Phasic alertness and intrinsic functional connectivity in healthy and pathological aging

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Abstract

Phasic alertness refers to a short-lived increase in the brain's sensitivity to upcoming events following brief external signals that do not provide any information about stimulus identity or location. In healthy younger adults, external warning signals speed up the processing of visual information. However, it is unclear whether this preparatory mechanism, optimizing the processing of information in complex visual environments, is preserved in healthy and pathological aging. In this thesis, we assessed the effects of auditory alerting cues on visual processing speed using a whole report paradigm based on the theory of visual attention. The results demonstrated that phasic alerting effects on visual processing speed are preserved in both healthy older adults and patients with amnestic mild cognitive impairment. Arguably, this preserved ability to temporarily enhance processing speed in response to a warning signal can help older individuals to compensate for age-related declines in their overall processing capacity. It is still an open question which brain mechanisms do underlie phasic alerting effects on visual processing speed and whether aging individuals rely on the same neural mechanisms as younger adults. In order to investigate brain mechanisms underlying phasic alertness, we related phasic alerting effects on visual processing speed to intrinsic functional connectivity (iFC) patterns, obtained from resting-state functional magnetic resonance imaging. We employed a combined multi-subject independent component and dual regression approach to identify resting-state networks in healthy younger and older participants. In younger participants, phasic alerting effects on visual processing speed were primarily related to iFC in the cingulo-opercular network. In contrast, phasic alerting effects on visual processing speed were significantly associated with iFC in the right fronto-parietal network in healthy older participants. A direct age group comparison revealed that the behaviour-iFC association in the cingulo-opercular network was significantly lower in healthy older compared to younger adults. Taken together, this thesis provides first evidence for age group specific iFC patterns underlying preserved phasic alerting effects on visual processing speed in aging individuals.

Graphical Abstract

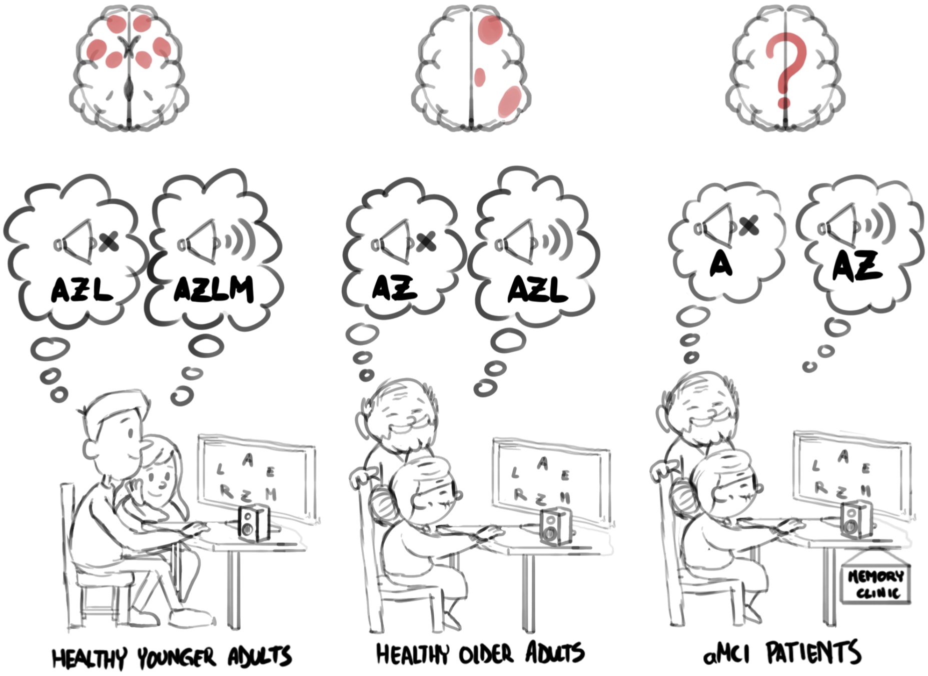

Figure 1: Graphical summary of the main findings of this thesis

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List of Abbreviations

AD	Alzheimer’s Dementia
aMCI	Amnestic Mild Cognitive Impairment
ANT	Attention Network Test
BOLD	Blood oxygenation level-dependent
CON	Cingulo-Opercular Network
CSF	Cerebrospinal Fluid
CTOA	Cue-Target Onset Asynchrony
ICA	Independent Component Analysis
iFC	Intrinsic Functional Connectivity
fMRI	Functional Magnetic Resonance Imaging
LC	Locus Coeruleus
MCI	Mild Cognitive Impairment
MRI	Magnetic Resonance Imaging
NA	Noradrenaline
NTVA	Neural Theory of Visual Attention
PET	Positron Emission Tomography
rFPN	Right Fronto-Parietal Network
RSN	Resting State Networks
TVA	Theory of Visual Attention
vSTM	Visual Short-Term Memory

Overview

The overarching aim of this thesis is to systematically link phasic alerting effects on visual processing speed to underlying intrinsic functional connectivity (iFC) patterns in healthy and pathological aging. Exploring whether phasic alerting effects are preserved in healthy and pathological aging is highly relevant as aging individuals are characterized by pronounced declines in their capacity to process information in complex visual environments. External warning signals, i.e. auditory cues, could help aging individuals to prepare for and process important upcoming information more efficiently. Such cue-induced, temporary increases in processing speed could compensate for age-related reductions of processing capacity and, by that, still allow aging individuals to flexibly adapt to upcoming situations. As the human brain undergoes a plethora of age-related changes, it appears to be essential to investigate the brain processes underpinning phasic alertness and address whether aging modifies the neural mechanisms underlying phasic alertness.

Chapter 1

General Introduction

The first section of the General Introduction defines phasic alertness and summarizes previous studies investigating phasic alerting effect in healthy younger adults, healthy older adults, and patients with Alzheimer's disease. The second section introduces the theory of visual attention (TVA) and explains how phasic alerting effects on visual processing speed can be measured using TVA-based whole report paradigms with auditory alerting cues. The third section explains the rationale for relating TVA-based estimates of phasic alerting effects on visual processing speed to iFC. Moreover, this section establishes why iFC can be measured using functional magnetic resonance imaging (fMRI) and presents the most suitable analysis approach for investigating associations between phasic alerting effects and iFC patterns. The General Introduction concludes with the aims of the thesis and the derived research questions for the four studies presented in the core part of this thesis.

1.1 Phasic alertness in healthy and pathological aging

1.1.1 Phasic alertness as a visual attention function

Our visual environment is highly complex - numerous objects are competing to be processed at any given time. As the visual processing resources of the human brain are limited, visual attention is required to select relevant and ignore irrelevant information. Selective attention can either be spatial, i.e. towards a location in space, or non-spatial, e.g. towards features such a colour or shape, objects, or points in time (for a review regarding aging see Zanto & Gazzaley, 2014). Spatially defined selection is also being referred to as orienting (Posner & Boies, 1971; Posner & Petersen, 1990). Apart from this selective component, attention also involves a rather general, non-selective component termed vigilance or alerting (Posner & Boies, 1971; Posner & Petersen, 1990). Alerting ensures that the brain maintains a sufficiently high state of sensitivity to sensory information over time so that continuous selectivity can be facilitated (Posner & Boies, 1971; Posner & Rothbart, 2007). Alerting can be subdivided into tonic and phasic alertness. Tonic alertness is defined as an intrinsically sustained state of readiness or wakefulness. In contrast, phasic alertness is a short-lived increase in the brain's state of readiness following a brief external signal (Sturm & Willmes, 2001). Although such external warning signals provide no information about the location or time of a stimulus' appearance, they increase the brain's sensitivity to imminent events (Oberlin et al., 2005).

1.1.2 Phasic alertness in healthy younger adults

Originally, it was suggested that phasic alerting cues only affect cognitive processes underlying the preparation and execution of motor responses (Posner, 1978; Sturm & Willmes, 2001). However, a later fMRI study reported increased brain activity in extrastriate, perceptual brain areas in phasic alerting cue trials of a target detection task (Thiel et al., 2004). This finding underlined the importance of measuring phasic alerting effects on both the (attentional) perceptual level and the level of motor responses.

Studies adopting Posner's cued reaction time task (Posner, 1980) or the Attention Network Test (ANT) (Fan et al., 2002) in healthy younger adults reported reduced reaction times in conditions with visual alerting cues as compared to conditions without phasic alerting cues (Coull et al., 2001; Fan et al., 2005; Posner, 1978; Posner & Boies, 1971). Phasic alerting cues also increased visual processing speed (Matthias et al., 2010; Petersen et al., 2017) and processing capacity (Wiegand et al., 2017b) in verbal letter report paradigms without required motor responses. Overall, phasic alerting cues consistently led to faster processing on the perceptual and motor level in healthy younger participants. While former studies have addressed brain mechanisms underlying response time benefits induced by alerting cues, brain correlates of phasic alerting effects on visual processing speed have not been investigated yet.

1.1.3 Phasic alertness in healthy older adults

The already limited brain resources for the processing of visual information in our environment further decline over the lifespan (McAvinue et al., 2012; Salthouse, 1996). When facing visually complex situations with such limited processing resources, the ability to utilize external warning signals in order to prepare for upcoming events appears to be even more essential. Interestingly, former studies addressing phasic alerting abilities in healthy aging yielded inconclusive results. Previous studies reported both intact (Fernandez-Duque & Black, 2006; He et al., 2020; Karpouzian-Rogers et al., 2019; Rabbitt, 1984) and impaired (Festa-Martino et al., 2004; Gamboz et al., 2010; Ishigami et al., 2016; Jennings et al., 2007; Wiegand et al., 2017a; Zhou et al., 2011) phasic alerting in healthy aging.

Varying task demands as well as diverse cue specifications can potentially explain these incongruent outcomes. The duration of the cue, the cueing modality, and temporal contingencies are potential sources of differing results. Several studies using visual cues with a duration of 100ms found decreased alerting abilities in healthy aging (Festa-Martino et al., 2004; Jennings et al., 2007; Zhou et al., 2011). In contrast to this, Fernandez-Duque and Black (2006) presented a visual alerting cue for 500ms and reported preserved phasic alerting in healthy older adults. Regarding differences in results based on cueing modality, Karpouzian-Rogers et al. (2019) compared alerting effects elicited by visual and auditory cues, both presented for 100ms. They observed that the auditory alerting effect is significantly higher in magnitude than the visual alerting effect, but both types alerting cues benefit performance in healthy older adults. A recent study corroborated the suggested preservation of auditory alerting effects in healthy aging. He et al. (2020) demonstrated that auditory cues presented for 100ms induce larger phasic alerting effects in healthy older participants compared to younger participants. Another important aspect is the temporal interval between the cue and stimulus onset. Even though phasic alerting cues do not carry any information about the upcoming location or features of a target, they inherently induce a temporal expectation as they, by definition, always precede a target display (Weinbach & Henik, 2012). Hence, participants know that a target will appear at some point in time after they have perceived the cue. If the temporal interval between a cue and target is constant (e.g. Zhou et al., 2011), participants can prepare for their response as the probability of a target appearing, given that is has not yet occurred, increases as time passes and participants can predict its occurrence (Nobre & van Ede, 2017). Jittering the intervals between cue and targets prevents participants from exactly anticipating the time of target appearance. Most importantly, the abovementioned studies measured response times by using speeded button presses as response modality. Crucially, aging is characterized by an overall, non-specific slowing of motor processes (Shalev et al., 2016). This emphasizes the need to measure phasic alerting effects on a perceptual level in order to minimize confounding effects of altered motor responses in aging individuals.

1.1.4 Pathological aging

Cognitive changes in aging can be thought of as a continuum. Healthy aging with cognitive functioning according to age standards and preserved everyday life functioning is located at one end of the continuum while the other end mirrors severe cognitive impairments which do not permit an independent life. One of the pathologies that can lead to such severe cognitive deteriorations is Alzheimer's disease - the most common cause of dementia. Other causes of dementia include cerebrovascular disease, Lewy body disease, frontotemporal lobar degeneration, Parkinson's disease, and mixed pathologies (Alzheimer's Association, 2019). Alzheimer's disease can be subdivided into three stages: preclinical stage, Mild Cognitive Impairment (MCI), and Alzheimer's dementia (AD).

In the preclinical stage of Alzheimer's disease, individuals do not exhibit cognitive impairments beyond their corresponding age standards on cognitive test batteries (Alzheimer's Association, 2019). This stage is, however, characterized by abnormal processing of β-amyloid peptide resulting in plaques which can be measured in the cerebrospinal fluid (reduced Aβ42) or via positron emission tomography (increased Pittsburgh compound B retention) (Jack et al., 2010). In addition, some individual's do perceive subjective declines in certain cognitive abilities that cannot (yet) be quantified on neuropsychological tests (Tales et al., 2015).

In contrast, MCI is defined as the stage in which individuals show both abnormalities in Alzheimer's disease biomarkers and cognitive decline exceeding their age norms but not interfering with their independent everyday life (Alzheimer's Association, 2019). MCI due to Alzheimer's disease primarily refers to impairments in the memory domain, also termed amnestic MCI (aMCI) (Roberts & Knopman, 2013).

The stage of Alzheimer's dementia is characterized by cognitive impairments in multiple cognitive domain as well as pathological brain changes in addition to β-amyloid plaques. Increased phosphorylated tau and total tau in the cerebrospinal fluid (CSF) indicate neuronal injury; decreased fluorodeoxyglucose uptake measured with positron emission tomography (PET) alludes to impaired synaptic activity (Jack et al., 2010). In addition, structural magnetic resonance imaging (MRI) can detect brain atrophies. Regarding cognition and behaviour, dementia due to Alzheimer's disease can be subdivided into three severity levels. In the mild level, patients can function independently in most areas of their life and only require some external support. The moderate level is marked by subsided communication, impaired activities of daily living and changed behaviour. Patients in the severe level of dementia require full time care and are likely to be bed-ridden (Alzheimer's Association, 2019).

Importantly, not every individual with an Alzheimer's disease pathology develops MCI or dementia (Bennett et al., 2006; Knopman et al., 2003). A systematic review addressing the rate of conversion from aMCI to AD has shown that about 32 percent of aMCI patients developed dementia over 5 years (Ward et al., 2013). Furthermore, in individuals who progress to the stages of MCI or dementia, a comparable pathology can result in a wide variety of cognitive symptoms (Husain, 2017). Overall, ageing is one of the primary risk factors for Alzheimer's disease (Hou et al., 2019) and the number of people above the age of 65 years is being estimated to increase from 9 to 16 percent over the next 30 years (United Nations, 2019). Due to this high prevalence and rate of conversion, there is an increasing need for the early detection of Alzheimer's disease. As opposed to MRI, PET, and CSF analysis, computerised cognitive tests depict a non-invasive, inexpensive, and less time consuming approach for early detection. Importantly, Alzheimer's disease is primarily associated with memory impairments, but memory is not a fully independent cognitive function. Several studies suggest that memory and attention functions are highly interrelated (e.g. Cabeza et al., 2011; Ciaramelli et al., 2008). In line with these findings, early stages of Alzheimer's disease are also characterized by alterations of visual attention processes (Baddeley et al., 2001; Fernandez-Duque & Posner, 2001; Parasuraman et al., 2002; Perry et al., 2000; Rizzo et al., 2000; Tales et al., 2005). It appears fundamental to address which aspects of attentional processing are preserved or deficient in healthy older adults and patients with early stages of Alzheimer's disease. Such differentiations could, potentially, be valuable markers for early diagnosis.

1.1.5 Phasic alertness in aMCI and AD

In large part, previous attention studies in Alzheimer's disease focused on spatial attention or orienting (Buck et al., 1997; Castel et al., 2007; Danckert et al., 1998; Faust & Balota, 1997; Ishizaki et al., 2013; Maruff et al., 1995; Oken et al., 1994; Parasuraman et al., 1992; Tales et al., 2002a). Only few studies investigated phasic alerting effects in patients with aMCI and AD (Fernandez-Duque & Black, 2006; Festa-Martino et al., 2004; Karpouzian-Rogers et al., 2019; Martella et al., 2014; Tales et al., 2002b; Tales et al., 2005; Tales et al., 2011). Comparable to the previously described studies in healthy older adults, studies addressing phasic alerting effects in aMCI and AD yielded inconclusive results.

Initially, studies assessing both target detection and discrimination performance reported significantly higher visual phasic alerting effects in healthy older participants than in aMCI and AD patients (Festa-Martino et al., 2004; Tales et al., 2002b; Tales et al., 2011). Later studies contradicted the finding that visual phasic alerting effects on target discrimination performance are diminished in patient populations. These studies reported alerting effects of comparable magnitude in healthy older adults and patients (Fernandez-Duque & Black, 2006; Tales et al., 2006; Tales et al., 2011). The described divergent findings suggest that outcomes of phasic alertness studies might be particularly sensitive to specified task demands (Tales et al., 2006). In addition, auditory and visual alerting cues appear to differ in how they affect patients' task performance. According to a study by Karpouzian-Rogers et al. (2019), aMCI patients' target discrimination performance only benefited from auditory alerting cues. In comparison, both healthy younger and older participants profited from both visual and auditory cues. However, across all three groups, auditory warning tones elicited the strongest alerting effects (Karpouzian-Rogers et al., 2019). In line with this finding, Martella et al. (2014) reported that auditory cues enhanced target detection performance in healthy older adults and aMCI patients.

Irrespective of varying task demands (target detection vs. discrimination), type of cueing (visual vs. auditory), and cueing specifications, all mentioned studies have one important aspect in common: they measured speeded motor responses. Whether, alerting cues already increase processing on a perceptual level in aMCI and AD patients remains an open question.

1.1.6 Interim summary

Phasic alertness is defined as a short-lived boost of the brain's sensitivity to upcoming events following an external warning signal. Younger participants' processing abilities consistently profit from such warning cues. However, the brain mechanisms underlying phasic alerting effects on visual processing speed have not been investigated yet. Former studies in healthy older participants and patients do not permit final conclusions regarding preserved or diminished phasic alerting effects in aging. In healthy older participants, aMCI patients, and AD patients, phasic alerting effects appear to be sensitive to varying task and response demands, hindering overarching conclusions. Most importantly, the informative value of studies addressing phasic alertness in healthy and pathological aging is limited by the use of speeded motor responses. It has not, yet, been investigated whether phasic alerting cues benefit processing on a purely perceptual level in healthy older adults and aMCI patients. Furthermore, it is an open question whether or not phasic alertness relies on the same neural mechanisms in younger and older adults.

1.2 Theory of visual attention based assessment of phasic alertness

The TVA provides a parameter-based approach to estimate attentional functions. By combining a TVA-based verbal whole report paradigm that does not require any motor responses with auditory alerting cues, phasic alerting effects on visual processing speed can be investigated on a purely perceptual level.

1.2.1 Theory of visual attention

The TVA is a unified theory of visual recognition and attentional selection (Bundesen, 1990; Bundesen & Habekost, 2008). In contrast to early-selection (Broadbent, 1958) or late-selection (Deutsch & Deutsch, 1963) theories, TVA does not treat recognition and selection as consecutive processes, taking place in a certain order, but defines them as two aspects of the same underlying process. According to TVA, this process mainly consists of perceptual categorizations. For the perceptual categorization of 'element x belongs to category j', this element has to enter visual short-term memory (vSTM). As vSTM is limited by its storage capacity, one can only retain K elements and if exceeding this limit, any additional categorizations of elements are lost. Accordingly, elements in the visual display compete for selection. Computing attentional weights for all elements prior to this race enables an appropriate distribution of processing resources. The current importance of each category is described by its pertinence value. The product of pertinence values π per category j and the sensory evidence η that a certain element x belongs to this category j, summed over all possible perceptual categories R, defines the attentional weight w for this specific element x.

$$w_x = \sum_{j \in R} \eta(x, j)\pi_j \qquad \text{weight equation}$$

Once the race starts, elements can be selected at any time. The probability for successful perceptual categorization at a certain time point, given that it has not occurred beforehand (the so-called hazard rate), can be thought of as the speed of the race. The rate of processing v is not only influenced by the already described sensory evidence η and attentional weights w but also by the perceptual bias β of the observer towards a certain category. In case selection happens in multi-element rather than single stimulus displays, the overall processing speed is defined as the sum of all v values (Bundesen, 1990).

$$v(x,i) = \eta(x,i)\beta_i \frac{w_x}{\sum\limits_{z \in S} w_z} \qquad \text{rate equation}$$

Overall, the consecutive recognition and selection process is implemented by two mechanisms: filtering and pigeonholing. Filtering refers to selecting elements of the visual input whereas pigeonholing classifies these selected elements into categories. Attentional weights depict the filtering mechanism. A higher pertinence value for a certain target category, compared to all other categories, results in higher attentional weights. Such an increase in attentional weight, in turn, speeds up processing of elements belonging to this category. Pigeonholing is described by the perceptual bias parameter. An increase in the observer's bias for a certain target category speeds up the categorization of elements belonging to this category. In sum, filtering defines which elements in the visual field are selected (selection); pigeonholing determines how these elements are classified (recognition).

1.2.2 Components of perceptual bias

Extending the rate equation, Bundesen et al. (2015) propose that the perceptual bias is composed of three factors. According to their multiplicative hypothesis, the perceptual bias is computed as the product of alertness, prior probability, and utility.

$$\beta_i = A p_i u_i \qquad \text{bias equation}$$

Prior probability refers to the phenomenon that being exposed to a certain feature more frequently will facilitate the processing of elements with exactly this feature. Utility is synonymous with subjective importance. Incentivizing features, for example by introducing monetary awards, will speed up the processing of such object features (Bundesen et al., 2015). In contrast to prior probability and utility, alertness is not linked to specific features. An increase in the level of alertness speeds up processing to the same extent for all possible features in the visual display.

1.2.3 Verbal whole report paradigms with alerting cues

Verbal whole report tasks enable measuring the number of correctly reported letters as a function of display size or exposure duration (Sperling, 1960). This is achieved by displaying a certain number of letters for a limited amount of time and asking participants to verbally report as many letters as possible. For displays with four or less letters, the number of reported letters mirrored the number of letters presented on the screen. For display sizes exceeding 4 letters, the number of reported letters is limited by the vSTM capacity. Most importantly, the number of letters reported does not only depend on the display size but also on their exposure duration (Sperling, 1960). TVA-based whole report paradigms commonly keep the number of letters constant and vary their exposure duration. TVA facilitates a theoretical least square fit to such whole report data with three free parameters: vSTM storage capacity *K* (in number of items), visual processing speed *C* (in items/second), and perceptual threshold *t0* (in milliseconds) (Bundesen & Habekost, 2008) (see Figure 2). Parameter *K* is defined as the asymptote of the smooth curve while parameter *C* is the slope of the curve at *t0*. Parameter *t0* represents the minimum effective exposure. The presented letters are either followed by a masked or by a blank display. In masked trials, the experimenter can set a specific effective exposure. In unmasked trials, the participants benefit from an after-image, also termed iconic memory buffering (Sperling, 1960). This prolonged effective exposure duration is estimated by the additional parameter μ (Bundesen, 1990; Kyllingsbæk, 2006).

