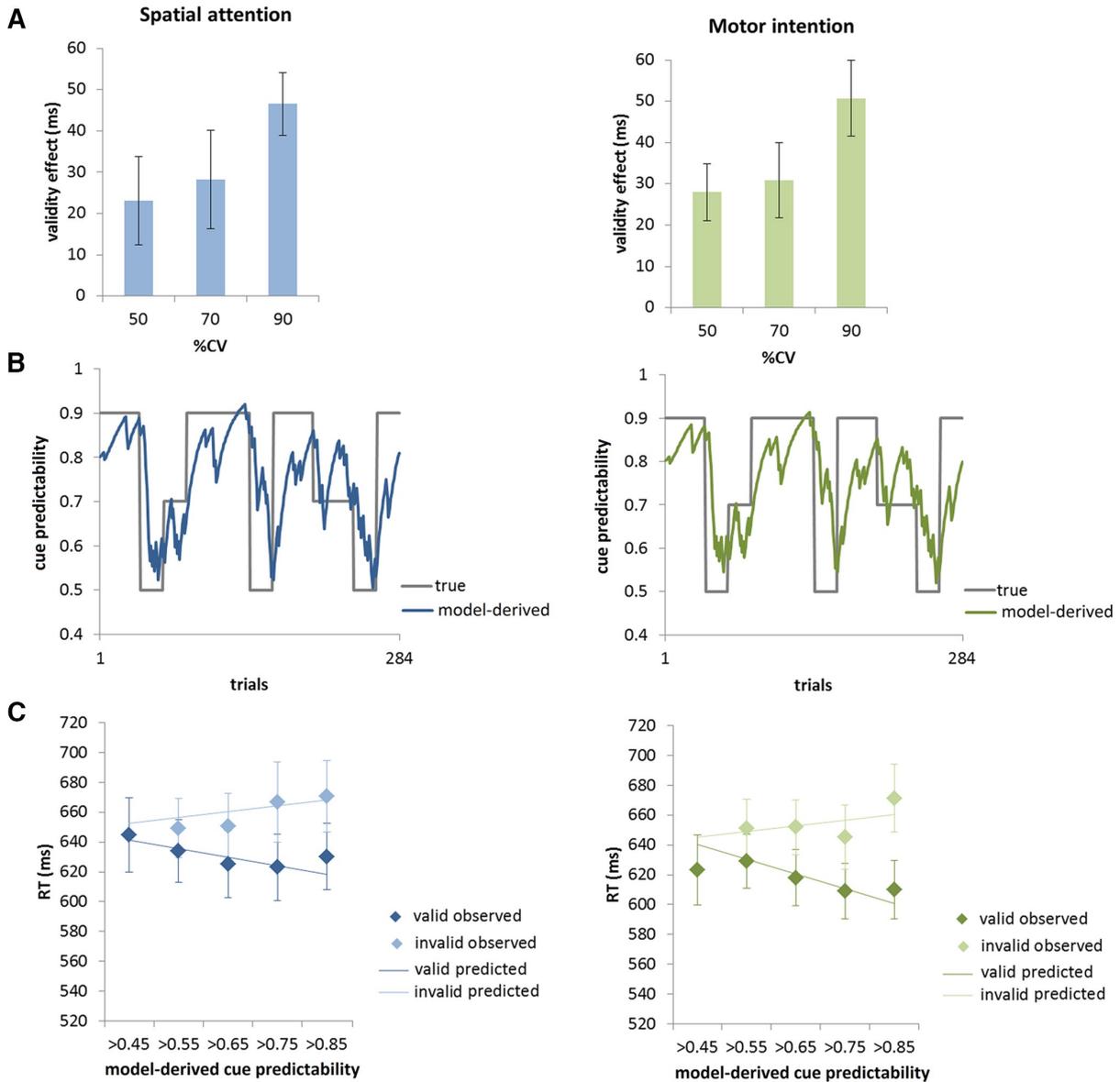
#### 3.3.1 Behavioral data

Table 1 provides an overview of mean RTs and accuracy in the different experimental conditions. Figure 4A depicts mean validity effects (RT invalid minus RT valid) for both tasks in the three experimentally manipulated %CV levels.

**Table 1. Behavioral data. Upper section: Mean RTs ( $\pm$  SEM), for spatial attention and motor intention, separately for valid and invalid trials in the three different %CV levels. Lower section: Mean accuracy (% correct responses) ( $\pm$  SEM) in the different experimental tasks and conditions.**

Task	Validity	%CV		
		50%	70%	90%
<i>Spatial attention</i>	Valid	628.1 ( $\pm$ 22.6)	629.6 ( $\pm$ 21.8)	626.1 ( $\pm$ 21.9)
	Invalid	651.3 ( $\pm$ 20.7)	657.8 ( $\pm$ 24.5)	672.6 ( $\pm$ 24.7)
<i>Motor intention</i>	Valid	618.2 ( $\pm$ 19.1)	622.7 ( $\pm$ 18.8)	611.7 ( $\pm$ 18.5)
	Invalid	646.2 ( $\pm$ 19.1)	653.6 ( $\pm$ 21.7)	662.4 ( $\pm$ 20.4)
<i>Spatial attention</i>	Valid	91.2 ( $\pm$ 1.2)	87.6 ( $\pm$ 1.7)	88.7 ( $\pm$ 0.9)
	Invalid	85.0 ( $\pm$ 2.0)	85.5 ( $\pm$ 2.0)	84.0 ( $\pm$ 2.0)
<i>Motor intention</i>	Valid	89.6 ( $\pm$ 1.4)	87.6 ( $\pm$ 1.7)	89.5 ( $\pm$ 1.2)
	Invalid	85.5 ( $\pm$ 1.3)	83.6 ( $\pm$ 1.7)	83.4 ( $\pm$ 1.8)

The 2 (*task*: spatial attention/motor intention)  $\times$  2 (*validity*: valid/invalid)  $\times$  3 (%CV: 50/70/90) within-subject ANOVA on individual mean RTs yielded a significant main effect of *validity* ( $F_{1,22}=27.56$ ,  $p<.001$ ), reflecting generally slower responses in invalid as compared to valid trials. As expected, the *validity*  $\times$  %CV interaction effect was significant (linear trend:  $F_{1,22}=13.77$ ,  $p=.001$ ), indicating higher differences between invalid and valid trials with higher %CV (see Figure 4A). There were no general differences in RTs between both task versions (non-significant main effect of *task*:  $F_{1,22}=1.45$ ,  $p=.24$ ). The same results were observed when task order was included as a between-subject factor in the above ANOVA and task order did not interact with any of the effects. The same ANOVA was performed on % accuracy, revealing only a main effect of *validity* ( $F_{1,22}=14.36$ ,  $p=.001$ ). Subjects were more accurate in valid than in invalid trials. Again, this effect was not influenced by the order of task administration, nor did it interact with any of the other factors.



**Figure 4. Behavioral data.** A) Validity effects (RT invalid minus RT valid) for each %CV block in each task. Error bars represent standard errors of the mean (SEM). B) Trial-by-trial changes in cue predictability  $\hat{\mu}_1^{(t)}$  (i.e., the subject's belief that the cue will be valid) in relation to the experimentally manipulated %CV over the 284 trials, for the spatial attention and motor intention task, respectively. For this graph  $\hat{\mu}_1^{(t)}$  was calculated on the basis of group average values of the model parameters which did not differ between the two tasks. Note, however, that the profiles look different for each individual subject in each task and that individual cue predictability values entered the fMRI analyses. C) Observed and predicted response times in valid and invalid trials as a function of the trial-by-trial estimate of cue predictability  $\hat{\mu}_1^{(t)}$ , for both task versions (calculated on the basis of group average values of the model parameters). Error bars depict the standard errors of the mean (SEM). Note that there was an insufficient number of trials for the invalid condition in the lowest probability bin, so that this data point is missing.

In a next step, trial-wise estimates of cue predictability  $\hat{\mu}_1^{(t)}$  were derived from the hierarchical Gaussian filter. These estimates are governed by the constant subject-specific parameters determining the step size of the random walks at the second ( $\omega$ ) and third level ( $\vartheta$ ). Comparing these parameters between both task versions revealed no significant differences in any of the parameters. Also, the response model parameters  $\zeta_{1v}, \zeta_{1i}, \zeta_{2v}$  and  $\zeta_{2i}$ , quantifying the absolute level of RTs, and the strength of the dependency on  $\hat{\mu}_1^{(t)}$  did not significantly differ between the two task versions. There were no significant correlations between the model parameters from the spatial attention and motor intention tasks, over subjects.

Figure 4B depicts  $\hat{\mu}_1^{(t)}$  calculated on the basis of the mean model parameters of the whole group. Figure 4C shows observed valid and invalid RTs in relation to predicted RTs for different values of model-derived cue predictability  $\hat{\mu}_1^{(t)}$ , (binned in 0.1 steps). A  $2 \times 4 \times 2$  within-subject ANOVA with the factors *validity* (valid/invalid), *cue predictability*  $\hat{\mu}_1^{(t)}$  (>.55/>.65/>.75/>.85) and *task* (spatial attention/motor intention) revealed a main effect of *validity* ( $F_{1,22}=33.03$ ,  $p<.001$ ) and, as expected, a significant *validity*  $\times$  *cue predictability*  $\hat{\mu}_1^{(t)}$  interaction (linear contrast:  $F_{1,22}=17.63$ ,  $p<.001$ ), showing that the differences between RTs in invalid and valid trials increased with higher values of  $\hat{\mu}_1^{(t)}$ . This was due to decreasing RTs in valid and increasing RTs in invalid trials.

In sum, these analyses showed that RTs in the two cueing paradigms followed the hypotheses from the predictive coding framework. Moreover, analyses revealed that the dynamics of the estimation of cue predictability were comparable between the two tasks, since there were no significant differences in the subject-specific parameters of the hierarchical Gaussian filter.

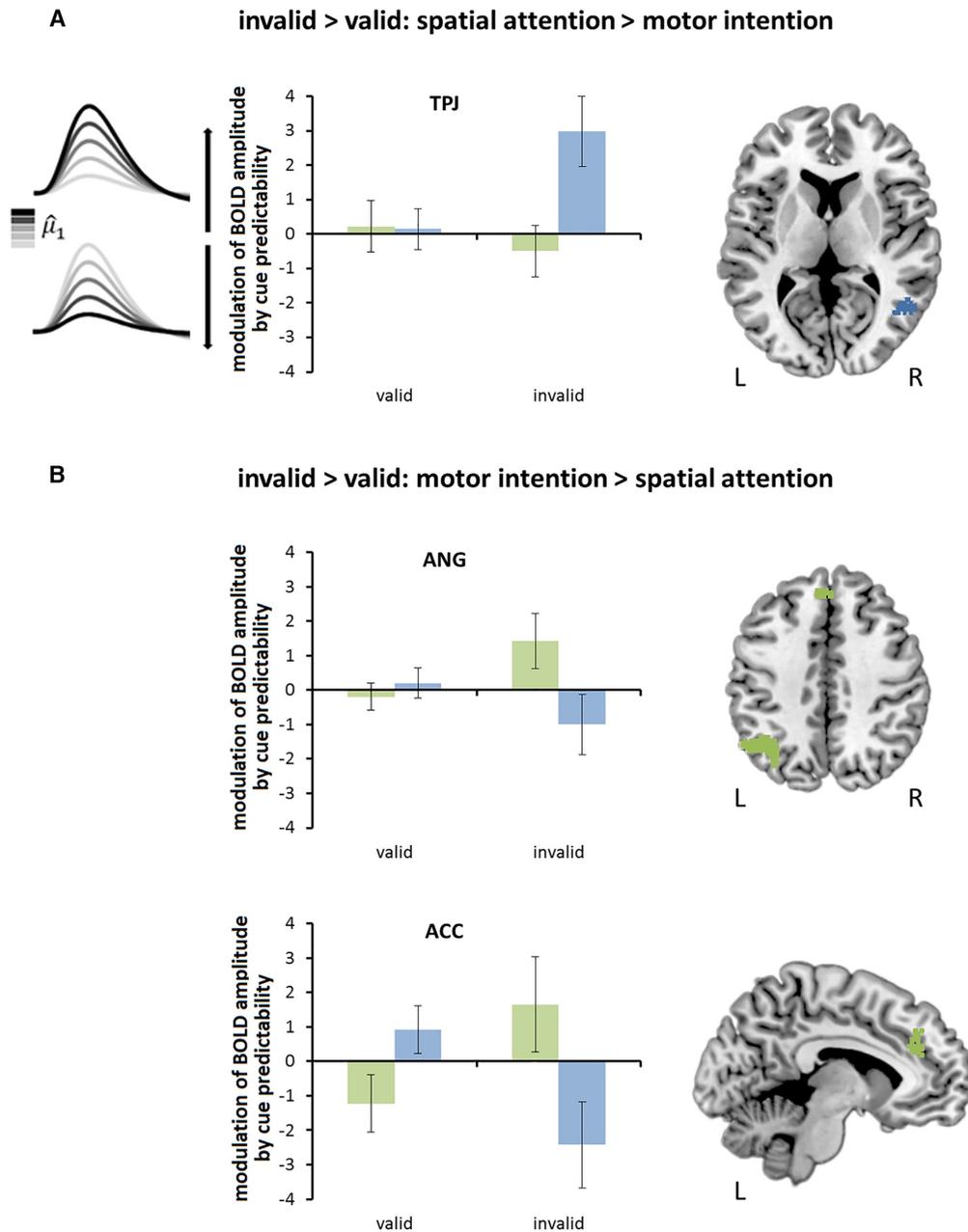
### 3.3.2 Eye movement data

Data of five subjects had to be discarded due to poor tracking inside the MR scanner. Nonetheless, eye-movements were monitored visually in these subjects on the camera screen. The remaining subjects fixated in (mean  $\pm$  SEM)  $97.7 \pm 0.45\%$  of the motor and  $97.5 \pm 0.59\%$  of the spatial cueing task, during the cue-target period. Fixation performance did not differ between the two tasks ( $t_{17}=0.73$ ,  $p=.47$ ). The  $2$  *task* (spatial attention/motor intention)  $\times$   $2$  *validity* (valid/invalid) within-subject ANOVA on the percentage fixation between target and response showed no significant effect of *task* ( $F_{1,17}=0.3$ ,  $p=.59$ ) or *validity* ( $F_{1,17}=0.02$ ,  $p=.89$ ), nor an interaction of the two factors ( $F_{1,17}=0.002$ ,  $p=.96$ ).