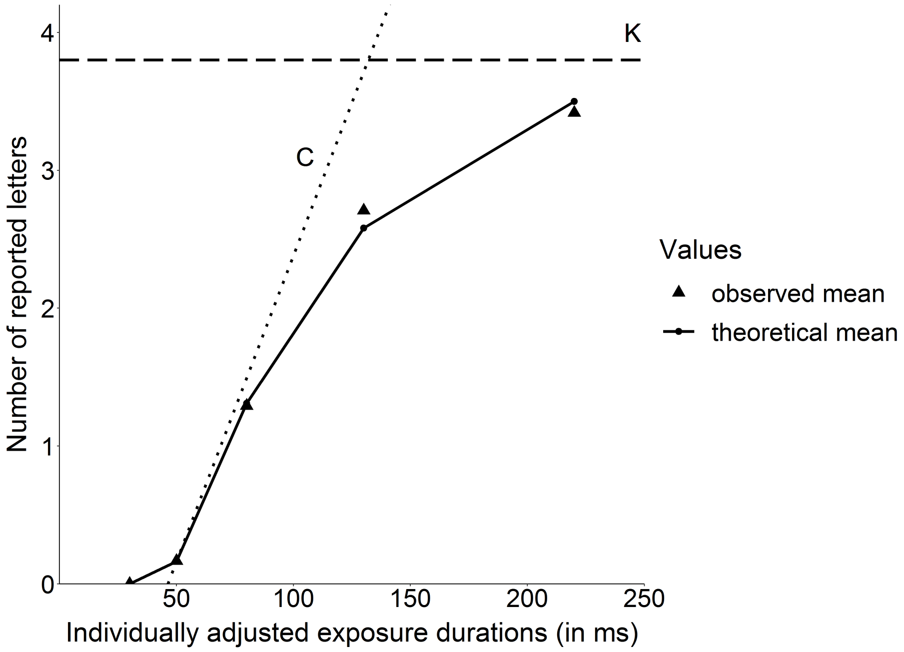

Figure 2: TVA fitting procedure

In a classical TVA whole report task, an identical prior probability and utility are allotted to all letters in the visual display. Therefore, a higher level of alertness will increase the perceptual bias and in turn result in a proportional increase in overall visual processing speed. When combining TVA-based whole report paradigms with auditory alerting cues, the speed of visual information uptake can be estimated separately for conditions with and without alerting cues. By comparing visual processing speed estimates in both conditions, TVA allows for the estimation of individual phasic alerting effects. Taken together, the studies presented in this thesis employ a TVA-based verbal whole report paradigm that does not require motor responses with auditory alerting cues in order to investigate phasic alerting effects on a purely perceptual level.

1.2.4 Neural theory of visual attention

The previously described computational principles of TVA can be extended to a neural level. The neural theory of visual attention (NTVA) (Bundesen et al., 2005) addresses filtering and pigeonholing at the single cell level. In general, the activation of a single neuron is defined as its increase in spiking in response to a certain stimulus compared to its baseline firing in the absence of any stimuli. As visual neurons are highly feature-selective, their instantaneous firing rate represents the sensory evidence that a given object has the feature represented by a particular neuron. In addition, the perceptual bias increases the spiking rate of a certain neuron to any stimulus independent of specific features. If several objects are present in the receptive field, a neuron will preferably respond to objects with high attentional weights. As these principles apply to all neurons, the filtering mechanism affects the number of spiking neurons while the pigeonholing mechanism changes their rate of firing (Bundesen & Habekost, 2008).

1.2.5 Interim summary

TVA-based whole report paradigms yield estimates of separate visual attention functions, e.g. visual processing speed, at the perceptual level. Adding phasic alerting cues to such paradigms allows for the comparison of visual processing speed estimates in cued and uncued conditions, a measure of the phasic alerting effect. Higher levels of alertness increase the perceptual bias and, by that, the overall speed of visual processing. On a neural level, this pigeonholing mechanism is reflected in an elevated firing rate of cortical neurons.

1.3 Intrinsic functional connectivity

1.3.1 Rationale for linking phasic alertness to iFC

None of the previous studies has addressed the neural underpinnings of phasic alerting effects on visual processing speed measured in TVA-based whole report paradigms. Therefore, it is unclear which neural mechanisms do underlie cue-induced temporary increases in visual processing speed, facilitating a faster processing of upcoming visual input. As described in the previous section, NTVA suggests that pigeonholing increases the firing rate of cortical neurons in response to visual stimuli in their receptive fields. According to NTVA, elevated spiking enables faster processing of visual stimuli with high perceptual bias, resulting in their encoding into vSTM. One of the key factors altering the perceptual bias and, correspondingly, the neuronal firing rate is the observer's level of alertness. Decisively, the spiking probability of cortical neurons is subject to spontaneous fluctuations. Propagating waves in the neocortex become manifest as subthreshold depolarizations of neurons (Wu et al., 2008). Neurons in such a spontaneous up state are characterized by an increased spiking probability, synaptic transmission efficacy, and sensitivity for upcoming sensory stimulation (Wu et al., 2008). Slow oscillations are a network mechanism, dynamically evolving as a mass phenomenon without a single exact origin and shaping the default activity of the cortex (Sanchez-Vives et al., 2017). Taken together, the neural interpretation of the TVA pigeonholing mechanism can be reconciled with intrinsic propagating waves that create an "unintentional focus of attention" (Wu et al., 2008) via subthreshold depolarizations of neuron populations in the sensory cortex. As we cannot measure subthreshold depolarizations of neurons in the human cortex, a different methodological approach is needed to capture intrinsic brain activity.

Global propagating calcium waves are significantly related to coactivations in cortical areas characterized by correlated hemodynamic signals (Matsui et al., 2016). Simultaneous calcium recordings with optic fibers and functional magnetic resonance imaging revealed that global cortical blood oxygenation level-dependent (BOLD) signals are specifically linked to the onset of slow calcium waves (Schwalm et al., 2017). Accordingly, BOLD signal fluctuations provide a window into intrinsic brain activity. We can measure BOLD signal fluctuations during resting-state fMRI. For the acquisition of such resting-state fMRI data, participants do not perform any cognitive or motor task. They are asked to rest with their eyes closed and intend to stay awake. We can then investigate whether spatial patterns of intrinsic fluctuations of the BOLD signal measured at rest are associated with phasic alerting effects measured in a TVA-based whole report paradigm.

1.3.2 Blood oxygenation level-dependent imaging

BOLD imaging is the most commonly used method in fMRI. BOLD fMRI relies on the magnetic properties of hemoglobin. While oxygenated hemoglobin is diamagnetic, deoxyhemoglobin is paramagnetic and, therefore, distorts the surrounding magnetic field leading to a decrease in T2* signal (Ogawa et al., 1990a; Ogawa et al., 1990b). Neuronal activity within a brain region requires oxygen for adenosine triphosphate production and, thus, leads to a rapid increase in deoxygenated hemoglobin. In addition, an excess of oxygenated hemoglobin is supplied to the brain region. The amount of oxygen supplied to a certain region is higher than its consumption. Accordingly, the BOLD signal following neural activity is increased as diamagnetic oxyhemoglobin replaces paramagnetic deoxyhemoglobin (Huettel et al., 2009).

1.3.3 Intrinsic fluctuations of BOLD signals

Decisively, the human brain does not only require oxygen for its energy production when performing cognitive tasks but also at rest. In fact, the additional energy consumption due to task-related increases in brain activity is estimated to be less than five percent. These estimates emphasize that most of the brain's energy consumption - a tremendous 20 percent of the body's overall energy consumption - is required for continuously ongoing intrinsic brain activity (Raichle, 2015). Ongoing slow fluctuations of the fMRI BOLD signal measured at rest form patterns of coherence (Biswal et al., 1995). These correlated time-courses of BOLD signal fluctuations with a frequency around 0.01-0.1Hz depict a measure of iFC (Fox & Raichle, 2007).

1.3.4 Resting-state networks

Spatial patterns of coherent slow intrinsic activity are termed resting-state networks (RSN). They have been identified in both primary sensory and associative brain areas (Allen et al., 2011; Smith et al., 2009; Yeo et al., 2011). For example, Allen et al. (2011) described auditory, visual, basal ganglia, sensorimotor, default mode, frontal, and attentional networks. RSN are reproducible across participants (Damoiseaux et al., 2006; De Luca et al., 2006). Moreover, they are characterized by a moderate to high test-retest reliability on the intra-subject level (Zuo et al., 2010). RSN are consistently found across species and differing levels of consciousness (Raichle, 2011). Animal studies provided evidence for comparable spatial patterns of coherent intrinsic activity in monkeys (Vincent et al., 2007) and rats (Lu et al., 2007). In humans, RSN can be replicated during conscious rest, anesthesia (Greicius et al., 2008; Stamatakis et al., 2010), and sleep (Fukunaga et al., 2006; Horovitz et al., 2008; Larson-Prior et al., 2009).

Importantly, iFC is not a measure of anatomical connectivity and does not provide information regarding directionality (Yeo et al., 2011). However, spatial patterns of coherent intrinsic activity correspond to structural connectivity patterns derived from diffusion spectrum imaging (Hagmann et al., 2008; Honey et al., 2009; Honey et al., 2007). A review of studies combining structural and intrinsic functional connectivity measures illustrates positive correlations between both types of connectivity but also reports functional connections in the absence of structural connections (Damoiseaux & Greicius, 2009).

IFC patterns are correlated with and explain a significant amount of trial-to-trial BOLD variability of button press responses, measured in event-related fMRI studies (Fox et al., 2007; Fox et al., 2006b). IFC does not only correspond to variability in motor responses but can also account for individual performance differences in tasks requiring higher cognitive functions, e.g. attention (Rosenberg et al., 2015; Visintin et al., 2015). With regard to alertness, iFC can predict reaction time increases in a condition with a phasic alerting cue as compared to a no-cue condition (Rosenberg et al., 2018). Connectivity patterns observed at rest are, in general, related to the individual variability in behaviour (Fox et al., 2007). In particular, they can predict individual performance differences in phasic alerting tasks (Rosenberg et al., 2018).

1.3.5 Independent component analysis

Spatial patterns of coherent BOLD activity can be identified by using a variety of analytical approaches: seed-based functional connectivity analysis (Biswal et al., 1995; Fox et al., 2006a), clustering (Yeo et al., 2011), independent component analysis (ICA) (Allen et al., 2011; Beckmann & Smith, 2004; Smith et al., 2009), and graph theory (Dosenbach et al., 2007). Seed-based approaches and ICA are, arguably, the two most popular techniques for analysing iFC (Fox & Raichle, 2007). Seed-based analysis is a simple and straightforward technique as it extracts the BOLD time course from a seed, i.e. region of interest, and correlates it with the time courses from all other voxels in the brain (Fox & Raichle, 2007). The main disadvantage of seed-based approaches is the requirement of defining seed regions a priori. In contrast, ICA is a data driven technique that does not require a priori definitions.

ICA is a blind separation technique that can decompose two-dimensional data (Bell & Sejnowski, 1995). Linear transformations are used to decompose the data set into separate components with minimized statistical dependence (Comon, 1994). This technique can be applied to fMRI data sets that contain matrices relating spontaneous BOLD signal time courses to specific voxels in space (Beckmann & Smith, 2004; Mckeown et al., 1998). It decomposes each time × space matrix into sets of time courses and spatial maps by applying three steps (Beckmann & Smith, 2004). First, probabilistic principal component analysis is used to identify a linear signal+noise subspace which contains the sources. Second, source signals in this subspace are estimated by employing a fixed-point iteration scheme, maximizing the deviation from Gaussianity for all source signal estimates. Third, the estimated sources, i.e. spatial maps, are extracted and converted into Z-maps (taking into account the estimated standard error of residual noise). A Gaussian mixture model enables the assessment of significant voxels within the Z-maps (Beckmann & Smith, 2004).

Taken together, ICA can separate spatial maps reflecting noise components from those reflecting RSN (Smith et al., 2004). This isolation of noise components constitutes the main advantage of ICA. However, the researcher has to visually inspect the components and decide if they reflect noise or RSN (Fox & Raichle, 2007). Apart from this potential bias, the analysis output also depends on the number of components chosen for the model. In general, the number of components cannot exceed the number of time points in the data matrix (Mckeown et al., 1998). A potential underestimation will result in information loss while a potential overestimation will lead to a higher amount of spurious components (Beckmann & Smith, 2004).

1.3.6 Dual regression

So far, we only covered how to identify RSN on the individual participant level. A combined multi-subject ICA and dual regression approach is needed to analyze RSN on the group level (Beckmann et al., 2009). In order to run an ICA on the group level, the time × space matrices of all participants have to be concatenated temporally (see Figure 3). The group ICA then decomposes the concatenated matrices into pairs of group time courses and group spatial maps. Subsequently, these group level files are further processed with a dual regression, i.e. combination of spatial and temporal regressions (Beckmann et al., 2009; Filippini et al., 2009). First, participant-specific temporal dynamics for each component are calculated by regressing the group-average spatial map into the individual time × space matrices (Beckmann et al., 2009). This step results in individual time points × components sets of beta coefficients (Smith et al., 2014b). Second, participant-specific spatial maps are identified by regressing the matrix of temporal dynamics into the same individual matrices (Beckmann et al., 2009). The individual spatial maps contained Z-scores indicating the similarity of a particular voxel's time course to the time course of a certain spatial map, i.e. component identified by the group ICA, controlling for the influence of all other components (Smith et al., 2014b).

Decisively, the individual spatial maps can be used to test hypotheses about behaviour-iFC associations in target RSN. Further, the individual time courses facilitate inter-network connectivity analyses. The combined ICA and dual regression approach appears to be particularly useful for relating individual differences in iFC to those in behaviour as it detects inter-individual variability more effectively than other analysis approaches (Smith et al., 2014a).

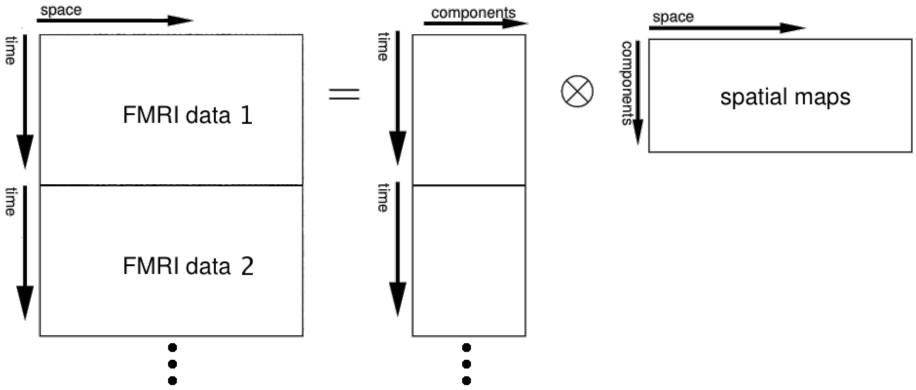

Figure 3: Temporal concatenation for group-level ICA

This image was taken from https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC with written permission from Stephen M. Smith.

1.3.7 Resting-state networks underlying TVA parameters

Applying a combined ICA and dual regression approach to resting-state fMRI data, a recent study related TVA-based estimates of visual attention functions to iFC in specific RSN (Ruiz-Rizzo et al., 2018). Ruiz-Rizzo et al. (2018) highlighted that, in younger healthy adults, individual differences in visual processing speed are inversely related to iFC in the ventral attention network, also referred to as salience network (Seeley et al., 2007) or cingulo-opercular network (CON) (Dosenbach et al., 2008). Both iFC in the cingulo-opercular network (He et al., 2014; Onoda et al., 2012) and visual processing speed (Espeseth et al., 2014; Habekost et al., 2013; McAvinue et al., 2012) decrease with age. Therefore, Ruiz-Rizzo et al. (2019) set out to address whether age-related iFC decreases in CON are associated with visual processing speed decline over the lifespan. They assessed 91 healthy adults in the age range of 20-77 years. The study could first replicate age-related decreases in both iFC in the CON and visual processing speed. Second, the authors extracted iFC values from cingulo-opercular network clusters characterized by age-related iFC reductions. Third, they correlated the iFC values with participants' TVA-based visual processing speed estimates. IFC extracted from a cluster located in the left insula was significantly associated with visual processing speed and mediated the effect of age on visual processing speed (Ruiz-Rizzo et al., 2019). Based on these results, the authors suggest that iFC in the CON could depict a potential marker for visual processing speed declines in healthy aging (Ruiz-Rizzo et al., 2019).

1.3.8 Interim summary

Coherent patterns of spontaneous fMRI BOLD signal fluctuations with a frequency around 0.01-0.1Hz depict a measure of iFC. Spatial patterns of such coherent intrinsic activity constitute RSN. On the group level, RSN can be identified using a combined multi-subject independent component analysis and dual regression approach. The individual spatial maps resulting from this approach allow for testing hypotheses regarding behaviour-iFC associations in RSN. Accordingly, TVA-based estimates of visual attention functions have been linked to specific RSN. In younger healthy adults, visual processing speed is inversely related to iFC in the CON. Both iFC in the CON and visual processing speed decline with age, and iFC in this RSN was suggested to mediate the effect of age on visual processing speed.

1.4 Aims of the thesis

The goal of this thesis was to identify systematic associations between phasic alerting effects on visual processing speed and iFC in healthy and pathological aging. In order to investigate these behaviour-iFC associations, we employed a TVA-based whole report paradigm with auditory alerting cues in healthy younger and older participants as well as aMCI patients and acquired resting-state fMRI data. The TVA-based whole report paradigm including auditory alerting cues enabled the measurement of phasic alerting benefits on a purely perceptual level. This type of measurement minimizes confounding effects of motor speed and is, therefore, especially insightful when studying phasic alertness in aging populations who are characterized by an overall slowing of motor processes. Spatial patterns of iFC depict a potential neural mechanism underlying phasic alertness. We used a combined ICA and dual regression approach to analyze resting-state fMRI data as this approach notably detects inter-individual variability and can be used to test for significant behaviour-iFC associations in RSN.

More precisely, the current thesis addressed the following research questions:

Project I: Do phasic alerting cues increase visual processing speed in healthy older participants? Are the degree and time course of these phasic alerting effects comparable between healthy younger and older adults?

Project II: Which iFC patterns do underlie phasic alerting effects on visual processing speed in healthy younger adults?

Project III: Which iFC patterns do underlie phasic alerting effects on visual processing speed in healthy older adults? Are the observed behaviour-iFC associations age group specific?

Project IV: Do phasic alerting cues increase visual processing speed in aMCI patients?

Chapter 2

Project I: Phasic alertness in healthy aging

The current chapter comprises the research article entitled "Phasic alertness cues modulate visual processing speed in healthy aging" that was published in Neurobiology of Aging in 2018. This first thesis project demonstrated that auditory alerting cues increase visual processing speed in healthy older adults. While basic visual processing speed was decreased in older as compared to younger participants, phasic alerting benefits were comparably strong across age groups.

Authors:

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Contributions:

M.H., K.F., and C.S. conceived and designed the study. N.N. programmed the behavioural paradigm. M.H. recruited participants, conducted the experiment, and analyzed the data. M.H. drafted the main manuscript. M.H., C.S., N.N., and K.F. critically revised the manuscript.

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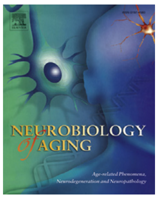

Phasic alertness cues modulate visual processing speed in healthy aging

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ABSTRACT

Warning signals temporarily increase the rate of visual information in younger participants and thus optimize perception in critical situations. It is unclear whether such important preparatory processes are preserved in healthy aging. We parametrically assessed the effects of auditory alertness cues on visual processing speed and their time course using a whole report paradigm based on the computational Theory of Visual Attention. We replicated prior findings of significant alerting benefits in younger adults. In conditions with short cue-target onset asynchronies, this effect was baseline-dependent. As younger participants with high baseline speed did not show a profit, an inverted U-shaped function of phasic alerting and visual processing speed was implied. Older adults also showed a significant cue-induced benefit. Bayesian analyses indicated that the cueing benefit on visual processing speed was comparably strong across age groups. Our results indicate that in aging individuals, comparable to younger ones, perception is active and increased expectancy of the appearance of a relevant stimulus can increase the rate of visual information uptake.

1. Introduction

Living in a rapidly changing and complex visual environment, the ability to prepare for upcoming stimuli or events is crucial for effective behavior. As such environments can be especially demanding in high age, it is important whether and how aging affects these preparatory mechanisms. The present study sets out to investigate the effect of normal aging on the benefit that warning signals exert on attentional performance.

External warning signals induce short-lived changes in preparatory states defined as phasic alertness (Sturm and Willmes, 2001). Although such alerting signals provide no information about the location or time of target appearance, several studies showed that they enhance the readiness of the observer's brain, leading to reaction time advantages in alerting conditions over conditions without warning signals (Coull et al., 2001; Fan et al., 2005; Posner, 1978; Posner and Boies, 1971). On a brain network level, phasic alerting cues induce increased activations in frontal and parietal areas, as well as thalamic and brainstem structures (Sturm and Willmes, 2001). These structures also include the noradrenergic and cholinergic systems, which exert neuromodulatory effects on the alerting system (Brown et al., 2015). As both systems are known to change over the lifespan (e.g., Robertson, 2013; 2014), the ability to prepare for upcoming visual events might as well undergo significant changes in healthy aging.

Previous studies on the effect of aging on phasic alerting, however, yielded nonconclusive results. Studies reporting a decrease or the absence of alerting effects (e.g., Festa-Martino et al., 2004; Gamboz et al., 2010; Ishigami et al., 2016) are opposed by findings indicating preservation of phasic alertness in aging (e.g., Fernandez-Duque and Black, 2006; Rabbitt, 1984). Furthermore, temporal orienting of attention (being closely linked to phasic alertness) has been shown to be preserved in healthy aging (Chauvin et al., 2016). Varying task demands and response modalities are potential sources of these incongruent results. It is important to differentiate whether and to which extent certain tasks measure phasic alerting effects on the (attentional) perceptual level and the level of motor responses. Both levels are not clearly dissociated in previous research. Originally, alerting stimuli were thought to solely affect "response readiness", that is processes underlying the preparation and execution of motor responses (Posner,

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1978; Sturm and Willmes, 2001). This assumption, however, was challenged by an functional magnetic resonance imaging study documenting increased brain activity under increased phasic alertness mainly in extrastriate, perceptual areas (Thiel et al., 2004). Therefore, behavioral paradigms addressing the perceptual level of phasic alertness have gained in importance. Especially in older populations, there is a necessity for nonresponse-related measures of the brain's preparatory state because measures based on speeded motor responses are confounded by the overall slowing of motor processes in aging (Shalev et al., 2016).