### 3.3.3 fMRI data

The purpose of this study was to compare the differential parametric modulation by cue predictability in invalid and valid trials between the two tasks (in analogy to the differential behavioral effects of cue predictability in valid and invalid trials). Common activity patterns should be revealed by a conjunction analysis (spatial attention invalid>valid  $\cap$  motor intention invalid>valid). However, this analysis did not yield any significant results - suggesting that there was no detectable overlap in the brain areas mediating predictability-dependent processing in the spatial attention and motor intention task.

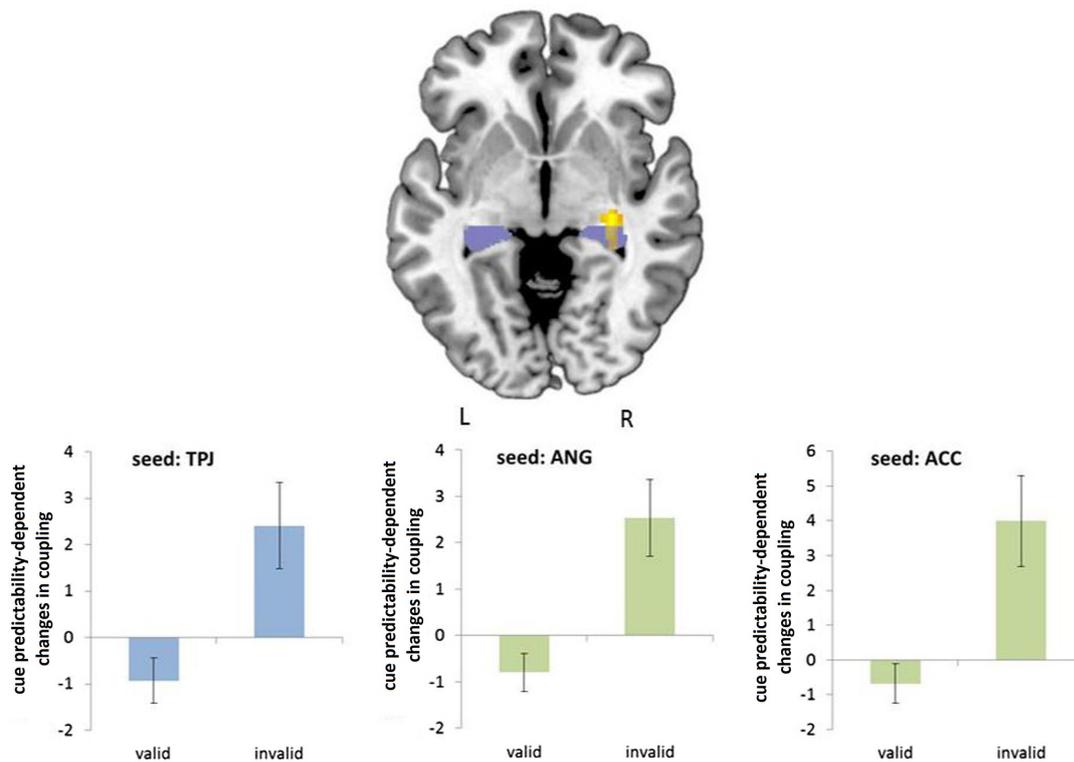
Differential (i.e., domain-specific) activity patterns should be reflected in the two interaction contrasts (spatial attention invalid>valid > motor intention invalid>valid; motor intention invalid>valid > spatial attention invalid>valid; each masked with the simple contrast of invalid>valid in the respective task). The first interaction contrast revealed that there were no whole-brain results reaching cluster-level significance for the spatial attention>motor intention effect. However, a significant effect was obtained in a ROI analysis of the right TPJ with a sphere centered on the coordinates from Vossel et al. (2015) ( $p_{\text{FWE}}$ -corrected for the search volume) ( $x=52, y=-56, z=8$ ; 10 voxel;  $t=3.7$ ). In this region, there was a positive parametric modulation effect for invalid trials, with beta estimates around zero for valid trials (see Figure 5A). For the reverse interaction contrast, we found differential parametric modulation effects for invalid versus valid trials in the left ANG ( $x=-38, y=-58, z=42$ ; 411 voxel;  $t=5.22$ ) and the left ACC ( $x=-8, y=36, z=24$ ; 156 voxel;  $t=4.92$ ), which were stronger in the motor intention than in the spatial attention task. The beta parameters for the parametric regressor cue predictability  $\hat{\mu}_1^{(t)}$  were positive for invalid trials, reflecting an increased response with higher estimated probability that the cue would be valid (see Figure 5B). In contrast, parameter estimates were zero or negative in valid trials, reflecting no or a decreasing modulation with higher estimated cue predictability.



**Figure 5. fMRI data: differential cue predictability-dependent effects for spatial attention and motor intention. A) Results of the first planned interaction contrast (spatial attention invalid>valid > motor intention invalid>valid): increasing BOLD responses in invalid trials and unmodulated BOLD responses in valid trials with higher values of model-derived cue predictability  $\hat{\mu}_1^{(t)}$  in the right temporoparietal junction (TPJ) in the spatial attention task (*blue*, in comparison with the motor intention task, *green*). B) Results of the second planned interaction contrast (motor intention invalid>valid > spatial attention invalid>valid): increasing BOLD responses in invalid trials and decreased or unmodulated BOLD responses with higher values of model-derived cue predictability  $\hat{\mu}_1^{(t)}$  in valid trials in the left ANG and left ACC in the motor intention task (*green*, in comparison with the spatial attention task, *blue*). L= left hemisphere; R=right hemisphere.**

### 3.3.4 PPI results

We used PPI analyses to investigate if there was a common brain region exhibiting predictability-dependent coupling changes with right TPJ during spatial attention and left ANG or ACC during motor intention, respectively. Figure 6 shows the results of the conjunction analysis testing for significant PPI effects in at least two of the three contrasts capturing the effects of validity- and predictability-dependent coupling with the three seeds. The only region in which a significant effect at the cluster-level could be observed was located in the anterior part of the right hippocampus ( $x=30, y=-24, z=-4$ ; 131 voxels;  $t=2.85$ ). Post-hoc analyses of the beta estimates of the parametric PPI regressors revealed that a significant difference between cue predictability-dependent coupling in valid and invalid trials was present for all three seed regions (two-sided paired t-tests: TPJ seed:  $t_{22}=-3.4, p=.003$ ; ANG seed:  $t_{22}=-3.8, p=.001$ ; ACC seed:  $t_{22}=-3.5, p=.002$ ; see bar charts in Figure 6).



**Figure 6. Results of the conjunction analysis of cue-predictability-dependent coupling changes with the right TPJ during spatial attention and the left ANG and ACC during motor intention (yellow). The hippocampus (violet) is shown according to the Automated Anatomical Labeling atlas provided in MRIcroN. Analysis of the parameter estimates for the parametric PPI regressors in valid and invalid trials revealed that a significant predictability-dependent coupling effect with the hippocampus was present for all three seed regions. Blue bars indicate the spatial attention task; green bars, the motor intention task. L, Left hemisphere; R, right hemisphere.**

### 3.4 Discussion

The present study combined computational modeling of behavior with fMRI to characterize common and distinct cortical mechanisms for predictive processing in spatial attentional and motor intentional systems. Manual RTs in two probabilistic cueing tasks were similarly affected by unsignaled changes in the predictability of a cue that indicated either the location of or the required response to a target stimulus. Differential parametric effects of BOLD responses by model-derived cue predictability in valid and invalid trials were regarded as signatures of the belief updating by precision-weighted prediction errors. Brain areas exhibiting such activity patterns were distinct for spatial attention and motor intention, with an involvement of the left ANG and ACC for motor intention and the right TPJ for spatial attention. In these areas, BOLD amplitudes were increased in invalid trials with higher estimated cue predictability (i.e., when an invalidly cued target was more unexpected) and decreased (ACC) or unmodulated (TPJ and ANG) in valid trials. There were no common areas in which cue predictability modulated neural activity in both domains. However, connectivity analyses revealed that the right hippocampus contributed to predictive processing in all three areas (TPJ during spatial attention; ANG and ACC during motor intention). Our results therefore suggest that, although the flexible control by inferred cue predictability recruited differential cortical structures in the two cognitive domains (i.e., spatial attention, motor intention), these structures all showed predictability-dependent coupling with the hippocampus.

#### 3.4.1 Behavior

In both the spatial attention and the motor intention task, RTs were equally affected by invalid cue information, as well as by experimentally manipulated changes in the probability that the cue would be valid. Moreover, there were no differences in the overall level of RTs or accuracy. Similarly, there were no significant differences in the parameters of the hierarchical Gaussian filter governing the trialwise estimation of cue predictability between the two tasks. This is consistent with previous studies showing the sensitivity of behavioral responses to probabilistic context during spatial attention (Vossel et al., 2014a) and motor intention (Bestmann et al., 2008). However, the model parameters were not correlated between the spatial attention and motor intention task. This contrasts with findings from the comparison of a spatial and a feature-based attention task, where the updating parameter of the second level of the model ( $\omega$ ) was significantly correlated between the two task versions (Dombert et al., 2016a). Consistent with these behavioral results, Dombert et al. (2016a) found a common modulation of reorienting-related activity in the left intraparietal sulcus, whereas the conjunction analysis in the present study did

not reveal any significant common effect.

### **3.4.2 Distinct and common mechanisms of cue-predictability-dependent processing**

Differential effects mediated (in our predictive processing model) by precision-weighted prediction errors were found in the left ANG and ACC for motor intention and in the right TPJ for spatial attention. Here, BOLD amplitudes increased with higher model-derived cue predictability in invalid trials. In TPJ and ANG, there was no substantial modulatory effect in valid trials. Although a negative parametric modulation effect would have been predicted from theoretical grounds, this finding is consistent with data from Lasaponara et al. (2011), who showed that effects of higher percentage of cue validity on RTs and ERPs can be stronger for cueing costs (invalid trials compared with neutral trials) than for benefits (valid trials compared with neutral trials).

The effect in the right TPJ replicates findings from previous studies using the same modeling approach with either saccadic responses (Vossel et al., 2015) or manual responses (Dombert et al., 2016a). It also extends these previous findings by showing that this effect was specific for the spatial attention condition because it was not observed for the motor intention task (cf. Fig. 5A). Because we were able to differentiate between attentional and motor intentional aspects in the present paradigm, we can ascribe the effect in TPJ to purely spatial attentional mechanisms. In other words, the preparation of eye movements or the allocation of covert spatial attention seem to involve different mechanisms than the preparation of limb movements.

Conversely, reorienting after invalid motor (but not spatial) cues was affected by model-derived cue predictability in the left ANG and the ACC extending into the left medial superior frontal gyrus. The finding that cue-predictability-dependent effects in a feature-based cueing task without a motor intentional component were observed in yet another brain region in the study by Dombert et al. (2016a) supports the interpretation that the effects in the present study were driven by the motor intentional component rather than by the expectation of a specific target feature. The area in the ACC has also been described as the rostral cingulate zone (RCZ). Our findings are consistent with a study on reward learning of actions, which reported that the RCZ responded stronger to negative events in a probabilistic reversal learning task when the reward rate was high (Jocham et al., 2009). Similarly, in our study, the BOLD response in this region to invalidly cued motor responses was increased with higher estimated cue predictability even though there was no reward associated with the action. The ACC has also been shown to be especially triggered

during cognitively demanding actions after context-specific behavioral surprise (Tobia et al., 2016), as well as during action selection when different response alternatives are competing (Botvinick et al., 1999), which would correspond to invalid trials in the present task. Similarly, predictability-dependent modulation of ACC activity during the motor intention task could also reflect the suppression of the previously prepared motor response. van Gaal and colleagues (2010) characterized a neural network comprising the ACC responsible for the inhibition of responses during a go/no-go task. Our results support the previous associations of ACC with response conflict and selection, but add that this area is modulated by the inferred cue predictability regardless of external reward.