A parameter-based approach to assess perceptual attentional processing, without confounds induced by individual variability in the preparation and execution of motor responses, is provided by verbal report paradigms based on the computational Theory of Visual Attention (TVA; Bundesen, 1990). The TVA model is closely linked to the biased competition view of attention (e.g., Desimone and Duncan, 1995). In a nutshell, TVA assumes that numerous visual objects are processed in parallel and compete for selection into a capacity-limited visual short term memory (vSTM) store. Speed, that is, the processing rate of individual objects (v), is the decisive criterion for its probability to get selected. Objects processed at greater rate compared to those at lower rate have a higher probability of being encoded into vSTM until its storage capacity is exceeded. The visual system's overall processing capacity is defined by the sum of all individual processing rates for the number of objects in the visual display and thus provides an estimate of the individual visual processing speed of a given participant (Habekost et al., 2013). TVA-based whole report paradigms with briefly presented letter displays are optimized for yielding precise parameters that characterize the visual attentional capacity of a given individual: visual perceptual threshold $t0$ (in ms), visual processing speed C (rate of information uptake per second), and vSTM storage capacity K (maximum number of objects that can be encoded and held available at a point in time).

By combining TVA-based paradigms with visual alertness cues, it was shown that incremented phasic alertness actually leads to an increase in visual processing speed (Matthias et al., 2010). Furthermore, a comparable increase in visual processing speed was found following auditory alerting cues, which additionally decreased the visual perceptual threshold (Petersen et al., 2017) and the latencies of lateralized event-related electroencephalography potentials that indicated early perceptual processing stages (Wiegand et al., 2017b). These studies strongly indicate that, in younger participants, phasic alertness increases the brain's readiness for perception and thus induces a preparatory state that affects the speed of visual information uptake.

According to a neural interpretation of TVA, namely NTVA (Bundesen et al., 2005), visual processing speed is determined by the number and the activation level of those neurons that are involved in the processing of visual information presented in a visual array. Furthermore, it is suggested that an increase of the level of alertness (A), that is, of the overall activation level of the brain, leads to an enhancement of the observer's readiness to form visual categorization. This will lead to an increased processing rate of categorizations (Bundesen et al., 2015). Thus, formally, all processing rates of multiple objects in a given display will be augmented by a common factor, resulting in an increase of the overall visual processing speed C of a given participant. Thus, by comparing conditions with and without alerting cues in a TVA-based whole report paradigm, quantitative estimates of an individual's phasic alertness gain on visual processing speed can be derived.

To date, the only TVA-based study using this approach to assess alerting effects in aging applied a partial report design. In this study, the authors did not find evidence for an enhancement of sensory effectiveness in elderly participants following auditory alerting cues (Wiegand et al., 2017a). However, the use of 1 constant exposure duration across the different experimental conditions of such partial report design does not allow retrieving separate quantitative measures of visual processing speed and visual perceptual threshold. Therefore, the present paper sets out to apply a TVA-based whole report paradigm with auditory alerting cues. First, we intend to replicate the previously reported alerting benefits in younger participants. We aim to extend those findings by assessing the time course of alerting effects. We applied jittered cue-target onset asynchronies (CTOAs) in a broad time range of 60–320 ms that cover most CTOAs used in prior TVA studies, which were either defined as relatively short (Matthias et al., 2010) or relatively long CTOAs (Petersen et al., 2017; Wiegand et al., 2017b). Second, we set out to investigate whether healthy older adults show significant benefits of alertness cues on their visual processing speed. Although alerting effects could not be demonstrated in a partial report paradigm with solely 1 presentation time, we assume that an assessment using a whole report task with different exposure durations is more sensitive to the subtle changes that are expected to follow cueing and reflects changes in processing speed more validly. In this task, we assume to find significant benefits induced by alerting cueing in healthy older participants. Third, we want to directly compare alerting benefits in both age groups. Overall, we hypothesize that a significant alerting effect is present in healthy aging but expect that both age groups could differ in the degree or time course of such an effect. Finally, we explore whether time on task affects visual processing speed in the different experimental conditions because, if they occur, such time-on-task effects might be influenced by cueing.

2. Material and methods

2.1. Subjects

Thirty-six healthy younger adults ($\leq$35 years) and 35 healthy older adults ($\geq$60 years) participated in the present study. Two younger and 3 older subjects were excluded because they reached extreme values of visual processing speed (>2 SDs from the group mean). Therefore, the final sample consisted of 34 younger and 32 older participants (see Table 1). All participants reported normal or corrected-to-normal vision, gave informed consent, and were either reimbursed for their participation or received course credits. The Edinburgh Handedness Inventory (Oldfield, 1971) and a

Table 1
Demographics of all participants

Variable	Young participants	Old participants	Significance test (p value)
	N = 34	N = 32	
Mean age (SD)	26.4 (4.7)	71.2 (4.7)	<0.001
Age range	18–35	60–77	
Sex (female/male)	21/13	11/21	0.026
Handedness (right/left/ambidextrous[b])	29/5/0	30/0/2	0.265
Mean education in years (SD)	12.6 (0.9)	11.8 (1.8)	0.146
Mean MWTB score (SD)[a]	28.6 (4.5)	32.7 (2.2)	<0.001
Mean MMSE score (SD)	/	28.8 (1.1)	/
MMSE range	/	27–30	

Chi square tests are calculated for handedness and sex; Mann-Whitney U tests are calculated for the other variables.

Key: handedness, assessed by Edinburgh Handedness Inventory; MWTB, Mehrfachwahl-Wortschatz-Intelligenztest, maximum score = 37 points; MMSE, Mini-Mental State Examination, maximum score = 30 points with values < 24 points indicating cognitive impairment; SD, standard deviation.

[a] Two younger and 2 older subjects have missing MWTB values.

[b] Due to historical pressure to "relearn" handedness, ambidextrous older participants are treated as left-handed in the comparison.

multiple choice German vocabulary test measuring crystallized intelligence, “Mehrfachwahl-Wortschatz-Intelligenztest” (MWTB; Lehrl et al., 1995) were administered (see Table 1). Older participants achieved significantly higher MWTB scores. This result can be explained by an accumulation of knowledge over the lifespan, which is generally reflected in higher crystallized intelligence measures (Deary et al., 2010). In addition, older participants were screened for cognitive impairments indicating beginning neurodegeneration using the Mini-Mental State Examination (MMSE; Folstein et al., 1975). None of the older participants had to be excluded based on a cutoff criterion for cognitive impairment of scores under 24/30 points (all scores ≥ 27 points). The study was reviewed and approved by the Ethics Committee of the Department of Psychology of the Ludwig-Maximilians-Universität München.

2.2. TVA-based whole report paradigm

On each trial of the TVA-based whole report paradigm, 6 equidistant target letters (each 1.2 cm high, 1.0 cm wide) were presented on an imaginary circle around the central fixation point (0.9 × 0.9 cm; see Fig. 1). The color of the letters varied randomly between red and blue with all 6 letters always appearing in the same color per trial. The luminance of all letters was set to 0.49 cd/m^2 (International Commission on Illumination $[\mathrm{CIE}]_{\mathrm{red}} = [0.49, 0.515, 0.322]$, $\mathrm{CIE}_{\mathrm{blue}} = [0.49, 0.148, 0.068]$). Subjects were instructed to report all letters recognized with “fair certainty” without any importance of speed or order. At the end of each test block, participants were presented with an accuracy rating on a scale based on all reported letters. They were asked to maintain an accuracy level between 70% and 90% with a higher or lower score leading to slightly adapted instructions for the next block. In case the participants’ accuracy rating exceeded 90%, they were asked to intend to also name letters that they believed to have recognized without being completely certain about it. If the accuracy score was lower than 70%, the participants were instructed to just report letters they have recognized with a high certainty even if that led to reporting less letters overall.

The experimenter entered all reported letters on the computer keyboard and started the next trial by pressing the space key. Per trial, 6 letters for the given display were randomly chosen from a set of 23 letters (ABCDEFGHJKLMNOPRSTUVWXZ) with every letter appearing only once in a given trial and trials differing between participants. Those letter arrays were presented either masked or unmasked. The masks consisted of squares matching the size of the letters (max. 1.8 × 1.8 cm) filled with red and blue colored blobs (see Fig. 1). They were presented for 500 ms ($\mathrm{CIE}_{\mathrm{red}} = [4.86, 0.605, 0.318]$, $\mathrm{CIE}_{\mathrm{blue}} = [2.99, 0.162, 0.088]$).

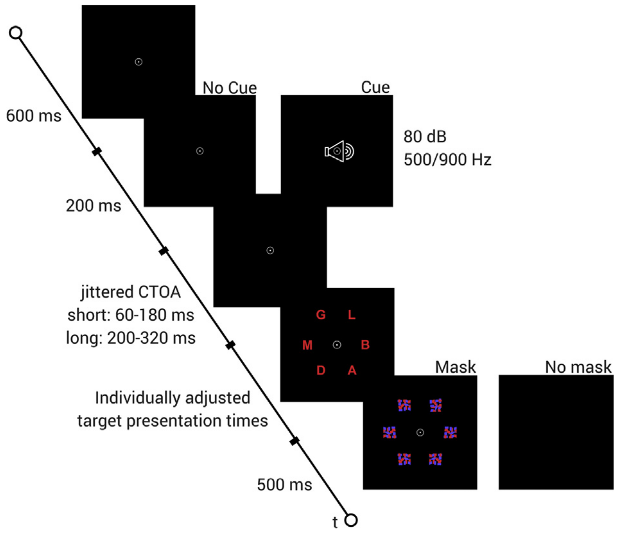

Fig. 1. Trial sequence in whole report paradigm. Abbreviation: CTOA, cue-target onset asynchrony.

Furthermore, 5 different target exposure durations were used. For each individual subject, the exposure durations were determined in a pretest phase and later used for all experimental blocks. This pretest phase consisted of 48 trials in total, grouped in 4 practice blocks with an accuracy rating following each block. The 12 trials in each block were composed of 4 triplets of trials. Each triple contained one masked calibration trial and 2 trials with long exposure durations, either masked with 250 ms or unmasked with 200 ms exposure duration, to not discourage the participant. Trials within each triple were randomized. The calibration trials started with an exposure duration of 100 ms. If the participant was able to report at least one of the 6 letters correctly, the exposure duration was decreased by 10 ms. In case none of the letters was named correctly, the exposure duration was increased by 10 ms. At the end of the adjustment block, the lowest adjusted exposure duration for the following test phase was determined as the shortest exposure duration used in the calibration trials. Hence, participants were not able to report any letter with this exposure duration. Four additional exposure durations were picked from a predefined list based on that value (e.g., if lowest exposure duration was 20 ms, adjusted exposure duration (AEDs) = [20, 40, 60, 120, 210]; if it was 90 ms, AEDs = [90, 120, 160, 210, 280]). Usually, iconic memory buffering leads to prolongation of the effective exposure durations by several hundred milliseconds when comparing unmasked to masked conditions (Sperling, 1960). In addition to masked versions of all 5 AEDs, 2 exposure durations were also presented without masks. This resulted in 7 effective exposure durations, generating a broad spectrum of performance, covering near-threshold and maximum performance levels.

Given that the exposure durations were adjusted to the individual accuracy levels and that responses were not speeded, the baseline performance of all participants is comparable for their shortest adjusted exposure duration. Thereby, the adjustment of exposure durations controls for differences in visual perceptual thresholds enabling a measurement of visual processing speed, which is not confounded by individual differences in visual perceptual threshold. Furthermore, participants were explicitly instructed to maintain fixation on the center of the screen as optimal preparation for the upcoming target letters, which always appeared in the same 6 locations positioned on an imaginary circle around the fixation point. Because of the instructions and short exposure durations, it is unlikely that eye movements affected the performance in a systematic way. Note that especially the estimation of visual processing speed relies on performance differences between near-threshold trials, that is, on performance in trials with the lowest exposure durations used throughout the experiment.

2.3. Alertness conditions

In the alerting-cue condition, an auditory cue containing no spatial information about the upcoming target location was presented for 200 ms. The 80 dB tone was chosen randomly, either with a frequency of 500 Hz or 900 Hz. During that time, the screen remained blank with only the fixation point being visible. The cue was assumed to enhance participants’ phasic alertness for a few hundred milliseconds. In the no-cue condition, participants saw a blank screen for 200 ms without hearing any tone. To familiarize the participants with the different alertness conditions, cue and no-cue trials were already randomized during practice trials.

2.4. CTOA variation

For the cue as well as no-cue conditions, 2 different CTOA spectrums, “long” and “short,” were used. The “short” CTOAs had an average of 120 ms and were jittered around the average value in steps of ± 20 ms, 40 ms, and 60 ms leading to an overall range of 60–180 ms. The “long” CTOAs had an average of 260 ms, with the same jittering steps leading to a range of 200–320 ms. For each trial, one CTOA was randomly drawn from the according CTOA distribution (short or long). In all conditions, the jittering was balanced with all jittered CTOAs having the same probability and appearing equally often across trials. This led to a total of 48 trials with the same CTOA, equally split into 24 cue trials and 24 no-cue trials.

2.5. Procedure

The whole report paradigm was conducted in a soundproof and dimly lit cabin. All stimuli were presented on a BenQ24 inch monitor (1920 × 1080 pixel screen resolution, 100 Hz refresh rate) and Trust Leto loud speakers were used for playing the tones. The approximate viewing distance of the subjects was 60 cm, controlled by the aid of a chin rest.

The sequence of frames presented on no-cue and cue trials can be seen in Fig. 1. After the experimenter initiated the trial, participants fixated on a white circle with a dot in the middle that was displayed in the center of a black screen for 600 ms. Following the fixation, the alerting tone was presented in cue trials while nothing happened in no-cue trails with participants still fixating on the circle in both conditions. A CTOA followed before the display array was presented with the adjusted exposure durations individually predetermined for each participant. In masked trials, the array was followed by a mask display for 500 ms. After entering the named letters, the experimenter started the next trial with a button press. Every block included an equal number of cue and no-cue trials with short and long CTOAs, presented in a random order.

The present experiment contained 8 blocks with 84 trials assigned randomly to each condition. The whole session lasted between one and one and a half hours. In the beginning, written instructions were displayed on the screen and 2 exemplary trials were presented.

2.6. Estimation of TVA parameters

The whole report paradigm offers the possibility to estimate visual processing speed, vSTM storage capacity, and visual perceptual threshold. Detailed underlying estimation algorithms were described by Kyllingsbaek (2006). Given an object *x*, the probability of identifying this specific object is mathematically modeled by an exponential growth function. Hence, the function is relating accuracy of report (mean number of reported items) to effective exposure duration. The origin of the function (coordinate: t0, 0) defines the visual perceptual threshold *t*0. The function’s slope at this coordinate indicates the visual processing speed *C* defined as the total rate of information uptake in objects per second. Furthermore, the asymptotic nature of the function shows that only a certain amount of information can be represented in vSTM. The according asymptote denotes the maximum number of represented object defined as vSTM storage capacity *K* (see Fig. 2).

2.7. Statistical analyses

When checking the assumptions for parametric testing in the younger participants, significant Shapiro-Wilk tests indicated non-normal distributions for visual processing speed and visual perceptual threshold in different conditions (Shapiro and Wilk, 1965). The vSTM storage capacity followed a normal distribution. In the older participants, visual processing speed did not follow a normal distribution in some experimental condition. The distributions of vSTM storage capacity and visual perceptual threshold did not violate the assumption of normality in older participants. Because of the described violations of the General Linear Model’s assumptions, an equivalent robust model was applied (Field and Wilcox, 2016; Wilcox, 2017). The robust model takes into account that even slight deviations from a normal distribution lead to higher tails of the distribution. These “heavy tails” substantially increase the standard error of the sample mean. Importantly, there are other location estimators (as opposed to mean or median) whose standard errors are significantly less affected by non-normal distributions. In this case, we chose the sample trimmed mean as location estimator. The sample trimmed mean can be calculated by removing the *x* largest and *x* smallest values in an ascending list of observations depending on which amount of trimming has been chosen. Generally, a trimming of 20% is recommended and is therefore also applied in the present paper (Wilcox, 2017). Nonparametric tests were applied for post hoc and exploratory comparisons.

We aimed to first replicate alerting effects in younger participants and explore the underlying time course of such effects. Second, we set out to investigate the degree and time course of alerting effects in older participants. Because of these specific research questions, the 2 samples were initially analyzed separately. For both, we used a robust method based on 20% trimmed means for a 2 × 2 repeated-measures design with the within subject factors cueing (cue vs. no-cue) and CTOA (short vs. long) for visual processing speed, vSTM storage capacity, and visual perceptual threshold. The analysis on visual processing speed was followed up by nonparametric post hoc Wilcoxon signed-rank tests. These analyses were performed using the WRS package (Wilcox and Schönbrodt, 2017) in RStudio version 1.0.136 (RStudio Team, 2016). Apart from orthodox statistics, we also ran the Bayesian counterpart of repeated-measures analysis of variances (ANOVAs) (Rouder et al., 2017) using JASP version 0.8.5.1 (JASP Team, 2018). A nonparametric, Bayesian counterpart for Wilcoxon signed-rank test is not available. JASP calculates the Bayes factor (B_{10}), which is a measure for the ratio of the likelihoods of 2 theories. By comparing those likelihood, the Bayes factor allows for a quantification of the evidence for each theory (e.g., null hypothesis and alternative, experimental hypothesis). Hence, if B_{10} is greater than 3, the present data substantially support the alternative hypothesis, whereas values smaller than 1/3 substantially favor the null hypothesis. B_{10} values between 1 and 3 (as well as 1 and 1/3 accordingly) solely yield anecdotal evidence for a hypothesis (e.g., Dienes, 2011; Wagenmakers et al., 2011).

The analysis of the younger subsample was followed up by an exploratory analysis on visual processing speed within the short CTOA, applying a median split based on the relative cueing effect. The resulting groups were contrasted using Mann-Whitney tests and their parametric, Bayesian counterpart (Rouder et al., 2009), which have to be interpreted keeping the normality violation in mind. For the variable sex, we used χ^2 tests and Bayes factors for contingency tables (Jamil et al., 2017). In a supplementary analysis, we analyzed the continuous sample of younger participants performing a logistic regression with cueing benefit as dichotomous outcome variable and initial visual processing speed as predictor (see Supplementary Materials).

For both, younger and older participants, we conducted exploratory analyses addressing time-on-task effects. Because of the number of trials needed for the TVA fitting algorithm to yield reliable estimates of visual processing speed, we could not analyze the data for each individual block but split the data according to the

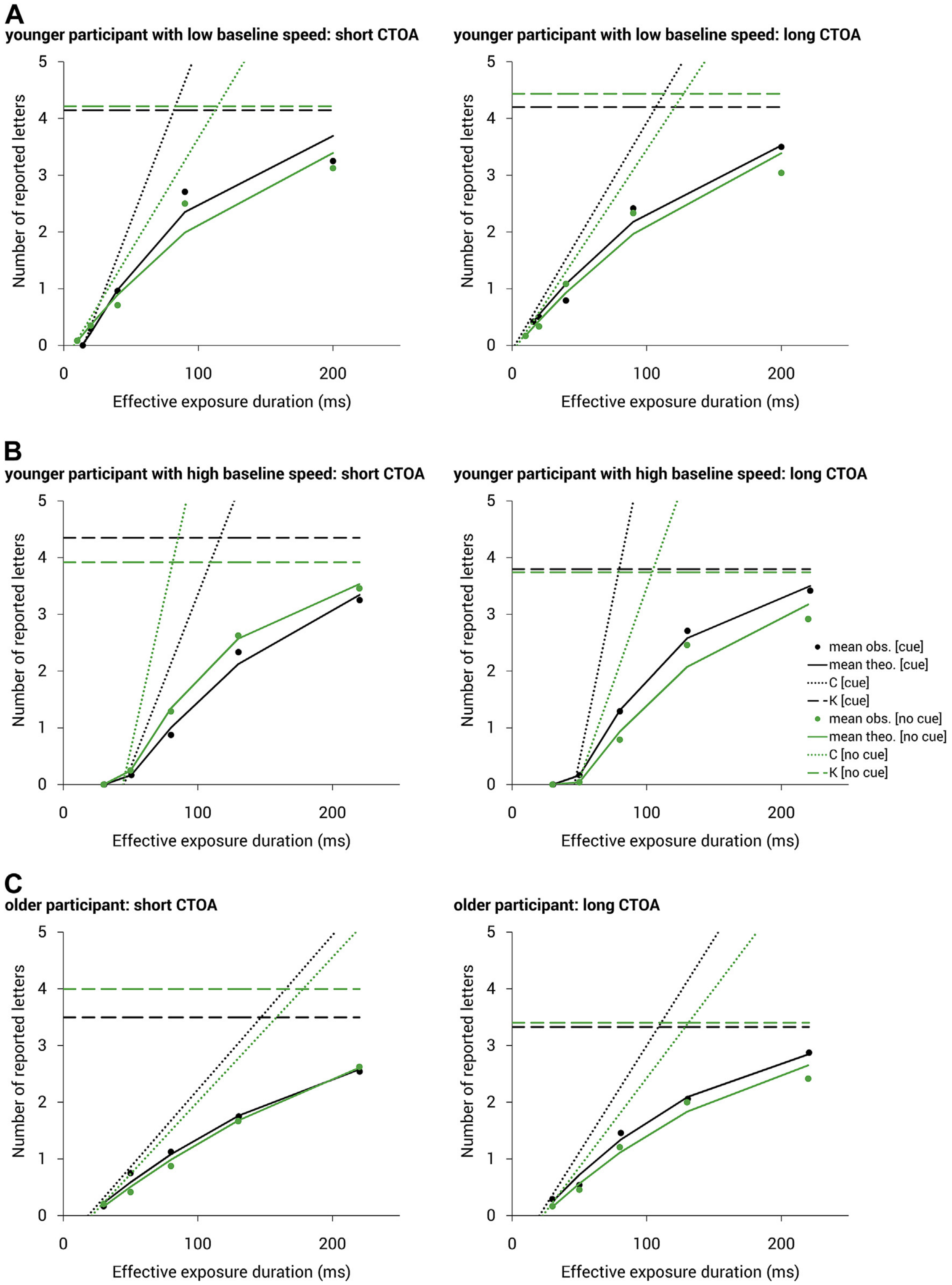

Fig. 2. Whole report performance for a representative younger participant with a relatively low baseline *C* value (no-cue condition) and a cueing benefit in the short CTOA (A); a representative younger participant with a relatively high baseline *C* value and a detrimental cueing effect in the short CTOA (B); a representative older participant (C). For each participant, separate graphs for the short and long CTOA are presented. Each graph contains a comparison between the cue and no-cue condition. The observed values are displayed as single data points (mean obs.). Solid curves represent the best theoretical fit from the TVA to the observations (mean theo.). The vSTM storage capacity *K* is defined as the asymptote of the function and is marked by a dashed line. The visual perceptual threshold *t*0 is defined by the origin of the function (coordinate: t0,0). Visual processing speed *C* is defined as the slope of the function in *t*0 and is represented by a dotted line. Abbreviations: CTOA, cue-target onset asynchrony; TVA, theory of visual attention; vSTM, visual short term memory.

test halves (blocks 1–4: first test half, blocks 5–8: second test half). Accordingly, we compared the estimates of visual processing speed in both test halves for all experimental conditions by running the Bayesian counterpart of 1-sided paired-sample t-tests for both CTOAs in younger and older participants separately. As a prerequisite for these analyses, we calculated Spearman's Rho for correlations between the visual processing speed estimates in the according test half and in the whole test.

Finally, we ran Bayesian counterparts of a repeated-measures ANOVA with the same within subject factors and age group as a between subject factor to compare alerting effects in younger and older participants. Because of significant sex and crystallized intelligence score difference between both groups, we calculated a follow-up repeated-measures ANOVA with the same factors, including sex and crystallized intelligence as covariates. To potentially account for generally lower visual processing speed values in the older participants, we additionally ran a Bayesian ANOVA for the relative cueing effect, comparing both CTOAs and age groups.

3. Results

3.1. Alerting effects in younger participants

The statistical analyses for the younger participants were run on the parameter estimates derived from TVA-based model fitting to the observed data. The mean correlations of observed and predicted scores in all 4 experimental conditions were >0.98. Such high correlations of the mean observed scores and predicted values in all conditions indicate a satisfactory goodness of fit of the TVA model.

The TVA parameter estimates for the different experimental conditions are found in Table 2. The analyses for all main effects and all interaction effects on the dependent variables vSTM storage capacity *K* (all $Q < 3.213$, all $p > 0.073$, all $B < 0.839$) and visual perceptual threshold *t0* (all $Q < 0.334$, all $p > 0.563$, all $B < 0.400$) did not reveal any significant results or evidence in favor of the alternative hypotheses. These results suggest that phasic alerting cues preceding a whole report task did not alter vSTM storage capacity or the visual perceptual threshold in younger participants. Therefore, the following analyses will solely focus on cueing effects on visual processing speed.

The robust 2 × 2 repeated-measures design for visual processing speed *C* revealed a significant main effect of cueing ($Qa = 6.475$, $p = 0.018$), as well as a trend for a significant cueing × CTOA interaction ($Qab = 2.857$, $p = 0.091$). The main effect of CTOA was not significant ($Qb = 0.036$, $p = 0.850$). Bayes factor comparisons favored the model assuming a main effect of cueing by estimating the observed data to be 4.759 times more likely under the alternative than the null hypothesis. The cueing × CTOA interaction yielded a Bayes factor of 3.000 favoring the alternative hypothesis. Regarding the effect of CTOA, the null hypothesis of no differences in visual processing speed between both CTOAs is more likely than the experimental hypothesis ($B_{10} = 0.182$).

The substantial evidence and significance trend for the cueing × CTOA interaction can be explained by a significantly higher visual processing speed in the cue compared to the no-cue condition in the long CTOA ($T = 493.000$, $p < 0.001$, $r_b = 0.657$), whereas no significant difference was found in the short CTOA ($T = 291.000$, $p = 0.919$, $r_b = (-0.022)$).

To gain insights into the reasons for an absence of a significant cueing effect at the short CTOA, we conducted an exploratory individual differences analysis. First, we calculated the relative cueing effect (RCE) in the short CTOA. Then, we applied a median split for the RCE ($Mdn = -1.01$). This resulted in 1 group with positive or rather neutral RCEs (ranging from −0.26 to 41.95) and another group with negative RCEs (ranging from −1.77 to −27.97). In exploratory analyses, we tested whether sociodemographic variables (age, education, sex) and/or baseline performance level, that is, TVA parameters *C*, *K*, and *t0* in the no-cue condition, differed between both median split groups (see Table 3). Visual processing speed *C* in the no-cue condition was the only parameter that differed significantly between both RCE groups. Participants in the low RCE group showed significantly higher visual processing speed baseline values [$M = 36.7$, $SD = 11.7$] compared to participants in the high RCE group [$M = 28.4$, $SD = 8.5$] (see Table 3).

For the exploratory analysis regarding time-on-task effects we, first, calculated Spearman's coefficients for correlations between visual processing speed estimates in the first test half and the whole test as well as the second test half and the whole test. In all 4 experimental conditions, the coefficients indicated strong correlations between the according test half and the full test (all $r_s \geq 0.80$). This result suggests that the visual processing speed estimates per test half are sufficiently reliable to use them as a factor in a time-on-task analysis. Bayesian counterparts of 1-sided paired-sample t-tests were conducted separately for all experimental conditions testing whether visual processing speed in the second test half is significantly lower than in the first test half. All tests yielded Bayes factors of $0.050 \leq B_{10} \leq 0.102$, therefore strongly favoring the null hypotheses. The results suggest that the visual processing speed estimates for all 4 experimental conditions do not deteriorate in the second test half compared to the first one.

3.2. Alerting effects in older participants

The statistical analyses for the older participants were also run on the parameter estimates derived from TVA-based model fitting to the observed data. The mean correlations of observed and predicted scores in both CTOAs were 0.97 for the cue condition and 0.98 for the no-cue condition. Again, such high correlations of the

Table 2
TVA parameter estimates for all conditions in younger participants

Variable	Cue condition	No-cue condition
Visual processing speed *C*		
Short CTOA	32.77 (11.06)	32.53 (10.91)
Long CTOA	34.63 (12.07)	30.95 (9.98)
vSTM storage capacity *K*		
Short CTOA	4.07 (0.56)	4.01 (0.52)
Long CTOA	4.05 (0.55)	4.08 (0.56)
Visual perceptual threshold *t0*		
Short CTOA	15.57 (12.12)	16.21 (11.94)
Long CTOA	16.06 (12.16)	15.24 (11.80)

Means and standard deviations (in parentheses) are reported.
Key: CTOA, cue-target onset asynchrony; TVA, theory of visual attention; vSTM, visual short term memory.

Table 3
Exploratory analysis comparing subgroups of younger participants based on a median-split of the relative cueing effect

Variable	U	*p* value	r_b	χ^2	B_{10}
Demographics					
Sex	–	0.724	–	0.125	0.438[a]
Age	125.000	0.511	−0.135	–	0.405
Education	142.500	0.954	−0.014	–	0.334
Initial TVA parameters					
Visual processing speed *C*	81.000	0.029	0.439	–	2.587
vSTM storage capacity *K*	124.000	0.496	0.142	–	0.356
Visual perceptual threshold *t0*	130.000	0.634	−0.100	–	0.371

Key: r_b: effect size given by rank biserial correlation; TVA, theory of visual attention; vSTM, visual short term memory.

[a] Independent multinomial.

mean observed scores and predicted values in all conditions indicate a satisfactory goodness of fit of the TVA model.

Table 4 presents the TVA parameter estimates for the different experimental conditions. The analyses for all main effects and all interaction effects on the dependent variables vSTM storage capacity K (all $Q < 2.237$, all $p > 0.135$, all $B_{10} < 0.288$) and visual perceptual threshold $t0$ (all $Q < 1.576$, all $p > 0.210$, all $B_{10} < 0.760$) did not reveal any significant results or evidence in favor of the alternative hypotheses. These results suggest that phasic alerting cues preceding a whole report task do not alter vSTM storage capacity or the visual perceptual threshold in older participants. Therefore, the following analyses will solely focus on cueing effects on visual processing speed.

A robust method for 2 × 2 repeated-measures revealed a significant main effect of cueing ($Qa = 7.750$, $p = 0.005$). Visual processing speed C was significantly higher in the cue compared to the no-cue condition. The main effect of CTOA ($Qb = 2.100$, $p = 0.148$) and the cueing × CTOA interaction ($Qab = 0.054$, $p = 0.817$) were not significant. Neither the mean visual processing speed nor the cueing effect was significantly different between the short and long CTOA.

Regarding the main effect of cueing, the Bayes factor of 1.417 indicates anecdotal evidence for the alternative hypothesis. The main effect of CTOA yields a Bayes factor of $B_{10} = 0.453$ (anecdotal evidence). The cueing × CTOA interaction ($B = 0.236$) demonstrates substantial evidence for the null hypothesis.

In contrast to the younger participants, the effects induced by the auditory alerting cues were comparable across the short and long spectrum in older participants. When adjusting the Bayesian analysis to the whole CTOA spectrum, the results yield an even stronger evidence for unequal means between the cue and no-cue condition (substantial in 1 factor vs. anecdotal in 2 factor design). Hence, the results can be interpreted as an overall preserved auditory alerting effect on visual processing speed in healthy aging.

For the exploratory analysis regarding time-on-task effects, we, first, calculated Spearman's coefficients for correlations between visual processing speed estimates in the first test half and the whole test as well as the second test half and the whole test. In all 4 experimental conditions, the coefficients indicated strong correlations between the according test half and the full test (all $r_s \geq 0.77$). This result suggests that the visual processing speed estimates per test half are sufficiently reliable to use them as a factor in a time-on-task analysis. Comparable to the analyses in younger participants, Bayesian counterparts of 1-sided paired-sample t-tests were conducted separately for all experimental conditions testing whether visual processing speed in the second test half is significantly lower than in the first test half. All tests yielded Bayes factors of $0.093 \leq B_{10} \leq 0.245$ and are, therefore, in substantial favor of the null hypotheses. The results suggest that the visual processing speed estimates for all 4 experimental conditions do not deteriorate in the second test half compared to the first one.

Table 4
TVA parameter estimates for all conditions in older participants

Variable	Cue condition	No-cue condition
Visual processing speed C		
Short CTOA	26.06 (7.76)	24.39 (6.64)
Long CTOA	27.37 (7.61)	25.48 (8.23)
vSTM storage capacity K		
Short CTOA	2.91 (0.52)	2.22 (0.51)
Long CTOA	2.95 (0.54)	2.93 (0.56)
Visual perceptual threshold $t0$		
Short CTOA	30.80 (14.10)	32.10 (17.03)
Long CTOA	33.63 (17.32)	32.03 (17.22)

Means and standard deviations (in parentheses) are reported.
Key: CTOA, cue-target onset asynchrony; TVA, theory of visual attention; vSTM, visual short term memory.

3.3. *Comparison of alerting effects between younger and older participants*

A Bayesian repeated-measures ANOVA using the within subject factors cueing and CTOA, as well as the between subject factor age group (see Fig. 3) shows significant main effects of cueing ($B_{10} = 29.200$) and age group ($B_{10} = 16.249$), strongly favoring the alternative hypotheses. The Bayes factor of $B_{10} = 0.189$ for the cueing × age group interaction provides substantial evidence for a comparable cueing effect between both age groups. The cueing × CTOA and CTOA × age group interactions are described by $B_{10} = 0.666$ and $B_{10} = 0264$, accordingly. Furthermore, the 3-way interaction cueing × CTOA × age groups yields an inconclusive Bayes factor of $B_{10} = 0.911$.

A follow-up analysis with sex and crystallized intelligence as additional covariates yielded comparable results [B_{10}(cueing) = 22.249; B_{10}(cueing × age group) = 0.251; B_{10}(cueing × CTOA) = 0.480; B_{10}(CTOA × age group) = 0.321; B_{10}(cueing × CTOA × age group) = 0.727].

An additional ANOVA with the relative cueing effect as dependent variable served the purpose to potentially account for generally lower visual processing speed values in the older participants. The main effect of age group yielded a Bayes factor of $B_{10} = 0.281$ (with included covariates: $B_{10} = 0.222$) and substantially favored the null hypothesis, that is, the relative cueing effect being comparable across age groups. The main effect of CTOA has a Bayes factor of $B_{10} = 1.823$ (with included covariates: $B_{10} = 1.035$) and the interaction age group × CTOA yields $B_{10} = 0.366$ (with included covariates $B_{10} = 0.379$). The results concerning the relative effects are thus very similar and confirm those of the previous ANOVA on the absolute cueing effects.

4. Discussion

In the present study, we applied a whole report task based on the TVA to assess alerting effects on visual processing in healthy younger and older adults. First, we set out to replicate alerting effects in younger participants and explore the underlying time course of such effects. Second, we investigated the degree and time course of alerting effects in older participants. Third, we addressed

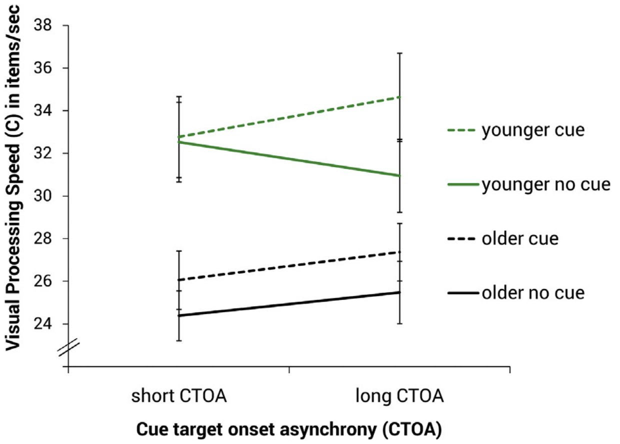

Fig. 3. Visual processing speed C results in all cueing (cue vs. no-cue) and CTOA (short vs. long) conditions for younger and older participants.

whether alerting effects remain stable over the lifespan by comparing younger and older participants.

4.1. Alerting effects in younger participants

The analysis in younger participants yielded a significant main effect of cueing on visual processing speed. The finding of alerting benefits on visual processing speed replicates former research using visual or auditory alerting cues (Matthias et al., 2010; Petersen et al., 2017). In line with a whole report task by Matthias et al. (2010), we neither found significant cueing effects on vSTM storage capacity or visual perceptual threshold. In contrast, Petersen et al. (2017) reported significant cueing effects on visual perceptual threshold when applying a single stimulus display. Hence, the differing stimulus displays, that is, single stimulus versus multi stimulus displays, can potentially account for these slightly varying findings.

Furthermore, the results reveal differential patterns for long and short CTOAs. Regarding the longer CTOA, the present results are in line with former studies. With respect to the finding of a nonsignificant difference between cue and no-cue trials in the short CTOA, the exploratory analysis revealed that the subgroup of participants without visual processing speed gain had a significantly higher initial (no-cue) visual processing speed. Thus, it seems that ceiling effects in high-performing participants can explain this result. It can be assumed that the relationship of phasic alertness and task performance, that is, visual processing speed, follows an inverted U-shaped function. In line with the Yerkes-Dodson law (Yerkes and Dodson, 1908), only a narrow window of arousal levels yields optimal task performance. Accordingly, participants with high initial arousal levels are likely to be overaroused by additional alertness cues, leading to an exceedance of the “optimal window”. The latter will derogate the task performance as can be seen in our results. Comparable effects have been found in a psychopharmacological study, investigating the effects of methylphenidate and modafinil on visual processing speed (Finke et al., 2010). While both psychostimulants substantially increased visual processing speed in the group of low performers, no such benefits could be seen in the high performance group.

An additional time-on-task analysis in the younger participants demonstrated that visual processing speed estimates for all experimental conditions are not reduced in the second compared to the first test half. This suggests that visual processing speed in both, the cue and no-cue condition, does not significantly deteriorate over the time course of the experiment.

4.2. Alerting effects in older participants

To the best of our knowledge, this study presents the first TVA-based investigation of auditory alerting effects on visual processing speed in an elderly group using a TVA-based whole report paradigm. The analyses yield a significant cueing effect on visual processing speed. These cueing effects are comparable between both CTOAs. The baseline *C* values of older participants were overall lower than in younger participants. Therefore, it can be assumed that older participants showed cueing benefits in both CTOAs because they were in the “optimal window” of arousal levels according to the Yerkes-Dodson law (Yerkes and Dodson, 1908). Neither vSTM storage capacity nor visual perceptual threshold is altered by the alertness cue. Comparable to the findings in younger participants, visual processing speed does not show time-on-task decrements. Overall, the results demonstrate significant alerting effects on the perceptual level, that is, visual processing speed, in healthy aging. Auditory alerting cues can facilitate visual processing in healthy elderly for a circumscribed period of time leading to a performance optimization in important situations.

4.3. Comparison of alerting effects between younger and older participants

The comparison of younger and older participants showed a significant main effect of cueing on visual processing speed. Moreover, it provided substantial evidence for the cueing effect being comparable in both age groups. Hence, the results suggest that alerting effects on visual processing speed are preserved in healthy aging.

This finding is in line with former research showing preserved alerting (Fernandez-Duque and Black, 2006; Rabbitt, 1984), as well temporal orienting of attention in healthy elderly (Chauvin et al., 2016). Nevertheless, the observed preservation of alerting effects on visual processing speed is in contrast to the formerly reported absence of alerting effects on sensory effectiveness in healthy older subjects (Wiegand et al., 2017a). Notably, different tasks were used for assessing alertness effects in this study. We used a whole report tasks with different exposure durations across trials that allows for a measurement of visual processing speed changes while controlling for individual differences in visual perceptual threshold. Such a differentiation was not possible with a partial report design using constant exposure durations. Furthermore, partial report paradigms also induce a selection requirement as participants need to focus on relevant targets and inhibit irrelevant distractors. It is not clear whether and how this requirement might interact with visual processing speed under high-arousing conditions. This renders whole report paradigms more precise and potentially more sensitive for the measurement of expectancy-induced changes in visual processing speed.

4.4. General discussion

Investigating alerting effects on visual processing speed in healthy younger participants replicated former studies regarding attentional benefits in long CTOAs. In contrast, no overall differences between cue and no-cue trials could be found in a short CTOA ranging from 60 to 180 ms. An exploratory follow-up analysis with participants being divided into groups with relatively high and low cueing effects in the short CTOA based on a median split, revealed that those 2 subgroups solely differ in their visual processing speed in the no-cue condition (baseline *C* values). This result implies an inverted U-shaped relation between phasic alertness and task performance, as measured by visual processing speed. Significantly higher visual processing speed in cue versus no-cue trials indicated that phasic alerting effects also affects visual processing speed in healthy aging individuals. These results suggest that, while healthy aging individuals do show an overall decline in their visual processing speed (Espeseth et al., 2014; Habekost et al., 2013; McAvinue et al., 2012), they are able to recruit additional attentional resources to temporarily increase their speed of processing when they are informed that relevant information will be presented soon. This finding has important implications for everyday life situations of seniors where fast visual processing is required, such as traffic scenarios. In these situations, it is essential to be able to use warning signals in critical situations to alter short-term information. Thus, it has been suggested that the ability to recruit additional attentional resources through external warning signals is crucial for efficient behavior in healthy aging. Expectancy inducing warning signals cannot solely be based on alerting but also on temporal expectations (for a review see Nobre and van Ede, 2017). The preservation of both, alertness and temporal expectancy (Chauvin et al., 2016), effects in aging suggests perception to be active, that is, expectancies can alter attentional and perceptional processes in healthy aging. This finding holds potential for future applied studies.

First, the present results of significant effects of auditory alerting cues on visual processing speed in healthy aging individuals are relevant for clinical diagnostics. It would be interesting to test whether such alerting effects might be decreased or even absent in patients at risk for pathological aging and cognitive decline.

Second, the reported findings have implications for training programs aiming to enhance cognition in healthy aging (e.g., Tennstedt and Unverzagt, 2014). Some of these intervention approaches in healthy elderly specifically aim to increase processing speed. Therefore, it would be of interest if a participant's short-term alerting cue benefit could predict the degree of long-term individual training gains. Such findings would have a high impact on personalized medicine approaches.

Third, the current task could be combined with neural measures to determine whether alerting processes in aging individuals rely on the same or different neural mechanisms compared to younger adults. One important approach to investigate underlying mechanisms of alertness is pupillometry. Petersen et al. (2017) used pupillometry as a physiological marker of alertness in a TVA-based alerting cue study. They report that the relation between pupillary responses and visual processing speed varies systematically based on the intensity of an auditory alerting cue (Petersen et al., 2017). Pupil dilations are closely linked to the norepinephrine production in the locus coeruleus (e.g., Joshi et al., 2016), which determines individual attention levels (e.g., Aston-Jones and Cohen, 2005).

The present study has critical limitations. It cannot provide a clear cut dissociation of alerting and temporal orienting of attention, that is, between 2 constructs whose definitions often overlap in literature (Weinbach and Henik, 2012). The common problem lies in the basic nature of phasic alerting signals. Even if such cues are neutral, that is, do not include any spatial-, temporal-, or feature-based information, they are inherently linked to a temporal expectation solely because participants know that they are preceding a target (Weinbach and Henik, 2012). Accordingly, in the present study, temporal expectancy could have been evoked by both, the start of a trial as well as the auditory alertness cue. In this case, the trial start would serve as the only "temporal expectancy cue" in the no-cue (alerting) condition, while both, the start of the trial and the alerting cue, could induce temporal expectancy effects in the cue condition. This leads to differing foreperiods in the no-cue and cue condition, further complicating the differentiation of alerting and temporal expectation effects. Therefore, the present study cannot precisely disentangle contributions of bottom-up alerting cues and top-down temporal expectations. Classical temporal expectancy paradigms demonstrate that the probability of a target appearing, given that it has not appeared yet, increases as time elapses if hazard rates are not dynamically manipulated (Nobre and van Ede, 2017). In these paradigms, the task performance, that is, speed or accuracy, increases with elapsed time. The present data in older participants do not resemble the described trend as the alerting effect in the long CTOA does not significantly differ from the short CTOA. This result suggests that visual processing speed benefits in the older participants do substantially rely on phasic alerting and cannot be explicitly explained by top-down temporal expectancy effects. In the younger participants, the alerting effect is significantly increased in the longer CTOA, which resembles the notion of an increased temporal expectancy over the time course of the trial resulting in behavioral benefits. However, the absence of the alerting effect in the short CTOA can be explained by younger participants' differences in initial processing speed (see RCE analysis), therefore supporting the substantial contribution of bottom-up alerting effects. Because of the overlapping time course of alerting and temporal orienting, a way to avoid temporal expectations resulting from a warning signal are non-aging foreperiods (Niemi and Näätänen, 1981; Weinbach and Henik, 2012) where behavioral benefits in the cue compared to the no-cue condition can be attributed to pure alerting effects. A recent study in younger participants reported significant auditory alerting effects on visual processing speed using CTOAs from 200 to 470 ms drawn from such a non-aging distribution (Petersen et al., 2017). In the future, it should be tested whether the use of paradigms with comparable foreperiods in cue and no-cue conditions and non-aging foreperiods lead to similar or different results on the effects of alerting cues on visual processing speed in healthy older participants.