According to probabilistic fiber tracking, the ACC is interconnected structurally with a subregion of the ANG (Caspers et al., 2011), which also showed predictability-dependent effects in the motor intention task. It has to be noted that this parietal activation was located more posteriorly than the activation reported by previous studies on motor intention in the supramarginal gyrus, which did not consider predictability-dependent effects (Rushworth et al., 2001b). Ranganath and Ritchey (2012) suggest that the ANG might be a candidate area for integrating contextual information due to its connection to the hippocampus and a wide-spread posterior medial system. Another view is that the ANG is a core region for providing an interface between the converging bottom-up multisensory inputs and the top-down predictions in the perception-to-action loop and that this can explain its involvement in a variety of functions (Seghier, 2013). Our data extend these previous findings by showing that activity in the ANG is modulated by probabilistic context on a short trial-by-trial time scale and that this effect is specific for situations with a motor intentional component.

The conjunction analysis of predictability-dependent processing did not detect any common brain regions for spatial attention and motor intention. This finding, together with the significant differential effects reflected in the interactions of task and validity discussed above, argue against a mere “frequency detector” module in the brain, which simply responds to rare events. Interestingly, however, the additional PPI analysis revealed a converging coupling pattern between all three seed regions (TPJ, ACC, and ANG) and the anterior hippocampus for predictability-dependent processing. The hippocampus has been shown to encode the predictability or expected uncertainty (entropy) in choice and sequential RT tasks (Strange et al., 2005; Harrison et al., 2006). Moreover, a recent study has shown that update signals in different brain structures lead to activity changes in the hippocampus and other medial temporal lobe structures, which may suggest that these latter regions provide an online store or neural representation of a current internal model

(Boorman et al., 2016). Our data, together with these previous results, provide evidence that the trialwise inference of predictability (involving the temporal integration and processing of relationships between events) recruits the hippocampal system regardless of the content of the encoded information (motoric or spatial). Therefore, the hippocampal system can process different types of (spatial and nonspatial) stimulus information flexibly (Viard et al., 2011) and support the formation of internal models to control perception and action in an uncertain world.

In conclusion, our findings provide novel insights into the generality and specificity of the computational anatomy underlying the flexible control of attention and intention in the human brain. Our data, together with previous findings in the attentional domain, argue for the notion that precision-weighted prediction errors induce belief updating in each cognitive domain separately, but that the necessity to relate new information to previous events and integrating it into memory involves crosstalk with the hippocampus in both systems regardless of the informational content. Therefore, our results confirm the previously reported dissociation and complementary lateralization of spatial attention and motor intention in the parietal cortex. At the same time, they highlight similarities of both systems in terms of computational principles and connectivity profiles.

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## 4. Reduced Bayesian belief updating with motor intentional cues in aging

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EMPIRICAL SECTION  
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## **Abstract**

Predicting upcoming events using past observations is a crucial component of an efficient allocation of attentional resources. The deployment of attention is sensitive to different types of cues predicting upcoming events. Here we investigated probabilistic inference abilities in spatial and feature-based attentional, as well as in motor intentional subsystems, focusing specifically on the age-related changes in these abilities. In two behavioral experiments, younger and older adults (20 younger and 20 older adults for each experiment) performed three versions of a cueing paradigm, where spatial, feature or motor cues predicted the location, color or motor response of a target stimulus. The percentage of cue validity (i.e. the probability of the cue being valid) changed over time, thereby creating a volatile environment. A Bayesian hierarchical model was used to estimate trial-wise beliefs concerning the cue validity on the basis of reaction times and to derive a subject-specific belief updating parameter  $\omega$  in each version of the task. We also manipulated task difficulty: in Experiment 1 participants performed an easier version of the task, whereas in Experiment 2 a more difficult version was employed. Results from Experiment 1 suggested a preserved ability to use the three different cues to generate predictions in the group of older adults. However, the increased task demands of Experiment 2 uncovered a difference in belief updating (i.e. the model parameter  $\omega$ ) between the two age groups, indicating a reduction of the ability to update predictions with motor intention cues in older compared with younger adults.

These results point towards a distinction of attentional and motor intentional subsystems, with more severe age-related differences in the motor intentional subsystem.

## 4.1 Introduction

Predictions concerning upcoming events play an important role in modulating our responses. Especially when facing an uncertain environment, our decisions and responses will depend on one side on the prior beliefs that we created during our past experiences in the same or in a similar situation, and on the other side on our ability to flexibly adapt to the ever-changing environment (Behrens, Woolrich, Walton, & Rushworth, 2007).

Previous research has shown that the deployment of attention is modulated by similar mechanisms (Vossel, Mathys, Daunizeau, Bauer, Driver, Friston & Stephan, 2014; Vossel, Mathys, Stephan, & Friston, 2015). Cueing paradigms, in which a cue predicts the location, a particular feature of a target, or the required motor response with a specific probability, are particularly useful to investigate the role of predictions for the attentional deployment (Posner, 1980; Rushworth, Ellison, & Walsh, 2001; Vossel et al., 2014; Dombert, Kuhns, Mengotti, Fink, & Vossel, 2016; Kuhns, Dombert, Mengotti, Fink, & Vossel, 2017). In these paradigms, validly cued targets induce faster responses, whereas slower responses are observed when predictions are violated, i.e. with invalidly cued targets. Moreover, reaction time (RT) differences between valid and invalid trials increase with increasing percentage of cue validity (%CV). Previous studies have shown that people are sensitive to changes in %CV, even when these changes are not explicitly signalled (Vossel et al., 2014; Dombert et al., 2016; Kuhns et al., 2017). In volatile environments, when the %CV is changing unpredictably over time, people tend to infer the validity of the cue on the basis of observations in past trials and this probabilistic inference process can be described using a hierarchical Bayesian learning model (Mathys, Daunizeau, Friston, & Stephan, 2011). This model formally quantifies the participants' estimates concerning the probability of the cue being valid, as well as the trial-wise updating of these beliefs. The hierarchical structure of the model allows a flexible estimate of the updating of the belief concerning the %CV. Such beliefs are influenced by the higher level of the model describing the estimate of the volatility of the environment and by a parameter describing the subject-specific speed of updating of these beliefs about volatility.

Recent evidence points towards a reduced ability in older adults to use uncertainty to guide learning in a predictive inference task (Nassar et al., 2016), and to flexibly adapt to changes in reward-based learning, particularly when reward information is uncertain (Eppinger, Haemmerer, & Li, 2011). The aim of the present study was to investigate age-related differences in flexibly adapting to changes in a volatile environment (i.e. belief

updating) in different cognitive subsystems. We used three distinct cueing versions to isolate the processes involved in spatial attention, feature-based attention and motor intention, and two different levels of difficulty of the tasks. Unsignaled changes in the %CV occurred during the course of the experiments, creating a volatile environment. A Bayesian hierarchical model was applied to estimate trial-wise predictions about cue validity based on individual RTs and to deduct and compare subject-specific updating parameters (Mathys et al., 2011). Recent research with healthy young participants combining this modelling approach with functional MRI (Dombert et al., 2016; Kuhns et al., 2017) identified common and distinct anatomical correlates of probabilistic inference in these three subsystems. Results showed that a common node located in the left anterior intraparietal sulcus (IPS) was involved in inferring trial-wise cue validity during spatial and feature-based attention (Dombert et al., 2016). However, distinct correlates were found for spatial attention and motor intention (Kuhns et al., 2017). Whereas for spatial attention the activity of the right temporo-parietal junction (TPJ) was modulated by trial-wise estimates of the cue being valid (see also Vessel et al., 2015 and Dombert et al., 2016), the same process for motor cues was supported by the left angular gyrus (ANG) and anterior cingulate cortex (ACC).

Based on these previous results, we hypothesized similar age-related changes for the spatial and feature-based attentional subsystems, but a possibly distinct pattern for belief updating in the motor intention system.

## 4.2 Experiment 1: Materials and Methods

### 4.2.1 Participants

Initially, twenty-one older and twenty-one younger volunteers participated in the current study. Inclusion criteria were an age between 18-30 years for the younger group and between 50-75 years for the older group. All participants were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), had normal or corrected-to-normal vision and no history of neurological or psychiatric disorders. The group of older participants underwent the Mini-Mental-State Examination (MMSE) to rule out general cognitive deficits (inclusion criterion: score  $\geq 29$ ; Folstein, Folstein, & McHugh, 1975). One participant in each group had to be excluded from further analyses since the error rate in the experimental tasks deviated more than two standard deviations from the group mean. Hence, the final sample consisted of 20 older (9 females; age:  $59 \pm 6.8$  ( $\pm$ SD) years; age range 50-71 years) and 20 younger participants (10 females; age:  $23 \pm 3.3$  ( $\pm$ SD) years; age range 18-30 years). All participants gave written informed consent prior to participation. The study had been approved by the local ethics committee and was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

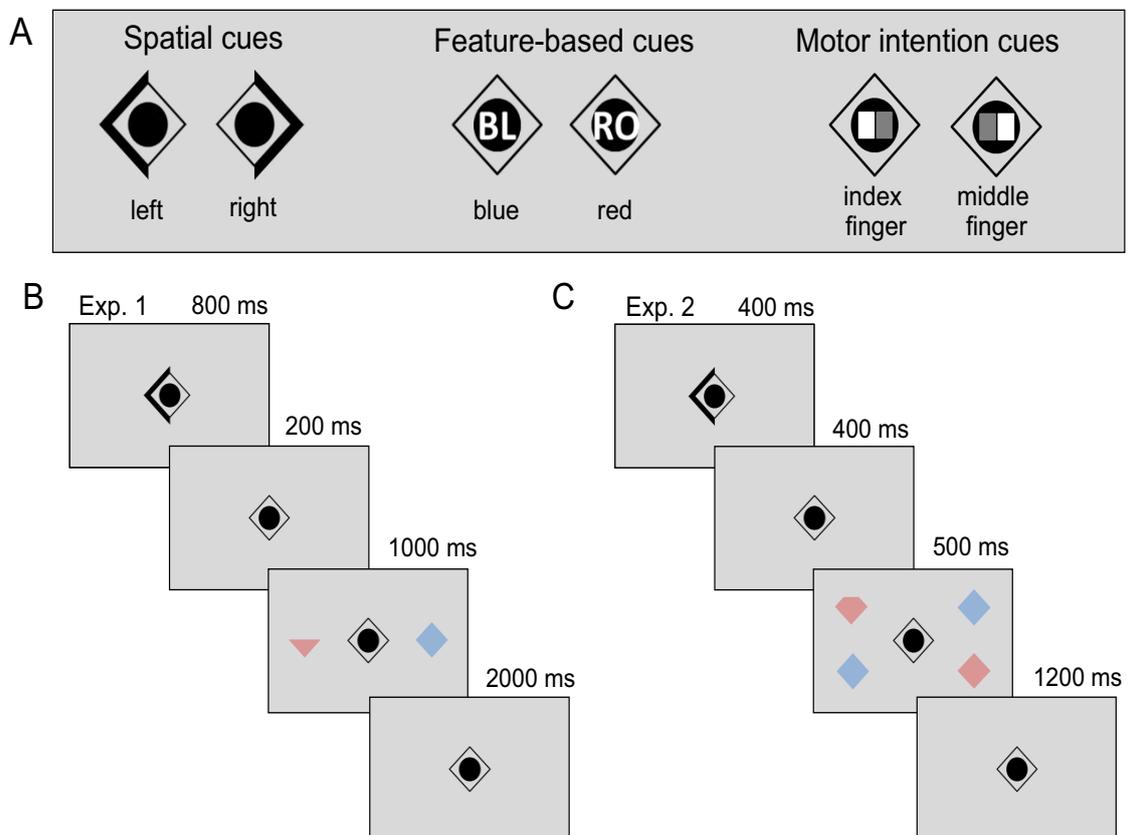
### 4.2.2 Stimuli and experimental paradigm

Three different cueing tasks (adapted from Dombert et al., 2016 and Kuhns et al., 2017) were presented consecutively on a laptop (resolution 1024 x 768, 60 Hz sampling rate) at a viewing distance of 52 cm.