5. Conclusions

In summary, the present study for the first time adopts a whole report task based on the TVA to assess alerting effects on visual processing speed in healthy younger and older adults. In addition and contrary to former studies, a jittered continuous CTOA spectrum is applied and analyzed contrasting short and long CTOAs. The results show that alerting effects on visual processing speed are preserved in healthy aging. Older participants show constant cueing benefits over the whole CTOA spectrum. Younger adults with a high baseline performance do not profit from an alerting cue followed by a short CTOA. This suggests that the short CTOA cue is overarousing for high-performing younger adults. In the longer CTOA, younger adults profit from the alerting cue irrespective of their baseline performance. Therefore, the results indicate an inverted U-shaped function of phasic alerting and visual processing speed.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.05.034.

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Chapter 3

Project II: IFC patterns underlying phasic alertness in healthy younger adults

The current chapter comprises the research article entitled "Phasic alerting effects on visual processing speed are associated with intrinsic functional connectivity in the cingulo-opercular network" that was published in NeuroImage in 2019. This second thesis project demonstrated that phasic alerting effects on visual processing speed are primarily associated with iFC in the cingulo-opercular network in healthy younger adults.

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K.F. and C.S. conceived and designed the study. M.H. led and coordinated the data acquisition. M.H. and A.L.R.-R. analysed the fMRI data. M.H. analysed the behavioural data. K.F. and C.S. aided in the interpretation of the data. M.H. drafted the main manuscript. M.H., A.L.R.-R., C.S., and K.F. critically revised the manuscript.

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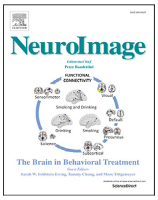

Phasic alerting effects on visual processing speed are associated with intrinsic functional connectivity in the cingulo-opercular network

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ABSTRACT

Phasic alertness refers to short-lived increases in the brain's “state of readiness”, and thus to optimized performance following warning cues. Parametric modelling of whole report task performance based on the computational theory of visual attention (TVA) has demonstrated that visual processing speed is increased in such cue compared to no-cue conditions. Furthermore, with respect to the underlying neural mechanisms, individual visual processing speed has been related to intrinsic functional connectivity (iFC) within the cingulo-opercular network, suggesting that this network's iFC is relevant for the tonic maintenance of an appropriate readiness or alertness state. In the present study, we asked whether iFC in the cingulo-opercular network is also related to the individual ability to actively profit from warning cues, i.e. to the degree of phasic alerting. We obtained resting-state functional magnetic resonance imaging (rs-fMRI) data from 32 healthy young participants and combined an independent component analysis of rs-fMRI time courses and dual regression approach to determine iFC in the cingulo-opercular network. In a separate behavioural testing session, we parametrically assessed the effects of auditory phasic alerting cues on visual processing speed in a TVA-based whole report paradigm. A voxel-wise multiple regression revealed that higher individual phasic alerting effects on visual processing speed were significantly associated with lower iFC in the cingulo-opercular network, with a peak in the left superior orbital gyrus. As phasic alertness was neither related to iFC in other attention-relevant, auditory, or visual networks nor associated with any inter-network connectivity pattern, the results suggest that the individual profit in visual processing speed gained from phasic alerting is primarily associated with iFC in the cingulo-opercular network.

1. Introduction

External warning cues induce short-lived changes in the brain's “state of readiness” defined as phasic alertness (Robertson et al., 1998; Sturm and Willmes, 2001). Numerous studies have demonstrated faster reaction times in conditions with warning cues compared to control conditions (e.g. Coull et al., 2001; Fan et al., 2005; Posner, 1978; Posner and Boies, 1971). While these phasic alerting benefits were initially suggested to reflect speeded preparation and execution of motor reactions (Posner, 1978; Sturm and Willmes, 2001), a fMRI study reported higher BOLD activity in perceptual areas, i.e. bilateral extrastriate regions and left precuneus, in target detection task trials preceded by alerting cues (without any spatial information) compared to no-cue trials (Thiel et al., 2004). In line with this finding, more recent studies have demonstrated benefits in preceding visual perceptual processes induced by visual (Matthias et al., 2010) and auditory warning cues (Haupt et al., 2018; Petersen et al., 2017). More precisely, these benefits pertain to an increase in the speed of visual information uptake.

Verbal report paradigms of briefly presented letter arrays combined with modelling based on the computational Theory of Visual Attention

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Abbreviations: TVA, Theory of Visual Attention of Bundesen; iFC, intrinsic functional connectivity; rs-fMRI, resting-state functional magnetic resonance imaging; vSTM, visual short term memory.

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(TVA) provide a parameter-based approach to measure attentional functions, particularly visual processing speed and – importantly for our study – changes in visual processing speed following alerting cues (Bundesen, 1990). TVA is closely related to the biased competition account (e.g. Desimone and Duncan, 1995) and implies parallel processing of several visual objects that are competing for selection into a visual short term memory (vSTM) store with limited capacity. The probability that an object gets selected before the store is filled is proportional to its processing rate. The processing rate at which the categorization "object x belongs to category i" is made is the product of the strength of sensory evidence that "x belongs to category i" and the visual bias of the observer towards category i.

$$v(x, i) = \eta(x, i)\, \beta_i \quad (1)$$

Critically for the present study, the extended model of components of visual bias suggests the visual bias to be computed as a product of three factors:

$$\beta_i = A\, p_i\, u_i \quad (2)$$

A reflects the level of alertness, p_i is the subjective prior probability of a certain feature, e.g. temporal expectancy (Vangkilde et al., 2013, 2012), and u_i refers to the utility or subjective importance of this feature (Bundesen et al., 2015). Accordingly, an increase of phasic alertness will lead to a proportional increase in the observer's bias towards an object and, thus, to a proportional increase in the processing rate of the object. The sum of the processing rates of all objects present in the visual display is defined as the overall visual processing speed C (in elements per second) of a given observer (Habekost et al., 2013). By definition, all items in a whole report share the same expectancy and subjective importance. An increase in the observer's alertness A induced by alerting cues will lead to a proportional increase in parameter C (Bundesen et al., 2015). Thus, by comparing visual processing speed in conditions with and without warning cues, the individual phasic alerting effect on visual information uptake can be measured.

It is assumed that TVA parameters depict relatively stable characteristics of a participant's attentional capability across different situations (Finke et al., 2005). We suggest that, comparable to other attentional parameters modelled based on TVA, an individual's ability to prepare for upcoming stimuli and optimize performance based on phasic alerting cues also depicts such a relatively stable capability or "trait-like" parameter. It is to be expected that the ability to optimize performance based on such cues varies among individuals. Accordingly, standard neuropsychological diagnostic procedures for the assessment of attention, e.g. Test Battery for Attentional Performance (TAP; Zimmermann and Fimm, 2002), include tasks measuring an individual's ability to profit from phasic alerting cues and relate this ability to the respective age norm. Therefore, stable inter-individual variations of alerting effects can be deployed to investigate the neural basis of this active perception mechanism, i.e. linking phasic alerting effects to intrinsic brain networks as they are both stable, "trait-like" parameters.

In previous TVA-based studies, individual visual attention functions have been linked to large-scale functional brain networks derived from resting-state functional magnetic resonance imaging (fMRI) data (Ruiz-Rizzo et al., 2019, 2018). In resting-state fMRI, ongoing fluctuations of the blood oxygen level dependent (BOLD) signal with a frequency around 0.01–0.1 Hz can be measured and analyzed (Fox and Raichle, 2007). Spatial patterns of coherent, i.e. correlated, BOLD fluctuations over time (termed intrinsic functional connectivity, iFC) constitute intrinsic brain networks. These intrinsic brain networks are stable on an intra- (Zuo et al., 2010) and inter-subject (Damoiseaux et al., 2006; De Luca et al., 2006) level. They are also highly consistent across species and states of consciousness, ranging from sleep to rest and task performance (Buckner et al., 2013; Fox and Raichle, 2007; Raichle, 2011). The spatial outlines of the networks largely correspond to underlying structural connectivity networks identified by diffusion tensor imaging (Hagmann et al., 2008; Honey et al., 2009, 2007). However, direct structural connections between two areas are not a prerequisite for intrinsic functional connections between them (Damoiseaux and Greicius, 2009; Raichle, 2011). The ongoing slow fluctuations in fMRI BOLD signal show cross-frequency correlations with slow cortical power ($<$4 Hz) and gamma band-limited power (50–100 Hz) measured with intracranial recordings (He et al., 2008) as well as with alpha, beta, and theta frequencies measured in magnetoencephalography (MEG) (Hipp et al., 2012; for a review see Engel et al., 2013). It is proposed that the phases of lower frequencies modulate the amplitudes of higher frequencies in an upward progression across the frequency spectrum (He et al., 2010). Such cross-frequency coupling is suggested to be of fundamental importance in the functional organization of the brain's activity (Raichle, 2011). Most importantly for the present study, iFC can be associated with (e.g. Visintin et al., 2015) and even predict (e.g. Rosenberg et al., 2018, 2017, 2015) individuals' behavioural performance in attention tasks. Connectome-based predictive modelling (Shen et al., 2017) can predict alerting scores assessed in the Attention Network Test (ANT), i.e. a more pronounced speeding of reaction times in central-cue compared to no-cue trials, from resting-state functional connectivity (Rosenberg et al., 2018). This finding provides evidence that connectivity patterns observed at rest, i.e. without any online administered task, contain a separable signature of the brain's ability to prepare for upcoming events (Rosenberg et al., 2018).

In particular, individual visual processing speed C values have been found to be related to iFC in the cingulo-opercular network (Ruiz-Rizzo et al., 2019, 2018), a brain network comprising regions such as the anterior prefrontal cortex, anterior insula, frontal operculum, dorsal anterior cingulate cortex, medial superior frontal cortex, and thalamus (Dosenbach et al., 2008). Importantly, iFC in this network, which has also been referred to as "salience network" (e.g. Seeley et al., 2007) or "ventral attention network" (e.g. Yeo et al., 2011), has been shown to be related to the intrinsic maintenance of an appropriate level of alertness during task performance (Coste and Kleinschmidt, 2016; Sadaghiani and D'Esposito, 2015) and has also been linked to indices of alertness, such as spontaneous upper alpha band oscillations (Sadaghiani et al., 2010) as well as spontaneous pupil dilations (Schneider et al., 2016). These findings are in line with a previous review of positron emission tomography (PET) and fMRI studies suggesting that phasic alertness is associated with activations of attention networks comprising bilateral frontal, parietal, and brainstem structures (Sturm and Willmes, 2001).

The present study sets out to investigate the neural correlate of active enhancements of visual processing speed. More specifically, we test whether the individual degree of phasic alerting effects, as measured by cue-induced changes in visual processing speed C in an offline administered TVA-based whole report paradigm, is linked to the individual iFC in the cingulo-opercular network acquired during resting-state fMRI. We hypothesize that phasic alerting effects are selectively associated with iFC in the cingulo-opercular network. In order to assure the specificity of the interrelation, we carry out control analyses to assess whether the phasic alerting effect, as predicted, is selectively associated with iFC in the cingulo-opercular network or whether it is rather globally linked to iFC within multiple intrinsic brain networks. To address this, we analyse associations of the phasic alerting effect with iFC in other attention-relevant, auditory, and visual networks. As we are employing a visual attention task with auditory cues, we additionally explore the inter-network connectivity between the cingulo-opercular network and the mentioned other intrinsic brain networks to gain insight into the question whether the functional connectivity between those networks is also associated with phasic alerting effects.

2. Material and methods

2.1. Participants

Thirty-six healthy adults at the age of 18–35 years participated in the present study. Two participants were excluded because of extreme visual processing speed *C* estimates that were not representative for the group (>2 SDs from the group mean). One further participant did not participate in the MRI session and one had to be excluded because of low functional imaging data quality. Therefore, the final sample consisted of 32 participants (see Table 1). All participants reported normal or corrected-to-normal vision. The study was reviewed and approved by the ethics committees of the Department of Psychology of the Ludwig-Maximilians-Universität München and the Klinikum rechts der Isar of the Technical University Munich. All participants gave informed consent, and were either reimbursed for their participation or received course credit. The data and code used in the present study are available upon direct request and the data sharing complies with the institutional ethics approval.

The acquisition of the resting-state fMRI (approx. 1 h) and the offline TVA-based behavioural assessment (approx. 1 h) took place on two different days. Participants also completed the Edinburgh Handedness Inventory (Oldfield, 1971) and a multiple choice German vocabulary test measuring crystallized intelligence, "Mehrfachwahl-Wortschatz-Intelligenztest" (MWTB; Lehrl et al., 1995) (see Table 1).

2.2. *Behavioural assessment*

The behavioural data presented here has already been reported in a previous publication (Haupt et al., 2018).

2.2.1. *TVA-based whole report paradigm*

The details of the applied TVA-based whole report procedure have been explained elsewhere (Haupt et al., 2018). All possible trial sequences can be seen in Fig. 1a. In summary, each trial consisted of six equidistant target letters (each 1.2 cm high, 1.0 cm wide) that were randomly chosen from a set of 23 letters (ABCDEFGHJKLMNOPRSTUVWXZ; every letter appeared only once per trial) and were presented on an imaginary circle (0.9 cm diameter) around the central fixation point. Participants were instructed to maintain central fixation and verbally report all letters recognized with "fair certainty" without any importance of speed or order. After entering all reported letters on the keyboard, the experimenter started the next trial with a button press. This variability in trial length was necessary to allow for the participants' unspeeded verbal report. A scale presenting the individual's accuracy rating based on all reported letters succeeded every test block. Participants were asked to maintain an accuracy level between 70% and 90% with a deviating score leading to adapted instructions for the next test block. If the participants' accuracy rating exceeded 90%, they were asked to also name letters that they believed to have recognized without complete certainty. If participants were less than 70% accurate, they were instructed to only report letters recognized with high certainty even if that meant that they would report less letters overall. For each participant, five individual target exposure durations were determined in a pretest phase and later used for all experimental blocks. The experiment consisted of 8 blocks with 84 trials each, resulting in an overall duration of one to one and a half hours. Throughout the experiment, target displays presented with the 5 adjusted exposure durations were followed by masks (max.1.8 × 1.8 cm, 500 ms). In addition, two exposure durations were also presented without a subsequent mask. Due to iconic memory buffering in unmasked compared to masked trials, this resulted in seven effective exposure durations (Sperling, 1960).

Table 1
Demographics and visual processing speed (*C*) estimates of all participants.

Variable	All Participants	p value
	N = 32	
mean age (SD)	26.6 (4.7)	–
sex (female/male)	20/12	–
handedness (right/left)	27/5	–
mean education in years (SD)	12.6 (0.9)	–
MWTB score (SD)	28.6 (4.6)	–
Number of days between behavioural session and rs-fMRI session	240.1 (294.7)	–
C in cue condition/no-cue condition	34.7 (11.6)/30.7 (9.3)	<.001

Note. SD: standard deviation; handedness: assessed by Edinburgh Handedness Inventory; MWTB: Mehrfachwahl-Wortschatz-Intelligenztest, maximum score = 37 points.

2.2.2. *Alerting conditions*

In the alerting-cue condition, the target display was preceded by an auditory cue (80 dB, randomly chosen with a frequency of either 500 Hz or 900 Hz) that contained no spatial information about the upcoming target location but was deployed to enhance participants' phasic alertness for a few hundred milliseconds. During the presentation of the tone (200 ms), the screen remained blank with only the fixation point being visible. Comparably, in the no-cue condition, participants saw a blank screen for 200 ms without any tone being presented. The cue target onset asynchrony (CTOA) had an average of 260 ms and was jittered around this value in steps of ± 20 ms, 40 ms and 60 ms leading to an overall range of 200–320 ms. For each trial, one CTOA was randomly drawn from the described CTOA range. As the whole behavioural experiment contained two different CTOA ranges (Haupt et al., 2018) but the present study only analyzes data from one CTOA range, 336 experimental trials are included in the estimation of TVA parameters and subsequent statistical analyses. In the present study, we only include data from the long CTOA range as participants showed consistent phasic alerting effects on visual processing speed when a longer CTOA was employed. In the shorter CTOA, high-performing individuals demonstrated ceiling effects of visual processing speed, derogating phasic alerting effects (Haupt et al., 2018).

2.2.3. *Estimation of TVA parameters*

The whole report task allows for the estimation of visual processing speed *C*, vSTM storage capacity *K*, and visual perceptual threshold *t0*. While the estimation of all parameters is needed for retrieving valid estimates of visual processing speed *C*, parameter *K* and *t0* are of no specific interest in the current study (note that alertness cues were repeatedly shown to predominantly affect visual processing speed, see Haupt et al., 2018; Matthias et al., 2010; Petersen et al., 2017). Furthermore, the variable of interest in the present study (C_{cue}) is not significantly correlated with K_{cue}, $K_{\text{no-cue}}$, $t0_{\text{cue}}$, and $t0_{\text{no-cue}}$ (all $\tau < 0.206$, all $p > .098$, all $BF < 0.854$). Hence, the present study sets out to address the specific relationship between visual processing speed *C* and iFC in the cingulo-opercular network.

For detailed underlying estimation algorithms please refer to Kyllingsbaek (2006). The mathematically modeled exponential growth function is relating the report accuracy (mean number of reported items) to the underlying effective exposure duration. Accordingly, the function's intersection with the x-axis defines the visual perceptual threshold *t0*. The slope of the function at this intersection indicates the visual processing speed *C* (total rate of information uptake in objects per second). Furthermore, the asymptote denotes the maximum number of represented object defined as vSTM storage capacity *K* (see Fig. 1b).

2.3. *Resting-state fMRI*

2.3.1. *Imaging data acquisition*

Imaging data were acquired on a 3T MR scanner (Philips Ingenia,

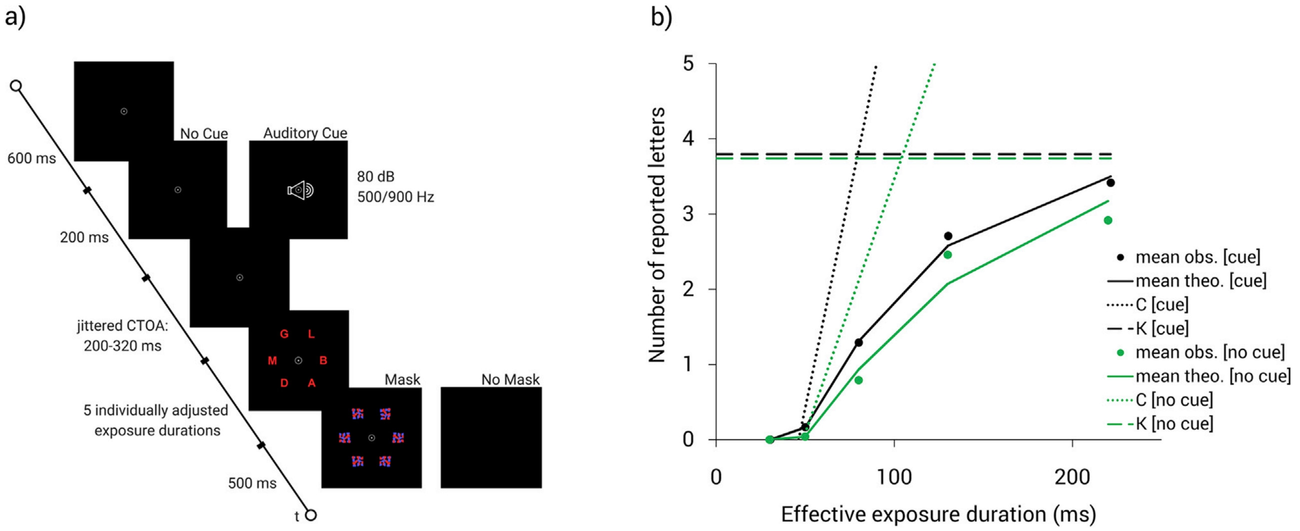

Fig. 1. Trial sequence in whole report paradigm (a) and whole report performance for a representative younger participant (b). The graph (b) contains a comparison between the cue and no-cue condition. The observed values are displayed as single data points (mean obs.). Solid curves represent the best theoretical fit from the TVA to the observations (mean theo.). The vSTM storage capacity *K* is defined as the asymptote of the function and is marked by a dashed line. The visual perceptual threshold *t0* is defined by the origin of the function (coordinate: t0,0). Visual processing speed *C* is defined as the slope of the function in *t0* and is represented by a dotted line.

Netherlands) using a 32-channel SENSE head coil. Small cushions stabilized participants' heads in the head coil to reduce head motion. Earplugs and headphones reduced scanner noise. Functional data acquisition lasted for 12.5 min and participants were instructed to keep their eyes closed, intend to stay awake, and to refrain from performing any cognitive or motor activity, i.e. be at rest, throughout the whole sequence. The functional data set consisting of 600 volumes was acquired by multi-band echo-planar imaging (EPI; Preibisch et al., 2015) with a multi-band SENSE acceleration factor of 2 (TR = 1250 ms; TE = 30 ms; phase encoding in anterior-posterior direction; flip angle = 70°; field of view (FOV) = 192 mm^2; matrix size = 64 × 64, 40 slices with 3 mm thickness and an inter-slice gap of 0.3 mm; reconstructed voxel size = 3 mm × 3 mm × 3.29 mm). Structural data were obtained by a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence (TR = 9 ms; TE = 4 ms; flip angle = 8°; FOV = 240 mm^2; matrix = 240 × 240, 170 sagital slices; reconstructed isotropic voxel size = 1 mm).

2.3.2. *Imaging data preprocessing*

The resting-state fMRI data were preprocessed in MATLAB (R2017b, version 9.3.0.713579; The Mathworks Inc.) using SPM 12 version 6225 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the Data Processing Assistant for Resting-State fMRI toolbox version 2.3 (DPARSF; Chao-Gan and Yu-Feng, 2010). After removing the first five functional volumes of every data set to account for T1 saturation effects, slice timing and head motion correction were performed by calling SPM functions. Slice timing correction is often omitted when imaging data are acquired by multi-band echo-planar imaging as, in this case, the repetition times are shorter than in conventional acquisition methods. However, up to our knowledge, it is still an open question whether repetition times in multiband image acquisition are actually short enough to completely omit slice time correction (Parker et al., 2017). Therefore, in general, slice timing correction depicts an advisable preprocessing step for functional imaging data (Sladky et al., 2011). None of the participants had to be excluded due to excessive head motion by the criterion of cumulative translation or rotation of 3 mm or 3° or due to more than 15% frame-wise displacements >0.5 mm (Power et al., 2012). All images were manually reoriented to the AC-PC axis. The functional images were normalized into Montreal Neurological Institute (MNI) space with a 2-mm isotropic voxel size by unified segmentation to the structural image (Ashburner and Friston, 2005). DPARSF integrates the three underlying procedures - coregistration, segmentation (grey matter, white matter, cerebrospinal fluid) and writing normalization parameters - into one processing step. The normalized images were smoothed using a 4 mm full-width-at-half-maximum (FWHM) Gaussian kernel. Additionally, band-pass filtering (0.01–0.1 Hz) was performed and the effects of nuisance covariates (whole-brain signal, white matter, cerebrospinal fluid, and scrubbing regressors for derivative 12 head motion parameters) were removed.

2.3.3. *Independent component analysis and dual regression analyses*

After preprocessing the functional data, we conducted a probabilistic Independent Component Analysis (ICA) in FSL (version 5.0.9) using the MELODIC command-line program version 3.14 (Beckmann and Smith, 2004; Smith et al., 2004). We specified 20 independent components aiming at decomposing the data into larger “primary networks” and avoiding to split up the data into relatively smaller “subnetworks” following the approach of Smith et al. (2009). The ICA decomposed each time × space matrix into pairs of time courses and spatial maps on the group level. Subsequently, these files were used as input and a dual regression was employed in order to estimate spatial maps and time courses for each participant (Beckmann et al., 2009; Filippini et al., 2009). The dual regression approach allows to quantify the functional connectivity of each voxel with each spatial map while controlling for all other spatial maps within each participant (Smith et al., 2014). Most importantly, we chose this approach as dual regression analysis is excelling in detecting inter-individual variability in functional connectivity compared to seed-based functional connectivity analysis (Smith et al., 2014). In a first step, the group-average spatial map was regressed into the individual participants' time × space matrices, resulting in a participant-specific time series. In a second step, the group-average time series was regressed into the same matrices, yielding 20 participant-specific spatial maps, i.e. one per independent spatial map on the group-level. The individual spatial maps contain Z-scores of every voxel within the according map. These Z-scores indicate the similarity of a particular voxel's time course to the time course of the respective component on the group-level while controlling for all other components. Therefore, the voxel-wise Z-scores were used as input for statistical tests to analyse whether the given component derived Z-scores do relate to behavioural variables. Importantly, the results of the statistical analyses are solely related to the specific output of the ICA, i.e. independent components. These components represent intrinsic brain networks, but the precise brain regions included may vary, so that results of statistical analyses might manifest in brain areas that belong to the independent component, but are not typically included in a certain brain network (Smith et al., 2014). In a last step, the randomize permutation-testing tool (5000 permutations, $p = .05$) within the FSL framework yielded group spatial maps (Beckmann et al., 2009; Filippini et al., 2009).

In order to identify typical intrinsic brain networks with our ICA-dual regression approach, we performed a spatial cross-correlation of our 20 independent components with intrinsic brain network templates derived from Allen et al. (2011). Accordingly, we identified the component with the strongest correlation coefficient with the “salience network” (component IC55, $r = 0.44$) of Allen et al. (2011) as the cingulo-opercular network in the present study.

2.4. Statistical analyses

2.4.1. Analyses of phasic alerting effects on visual processing speed

Visual processing speed C values in the cue and no-cue conditions did not follow a normal distribution. Therefore, the data were analysed with a nonparametric Wilcoxon signed-rank test. In addition, the Bayesian equivalent of a paired samples *t*-test (Rouder et al., 2009) was conducted using JASP version 0.8.5.1 (JASP Team, 2018). The Bayes factor (BF) is a measure for the ratio of the likelihoods of two theories. Hence, the Bayes factor allows for a quantification of the evidence for the null hypothesis and the alternative, experimental hypothesis. If BF_{10} is greater than 3 the present data substantially support the alternative hypothesis while values smaller than 1/3 substantially favor the null hypothesis (Dienes, 2011; Wagenmakers et al., 2011).

2.4.2. Analyses of phasic alerting effects on visual processing speed and iFC in the cingulo-opercular network

The individual spatial maps resulting from the described second step of the dual regression served as input for the intra-network analyses conducted in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and additional nonparametric analyses using the Statistical NonParametric Mapping toolbox (SnPM13, http://warwick.ac.uk/snpm). According to Hayes and Rockwood (2017), modelling post-scores or difference scores using pre-scores as covariates yields more precise estimates of change than pure differences scores because it accounts for regression to the mean. Thus, we performed a voxel-wise multiple regression of visual processing speed C in the cue condition on iFC in the cingulo-opercular network while controlling for visual processing in the no-cue condition ($p < .05$ FWE corrected for multiple comparisons at the cluster level, voxel-wise height threshold $p < .001$).

To further confirm the robustness and validity of the association between phasic alerting effects on visual processing speed and iFC in the cingulo-opercular network, we ran additional multiple regressions using alternative indices of the individual alertness cueing benefit as regressor of interest, i.e. absolute difference ($C_{\text{cue}} - C_{\text{no-cue}}$), relative cueing effect $(C_{\text{cue}} - C_{\text{no-cue}})/(C_{\text{no-cue}})$, and the standardized cueing effect $(C_{\text{cue}} - C_{\text{no-cue}})/(C_{\text{cue}} + C_{\text{no-cue}})$. Furthermore, we assessed whether the choice of a specific covariate influences the outcome of the multiple regression by keeping the regressor of interest constant (absolute difference) while adding either C in the no-cue condition or overall C (averaged over cue and no-cue trials) as a covariate of no interest.

In all voxel-wise analyses, we added age, education, and sex as planned covariates. The variable of interest (C_{cue}) is not significantly correlated with any of these control variables ($-0.149 < \text{all } \tau < 0.058$, all $p > .241$, all $BF_{10} < 0.458$). However, differences in sex, age, and cognitive ability (possibly related to years of education) are suggested to be reflected in distinct connectivity patterns and power spectra within multiple resting state networks (e.g. Allen et al., 2011; Smith et al., 2014; Zhang et al., 2016). To ensure that our results are not driven by the added covariates, we also repeated the voxel-wise multiple regression of visual processing speed C in the cue condition on iFC in the cingulo-opercular network without age, sex, and education as covariates (only controlling for visual processing speed in the no-cue condition).

In addition, we repeated our analysis twice to account for the influence of head motion and time between the behavioural and fMRI session. Firstly, we controlled for the influence of head motion by re-running the mentioned multiple regression with mean volume-to-volume head motion, i.e. frame-wise displacement, as an additional covariate. We chose the measure by Jenkinson et al. (2002) as it considers voxel-wise differences in its derivation (Yan et al., 2013). We also directly correlated frame-wise displacement with the behavioural variable of interest. Secondly, we added days between sessions as a covariate to the voxel-wise multiple regression. Again, we also correlated the variable days between sessions with the behavioural variable of interest.

2.4.3. Control analyses regarding the specificity of the association between phasic alerting effects and iFC in the cingulo-opercular network

In order to address the specificity of the relationship between phasic alerting effects on visual processing speed C and the cingulo-opercular network, we additionally performed control analyses in other attention-related, auditory, and visual networks. We identified them by visual inspection and cross-correlation ($0.37 < \text{all } r < 0.48$) with templates by Allen et al. (2011) (IC71, IC52, IC60, IC17, IC39 and IC46). Firstly, we chose to control for alerting associations with iFC in the executive control network (IC71) as this network has been reported to be co-activated with the cingulo-opercular network during fMRI tasks but its iFC is dissociable from iFC within the cingulo-opercular network (Seeley et al., 2007). Seeley et al. (2007) suggest that iFC in the executive control network is associated with higher order cognitive processes such as working memory and sustained attention. Secondly, we analyzed the association of phasic alerting effects with iFC in left (IC52) and right (IC60) lateralized fronto-parietal networks as these intrinsic brain networks comprise the main alerting-related structures reported by a review of PET and fMRI task studies (Sturm and Willmes, 2001). Thirdly, we tested for a significant relation between alerting effects and iFC in the auditory network (IC17) as our behavioural task contains an auditory cue. Lastly, we repeated the analyses in two visual networks (IC39 and IC46) as we are employing a behavioural task consisting of visual stimuli.

For all mentioned networks, we repeated the analyses using a nonparametric regression approach with 10000 permutations in order to yield an empirical cumulative distribution function of the statistic under the null hypothesis and to control for type I errors.

2.4.4. Analyses of inter-network connectivity between the cingulo-opercular network and other attention-relevant and sensory networks

Finally, we investigated whether the cingulo-opercular network's inter-network functional connectivity with attention-related, auditory, or visual networks is also significantly associated with phasic alerting effects. We addressed this question by entering the individual time courses of the mentioned intrinsic brain networks (yielded by the first step of dual regression) into an inter-network analysis (using custom

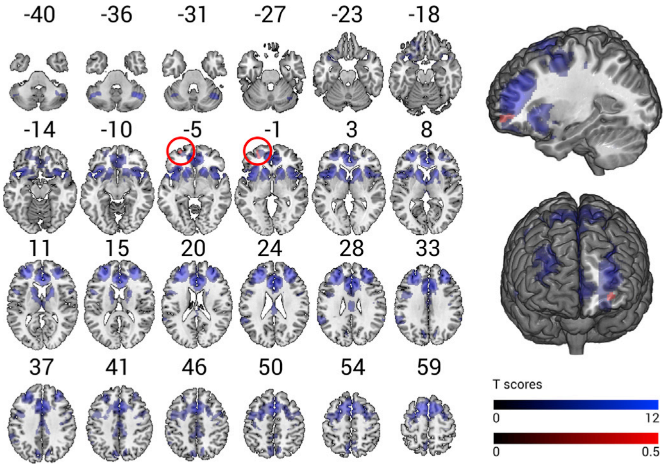

Fig. 2. Statistical Parametric Mapping of voxel-wise multiple regression of visual processing speed in alerting cue condition (red) on iFC in cingulo-opercular network (blue). The results are obtained by independent component analysis of resting-state fMRI data and are overlaid onto standard anatomical MNI152 templates using the software MRIcroGL (available at: https://www.mccauslandcenter.sc.edu/mricrogl/source); slice numbers in transverse plane are indicated. The results of the multiple regression are controlled for visual processing speed in the no-cue condition, age, sex, and education ($p < .05$ FWE corrected at cluster level).

code written in MATLAB; also see Ruiz-Rizzo et al., 2018). We correlated the time course of the cingulo-opercular network with the ones derived from the other six independent components of interest per participant. Subsequently, we performed Fisher r-to-Z transformation and partial correlation analyses to test whether the inter-network connectivity of the cingulo-opercular network with any other network was significantly correlated with visual processing speed C in the cue condition when controlling for visual processing speed C in the no-cue condition.

3. Results

3.1. Phasic alerting effects on visual processing speed

The Wilcoxon signed-rank test was employed to compare visual processing speed in the cue ($M = 34.7$, $SD = 11.6$, letters per second) and no-cue ($M = 30.7$, $SD = 9.3$, letters per second) condition. The test yields a significant difference between both conditions ($Z = 338$, $p < .001$, $r_b = 0.697$), i.e. visual processing speed C in the cue condition was significantly higher than in the no-cue condition, indicating a successful phasic alerting effect of the auditory warning cue. The Bayesian analysis confirms the significant alerting effect on visual processing speed C. The Bayes Factor of $BF_{10} = 43.17$ very strongly supports the alternative hypothesis of the visual processing speed estimates in both alerting conditions being significantly different from each other.

3.2. Relation of phasic alerting effects on visual processing speed and iFC in the cingulo-opercular network

The cingulo-opercular network encompasses the cerebellum, amygdala, insula, basal ganglia, thalamus, paracingulate gyrus, anterior cingulate cortex, orbital gyrus and frontal gyri (inferior, middle and superior) (see Fig. 2).

The voxel-wise multiple regression analysis yielded a significant relationship between the individual degree of phasic alerting effects on visual processing speed C and iFC in the cingulo-opercular network. Specifically, when controlling for age, sex, education, and also for baseline visual processing speed C values in the no-cue condition, higher individual alerting effects on visual processing speed were significantly associated with lower individual iFC in the cingulo-opercular network, with a peak in the left superior orbital gyrus (MNI coordinates in mm: [-26 46–2], cluster size: 66 voxels, $T = 4.91$, $p = .003$, FWE corrected for multiple comparisons at the cluster level with applied voxel-wise height threshold of $p = .001$) (see Fig. 2).

To confirm the robustness and validity of the association between phasic alerting effects on C and iFC in the cingulo-opercular network, we conducted the same analysis with the absolute difference (C in no-cue trials as covariate), absolute difference (overall C, averaged over cue and no-cue trials, as covariate), relative cueing effect, and the standardized cueing effect as regressor of interest. All analyses yielded the same significant peak within the cingulo-opercular network (see Supplements Table 1). This indicates that the association of phasic alerting effects with the iFC in the cingulo-opercular network is robust regardless of which specific measure of phasic alerting effects on C and the specific baseline C that were chosen as the regressor of interest and covariate.

In addition, we repeated the voxel-wise multiple regression of visual processing speed C in the cue condition on iFC in the cingulo-opercular network without age, sex, and education as covariates (only controlling for visual processing in the no-cue condition). The analysis yields a significant association of a higher alerting effect on visual processing speed with lower iFC in the cingulo-opercular network in a comparable, only slightly extended, cluster (MNI coordinates in mm: [-30 56–4], cluster size: 85 voxels, $T = 4.77$, $p = .001$).

This result is also stable when either frame-wise displacement (MNI coordinates in mm: [-26 46–2], cluster size: 65 voxels, $T = 4.78$, $p = .003$) or days between sessions (MNI coordinates in mm: [-28 60–6], cluster size: 76 voxels, $T = 5.11$, $p = .001$) are added as a covariate to the described voxel-wise multiple regression with sex, age, and education as covariates. Further, we controlled for head motion and time between sessions by calculating nonparametric correlation of C_{cue} with frame-wise displacement ($\tau = 0.137$, $p = .270$, $BF_{10} = 0.410$) and days between sessions ($\tau = -0.218$, $p = .080$, $BF_{10} = 1.002$).

These additional analyses show that the results of the voxel-wise multiple regression of visual processing speed C in the cue condition on iFC in the cingulo-opercular network remain constant whether or not the planned covariates are added. Furthermore, the results demonstrate that estimates of head motion, i.e. frame-wise displacement, and time between sessions are neither correlated with visual processing speed, nor change the results of the voxel-wise multiple regression when added as an additional covariate. Taken together, these findings suggest that none of the covariates are driving the observed brain-behaviour relationship.

3.3. Control analyses regarding the specificity of the association between phasic alerting effects and iFC in the cingulo-opercular network

To determine whether phasic alerting effects on C are specifically linked to iFC in the cingulo-opercular network, we controlled for phasic alerting associations with iFC in other networks. The parametric and non-parametric multiple regression analyses yielded no significant association of the individual degree of phasic alerting effects on visual processing speed with iFC in the executive control network, left and right fronto-parietal networks, auditory network, as well as visual networks (all $p > .05$). As in the main analyses, all control analyses included age, sex, education and visual processing speed C values in the no-cue condition as covariates. Importantly, the result in favour of the null hypothesis in the executive control network, left and right fronto-parietal networks, auditory network, as well as visual networks demonstrate that phasic alerting effects on C are not significantly associated with iFC in these networks. The non-parametric analysis confirmed that the null results were not due to violations of the normality assumption. However, we cannot directly compare the behaviour-iFC relationship in the cingulo-opercular network with the behaviour-iFC relationships in the control networks as we used a voxel-wise analysis approach.[2] Considering this limitation, we can summarize that the iFC of the assessed auditory, visual, and attention-related networks is not significantly associated with phasic alerting, suggesting a primary association of phasic alerting effects on C and iFC in the cingulo-opercular network.

3.4. Inter-network connectivity between the cingulo-opercular network and other attention-relevant and sensory networks

In order to trace whether the inter-network connectivity of the cingulo-opercular network is also significantly associated with phasic alerting effects on *C*, we entered the above mentioned attention-related, auditory, and visual networks into an inter-network analysis. The analysis yielded a significant positive correlation of the cingulo-opercular network with the right fronto-parietal network (IC60) as well as significant negative correlations with the auditory network (IC17), and both visual networks (IC39, IC46). The correlations of the cingulo-opercular network with the left fronto-parietal network (IC52) and the executive control network (IC71) were not significant (see Supplements Fig. 1).

Importantly, partial correlation analyses revealed that none of the described significant inter-network correlations were, in turn, significantly correlated with visual processing speed *C* in the cue condition when controlling for *C* in the no-cue condition ($-0.254 \leq$ all $r \leq 0.206$, all $p \geq 180$). These results indicate that the decisive link between the phasic alerting effect on visual processing speed *C* and the cingulo-opercular network is its intra-network iFC and not its inter-network connectivity with other attention-relevant, auditory, or visual networks.

4. Discussion

When provided with warning signals, observers can temporarily increase their arousal state. In particular, they can speed up their rate of visual information uptake by recruiting additional attentional processing resources (Haupt et al., 2018; Matthias et al., 2010; Petersen et al., 2017). Such active optimization is decisive for efficient behaviour in situations where fast visual perception is essential for quick and accurate responses, such as traffic, sports, and social communication scenarios.

The present study set out to identify the underlying neural network mechanisms of this relevant phasic alerting effect by relating individual differences in the degree of phasic alerting effects on visual processing speed *C* measured in an offline administerd TVA-based paradigm to those in intrinsic functional connectivity (iFC) in the cingulo-opercular network (acquired by resting-state fMRI). We chose iFC in the cingulo-opercular network as it was previously suggested to play a significant role in alertness (Coste and Kleinschmidt, 2016; Sadaghiani et al., 2010; Sadaghiani and D'Esposito, 2015; Schneider et al., 2016) and visual processing speed (Ruiz-Rizzo et al., 2019, 2018). Furthermore, the cingulo-opercular network comprises some of the structures that have been suggested to be particularly relevant for the phasic component of alertness induced by warning cues, i.e. bilateral frontal, and brainstem structures (Sturm and Willmes, 2001).

In our study, a voxel-wise multiple regression analysis revealed that, indeed, more pronounced cueing effects on visual processing speed were significantly related to iFC in the cingulo-opercular network. The relationship was inversed, i.e. phasic alertness effects were negatively associated with iFC in the cingulo-opercular network. The result proved to be robust regardless of which alerting score (score in cue condition controlled for score in no-cue condition, absolute difference, relative difference, or standardized cueing effect) was used as dependent variable in the analysis. This result underlines that the association between phasic alerting effects on visual processing and iFC in the cingulo-opercular network does not solely rely on the chosen definition of the alerting effect but can be generalised across measures of phasic alerting effects. We also addressed the specificity of the association between phasic alerting and iFC in the cingulo-opercular network by employing control analyses regarding the intra-network connectivity in other relevant attention-related and sensory networks. IFC in the executive control network, left and right fronto-parietal networks, auditory, and visual networks were not significantly related to phasic alerting effects. Additional inter-network connectivity analyses of the cingulo-opercular network and other attention-related, auditory, and visual networks indicated that inter-network connectivity could not account for inter-individual differences in phasic alerting. In sum, the results indicate that phasic alerting effects on visual processing speed are robustly and primarily associated with iFC in the cingulo-opercular network with a peak in the left superior orbital gyrus.

According to the extended TVA model of visual bias, an increase in the perceptual bias parameter β leads to a proportional increase in visual processing speed *C* in a whole report paradigm. The perceptual bias β is a product of three factors including alertness *A* (Bundesen et al., 2015). Hence, if the other two factors are held constant, the increase in *C* is proportional to the increase in alertness (induced by the auditory cues). In the present study, the estimated average processing speed *C* is 34.7 items per second in the cue condition, and 30.7 items per second in the no-cue condition. This translates to a phasic increase in the alertness parameter *A* of around 13%, i.e. an alertness factor of 1.13. The neural interpretation of TVA (NTVA; Bundesen et al., 2005) suggests that the perceptual decision bias parameter influences the level of activation in neurons induced by a visual display. Hence, the theory suggests that enhancing phasic alertness by cues increases the activation levels of cells. It has been suggested that slow fluctuations in BOLD signal, measuring the brain's default activity pattern, reflect slow propagating waves providing sub-threshold depolarization to individual neurons, resulting in an increased spiking probability of those neurons (Matsui et al., 2016; Sanchez-Vives et al., 2017; Wu et al., 2008). In a recent study, Schwalm et al. (2017) suggested that local calcium events do underlie these slow waves and are directly linked to a global cortical fMRI BOLD signal. Therefore, it seems plausible that spontaneous fluctuations of cortical excitability on the basis of propagating waves influence brain's “state of readiness” regarding the processing of incoming information. Our data suggest that the individual spatial patterns of coherent fluctuations among regions of the cingulo-opercular network are related to the

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[2] For every individual, the Dual Regression succeeding the Independent Component Analysis yields one spatial map per component (relating to a specific intrinsic brain network) containing Z-scores of every voxel. These Z-scores indicate the similarity of the time course of a particular voxel to the time course of the respective component on the group-level. Accordingly, we do not obtain one meaningful value representing the intrinsic functional connectivity (iFC) in a given component (intrinsic brain network) per participant. Therefore, we cannot calculate a correlation between one behavioural score and one iFC score in a certain network for every participant. Rather, we employ a voxel-wise multiple regression approach, i.e. for every participant we quantify the degree to which the behavioural score (while controlling for covariates) is related to the Z-score (of a given voxel) separately for every voxel that is part of the network. We either compare the observed differences in behaviour-iFC relationships with the null distribution of differences (permutation tests in SnPM) or the t-distribution (in SPM). We then (1) apply a voxel-wise height threshold ($p < .001$) and (2) correct for multiple comparisons at the cluster level (FWE correction, $p < .05$). Clusters of significant associations between the behavioural score and the Z-scores of the comprised voxels are interpreted as a proof-of-principle of a significant association between the behavioural variable of interest and iFC in the according intrinsic brain network. Accordingly, we would be able to compare iFC-behaviour relationships across networks if clusters in other networks would have surpassed the cluster-level significance threshold. In this case, for every network, we could have calculated the correlation between the behavioural score and Z-scores of voxels in the significant cluster, and could have, later on, statistically compared those correlation scores across networks. However, we do not find significant clusters in any network but the cingulo-opercular network. In summary, we cannot directly compare behaviour-iFC relationships between networks as, based on our voxel-wise analysis approach, we neither have one meaningful value representing iFC on the network-level, nor do we have one cluster-based iFC value for each network.

individual excitability, i.e. to the relevant ability to arouse the visual processing system in order to increase the readiness to perceive information in a fast manner, specifically in situations that require speeded processing.