At the beginning of each trial the cue stimulus was shown for 800 ms. The cues in the three task versions contained either spatial or feature information about the upcoming target, or were preparatory for a motor response. In the spatial attention version, an arrowhead presented at the central fixation diamond pointed to the left or right side of the display, thereby indicating the most likely target location (Figure 1A). In the feature-based attention task, feature cues provided information about the most likely colour of the target. These cues consisted of two-letter abbreviation of the colour word in the centre of the fixation diamond ('BL' or 'RO'; [i.e. 'BL', 'RE', in German, respectively) (Figure 1A). This cue has been shown to elicit most effective cueing effects when compared to the presentation of the physical colour or the whole colour word (Dombert, Fink, & Vossel, 2016). Finally, in the motor intention task, the cue illustrated the two response buttons within the fixation diamond, with one being white and the other one being grey. Participants were asked to prepare the motor response corresponding to the white button,

cueing either the right index or middle finger in preparation towards the upcoming target (Figure 1A).

After a 1000 ms stimulus onset asynchrony, the target display appeared for 1000 ms, consisting of one target stimulus, an upward or downward triangle located either on the left or right side of the fixation diamond (4.1° eccentric in each visual field, see Figure 1B), and a distractor stimulus (a diamond, located on the opposite side). When the distractor was red, the target was blue and vice versa. Participants were asked to respond to upward or downward triangles by button presses with two different response buttons for their right index and middle finger. The response mapping (upward/downward triangle - index/middle finger) was counterbalanced between participants. Participants were instructed to maintain central fixation and to respond as fast as possible to the target.



**Figure 1. Experimental paradigm in Experiment 1 and 2. A. Three different cue stimuli were used for guiding spatial attention, feature-based attention, and motor intention. The spatial cue guided the attention towards one hemifield of the search display, whereas the feature cue was informative about the target colour (RO for 'red' and BL for 'blue'). Motor responses were indicated by the salient white button cueing for index or middle finger response. B. Timeline of a valid trial for the spatial**

### **attention task in Experiment 1. C. Timeline of a valid trial for the spatial attention task in Experiment 2.**

The order in which the three different cueing tasks testing spatial attention, feature-based attention, or motor intention were administered was counterbalanced across participants. In each cueing task, the proportion of valid and invalid trials determining the validity of the cue information (%CV; i.e. the probability that the cue will be valid) changed over the course of the experiment between levels of 50% and 80% (Figure 2B). Participants were informed about possible changes in %CV, but not about when they would occur or how high the %CV would be. A total of 200 trials per cueing version were shown, with alternating %CV blocks, each block consisting of 40 trials (Figure 2B). The position of the target, as well as its colour, was counterbalanced across the cueing conditions and the %CV blocks. Following standard procedures in computational studies of trial-wise inference, target stimuli and trial sequence were identical between cueing versions. Halfway through each version, a one-minute break was introduced by displaying the word "Pause". A practice session preceded each task of the experiment, so that participants could get used to the fixation, manual response and cueing conditions. The practice consisted of two short separate runs; one run with a constant 80 %CV followed by a second run with changes in %CV. The total duration of the experiment (three runs with practice in between) amounted to approximately 70 minutes.

#### **4.2.3 Statistical analysis of general task performance and cueing effects in relation to task domain and age**

In a first step, we investigated the differences in general performance between the two age groups in the three different cueing tasks. Each subject's mean RT for correct trials was calculated across all cueing and %CV conditions. Responses deviating more than two standard deviations from the overall individual mean were discarded. Mean RT for each subject in each task version entered a  $3 \times 2$  ANOVA with the within-subject factor *Task* (spatial attention/feature-based attention/motor intention) and *Age* (younger/older) as between-subject factor. A similar ANOVA was performed on accuracy (% correct responses).

Moreover, we tested whether the participants showed general differences in cueing effects in the different versions of the task and between the two age groups. To account for the generally slower responses in older participants revealed by the first ANOVA, we calculated normalized cueing effects by dividing the difference between valid and invalid RT by mean overall RT. These normalized cueing effects were analyzed with a 3 (*Task*:

spatial attention/feature attention/motor intention)  $\times$  2 (Age: younger/older) ANOVA. In addition, the normalized cueing effects were tested against zero with one-sample t-tests to ensure that the subjects paid attention to the cues. Results of the ANOVAs are reported after Greenhouse-Geisser correction at a significance level of  $p < 0.05$ . Post-hoc t-tests (with Bonferroni correction) were computed to interpret the significant effects when appropriate.

#### 4.2.4 Bayesian modeling and statistical analysis of age and domain-specific inference on cue predictability

To investigate age-related differences in belief updating under uncertainty during spatial attention, feature-based attention, and motor intention, a Bayesian hierarchical learning model was applied, estimating the individual trial-wise beliefs about cue validity (Mathys et al., 2011; Vossel et al., 2014). Single-trial RTs of each participant were used to derive learning parameters for each task. Since the general speed of responding differed between the two age groups, these analyses were based on normalized RTs (RT divided by overall mean RT).

The model, applied separately in the three tasks, incorporates a *perceptual* and a *response* model (Figure 2A). While the perceptual model describes updating of beliefs based on the cue-target outcomes (observations), the response model is used to derive responses (i.e. RTs) based on these beliefs. For a more in depth description of the model, please refer to Mathys et al. (2011). In what follows, we will describe the model parameters as relevant for the present study.

The perceptual model consists of hierarchically coupled Gaussian random walks enabling a flexible control of updating of the beliefs about cue validity in each trial, in relation to beliefs about volatility and subject-specific parameters. It comprises three states denoted by  $x$ . The state  $x_1^{(t)}$  represents the environmental state of each trial  $t$ , which, in the present paradigm, consisted of either a validly or invalidly cued target (with  $x_1^{(t)} = 1$  for valid and  $x_1^{(t)} = 0$  for invalid trials). The distribution of the probability of a trial being valid (i.e.  $x_1^{(t)} = 1$ ) is a Bernoulli distribution governed by the next higher state  $x_2^{(t)}$ , which in turn changes over time as a Gaussian random walk. The volatility of  $x_2^{(t)}$  (i.e. how fast  $x_2^{(t)}$  changes after new observations) is determined by two quantities:  $x_3^{(t)}$  (the state of the next upper level of the hierarchy) and a subject-specific updating parameter  $\omega$ . The third state  $x_3^{(t)}$  also changes as a Gaussian random walk, with the dispersion of the random walk being determined by a second fixed subject-specific parameter  $\vartheta$ .  $\omega$  determines the step size of the random walk at the second level of the model, or in other

words, the speed of the belief update about cue validity from trial-to-trial.  $\vartheta$  determines the speed of the update about the stability of cue validity (i.e. volatility, third level of the model).

**A**

Level 3: Volatility of cue predictability

$$p(x_3^{(t)}) \sim N(x_3^{(t-1)}, \vartheta)$$

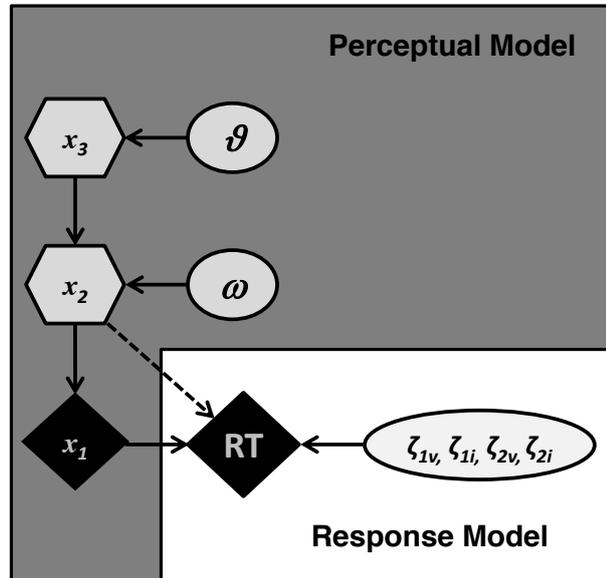
Level 2: Tendency towards valid trials

$$p(x_2^{(t)}) \sim N(x_2^{(t-1)}, e^{x_3 + \omega})$$

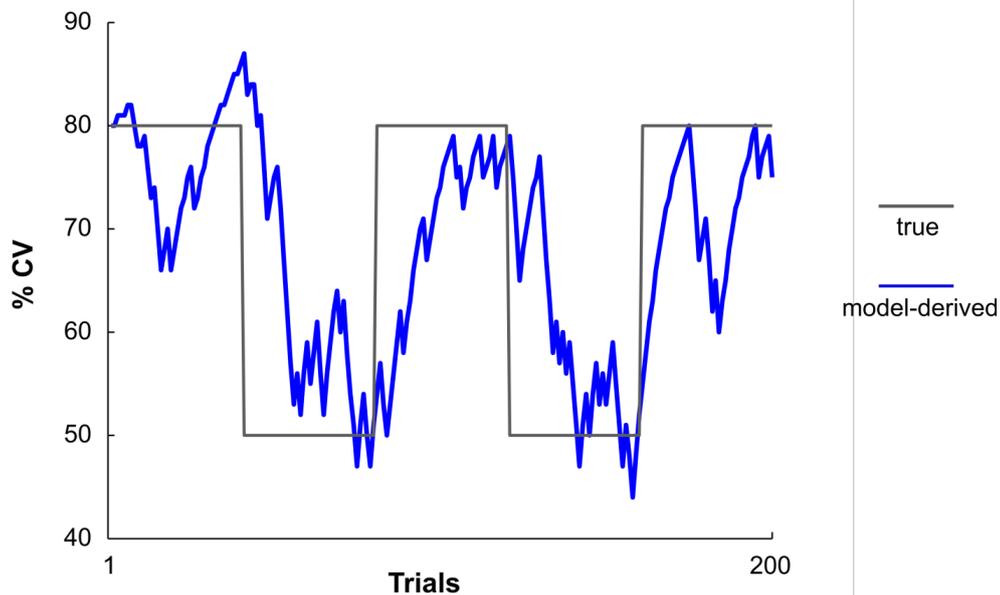
Level 1: Observations (valid/invalid trials)

$$p(x_1 = 1) = s(x_2) \text{ valid trial}$$

$$p(x_1 = 0) = 1 - s(x_2) \text{ invalid trial}$$



**B**



**Figure 2.** Illustration of the Bayesian hierarchical model for belief updating and example of behavioural output. **A.** The perceptual model (shown on the dark grey background) incorporates the three states ( $x_1, x_2, x_3$ ). Higher levels are influenced by constant parameters  $\omega$  and  $\vartheta$ , which affect trial-wise changes on the respective level. Whereas the variables shown in diamonds and hexagons are quantities evolving with time (trials), circled variables are constants. Additionally, the quantities in the hexagons rely upon their previous states in a Markovian fashion. **B.**

**Percentage of cue validity (%CV) was manipulated over the course of the experiments, alternating between 80 and 50% (grey line). Here, trial-by-trial changes in probability-dependent processing  $\hat{\mu}_1^{(t)}$  (i.e. the subject's belief that the cue will be valid) in relation to the volatile environment over the course of 200 trials is shown. For this graph  $\hat{\mu}_1^{(t)}$  was calculated for one subject to exemplify the model.**

To infer the subject-specific beliefs about trial-by-trial variations in probabilistic contingencies from the RTs, the perceptual model needs to be inverted; this yields the posterior densities of the three hidden states  $x^{(t)}$ . In the following, the sufficient statistics of the subject's posterior belief will be denoted by  $\mu^{(t)}$  (mean),  $\sigma^{(t)}$  (variance), and  $\pi^{(t)} = \frac{1}{\sigma^{(t)}}$  (precision). As described in detail in Mathys et al. (2011), variational model inversion under a mean field approximation yields simple analytical update equations – where belief updating rests on precision-weighted prediction errors. These update equations provide approximately Bayes-optimal rules for the trial-by-trial updating of the beliefs. In this experiment, they provide us with the subject's estimate of the probability that the target appears at the cued location, the target color matches the cue, or that the target will require the cued motor response in a particular trial (note that this is an individualized approximate Bayes-optimality, in reference to the subject-specific values for the updating parameters  $\omega$  and  $\vartheta$ ).

A response model was used to map the derived posterior beliefs to the observed RTs. In previous work (Dombert et al., 2016; Kuhns et al., 2017) a response model in which RTs were directly governed by the estimated cue validity before the observation of the trial outcome  $\hat{\mu}_1^{(t)}$  described the data most plausibly. Variational Bayesian estimation was used to derive the model parameters based on RTs, as implemented in the HGF toolbox (<http://www.translationalneuromodeling.org/tapas/>) running on MATLAB® (2012b, The MathWorks, Inc., Natick, Massachusetts, United States). The two response model parameters  $\zeta_1$  and  $\zeta_2$  parameterize the intercept and the slope of the linear function:

$$RT^{(t)} = \begin{cases} \zeta_{1v} - \zeta_{2v}\hat{\mu}_1^{(t)} & \text{for } x_1^{(t)}=1 \text{ (i.e. valid trial)} \\ \zeta_{1i} + \zeta_{2i}\hat{\mu}_1^{(t)} & \text{for } x_1^{(t)}=0 \text{ (i.e. invalid trial)} \end{cases}$$

Again, like the subject-specific parameters  $\omega$  and  $\vartheta$  of the perceptual model, these response model parameters were estimated for each subject from the individual RT data (normalized RTs).

### 4.3 Results

An overview over mean RTs and accuracy in the three versions of the cueing tasks for each age group is given in Table 1.

**Table 1. Behavioural data for Experiment 1. Mean RTs ( $\pm$  SEM) and mean accuracy ( $\pm$  SEM), for spatial attention, feature-based attention and motor intention, separately for younger and older adults.**

Task	Mean RT (ms)		Accuracy (%)	
	Younger	Older	Younger	Older
<i>Spatial attention</i>	507 ( $\pm 16$ )	655 ( $\pm 19$ )	97.6 ( $\pm 0.3$ )	98.3 ( $\pm 0.3$ )
<i>Feature-based attention</i>	502 ( $\pm 17$ )	648 ( $\pm 16$ )	96.5 ( $\pm 0.5$ )	98.0 ( $\pm 0.3$ )
<i>Motor intention</i>	486 ( $\pm 18$ )	607 ( $\pm 16$ )	96.0 ( $\pm 0.5$ )	98.0 ( $\pm 0.4$ )

The ANOVA on accuracy with the within-subject factor *Task* (feature-based attention/spatial attention/motor intention) and the between-subject factor *Age* (younger/older) yielded to a main effect of *Task* ( $F_{(1.8,68.1)} = 5.91$ ,  $p = 0.006$ ). Post-hoc paired samples t-tests (Bonferroni corrected threshold:  $p = 0.017$ ) comparing the tasks revealed better performance in the spatial attention task ( $97.9 \pm 0.2\%$ ; mean  $\pm$  SEM) compared to the motor intention task ( $97 \pm 0.36\%$ ;  $t_{(39)} = -2.92$ ,  $p = 0.006$ ) and compared to the feature-based attention task ( $97.3 \pm 0.34\%$ ;  $t_{(39)} = -2.89$ ,  $p = 0.006$ ). The main effect of the between-subject factor *Age* was significant ( $F_{(1,38)} = 7.96$ ,  $p = 0.008$ ), indicating higher accuracy for older than younger participants ( $98 \pm 0.35\%$  vs.  $97 \pm 0.35\%$ ). The interaction *Age*  $\times$  *Task* was not significant ( $F_{(1.8,68.1)} = 2.4$ ,  $p = 0.1$ ).

The ANOVA on individual mean RT (across all conditions) revealed a significant main effect of *Task* ( $F_{(1.9,72.9)} = 9.74$ ,  $p = 0.0002$ ). Post-hoc paired samples t-tests (Bonferroni corrected threshold:  $p = 0.017$ ) comparing the tasks revealed significantly faster RTs in the motor intention task ( $546 \pm 15$  ms; mean  $\pm$  SEM) as compared to the spatial attention ( $581 \pm 17$  ms;  $t_{(39)} = -4.4$ ,  $p = 0.00007$ ) and the feature-based attention task ( $575 \pm 16$  ms;  $t_{(39)} = 3.18$ ,  $p = 0.003$ ). Additionally, the between-subject factor *Age*

was significant ( $F_{(1,38)} = 39.67$ ,  $p = 0.0000002$ ), indicating generally slower RTs for the older participants ( $636 \pm 15$  ms vs.  $498 \pm 15$  ms). The interaction *Age*  $\times$  *Task* was not significant ( $F_{(1,9,72.9)} = 1.58$ ,  $p = 0.21$ ).

The ANOVA on normalized cueing effects yielded to no significant main effect of *Task* ( $F_{(2,75.3)} = 1.35$ ,  $p = 0.27$ ) or *Age* ( $F_{(1,38)} = 0.21$ ,  $p = 0.65$ ), nor an interaction between *Task*  $\times$  *Age* ( $F_{(2,75.3)} = 0.34$ ,  $p = 0.71$ ). We additionally performed one-sample t-test against zero to investigate whether younger and older adults show significant cueing effects in all task versions. Indeed, all t-tests were significant (all  $ps < 0.005$ ), showing that both age groups were using the cues during the three tasks versions.

The main focus of our study was the assessment of trial-wise inference on cue validity using Bayesian modeling. For this reason, we analyzed the task- and subject-specific parameters  $\omega$  and  $\vartheta$  which determine the speed of the trial-wise updating of belief that the cue will be valid ( $\omega$ ) and beliefs about volatility of cue validity ( $\vartheta$ ). The ANOVA with the within-subject factor *Task* (feature-based attention/spatial attention/motor intention) and the between-subject factor *Age* (younger/older) on the updating parameter  $\omega$  did not reveal any significant main effect (*Task*:  $F_{(2,75.1)} = 0.25$ ,  $p = 0.78$ ; *Age*:  $F_{(1,38)} = 3.3$ ,  $p = 0.08$ ) or interaction (*Task*  $\times$  *Age*:  $F_{(2,75.1)} = 0.06$ ,  $p = 0.94$ ). The ANOVA on the parameter  $\vartheta$  quantifying updating about volatility did also not reveal any significant main effect (*Task*:  $F_{(1,38.3)} = 1.28$ ,  $p = 0.27$ ; *Age*:  $F_{(1,38)} = 0.73$ ,  $p = 0.4$ ) or interaction (*Task*  $\times$  *Age*:  $F_{(1,38.3)} = 0.87$ ,  $p = 0.36$ ).

Figure 3 shows observed RT costs in relation to predicted RTs costs for different values of estimated cue validity  $\hat{\mu}_1^{(t)}$  (binned in higher or lower/equal to 0.7).

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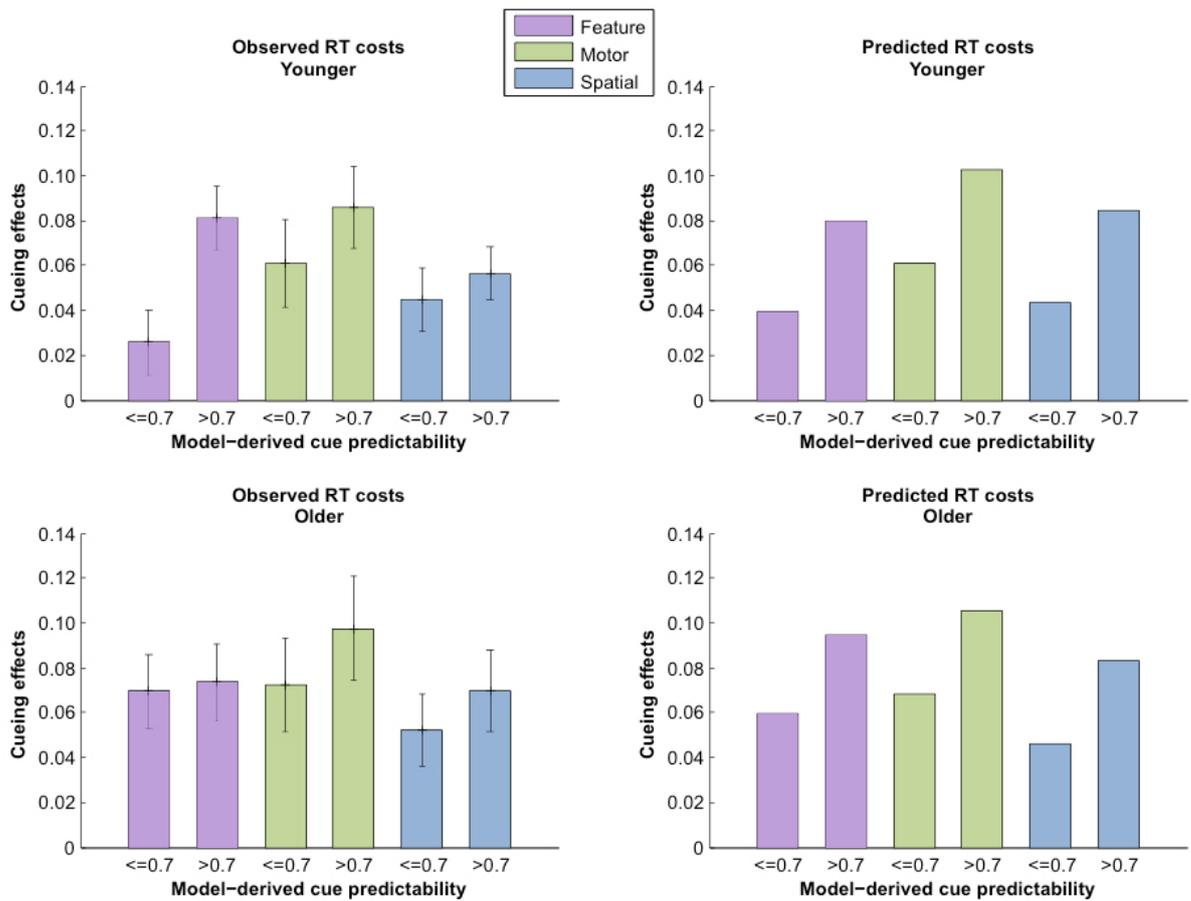


Figure 3. Observed and predicted pattern of RT costs from the Bayesian hierarchical model in Experiment 1. RT costs were calculated by subtracting normalized RTs of invalid trials from valid trials and they are shown in relation to the participants' trial-by-trial estimate of the cue predictability  $\hat{\mu}_1^{(t)}$  for all three tasks versions and the two age groups, binned in cue validity higher or lower/equal to 0.7. Error bars indicate SEM.

## 4.4 Discussion

The first experiment was designed to explore putative age-related differences in the ability to use trial-by-trial observations to estimate the cue validity, i.e. to update predictions concerning upcoming stimuli. In addition, we tested whether the attentional deployment and the updating behaviour differed between three different versions of the cueing paradigm, namely the spatial attention, the feature-based attention, and the motor intention tasks.

We found no evidence of age-related differences in belief updating abilities. None of the learning parameters from the Bayesian learning model analyzed showed group differences between older and younger participants. There was also no evidence of differences in updating between the three different tasks. As for the attentional deployment, measured from the normalized cueing effects, we again did not find any age-related differences, nor differences in the different tasks. However, we did find age-related differences in the general performance, with older participants being more accurate but slower in reacting than the younger participants, indicating a speed-accuracy trade-off. In addition, we found a higher accuracy for the spatial task, compared with the feature-based and the motor intention tasks, and faster RTs for the motor intention task, compared with the spatial and the feature-based tasks. Although the reaction to the target involves motor preparation across conditions, the motor intentional cue allows building a representation of the movement at an earlier stage and this might explain these RT differences.

Given the results from Experiment 1, we could not conclude that older participants differ from younger participants in their probabilistic inference abilities. Therefore, in Experiment 2 we used a more difficult version of the cueing paradigm, more similar to the ones used in previous neuroimaging studies with younger participants (Dombert et al., 2016; Kuhns et al., 2017).

## 4.5 Experiment 2: Materials and Methods

The results of Experiment 1 revealed comparable abilities of inferring cue validity in older and younger adults across different cueing conditions in a simple task setting. Therefore, Experiment 2 employed more difficult versions of the cueing tasks to investigate whether increased task difficulty may uncover age-related decline in belief updating in any of the three attentional-intentional domains. We exacerbated the task by shortening the cue and target appearance time, as well as the time window to respond to the target. In addition, the target stimuli and search display were made more complex, the latter by adding two distractor stimuli.

### 4.5.1 Participants

Twenty-one older and twenty-two younger participants who did not participate in Experiment 1 participated in Experiment 2. Two participants from the young age group and one subject in the older group had to be excluded due to a high error rate ( $>2$  SD). Therefore, the final sample comprised twenty older participants (10 females; age:  $61 \pm 8.2$  (SD) years; age range 50-77 years) and twenty younger participants (10 females; age:  $26 \pm 3.3$  (SD) years; age range 19-30 years). The group of younger adults in Experiment 2 differed from the one of Experiment 1 by age ( $t(38) = -2.13$ ,  $p = 0.04$ ), with participants of the younger group being slightly younger in Experiment 1 than in Experiment 2 ( $23.4 \pm 0.75$  vs.  $25.7 \pm 0.75$  years; mean  $\pm$  SEM). No differences in age were found between older participants in Experiment 1 and Experiment 2 ( $59 \pm 1.5$  vs.  $61.4 \pm 1.8$  years;  $t(38) = -1.02$ ,  $p = 0.31$ ). The inclusion criteria matched those of Experiment 1.

### 4.5.2 Stimuli and experimental paradigm

Experiment 2 used the same cue stimuli for the three task versions and manual responses towards target stimuli as Experiment 1. However, the cue and target presentation were shortened to 400 ms and 500 ms, respectively, and the intertrial interval was reduced (1200 ms vs. 2000 ms in Experiment 1) (see Figure 1C). The complexity of the search display was increased, containing three distractor diamonds and one target diamond peripherally arranged in the corners of an imaginary rectangle centered on the fixation diamond ( $4.1^\circ$  eccentric in each visual field). The target diamond had a missing corner in its upper or lower half and participants were asked to indicate which corner was missing. The response mapping was counterbalanced across participants. Each hemifield always contained one red and one blue diamond with counterbalanced positions across %CV blocks and valid and invalid trials, resulting in an equal number of diagonally and

horizontally arranged trials. All other aspects of the task including the trial sequence and %CV manipulation were kept constant with regard to Experiment 1.