The results of the present study complement previous findings demonstrating that resting-state functional connectivity patterns can predict alerting scores measured in the Attention Network Test (ANT; Rosenberg et al., 2018). Rosenberg et al. (2018) demonstrated that intra-temporal, occipital-parietal, and temporal-motor connections significantly predicted higher alerting scores. However, specific whole-brain functional connectivity networks cannot be directly compared to the network findings in the present study. Firstly, while the present study employs a voxel-wise multiple regression preceded by an ICA and Dual regression approach, Rosenberg et al. (2018) use a 268 node functional brain atlas as the basis of network definition. Accordingly, the behaviour is related to the time courses of each of these nodes, which in turn are defined as the averaged time courses of all voxels in each node. Secondly, both tasks yield distinct measures of alerting (for a comparison of the ANT and TVA-based assessment also see: Habekost et al., 2014). The ANT measures phasic alerting effects as the difference between reaction time in a no-cue and a cue condition. The association between temporal-motor connections and high alerting scores might thus reflect an increase in the readiness to prepare and execute motor reactions (Rosenberg et al., 2018). As, in contrast, the TVA-based measure of alertness is a pure measure of visual attention, i.e. perceptual effects of alerting cues, we do not see such a relationship. However, both studies provide crucial evidence that functional connectivity patterns observed in resting-state fMRI, i.e. when no behavioural task is administered during fMRI acquisition, can be linked to individuals' ability to prepare for upcoming stimuli, i.e. phasic alertness.

Importantly, our result should not be interpreted as the peak region, i.e. left superior orbital gyrus, being particularly “responsible” for phasic alerting effects. As we employed a voxel-wise approach, the iFC values of the significant voxels in the left superior orbital gyrus (Z scores) are in principle relative values. This means that they can only be interpreted in relation to iFC of other voxels within in the brain. Regarding the cingulo-opercular network, we can, therefore, solely predicate that the inverse relationship between phasic alerting effects on visual processing speed and iFC in the cingulo-opercular network was best represented in the left superior orbital gyrus. Such representation of the phasic alertness iFC relationship in the left hemisphere is principally in line with former studies reporting a left-hemispheric involvement during tasks employing phasic alerting cues (Coull et al., 2001) as compared to tonic alertness conditions (Sturm and Willmes, 2001). However, the results do not imply a specific role of the left superior orbital gyrus for phasic alertness.

Interestingly, the present study reveals a negative association between phasic alerting effects on visual processing speed and iFC in the cingulo-opercular network. This finding can be reconciled with results from a previous resting-state fMRI study (Ruiz-Rizzo et al., 2018). Ruiz-Rizzo et al. (2018) demonstrated that young, healthy participants with higher (vs. lower) visual processing speed C as obtained in a standard TVA-based whole report task without alerting cues, were characterized by lower iFC in the cingulo-opercular network as assessed in a separate rs-fMRI session. Visual processing speed in such uncued conditions is assumed to reflect an individual's level of intrinsic (tonic) alertness (Matthias et al., 2010). Taken together, the results of these two studies might imply that participants with a low iFC in the cingulo-opercular network have a relatively efficient processing system. This could lead to both relatively high processing speed C in paradigms that require the intrinsic maintenance of arousal, i.e. tonic alertness, and a relatively efficient active utilization of exogenous cues to improve their visual processing speed, i.e. phasic alertness. Our finding relates to a task-evoked fMRI study by Sadaghiani and D'Esposito (2015). The authors found that participants with a high overall accuracy in a pitch discrimination paradigm show lower BOLD activity in the cingulo-opercular network compared to low performing individuals. The authors suggested that, for these high performers, the task might have imposed lower demands on their alerting system (Sadaghiani and D'Esposito, 2015). Thus, the results from the present study might suggest that participants with a rather efficient alertness system might not be forced to recruit the cingulo-opercular network to the same extent as less efficient and lower performing participants. Potentially, this pattern could already be reflected in iFC patterns measured in a resting-state condition, in which the only task for the participants is to keep an appropriate arousal level in order not to fall asleep while they are not engaged in any particular task.

We suggest individual effects of phasic alertness on visual processing speed to have a trait-like character. Such a relatively constant parameter could potentially be associated with intra-network and, importantly, also inter-network connectivity between different intrinsic brain networks. For example, it was previously demonstrated that visual processing speed in uncued conditions showed both, a negative association with intra-network connectivity in the cingulo-opercular network and a positive one with inter-network connectivity between the cingulo-opercular and right fronto-parietal network (Ruiz-Rizzo et al., 2018). While in the present study, we did not find such significant associations for phasic alerting effects with inter-network connectivity, this does not necessarily indicate that coupling to other intrinsic brain networks is not relevant. Potentially, effective connectivity measures constitute a promising approach to reveal relevant directed, i.e. effective, connectivity patterns between brain networks or within the same network (Mottaghy et al., 2006; Périn et al., 2010; Riedl et al., 2016) that might not be depictable with iFC measures. Importantly, such interactions of the cingulo-opercular network with other networks or brain stem structures could potentially also explain a negative relationship of behaviour and intra-network connectivity as recently suggested by Ruiz-Rizzo et al. (2018). A candidate structure relevant for phasic alerting effects is the locus coeruleus, which was shown to be functionally connected to some nodes of the cingulo-opercular network in healthy younger (Zhang et al., 2016) and older (Serra et al., 2018) participants during resting state. Accordingly, a TVA-based study demonstrated that increases in visual processing following phasic alerting cues were accompanied by increases in pupil dilation (Petersen et al., 2017), a measure known to correlate with BOLD activity in the locus coeruleus (Murphy et al., 2014). Therefore, phasic alerting effects on visual processing speed could be associated with iFC of the locus coeruleus and brain structures forming the cingulo-opercular network. The present study could not address this question as we did not acquire physiological data to account for physiological noise in the brainstem originating from adjacent arteries and cerebrospinal fluid filled spaces. Future studies will be needed to shed light on this question.

Beyond the specific questions derived from the negative association of phasic alerting effects and iFC in the cingulo-opercular network, the present findings also potentially have several overarching implications for future studies. First, the question arises how the brain regions of the cingulo-opercular network interact with visual areas in order to accelerate the uptake of visual information. It has been suggested that brain regions within the cingulo-opercular network, especially the insula, play a decisive role in phasic alertness, i.e. mediate sensory alertness by heightening the readiness to respond to stimuli in sensory cortices (Sterzer and Kleinschmidt, 2010). It also seems plausible that specific intrinsic brain networks are connected with each other. In the present study, we could not find associations of phasic alerting effects on visual processing speed with inter-network connectivity of the cingulo-opercular network and visual networks. This might indicate that iFC as a measure is not sensitive enough to capture uni- or bidirectional communication between brain areas. Methods such as metabolic connectivity mapping could aid in revealing effective connectivity patterns (Riedl et al., 2016). Furthermore, studies using brain stimulation techniques constitute a promising approach to address the directionality of connections between brain areas within specific networks. Finally, a recent establishment of a TVA-based mouse paradigm opens the avenue to experimentally study the brain system functions underlying alertness effects on visual processing speed (Fitzpatrick et al., 2017).

Secondly, establishing a neural correlate of phasic alerting in the optimally functioning brain systems of young healthy persons allows to test whether such an association is altered in populations that are known to show changes in visual processing speed, phasic alertness functions, and/or iFC. For example, iFC in the cingulo-opercular network is prone to age-related changes (He et al., 2014; Onoda et al., 2012; Ruiz-Rizzo et al., 2019). It has, however, been shown that phasic alerting effects on visual processing speed are preserved in healthy aging (Haupt et al., 2018), although older participants' phasic alerting benefits might be more vulnerable to paradigm changes than the ones found in young participants (Wiegand et al., 2017). Thus, the question arises whether phasic alerting effects in healthy aging individuals rely on the same or differing underlying spatial patterns of iFC. Furthermore, visual processing speed is significantly reduced in pathological aging, i.e. in patients suffering from mild cognitive impairment and Alzheimer's disease (Bublak et al., 2011; Neitzel et al., 2016; Ruiz-Rizzo et al., 2017), psychiatric disorders (Gögler et al., 2017b, 2017a; McAvinue et al., 2015), and in diverse neurological patient populations (for a review on clinical TVA-based studies, see Habekost, 2015). Improved knowledge on the residual degree to which phasic alerting can improve visual processing speed in these patient populations and the relationship to iFC changes in the cingulo-opercular network could pave the way for new treatment options.

Thirdly, establishing a link for the degree of short-term enhancement of visual processing speed also opens the avenue to assess whether the individual degree of more long-term excitability might be related to iFC in the cingulo-opercular network. Future studies might address the question whether iFC in the cingulo-opercular network allows for individualized prediction of the individual response to phasic alertness training (e.g. Tennstedt and Unverzagt, 2014), and might, therefore, be used for tailoring interventions for persons with alertness dysfunctions.

5. Conclusions

In summary, the present study demonstrates that phasic alerting effects on visual processing speed are primarily associated with iFC in the cingulo-opercular network.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.04.019.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Chapter 4

Project III: IFC patterns underlying phasic alertness in healthy older adults

The current chapter comprises the research article entitled "Right-lateralized fronto-parietal network and phasic alertness in healthy aging" that was published in Scientific Reports in 2020. This third research project demonstrated that, in healthy older adults, phasic alerting effects on visual processing speed are primarily associated with iFC in the right fronto-parietal network. An additional age group comparison revealed that the association between phasic alerting effects on visual processing speed and cingulo-opercular network iFC is significantly lower in healthy older than in younger adults.

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Contributions:

K.F. and C.S. conceived and designed the study. M.H. led and coordinated the data acquisition. M.H. and A.L.R.-R. analysed the fMRI data. M.H. analysed the behavioural data. K.F. and C.S. aided in the interpretation of the data. M.H. drafted the main manuscript. M.H., A.L.R.-R., C.S., and K.F. critically revised the manuscript.

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Right-lateralized fronto-parietal network and phasic alertness in healthy aging

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Phasic alerting cues temporarily increase the brain's arousal state. In younger and older participants, visual processing speed in a whole report task, estimated based on the theory of visual attention, is higher in cue than no-cue conditions. The present study assessed whether older participants' ability to profit from warning cues is related to intrinsic functional connectivity (iFC) in the cingulo-opercular and/or right fronto-parietal network. We acquired resting-state functional magnetic resonance imaging data from 31 older participants. By combining an independent component analysis and dual regression, we investigated iFC in both networks. A voxel-wise multiple regression in older participants yielded that higher phasic alerting effects on visual processing speed were significantly related to lower right fronto-parietal network iFC. This result supports a particular role of the right fronto-parietal network in maintaining phasic alerting capabilities in aging. We then compared healthy older participants to a previously reported sample of healthy younger participants to assess whether behaviour-iFC relationships are age group specific. The comparison revealed that the association between phasic alerting and cingulo-opercular network iFC is significantly lower in older than in younger adults.

Phasic alertness refers to momentary enhancements of the brain's "state of readiness" due to warning cues[1]. Previous studies, using a whole report task with briefly presented letter arrays and parametric modelling of report performance based on the theory of visual attention (TVA)[2], demonstrated that perceptual speed of visual processing is enhanced by visual[3] and auditory warning cues[4]. Furthermore, auditory alerting was shown to be effective in both healthy younger and older participants[5]. Concerning neural correlates underlying phasic alerting effects in younger adults, we found that the individual cueing benefits were significantly related to intrinsic functional connectivity (iFC) in the cingulo-opercular network (CON)[6]. IFC refers to spatial patterns of correlated blood oxygen level dependent (BOLD) signal with a frequency of 0.01–0.1 Hz over time[7]. These BOLD fluctuations can be measured using resting-state functional magnetic resonance imaging (rs-fMRI).

With respect to older adults, it is unclear whether their preserved phasic alertness response relies on the same intrinsic brain network as in younger adults or a different one. Reviewing the importance of right-hemispheric structures for cognitive reserve[8], Robertson suggested that the integrity and functional connectivity of the right fronto-parietal network (rFPN) is decisive for the late-life maintenance of attentional abilities and, especially, alertness functions[9,10]. He summarized evidence for a close, bidirectional relationship of the availability of noradrenaline provided by the locus coeruleus, which is decisive for the ability to increase arousal[11,12], and the integrity of the right fronto-parietal network in aging individuals. The model is supported by a study demonstrating that activating the noradrenergic system by applying a handgrip task increased functional connectivity between the locus coeruleus and the fronto-parietal network in older compared to younger adults[13]. Taken together, previous evidence and relevant cognitive reserve models suggest that connectivity in the rFPN could be essential for alertness functions in healthy older participants.

The present study, therefore, sought out to investigate whether iFC in the CON and/or rFPN do underlie phasic alerting effects in healthy aging. In order to address this question, we first examined the relationship between

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individual iFC in the CON as well as rFPN and the individual degree of the phasic alerting effects in a group of healthy older adults. Second, we investigated iFC-behaviour relationships in task-related sensory networks. The degree of the phasic alerting effects could potentially be related to auditory networks as they were induced by auditory cues. They could also be associated with visual networks as we measured the effect of these auditory cues on visual processing speed. All networks were identified by visual inspection and cross-correlation with networks reported in a prior relevant study[14]. As iFC in visual areas usually splits up into several visual networks and two visual networks yielded high cross-correlations, we decided to include both networks in our analyses (see Supplements for visualization of sensory networks). In addition to these intra-network analyses, we explored inter-network connectivity patterns between the CON, rFPN, auditory, and visual networks. In order to ensure the specificity of observed associations, we carried out intra-network and inter-network control analyses in other attention-relevant intrinsic brain networks, expecting that they would not be significantly related to phasic alerting effects. Lastly, we compared healthy older adults to a previously assessed sample of healthy younger participants[6] in order to determine whether associations between phasic alerting effects and iFC are age group specific.

The analyses of rs-fMRI data follow the pipeline of a previous publication[6]. To facilitate the reading process, specifications concerning the acquisition, preprocessing, and analyses of rs-fMRI data are also added to the Methods section of the current manuscript. For all analyses, phasic alerting effects are quantified as differences in visual processing speed between a condition with an auditory cue compared to a no-cue condition. Visual processing speed is measured in a whole report paradigm based on the TVA[2]. For details regarding the TVA-based whole report procedure and estimation of visual processing speed, please refer to the previous publication of purely behavioural results[5] and the Methods section.

Results

Phasic alerting effects in healthy older participants.

The behavioural data of the original sample of 32 healthy older participants have already been analysed and reported elsewhere[5]. As one older participant was excluded from the present study due to extensive head motion, we report the behavioural results for 31 healthy older participants included in the present rs-fMRI study.

All participants completed a verbal whole report paradigm with half of the trials being preceded by an auditory cue. On the behavioural level, we are comparing estimates of visual processing speed in cue and no-cue conditions. Due to non-normal distributions of visual processing speed values, we applied both robust and Bayesian analyses. The main effect of cueing was significant ($Qa = 6.333$, $p = 0.012$). In Bayesian terms, it yielded anecdotal evidence that visual processing speed differed between the cue and no-cue condition ($B_{10} = 1.016$). We also analyzed whether two different cue target onset asynchronies (CTOA) would influence visual processing speed estimates. Neither the CTOA main effect ($Qb = 1.899$, $p = 0.168$, $B_{10} = 0.406$), nor its interaction with cueing ($Qab = 0.046$, $p = 0.830$, $B_{10} = 0.247$) were significant.

As phasic alerting effects did not differ in both CTOAs, we are using the absolute cueing effect averaged over both CTOAs as the behavioural variable of interest for the subsequent rs-fMRI analyses.

Associations between phasic alerting effects and iFC in healthy older participants.

Cingulo-opercular and right fronto-parietal network. We ran voxel-wise multiple regression analyses in the group of healthy older participants. First, we analyzed the behaviour-iFC associations in the rFPN, controlling for age, sex, education, and head motion. The analysis demonstrated that higher absolute cueing effects, averaged over both CTOAs, were significantly related to lower iFC in the rFPN, peaking in the right superior temporal gyrus (MNI coordinates in mm: [54 −52 22], cluster size: 647 voxels, $T = 4.11$, $Z = 3.56$, $p = 0.022$, FWE cluster-corrected) (see Fig. 1). Second, we analyzed behaviour-iFC relationships in the CON. We did not find significant associations of cueing effects and iFC in the CON.

Decisively, the significant peak of the behaviour-iFC relationship in the rFPN does not mean that the right superior temporal gyrus is specifically responsible or essential for phasic alertness. The interpretation of this finding is limited to the mentioned cluster best representing the behaviour-iFC association observed in the rFPN. This limitation applies because we used a voxel-wise analysis approach. By definition, iFC values of all voxels are relative values - they indicate the similarity of a voxel's time course to the time courses of all other voxels in a certain network. Hence, we cannot interpret absolute values of voxels forming a significant cluster.

Auditory and visual networks. In order to address whether iFC in sensory networks is related to auditory phasic alerting effects on visual processing, we ran additional multiple regression analyses in the auditory and two visual networks (see Supplementary Figs. 1–3). The analyses yielded significant negative associations of phasic alerting effects and iFC in the auditory network, peaking in the left middle frontal gyrus (MNI coordinates in mm: [−28 12 48], cluster size: 521 voxels, $T = 4.32$, $Z = 3.70$, $p = 0.042$ FWE cluster-corrected), and visual networks. For visual network I (Allen component IC39) the peak was located in the left fusiform gyrus (MNI coordinates in mm: [−12 −82 −16], cluster size: 1434 voxels, $T = 4.46$, $Z = 3.79$, $p < 0.001$ FWE cluster-corrected); for visual network II (Allen component IC46) the peak was located in the left lingual gyrus (MNI coordinates in mm: [−30 −58 8], cluster size: 2135 voxels, $T = 5.99$, $Z = 4.67$, $p < 0.001$ FWE cluster-corrected).

Control analyses in other attention-relevant networks. To determine whether phasic alerting effects on visual processing speed are specifically linked to iFC in the right fronto-parietal network, we controlled for phasic alerting associations with iFC in other attention-relevant networks. The analyses yielded no significant association of phasic alerting effects on visual processing speed with iFC in the executive control and left fronto-parietal network (all $p > 0.05$ FWE cluster-corrected).

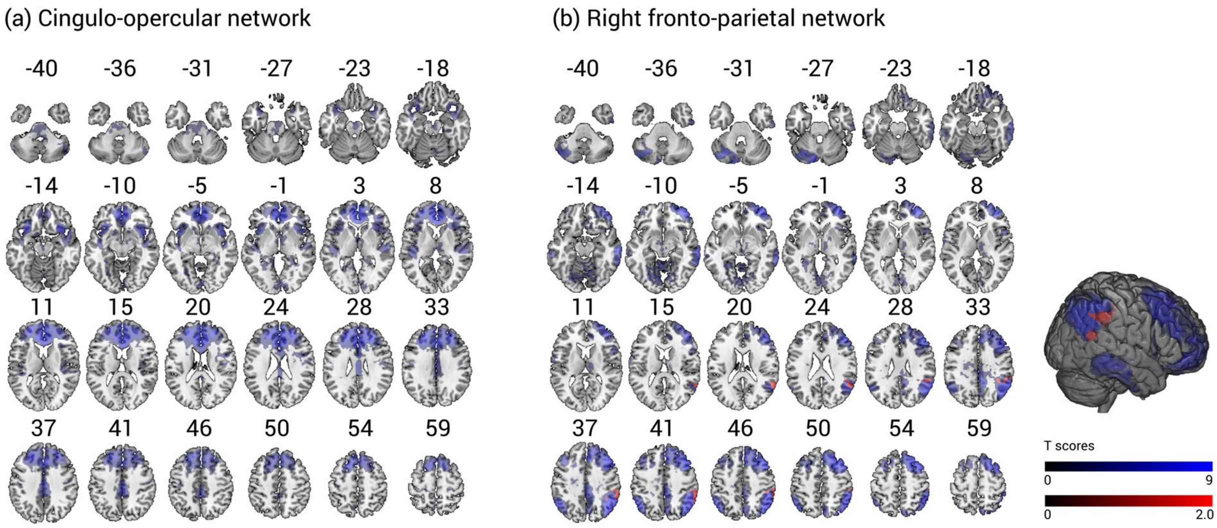

Figure 1. IFC in the cingulo-opercular network (**a**) and right fronto-parietal network (**b**) in older healthy participants. The clusters significantly related to phasic alerting effects (red) are overlaid on intra-network iFC (blue). The spatial maps are obtained by a combined independent component analysis dual regression approach. Behaviour-iFC associations were tested using a voxel-wise multiple regression, controlling for age, sex, head motion, and education ($p < 0.05$ FWE corrected at cluster level). The results are presented on a standard anatomical MNI152 template using MRIcroGL (https://www.mccauslandcenter.sc.edu/mricrogl/source); slice numbers in transverse plane are indicated.

Inter-network connectivity analyses. Following the analyses of intra-network connectivity, we addressed whether, in addition, inter-network connectivity patterns of the CON or rFPN with other attention-related, auditory, and visual networks do underlie phasic alerting effects. The analysis yielded significant negative correlations of both visual networks with the CON. The left fronto-parietal, executive control, and auditory networks were positively correlated with the rFPN; both visual networks were negative correlated with the rFPN (see Supplementary Fig. 4). Importantly, none of these inter-network connectivity patterns were significantly related to the behaviour of interest, i.e. phasic alerting effects ($-0.229 \leq$ all $r \leq 0.259$, all $p \geq 0.159$).

In summary, the individual degrees of phasic alerting effects on visual processing speed in healthy older adults are primarily associated with their intra-network iFC in the rFPN, auditory, and visual networks. The results of the present study do not provide evidence for a relevant link between observed phasic alerting effects and inter-network connectivity patterns or intra-network iFC in any network but the rFPN.