#### **4.5.3 Statistical analyses**

The same analyses as in Experiment 1 were performed.

#### **4.5.4 Eye movement recording and analysis**

Previous evidence showed that age correlates with an increased difficulty in voluntary saccade control (Peltsch, Hemraj, Garcia, & Munoz, 2011). Since we introduced additional distractor stimuli to make the task more complex, eye movements were recorded to control for fixation ability. An EyeLink® 1000 MR-compatible eye-tracker system (SR Research Ltd.) was employed at a sampling rate of 500 Hz. A 9-or 5 point calibration was performed, followed by a validation to ensure that errors were  $<1^\circ$ . Data were processed using the ILAB toolbox (Gitelman, 2002) in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States). The time between cue and target onset was analyzed for the amount of time spent in a predetermined fixation zone of  $1.5^\circ$  around the central fixation diamond. Consequently, the percentage of fixation time within the central ROI was compared using independent samples t-tests for each task, between the age groups.

## 4.6 Results

### 4.6.1 Behavioral data

Table 2 provides the mean RTs and accuracy in the three experimental conditions for each age group.

**Table 2. Behavioural data for Experiment 2. Mean RTs ( $\pm$  SEM) and mean accuracy ( $\pm$  SEM), for spatial attention, feature-based attention and motor intention, separately for younger and older adults.**

Task	Mean RT (ms)		Accuracy (%)	
	Younger	Older	Younger	Older
<i>Spatial attention</i>	662 ( $\pm$ 21)	809 ( $\pm$ 26)	93.4 ( $\pm$ 0.5)	84.8 ( $\pm$ 2.7)
<i>Feature-based attention</i>	653 ( $\pm$ 22)	824 ( $\pm$ 22)	93.0 ( $\pm$ 1.1)	84.4 ( $\pm$ 2.3)
<i>Motor intention</i>	603 ( $\pm$ 22)	803 ( $\pm$ 23)	92.2 ( $\pm$ 1.0)	84.4 ( $\pm$ 2.2)

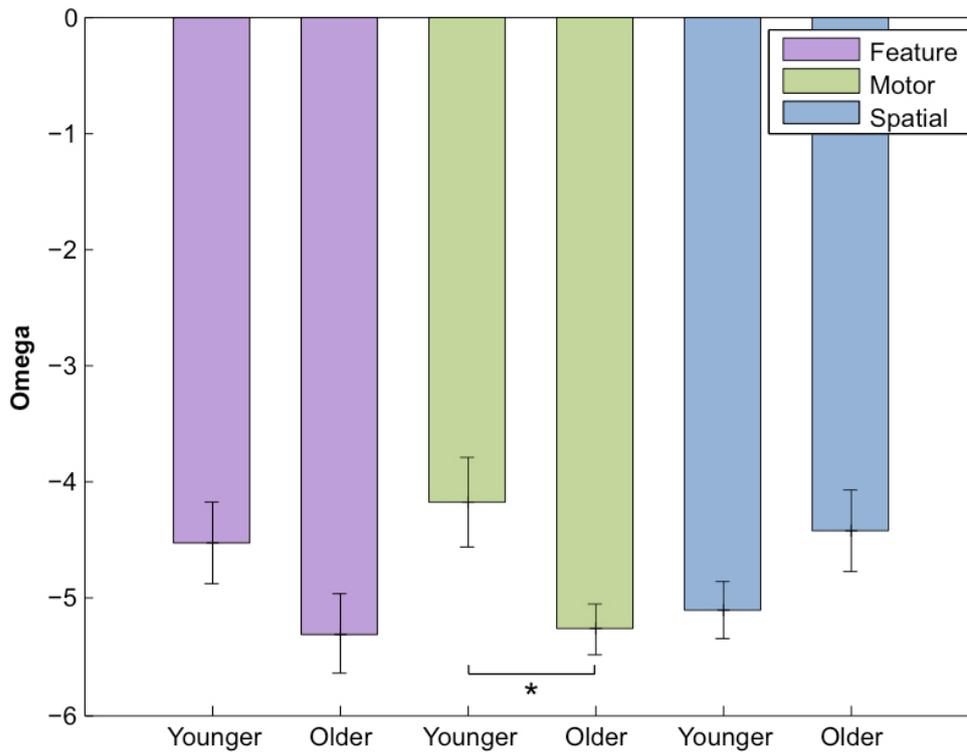
The 3 (*Task*: feature-based attention/spatial attention/motor intention)  $\times$  2 (*Age*: younger/older) ANOVA on accuracy revealed a significant main effect of *Age* ( $F_{(1,38)} = 12.1$ ,  $p = 0.001$ ). In contrast with the results of Experiment 1, the younger participants were more accurate than the older participants in Experiment 2 ( $93 \pm 1.7\%$  vs.  $84 \pm 1.7\%$ ). No main effect of *Task* ( $F_{(1.9,71.6)} = 0.52$ ,  $p = 0.59$ ) nor a significant *Task*  $\times$  *Age* interaction were found ( $F_{(1.9,71.6)} = 0.18$ ,  $p = 0.82$ ).

The same ANOVA on mean RTs revealed a significant main effect of *Task* ( $F_{(1.77,67.4)} = 8.75$ ,  $p = 0.0007$ ). Post-hoc paired samples t-tests (Bonferroni corrected threshold:  $p = 0.017$ ) comparing the tasks revealed that RTs in the motor intention task ( $703 \pm 22$  ms) were significantly faster than in the spatial attention task ( $736 \pm 20$  ms;  $t_{(39)} = -3.8$ ,  $p = 0.001$ ) and in the feature-based attention task ( $738 \pm 20$  ms;  $t_{(39)} = 3.6$ ,  $p = 0.001$ ). A main effect of *Age* ( $F_{(1,38)} = 32.5$ ,  $p = 0.000001$ ) was found, with slower RTs for older compared with younger participants ( $812 \pm 21$  ms vs.  $639 \pm 21$  ms). In addition, the *Task*  $\times$  *Age* interaction ( $F_{(1.77,67.4)} = 3.97$ ,  $p = 0.028$ ) was significant. Post-hoc independent samples t-tests (Bonferroni corrected threshold:  $p = 0.017$ ) comparing tasks between the age groups indicated that younger participants were significantly faster in all tasks (feature-based

attention:  $t_{(38)} = -5.55$ ,  $p = 0.000002$ ; motor intention:  $t_{(38)} = -6.3$ ,  $p = 0.0000002$ ; spatial attention:  $t_{(38)} = -4.3$ ,  $p = 0.0001$ ). In order to test for differences between task versions within the two age groups, we calculated post-hoc paired samples t-tests (three tests per age group; Bonferroni corrected threshold:  $p = 0.017$ ). Results revealed faster RTs in younger participants for the motor intention task ( $603 \pm 21$  ms) compared with the spatial attention task ( $662 \pm 21$  ms;  $t_{(19)} = -4.78$ ,  $p = 0.0001$ ) and with the feature-based attention ( $639 \pm 24$  ms;  $t_{(19)} = 3.34$ ,  $p = 0.003$ ). No differences were found between task versions within the group of the older participants.

The ANOVA on normalized cueing effects yielded no significant main effect of *Task* ( $F_{(1.9,73.1)} = 0.05$ ,  $p = 0.95$ ), nor a *Task*  $\times$  *Age* interaction ( $F_{(1.9,73.1)} = 0.06$ ,  $p = 0.93$ ). However, there was a significant main effect for *Age* ( $F_{(1,38)} = 5.7$ ,  $p = 0.02$ ), with higher normalized cueing effects for younger than older adults ( $0.11 \pm 0.01$  ms vs.  $0.07 \pm 0.01$  ms). We additionally performed one-sample t-test against zero to investigate whether younger and older adults show significant cueing effects in all task versions. Indeed, all t-tests were significant (all  $ps < 0.005$ ), showing that both age groups were using the cues during the three tasks versions.

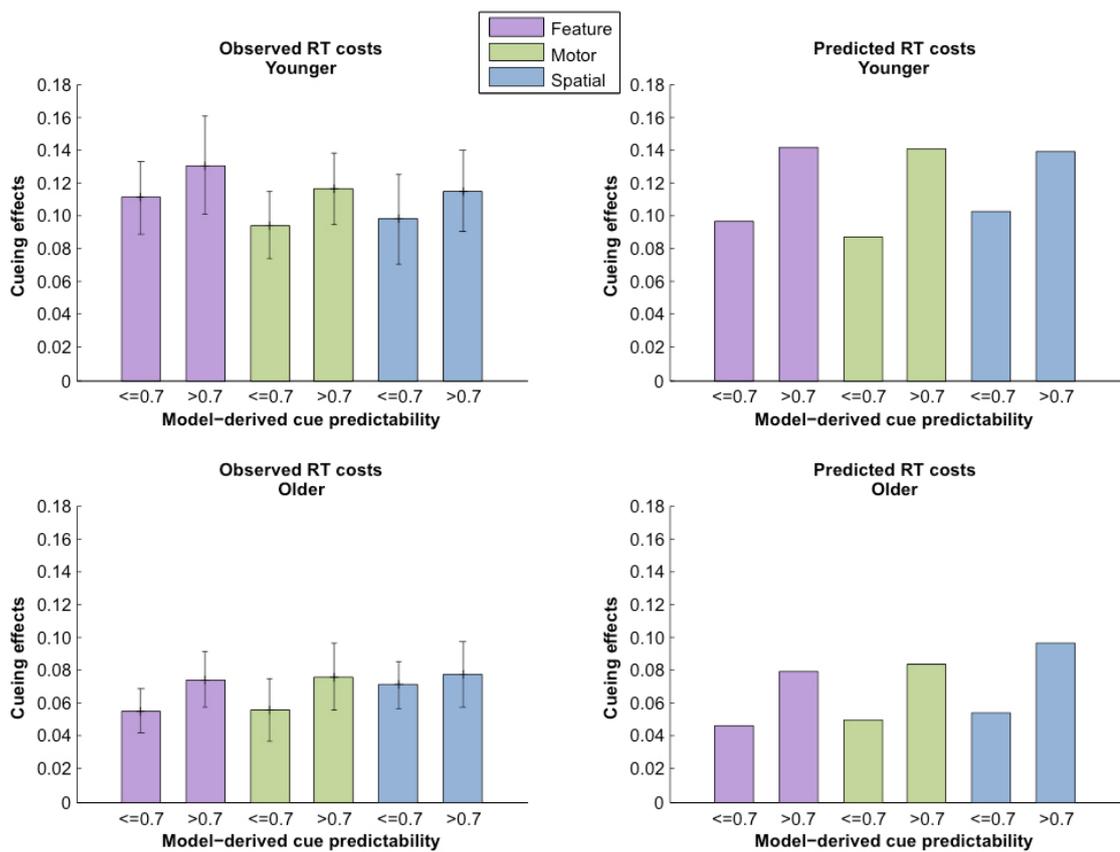
As in Experiment 1, the subject-specific updating parameter  $\omega$  was compared in an ANOVA with the within-subject factor *Task* (spatial attention/feature-based attention/motor intention) and the between-subject factor *Age* (younger/older). The main effects of *Task* ( $F_{(2,75)} = 0.21$ ,  $p = 0.81$ ) and *Age* ( $F_{(1,38)} = 2.4$ ,  $p = 0.13$ ) were not significant. However, a significant *Task*  $\times$  *Age* interaction ( $F_{(2,75)} = 4.33$ ,  $p = 0.017$ ) was observed. Post-hoc independent samples t-tests (Bonferroni corrected threshold:  $p = 0.017$ ) showed that the learning parameter  $\omega$  in the motor intention task tended to be reduced in older compared with younger adults ( $t_{(38)} = 2.49$ ,  $p = 0.019$ ; see Figure 4). Thus, younger participants tended to be faster than the older participants in updating their beliefs about cue validity in the motor intention task. No differences were found between task versions for each of the two groups.



**Figure 4. Results from the Bayesian hierarchical Model in Experiment 2. Between-group comparison of the individual updating parameter  $\omega$  for spatial attention, feature-based attention, and motor intention. Bigger values of  $\omega$  indicate faster updating. In the motor intention task, younger participants are significantly more flexible in their tendency to adapt their predictions, as opposed to older adults.**

The ANOVA on  $\vartheta$  parameter (updating of volatility) did not reveal any significant main effect (*Task*:  $F_{(1,1,43)} = 0.77$ ,  $p = 0.4$ ; *Age*:  $F_{(1,38)} = 0.26$ ,  $p = 0.61$ ) nor a *Task*  $\times$  *Age* interaction ( $F_{(1,1,43)} = 1.34$ ,  $p = 0.26$ ).

Figure 5 shows observed RTs cost in relation to predicted RTs costs for different values of  $\hat{\mu}_1^{(t)}$ , (binned in higher or lower/equal to 0.7).



**Figure 5. Observed and predicted pattern of RT costs from the Bayesian hierarchical model in Experiment 2. RT costs were calculated by subtracting normalized RTs of invalid trials from valid trials and they are shown in relation to the participants' trial-by-trial estimate of the cue predictability  $\hat{\mu}_1^{(t)}$  for all three task versions and the two age groups, binned in cue validity higher or lower/equal to 0.7. Error bars indicate SEM.**

#### 4.6.2 Eye movement data

A total of 19 of the 120 datasets (one for each of the three task versions for the younger and older adults) had to be discarded from further analysis due to poor tracking quality and technical difficulties. Independent samples t-tests on percentage of fixation time in the cue-target period were conducted for each task version, between age groups. In the feature-based attention RT costs task, five datasets of older participants could not be included. Analysis showed significantly higher fixation time in younger adults ( $99 \pm 0.3\%$ ; mean  $\pm$  SEM) compared to older adults ( $98 \pm 0.2\%$ ; ( $t_{(33)} = 2.6$ ,  $p = 0.01$ ). In the motor intention task, datasets of five younger and four older adults did not enter the analysis. Again, younger participants had a significantly better fixation performance ( $99 \pm 0.2\%$ ) than the older group ( $98 \pm 0.3\%$ ;  $t_{(29)} = 3$ ,  $p = 0.005$ ). As for the spatial attention task, five datasets from older adults had to be discarded. The remaining participants showed no

significant differences ( $t_{(33)} = 0.7$ ,  $p = 0.49$ ) in fixation time (younger:  $99 \pm 0.4\%$ ; older:  $98 \pm 0.2\%$ ). Despite of the differences between age groups in some of the task versions, mean fixation values showed that also older adults were able to keep good fixation during the task.

## 4.7 Discussion

In Experiment 2, we employed a more difficult version of the cueing paradigm used in Experiment 1, with the aim of challenging the participants' ability of inferring the cue validity and updating their beliefs in a volatile environment. Age-related differences were found in both behavioral performance and in the model parameters. Younger participants were faster and more accurate in their responses than older participants, suggesting that the latter group was more challenged by the difficult version of the paradigm. This was also reflected in the results of the cueing effects, where younger participants showed higher cueing effects than older participants, suggesting that the former group was more sensitive to the cue information and showed stronger orienting towards the cues. In addition, age-related and task differences were found when analyzing the subject-specific updating parameter  $\omega$ . More specifically, younger participants showed faster belief updating in the volatile environment in the motor intention task than older participants. Whereas probabilistic inference abilities did not differ with age in Experiment 1, increased task demands in Experiment 2 unraveled a slowing of belief updating with motor intention cues for older participants.

Concerning task differences, similarly to Experiment 1, the motor intention task induced faster RTs than the spatial and the feature-based attention tasks. The same pattern was found for RTs in the group of the younger participants, whereas no difference in RTs between tasks was found for the group of the older participants.

## 4.8 General discussion

Using three different versions of a cueing paradigm and two task difficulty levels, we investigated age-related changes in the ability to use recent observations and environmental cues to infer the probability of upcoming events for an efficient attentional deployment. Formal computational modeling with a generic Bayesian learning scheme allowed us to characterize individual updating of beliefs concerning the occurrence of upcoming events in a volatile environment, when different stimulus properties were predicted by spatial, feature, or motor cues.

The results point towards a reduced ability to update predictions in older participants in the difficult motor intention task, i.e. when the finger required for the response was cued. Previous neuroimaging studies (Dombert et al., 2016; Kuhns et al., 2017) used the same three versions of the task and showed that probabilistic inference for spatial attention, feature-based attention, and motor intention engages different brain regions. Specifically, the right TPJ is pivotal for probabilistic inference for spatial attention, whereas the left ANG and the ACC support the same cognitive process for motor intention. The difference in the neural substrates of probabilistic inference processing can explain the selective age-related differences in belief updating abilities in the motor intention task. Indeed, there is evidence that the functionality of the prefrontal cortex is reduced with aging (for a review see Hedden and Gabrieli, 2004), and previous studies also point to a decline of ACC function and volume with age (Pardo et al., 2007; Mann et al., 2011).

A recent paper (Nassar et al., 2016) has highlighted the difficulty of older adults in using uncertainty estimates to guide behavior in a predictive inference task involving reward. Previous evidence similarly suggested that older adults might be impaired in probabilistic reinforcement learning when reward information is uncertain, however they do not show the same level of impairment when the reward contingencies are fully predictable (for a review see Eppinger, Haemmerer, & Li, 2011).

Nevertheless, the present results suggest a reduced probabilistic belief updating in older adults only when motor cues are used to predict the appearance of the target, whereas no differences were found for the spatial attention and feature-based attention tasks. In line with our results, previous studies reported preserved cueing effects in older adults for endogenous attention (Curran, Hills, Patterson, & Strauss, 2001; Tales, Muir, Bayer, & Snowden, 2002), despite of slower latencies for early visual ERP components, i.e. N1 and P1, as well as later components such as the P3, in older compared with younger adults (Curran et al., 2001).

Using a cueing task with spatial cues predicting the hand needed for the response, Sterr and Dean (2008) found absence of validity effects (difference in RTs between validly and invalidly cued responses) in a group of older adults compared with younger participants. In addition, they found differences in ERP components, such as the foreperiod contingent negative variation and the lateralized readiness potential, between the two age groups indicating reduced lateralized motor preparation in the group of older participants. These results suggested differences in processing of motor cues with healthy aging, in line with the present results. However, in the abovementioned study, no

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manipulation of the cue predictability during the task was performed. It is indeed by manipulating the cue predictability over time that allowed us to unveil differences in the updating of predictions with aging. Hence, by combining the analysis of behavior with a formal computational model, the present work provides new insights into the efficiency of attentional and motor intentional mechanisms in healthy aging.

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## 5. Summary and Conclusion

In what follows, results drawn from the experiments will be embedded into the current opinions of the scientific community. In particular, conclusions on the distinct neural correlates of learned trial-wise expectancies for spatial attention and motor intention (3.), as well as possible age-differences (4.) will be drawn.

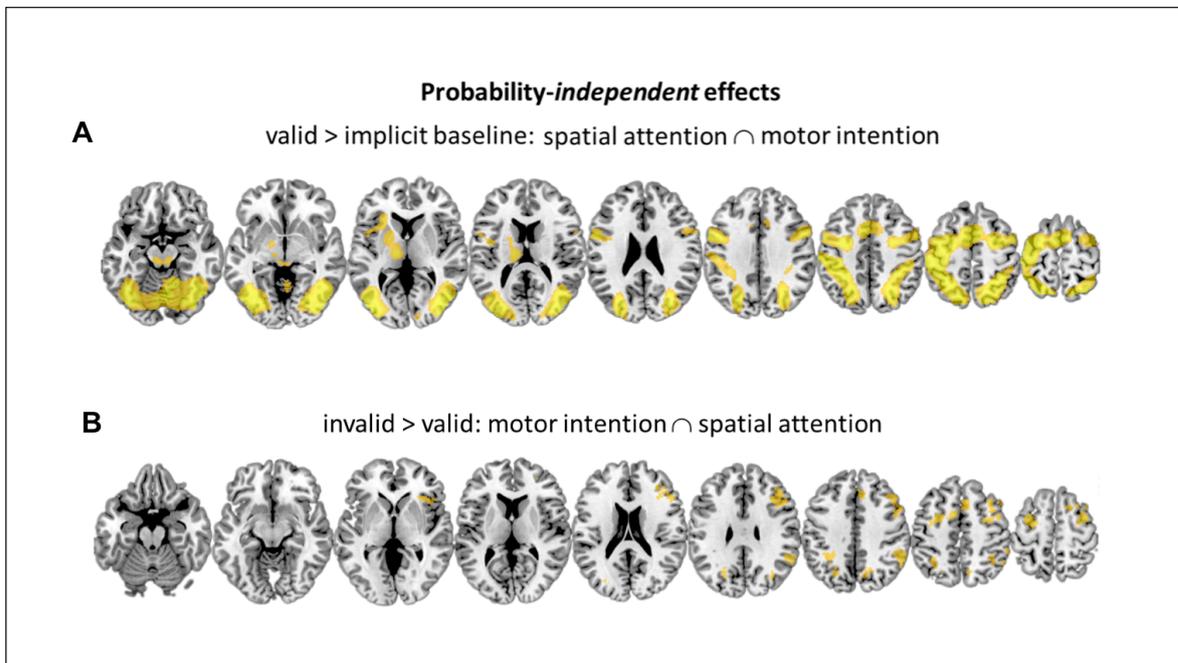
### 5.1 Distinct neural correlates for learning under uncertainty

Whenever the statistical environment needs to be inferred, the brain computes predictions about events and adapts when expectancy violations occur. These processes may be associated with activity changes in right FEF, TPJ, and putamen for spatial attention and saccadic eye movements, and have been found to adapt as a measure of precision of belief about the validity of spatial cues. In other words, when the confidence in the cue validity is high, and reorienting due to violations thereof becomes necessary (i.e. invalid cues), activity is enhanced in these regions (Vossel et al., 2015). The first experiment (3.) extends current findings by separating the neural implementation of *probability-independent* and *probability-dependent* effects for spatial attention and motor intention.

First, to address the commonalities of functional orienting and reorienting processes following spatial attention and motor intention cues, *predictability-independent* analyses were conducted. A conjunction analysis investigating mere orienting-related activity (valid trials) activated a *common* widespread frontoparietal network for spatial attention and motor intention (see figure 8 A). This is in line with the well-described dorsal network (Corbetta & Shulman, 2002). Contrasting valid trials between motor and spatial (motor>spatial), revealed no distinction for motor intention orienting, although prior studies show a more pronounced left parietal involvement for motor cues (Hesse et al., 2006; Astafiev et al., 2003). This discrepancy might be due to our more abstract set-up and subtle cue, compared to cueing of an entire hand (Hesse et al., 2006) or preparing the pointing finger (Astafiev et al., 2003).

Reorienting-related activity (invalid>valid) for both tasks *commonly* involved dorsal frontoparietal regions such as bilateral FEF and right IPS, as well as right-lateralized activity in inferior frontal gyrus and angular gyrus (see figure 8 B). Co-activation of ventral and dorsal regions is commonly observed and may reflect the bi-directional interaction of the two attention networks to establish flexible attentional control (see, e.g. Corbetta &

Shulman, 2011). Thus, we extend these results by suggesting a shared network for reorienting in spatial attention and motor intention. In other words, we provide evidence that these areas also respond to invalid information about an imminent motor response, when the planned action needs to be revised accordingly.



**Figure 8. A Conjunction analysis of orienting-related neural activity following valid spatial attention and motor intention cues. B Conjunction analysis of reorienting-related activity contrasting invalid>valid in spatial attention and motor intention task.**

Second, the question was addressed regarding the generality of the neural implementation of *predictability-dependent* processing for the two domains of interest. The results suggested domain-specific results for *predictability-dependent* effects contrasting reorienting in spatial attention and motor intention, respectively. Enhancements in activation following invalid trials modulated by estimated cue predictability were found in rTPJ for spatial attention and ANG and ACC in the left-hemisphere for motor intention. Differently put, BOLD responses in these areas and RT costs were increased, the more unexpected an invalid trial was estimated to occur. Behaviorally no differences between task versions in accuracy, RT, or model parameters  $\omega$  and  $\vartheta$  were observed, hinting at similar learning rates for the two task versions. Notably, no correlations between the learning parameter of both versions, nor significant conjunction of *predictability-dependent* reorienting were found supporting the domain-specificity of functional neuroanatomy in these domains. Differently, Dombert et al. (2016) reported a correlation of the subject-specific learning parameter  $\omega$ , for spatial and feature-based attention. These attention

domains seem to be closer associated than spatial attention with motor intention, in which individual learning differences in one domain cannot be applied to predict learning in the other. In addition, an explorative connectivity analysis with the seed areas (ANG, ACC and TPJ) was conducted, since we also expected a supramodal neural correlate for *predictability-dependent* processing. This analysis revealed common coupling and *predictability-dependent* effect (i.e. stronger coupling after invalid cues) with right anterior hippocampus.

Taken together, the abovementioned results challenge the assumption of a global role of rTPJ and ascribe its engagement primarily to spatial attention (see 3.; Dombert et al. 2016). Moreover, instead of redirecting attention towards any novel event and acting as a 'circuit breaker', rTPJ is more specifically engaged in reacting upon unexpected but behaviorally relevant stimuli (e.g. when predictions about upcoming events need to be inferred) and is context-sensitive. This observation also fits well with recent views of rTPJ involvement in carrying stimulus-driven representations of task-relevant information (Geng & Mangun, 2011; Geng & Vossel, 2013) and with the observation that behavioral deficits in right brain damaged individuals might arise due to a deficit in learning the statistical structure of target locations (Shaqiri & Anderson, 2012; Shaqiri, Anderson & Danckert, 2013). Dynamic Causal Modeling (DCM) of neuroimaging data sheds light into effective connectivity by estimating coupling among brain regions, in response to experimental factors (Daunizeau, David & Stephan, 2011; Friston, Harrison & Penny, 2003). TMS and DCM studies further support the prominent role of rTPJ in belief updating in spatial attention. As such, interference with TMS disrupts updating of prior beliefs post-target (Mengotti, Dombert, Fink & Vossel, 2017) and analyses of connectivity-strength between FEF and TPJ revealed a decrease of FEF control over TPJ, following reorienting towards task-relevant but unattended information (DiQuattro, Sawaki & Geng, 2013). Thus, instead of sending an interrupt signal to the dorsal system (e.g. FEF) preceding an attention shift, rTPJ is interpreted to update internal models. Additionally, the specific *predictability-dependent* activity in left ANG and ACC for motor intention might offer a novel account for understanding deficits in redirecting motor attention in left brain damaged patients. Especially, apraxic patients have difficulties selecting movements and display lesion clusters around left IPS and parts of the frontal lobe (Rushworth et al., 2003). A possible link between disturbances of predicting upcoming motor intention with conceptual apraxia seems feasible. In this certain type of apraxia, symptoms entail an inability to select and carry out an appropriate motor program and difficulties to voluntarily perform learned tasks have been reported (Gross & Grossman, 2008).

## SUMMARY AND CONCLUSION

Perception has been described as a cascade of continuous matching of incoming sensory input (i.e. unpredicted activity) with predictions. Our null-finding or slight decrease in *predictability-dependent* modulation in valid trials could be explained under the assumption of a bi-directional hierarchical learning architecture of the brain. As long as higher levels correctly predict lower level activity no adjustments need to take place. In turn, increased *predictability-dependent* coupling-changes of the seed-regions with right anterior hippocampus after invalid trials could be associated with the propagation of prediction error to higher-level structures. This cascade of events initiates adaption of probabilistic representations, ultimately leading to learning (Clark, 2013). Therefore, using a Bayesian computational approach, resembling the brain's updating ability, offers a more naturalistic approximation of attentional performances.

Concluding, probabilistic inference is performed within each cognitive subsystem, but shared connectivity profiles with anterior hippocampus are suggested. The results pave the way for a deeper understanding of the specificity of computational mechanisms of flexible attentional control in the human brain and aim at offering a more unified account of perception and action.

## 5.2 The modulation of probabilistic cueing on different attentional systems in ageing

It is well known that a decline in attention allocation and response speed is a natural phenomenon in age (Madden, 1992). Until now, there is no common consent on whether older adults have a preserved ability to update predictions (Curran et al., 2001) or indeed have difficulties in encoding the structure of uncertain environments (Nassar et al., 2016). For that reason, the second study (4.) tested if older adults retained the ability to learn the predictability of different cues in a volatile cueing-paradigm, compared to young adults. We chose to introduce three cues guiding spatial- and feature attention and motor intention, since our results from the first study (3.) and work by our group (Dombert et al. 2016) point at distinct neural correlates for updating probabilities.

In the first experiment of the second study, inference of cue predictability did not significantly differ between age groups. All three cue types guided attention equally well between and within the age groups and learning parameters extracted from the Bayesian model did not yield significant learning differences. These findings fit well with previous literature, describing a preserved ability to identify statistical regularities in contextual spatial attention tasks (Jiang, Koutstaal, & Twedell, 2016). Here younger and older participants learned the location-probability of a target in a spatial layout and the effect was ascribed to habitual learning. Further, when spatial cueing effects were tested within the visual and auditory modality, age remained an insignificant determinant of performance (Guerreiro, Adam, & Van Gerven, 2012). However, none of the present studies have described adaptive behavior in a volatile environment and disentangled different cueing modalities.

Since task complexity is an important determinant of age differences in performance (Madden, 1992; Zanto & Gazzaley, 2014), we included a second experiment. This difficult set-up was more similar to the original one used in the first study (3.; Dombert et al., 2016) and comprised two additional possible target positions and the target itself was not as intuitive as in the first experiment. Estimates of the computational model allowed to unravel a reduced updating parameter  $\omega$  for the motor intention condition in older, as compared to younger adults. This result reflects slowing of individual trial-by-trial updating speed with age.

The finding of differential updating behavior in older adults following motor intention cues indicates the necessity of separately investigating different attentional domains. We also demonstrated the scope of computational modeling, which was essential to unveiling

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the age-differences. Most importantly, our results establish an account of trial-by-trial belief updating in different cognitive system in healthy ageing. We provide evidence for retained attentional and intentional updating mechanisms and a slight decline in updating motor cues in complex tasks. Additionally combined with the identified distinct neural correlates of belief updating (3.), it can be particularly helpful for interpreting results from lesion studies reporting deficits in statistical learning (Shaqiri & Anderson, 2012; Shaqiri, Anderson & Danckert, 2013).

What could be the reason for the detected learning difference for motor cues? Aging leads to decreased functional connectivity and modularity (i.e. less differentiation) of frontoparietal networks (Geerligs, Renken, Saliassi, Maurits & Lorist, 2015). A recent neuroimaging study on short-term memory, focused on describing interactions between the dorsal and ventral attention network in aging. In comparison, older adults overly engaged the dorsal attention network while showing significantly less activation of the ventral network following distracting stimuli, especially when short-term memory load was high. This increase of top-down control was proposed to counteract decreased reactivity of the ventral system (Kurth et al., 2016). More specifically, lower engagement of occipital areas leads to a deterioration of bottom-up sensory input, which in turn needs to be compensated by increased activation of the frontoparietal network (Madden et al., 2007). Compensation seemed to work for the spatial and feature-based attention domains, but motor intention might have had a disadvantage in reacting towards unexpected information, due to the specific involvement of the ANG in predictability-dependent reorienting (Kuhns, Dombert, Mengotti, Fink & Vossel, 2016). This area was proposed to be a core region for converging bottom-up information and top-down predictions (Seghier, 2013). In other words, when bottom-up signals decrease in quality due to age and cognitive task load increases (as it did in our difficult task by introducing two additional distractors, see 4.) learning might be slowed due to the strong compensatory influence of the dorsal attention system and the prominent role of the ANG in motor intention. Another explanation might be found at an earlier stage, namely during the integration of motor preparatory information (i.e. cueing of motor response). Preparatory electrophysiological activity is attenuated in older adults and explains prolonged RTs during valid trials. The alteration in motor intention becomes apparent in complex and time restrained tasks (Sterr & Dean, 2008).

From the aging experiment, we could not conclude whether the increased number of possible targets, the change in SOA, or a combination of both was pivotal for the observed differences in learning the statistical structure following motor intention cues in older adults. Nonetheless, we have provided an informative base for retained perceptual

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inference for all domains, with learning decrements only for motor intention in complex environments in healthy age. Thus, we extend the current literature, by proposing that ability of learning environmental statistics *per se* is retained in perceptual- and intentional domains, but that updating predictions following motor intention cues is slightly affected in difficult task environments. Future studies should consider learning deficits on a continuous age scale rather than in dichotomous groups and it is important to keep in mind that behavioral-invariant results do not provide the entire picture and additional measures from e.g. trial-by-trial learning or functional measures are needed to detect aging-effects.

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### 5.3 Future prospects

The present studies have provided the following insights: (i) Modulation of neural mechanisms induced by updating in volatile environments seems to be domain-specific for spatial attention and motor intention. (ii) Anterior hippocampus shows common connectivity patterns with seed regions involved in inference processes for the attentional and intentional subsystems. (iii) Updating expectancies following motor intention, but not spatial- or feature-based attention in demanding task-environments seems depleted as a function of age.

First, no correlation between updating parameters ( $\omega, \vartheta$ ) of spatial attention and motor intention in individual subjects have been found, dissimilar to results obtained by Dombert et al. (2016). There the correlation between the individual updating parameter of feature- and spatial attention, hints at similar rates of learning. Hence, one can use an individuals updating parameter of one version to predict learning in the other. Future connectivity analyses are necessary to unveil the underlying dynamics within the motor intention and spatial attention system. Recent takes on deficits seen in neglect, point towards an inability to learn statistical regularities from spatial information (see e.g. Shaqiri et al., 2013). Our studies add that probabilistic inference for spatial attention is retained in healthy age and propose rTPJ as the neural correlate for specifically updating spatial predictions. It would be intriguing to characterize how brain lesions affect trial-by-trial updating in feature attention and motor intention. Based on our findings, one could assume retained updating in neglect patients for feature-based and motor intention cues in easy task set-ups. Apraxic patients, however, with lesions to the left hemisphere are also of interest since their motor intention updating mechanism could be disrupted. Next to these behavioral studies, valuable information could be drawn from lesion-symptom analysis techniques. A promising methodology is offered by multivariate pattern analysis (MVPA), since it assumes joint instead of independent contribution (i.e. mass-univariate approach) of brain areas to perception and behavior (see, e.g., Karnath & Smith, 2014; Mah, Husain, Rees & Nachev, 2014). It has been successfully applied to investigate damage patterns predicting spatial neglect (Smith, Clithero, Rorden & Karnath, 2013). Thus, future studies could link Bayesian model parameters determining individual updating ( $\omega$  and  $\vartheta$ ) and RT cost modulation by %CV to different lesion patterns. In the long run, this could pave the way for new rehabilitation approaches more customized to the retained learning abilities. For instance, neglect patients having difficulty with spatial information will be guided by feature-based or motor intention cues during rehabilitation interventions.

Common coupling of the distinct neural updating hubs with anterior hippocampus has been found. Latest study results propose the hippocampus to be responsible for mapping choices to potential outcomes, thereby creating an internal model (Boorman, Rajendran, O'Reilly & Behrens, 2016). DCM of our seed regions (left ANG, ACC and rTPJ) with the anterior hippocampus during predictability-dependent reorienting could illuminate the causal architecture of neural dynamics.

Moreover, since our work focused on healthy participants, the question arises how computational modeling can help to define learning behavior in psychiatric disease. For instance, patients with attention deficit hyperactivity disorder (ADHD) (Cortese et al., 2012) and schizophrenia (Stephan, Baldeweg & Friston, 2006) show aberrant learning behavior and alterations in brain connectivity in several networks. ADHD-related deficits in adults have been suggested to result from a hypo-engagement of the ventral attention network (Helenius, Laasonen, Hokkanen, Paetau & Niemivirta, 2011). This is in line with a theoretical framework stating that a cardinal symptom of ADHD, manifested as difficulties in modulating behavior, arises as a result of deficits in learning statistical regularities (Nigg & Casey, 2005).

In schizophrenia, synaptic plasticity is compromised, demonstrated by abnormalities in intra-areal connectivity. Further, electrophysiological markers for processing of prediction error are indexed by the mismatch negativity (MMN) in the ERP (Stephan et al., 2006). MMN amplitude is significantly reduced in schizophrenia, which has led to a recent theory of explaining psychotic symptoms and sensory learning deficits as abnormal encoding of prediction error (Schmidt et al., 2012). What is more, in an fMRI study, prediction error processing has been linked to the right PFC as shown by disrupted processing under ketamine. So far oddball paradigms and auditory cues have been primarily used. Since very similar psychotic symptoms can be induced in healthy volunteers with N-methyl-D-aspartate receptors (NMDAR) antagonists like ketamine and they are more easily accessible, this cohort should be considered for a first study. Since learning novel information distinctly affects spatial attention and motor intention, it would be of interest to separately investigate predictability-dependent updating in a psychosis model. Thus, the pharmacological effects in a double-blind within-subjects design could be used to unveil the alleged behavioral effects on updating predictions utilizing the methodology of the first study (3.). Participants would not be informed under which condition (ketamine or placebo) they were. Subsequently, individual updating parameters of the Bayesian model between the two conditions would be compared. If prediction error were truly disrupted, this would be apparent in significantly slower adaption towards the manipulated volatile environment in participants under pharmacological influence

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compared to placebo. If this is the case time-consuming and costly EEG or fMRI data acquisition could be replaced in the future and individual learning parameters might suffice as a faster complementary diagnostic tool, next to biographical anamnesis and medical record. If aberrant learning parameters are indeed significant determinants of psychosis, the next step could be to illuminate which antipsychotic drug might have the best effect on alleviating impairments in trial-by-trial inference. This could be a valuable addition to the measure of effectiveness, since it is currently quantified by e.g. continuation of the drug, weight gain or lipid metabolism (Lieberman et al., 2005). Finally, this novel approach of characterizing false inference in neuropsychological deficits has been subsumed under the term 'computational phenotyping' (Parr, Rees & Friston, 2018).

Our results combined with recent findings inaugurate promising avenues for future studies in understanding computational mechanisms in psychopathology and to elucidate the causal dynamics in the different attentional- and intentional domains. Future results could for example lead to improved diagnostics in schizophrenia and tailored rehabilitation programs in patients suffering from neglect.

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