Age group comparison of associations between phasic alerting effects and iFC. Following the analyses in healthy older participants, we set out to compare the results of these participants to those of the previously analysed and reported sample of healthy younger adults who underwent the same behavioural and fMRI assessment procedures[6]. This comparison allows us to determine whether associations between phasic alerting effects and iFC in the CON or rFPN are age group specific.

First, we ran a voxel-wise multiple regression comparing behaviour-iFC relationships between healthy older and younger participants in the CON. This analysis revealed that the association between alerting benefits and iFC in the CON is significantly lower in older than in younger adults. The significant cluster is located in the superior orbito-frontal gyri bilaterally (peak MNI coordinates in mm: [14 40 16], cluster size: 1061 voxels, $T = 4.20$, $Z = 3.90$, $p < 0.05$ FWE cluster-corrected) (see Fig. 2a). While younger adults are characterized by a strong positive association between alerting benefits and iFC extracted from this cluster, older adults present a slight negative association (see Supplementary Fig. 5).

Second, we ran the same analysis in the rFPN. This analysis did not yield significant differences between age groups in their behaviour-iFC relationship ($p < 0.05$ FWE cluster-corrected).

Interestingly, the preceding analysis in healthy older participants provided strong evidence for a primary behaviour-iFC association in the rFPN. Therefore, we decided to perform an additional exploratory analysis without cluster correction but with a conservative voxel-wise threshold of $p < 0.001$. This exploratory multiple regression without cluster-level correction suggests that the association between phasic alerting effects and iFC in the rFPN is higher in older than younger participants (see Fig. 2b). The peak of the association was located in the right posterior cingulate cortex (MNI coordinates in mm: [10 −46 30], cluster size: 18 voxels, $T = 3.87$, $Z = 3.62$, $p = 0.039$ at cluster level, uncorrected). This result suggests that there is a trend for a stronger behaviour-iFC association in the rFPN in older versus younger participants.

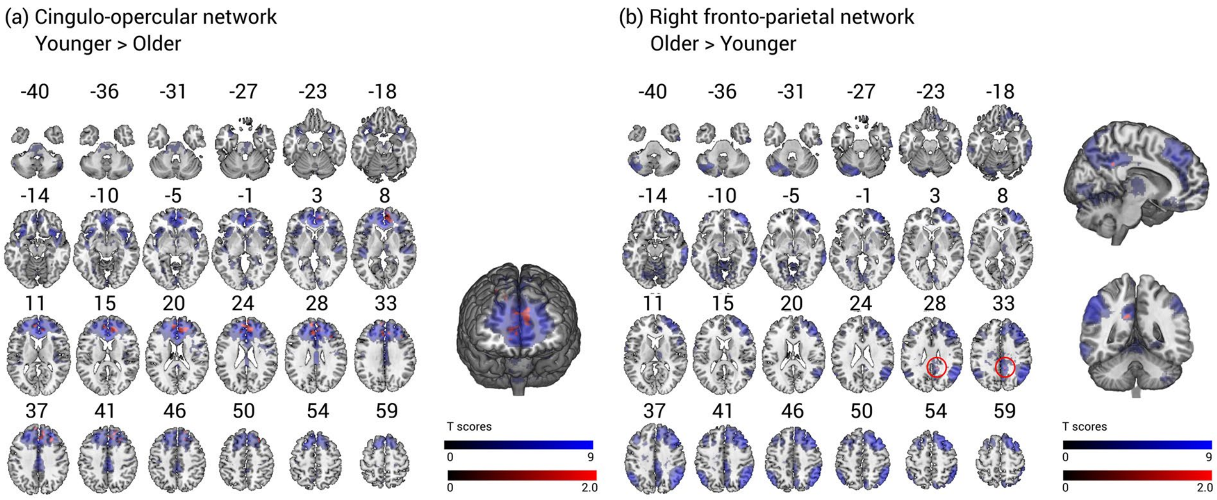

Figure 2. Age group differences of associations between phasic alerting effect on visual processing speed and iFC in the cingulo-opercular (**a**) and right fronto-parietal network (**b**). Panel a illustrates that the association between phasic alerting effects on visual processing speed and iFC in the cingulo-opercular network is significantly lower in older than in younger adults ($p < 0.05$ FWE corrected at cluster level, significant cluster in red). Panel b represents an exploratory analysis ($p < 0.05$ uncorrrected at cluster level) in the right fronto-parietal network. The spatial maps (blue) are obtained by a combined independent component analysis dual regression approach. Behaviour-iFC associations were tested using a voxel-wise multiple regression, controlling for age, sex, head motion, and education. The results are presented on a standard anatomical MNI152 template using MRIcroGL (https://www.mccauslandcenter.sc.edu/mricrogl/source); slice numbers in transverse plane are indicated.

Discussion

Auditory warning cues increase visual processing speed in healthy younger and older participants[4,5]. In healthy younger adults, such phasic alerting effects have been linked to iFC in the CON[6]. The present study investigated whether the same or distinct functional connectivity patterns do underlie preserved phasic alerting effects in healthy older participants. Previous studies suggested that the rFPN could be essential for preserved alertness functions in healthy older participants[10,13,15].

The present study sought out to identify iFC patterns underlying phasic alertness in healthy older participants. We addressed this question by measuring phasic alerting effects on visual processing speed in a TVA-based whole report and recording resting-state fMRI data. First, we analysed iFC-behaviour relationships in the CON and rFPN in healthy older adults. Second, we compared these iFC-behaviour relationships between healthy younger and older adults in order to determine whether associations in the CON and/or rFPN are age group specific.

In healthy older participants, higher absolute cueing effects were significantly related to lower iFC in the rFPN. In contrast to the results in younger participants[6], we did not find significant behaviour-iFC associations in the CON in healthy older participants. Importantly, greater connectivity does not automatically imply better behavioural performance. Previous studies have demonstrated that lower behavioural scores were associated with higher iFC in the brain networks of interest[16,17]. Based on such evidence, Ferreira and Busatto[18] summarised that the assumption "the more, the better" is overly simplistic and might be misleading in the interpretation of findings.

We also addressed iFC in the auditory network as we used auditory cues and in visual networks because we assessed the effect of alerting cues on visual processing. The analyses yielded significant negative associations of phasic alerting effects and iFC in the auditory network as well as both visual networks. Inter-network connectivity analyses of both the rFPN and CON with these task-relevant networks did not reveal significant relationships related to phasic alertness. However, as we have found significant behaviour-iFC associations in the auditory as well as two visual networks, we suggest that the rFPN in healthy older participants is in permanent, bi-directional exchange of information with sensory networks. On the one hand, the information it receives might be dependent on the efficiency of the auditory system to perceive auditory warning signals. On the other hand, the rFPN might accelerate the uptake of visual information by heightening the readiness of visual networks. The fact that we did not find significant behaviour-related connectivity patterns between networks, arguably, suggests that our connectivity measure lacks the sensitivity to reflect uni- or bi-directional communication between these brain areas. In this case, effective connectivity measures could facilitate the measurement of relevant directed connectivity patterns between the rFPN and the sensory network[19–21]. In addition, neither the intra-network connectivity of other attention-related networks nor their inter-network connectivity with the CON or rFPN were found to be significantly related to phasic alerting effects. These control analysis support the notion of the rFPN playing a specific role for phasic alerting effects in older participants.

Overall, the results of the behaviour-iFC analyses in healthy older participants indicate that right-hemispheric fronto-parietal structures are important for noradrenaline-mediated attentional and, particularly, alertness processes

	Younger participants	**Older participants**
Variable	**N = 32**	**N = 31**
mean age (SD)	26.6 (4.7)	71.1 (4.8)
sex (female/male)	20/12	10/21
handedness (right/left)	27/5	29/2
mean education in years (SD)	12.6 (0.9)	11.8 (1.8)
MWTB verbal intelligence score (SD)	28.6 (4.6)	32.7 (2.3)
MMSE score (SD)	—	28.9 (1.1)
Days between sessions[1]	240.1 (294.7)	255.0 (124.3)
Absolute Cueing Effect (over both CTOAs)[2]	—	1.65 (3.65)
Absolute Cueing Effect (long CTOA)[3]	3.92 (5.91)	1.69 (6.75)

Table 1. Demographics and visual processing speed (C) estimates of all participants. *Note*. SD: standard deviation; handedness: assessed by Edinburgh Handedness Inventory; MWTB: Mehrfachwahl-Wortschatz-Intelligenztest, maximum score = 37 points; MMSE, Mini-Mental State Examination, maximum score = 30 points with values < 24 points indicating cognitive impairment; [1]Number of days between behavioural and rs-fMRI session; [2]$((C_{cue}\ [long] - C_{no\text{-}cue}\ [long]) + (C_{cue}\ [short] - {}_{Cno\text{-}cue}\ [short]))/2$; [3]$C_{cue}\ [long] - C_{no\text{-}cue}\ [long]$.

in aging[10,13,14]. Robertson[10] summarized evidence suggesting that the integrity and functional connectivity in this network may facilitate attentional functions in old age. Enhancing visual processing speed in response to a warning signal depicts a central cognitive ability that can temporarily reduce the detrimental impact of age-related declines of general processing resources. Accordingly, older individuals with a high capability to mobilize additional capacity when faced with external warning signals are able to improve their rate of visual information uptake in critical situations. Older adults with lower phasic alertness capabilities might be characterized by a relatively stable capacity that is i) reduced due to aging effects and ii) does not flexibly adopt to task demands, even when provided with alerting environmental cues. A recent study, using a TVA-based paradigm with auditory alerting cues and measuring cue-related power and phase-locking effects in electroencephalography (EEG), documented that the variability of phasic alertness effects in older adults is reflected in the neural response. Namely, it was found that only those older participants with a relatively youth-like pattern of phase-locking showed reliable performance benefits[22]. The results of the present study suggest that these inter-individual differences in the ability to utilize auditory phasic alerting cues to increase visual processing speed are linked to iFC in the rFPN. They, thereby, support the importance of the integrity and connectivity of this network for active perception mechanisms and cognitive reserve in old age.

The comparison of healthy older participants with a previously reported sample of younger adults revealed that associations between phasic alerting effects and iFC in the CON are age group specific. The association between phasic alerting benefits on visual processing speed and iFC in the CON is significantly lower in older than in younger adults. This finding can be consolidated with a recent resting-state like fMRI study demonstrating reduced functional connectivity between the locus coeruleus, depicting the brain's primary source of noradrenaline, and core salience network structures in healthy older compared to younger adults[23]. The age group comparison in the rFPN showed that behaviour-iFC pattern does not significantly differ between healthy younger and older participants. A potentially more important role of the rFPN in healthy aging is, however, suggested by an additional exploratory analysis without cluster correction. Based on the specific role of the CON in younger adults[6] and the primary role of the rFPN in healthy older adults suggested by both current results and former studies[9,10,13], we expected to observe an age group specific dissociation of iFC patterns underlying alerting effects in both networks. It is possible that our sample of healthy older participants is heterogeneous with regard to the relevance of iFC in the rFPN for phasic alerting effects. A recent study suggested that there are substantial individual differences in neural responses underlying phasic alerting effets in aging individuals[22]. Some aging individuals might preserve a youth-like functioning while others might be characterized by obvious changes. Such variance could also affect associations between phasic alerting effects and iFC in the CON and rFPN. The interpretation of results is, further, complicated by the question whether the relevance of the rFPN in aging individuals indicates a (more or less intact) compensatory mechanism relying on this system. Overall, future studies are needed to establish whether the association between alertness and iFC in the rFPN is age group specific.

The present study has several limitations. First, the cross-sectional design and regression analyses do not allow for inferences being drawn regarding directionalities between phasic alertness, aging, and iFC in the CON and rFPN. Second, our study lacks a direct link to the locus coeruleus-noradrenaline system as we did not include a specific readout. Neuromelanin-sensitive magnetic resonance imaging sequences are a promising tool for quantifying locus coeruleus intergrity[24,25]. In addition, measuring pupil dilation would provide a window into locus coeruleus activity (for a review see[15]). Third, our voxel-wise analysis approach does not allow for a direct comparison of behaviour-iFC relationships between networks as such analyses do not yield one value describing iFC on the network-level.

Methods

Participants. Thirty-two older adults ($\geq$60 years) participated in the present study. One older participant had to be excluded due to extensive head motion. For the age group comparison, they were contrasted with 32 healthy younger (18–35 years) participants whose rs-fMRI data have been reported in a previous study[6]. The behavioural data of both younger and older participants have already been reported elsewhere[5]. The final sample of the present

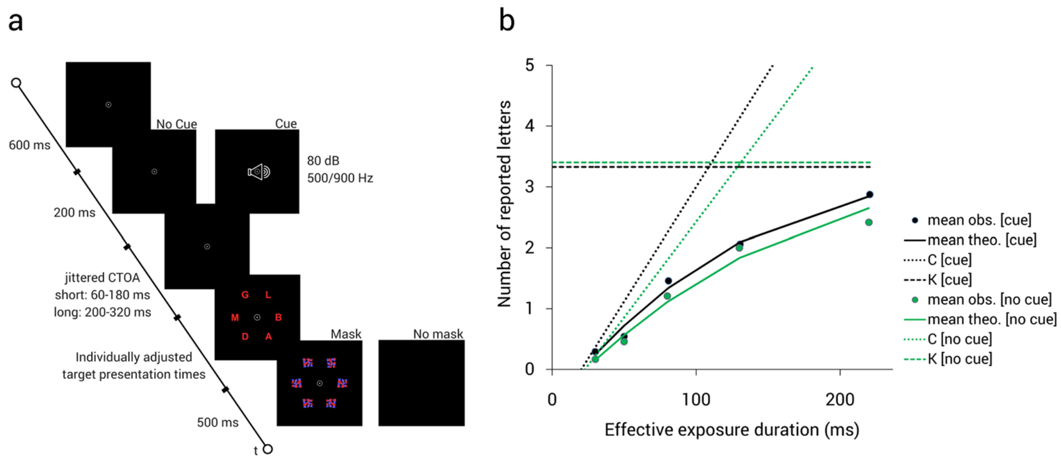

Figure 3. Exemplary trial sequence of the presented TVA-based whole report task (**a**) and summary of performance in cue and no-cue conditions for a representative healthy older participant (**b**). Solid curves (mean theo.) depict the best TVA-based fit to acquired data points (mean obs). The dashed line represents the model-based estimate of vSTM storage capacity *K*; the dotted line represents the model-based estimate of visual processing speed *C*.

study consisted of 32 younger and 31 older participants (see Table 1). All participants reported normal or corrected-to-normal vision, and they were reimbursed for their participation. The study was reviewed and approved by the ethics committees of the Department of Psychology of the Ludwig-Maximilians-Universität München and the Klinikum rechts der Isar of the Technical University Munich. All methods were performed in accordance with the ethics protocol's relevant guidelines and regulations. Written informed consent was obtained from all study participants in agreement with the ethics protocols.

As in the younger sample, the acquisition of the rs-fMRI (approx. 1 hour) and the TVA-based behavioural assessment (1–1.5 hours) of the older sample took place on two different days. Participants also completed the Edinburgh Handedness Inventory[26], a multiple choice German vocabulary test measuring crystallized intelligence called "Mehrfachwahl-Wortschatz-Intelligenztest" (MWTB)[27], and the Mini-Mental State Examination (MMSE) as a screening for cognitive impairments indicative of beginning dementia[28]. None of the participants had to be excluded based on a cut-off criterion for cognitive impairment, i.e. a score below 27/30 points. Demographic information of both study groups is presented in Table 1.

TVA-based whole report paradigm with alerting cues.

The details of the applied TVA-based whole report procedure have already been reported elsewhere[5]. In short, TVA is closely related to the biased competition account[29] and implies parallel processing of several visual objects competing for selection into a capacity-limited visual short term memory (vSTM) store. The probability that an object gets selected before the store is filled is proportional to its processing rate[2]. An increase of phasic alertness leads to a proportional increase in the processing rate of the object[30]. The sum of the processing rates of all objects present in the visual display is defined as the observer's overall visual processing speed C (in elements per second)[31]. By definition, all items in a whole report paradigm share the same expectancy and subjective importance. Hence, an increase in the observer's alertness induced by auditory warning cues will lead to a proportional increase in parameter C[30]. By comparing visual processing speed in conditions with and without warning cues, the individual phasic alerting effect can be estimated.

All possible trial sequences can be seen in Fig. 3a. Participants were instructed to maintain central fixation throughout the task and verbally report all letters recognized with "fair certainty", without any importance of speed or order. After entering all reported letters on the keyboard, the experimenter started the next trial with a button press. A scale presenting the individual's accuracy rating based on all reported letters succeeded every test block. Participants were asked to maintain an accuracy level between 70% and 90%, with a deviating score leading to adapted instructions for the next test block. If the participants' accuracy rating exceeded 90%, they were asked to also name letters that they believed to have recognized without complete certainty. If participants were less than 70% accurate, they were instructed to only report letters recognized with high certainty even if that meant that they would report fewer letters overall.

The whole behavioural experiment consisted of 8 blocks with 84 trials each. Half of the trials were preceded by an auditory cue and the other half of trials were uncued[5]. For the cue as well as no-cue conditions, 2 different CTOA spectrums, "long" and "short", were used. The "short" CTOA had an average of 120 ms and was jittered around the average value in steps of ±20 ms, 40 ms, and 60 ms resulting in an overall range of 60–180 ms. The "long" CTOAs had an average of 260 ms with the same jittering steps leading to a range of 200–320 ms. For each trial, one CTOA was randomly drawn from the according CTOA distribution (short or long). In all conditions, the jittering was balanced with all jittered CTOAs having the same probability and appearing equally often across trials. The effects induced by the auditory alerting cue were comparable across the short and long CTOA spectrums in older participants[5]. Therefore, we used the average absolute cueing effect calculated as $((C_{cue}\ [long] - C_{no\text{-}cue}\ [long]) + (C_{cue}\ [short] - {}_{Cno\text{-}cue}\ [short]))/2$ as the behavioural variable of interest in the subsequent iFC analyses in healthy older participants. Importantly, high-performing younger individuals demonstrated ceiling effects of visual processing speed in the short CTOA, derogating phasic alerting effects. As both age groups demonstrated stable phasic alerting effects in the long CTOA, we only analyzed the absolute cueing effect derived from long CTOA trials in the age group comparison (see Table 1).

The whole report task allows for the estimation of visual processing speed C, vSTM storage capacity K, and visual perceptual threshold $t0$. For detailed underlying estimation algorithms please refer to Kyllingsbaek[32]. Figure 3b shows the mathematically modeled exponential growth function of a representative older participant which is relating report accuracy (mean number of reported items) to effective exposure durations. The present study addresses the specific relationship between visual processing speed C and iFC as alertness cues predominantly affect visual processing speed[3–5].

Resting-state fMRI. The analyses of rs-fMRI data in the present study follow the pipeline described in a previous publication[6]. In order to facilitate the reading process, we repeat the specifications regarding data acquisition, preprocessing, Independent Component Analysis, Dual Regression, and statistical analyses in the following paragraphs. Previously reported rs-fMRI data of the younger participants[6] are added to the present study to address potential differences between older and younger participants.

Imaging Data Acquisition. Imaging data were acquired on a 3 T MR scanner (Philips Ingenia, Netherlands) using a 32-channel SENSE head coil. Small cushions stabilized participants' heads in the head coil to reduce head motion. Earplugs and headphones reduced scanner noise. Functional data acquisition lasted for 12.5 minutes, and participants were instructed to keep their eyes closed, intend to stay awake, and to refrain from performing any cognitive or motor activity, i.e. be at rest, throughout the whole sequence. At the end of the sequence, all participants reported that they had stayed awake. The functional data set consisting of 600 volumes was acquired by multi-band echo-planar imaging (EPI)[33] with a multi-band SENSE acceleration factor of 2 (TR = 1250 ms; TE = 30 ms; phase encoding in anterior-posterior direction; flip angle = 70°; field of view (FOV) = 192mm^2; matrix size = 64 × 64, 40 slices with 3 mm thickness and an inter-slice gap of 0.3 mm; reconstructed voxel size = 3 mm × 3 mm × 3.29 mm). Structural data were obtained by a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence (TR = 9 ms; TE = 4 ms; flip angle = 8°; FOV = 240mm^2; matrix = 240 × 240, 170 sagital slices; reconstructed isotropic voxel size = 1 mm).

Imaging data preprocessing. The rs-fMRI data were preprocessed in MATLAB (R2017b, version 9.3.0.713579; The Mathworks Inc.) using SPM 12 version 6225 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the Data Processing Assistant for Resting-State fMRI toolbox version 2.3 (DPARSF)[34]. After removing the first five functional volumes of every data set to account for T1 saturation effects, slice timing and head motion correction were performed by calling SPM functions. One older participant had to be excluded due to excessive head motion by the criterion of cumulative translation or rotation of 3 mm or 3° or due to more than 20% frame-wise displacements >0.5 mm (382/594 displaced frames)[35]. All images were manually reoriented to the AC-PC axis. The functional images were normalized into Montreal Neurological Institute (MNI) space with a 2-mm isotropic voxel size by unified segmentation to the structural image[36]. DPARSF integrates the three underlying procedures - coregistration, segmentation (grey matter, white matter, cerebrospinal fluid) and writing normalization parameters - into one processing step. The normalized images were smoothed using a 4 mm full-width-at-half-maximum (FWHM) Gaussian kernel. Additionally, band-pass filtering (0.01–0.1 Hz) was performed and the effects of nuisance covariates (whole-brain, white matter, and cerebrospinal fluid signals, as well as 12 head motion parameters, their derivatives, and scrubbing regressors) were removed.

Independent component analysis and dual regression analyses. After preprocessing the functional data, we conducted a probabilistic Independent Component Analysis (ICA) in FSL (version 5.0.9), using the MELODIC command-line program version 3.14[37,38]. We specified 30 independent components aiming at decomposing the data of the rather heterogeneous sample of healthy younger and older adults into larger networks. We refrained from using more components in order to avoid a split-up of the data into smaller subnetworks. The ICA decomposed each time × space matrix into pairs of time courses and spatial maps on the group level. Subsequently, these files were used as input and a dual regression was employed in order to estimate spatial maps and time courses for each participant[39,40]. The dual regression approach allows to quantify the functional connectivity of each voxel with each spatial map while controlling for all other spatial maps within each participant[41]. Most importantly, we chose this approach as dual regression analysis is excelling in detecting inter-individual variability in functional connectivity compared to seed-based functional connectivity analysis[41]. In a first step, the group-average spatial map was regressed into the individual participants' time × space matrices, resulting in 30 participant-specific time series. In a second step, the group-average time series was regressed into the same matrices, yielding 30 participant-specific spatial maps, i.e. one per independent spatial map on the group-level. The individual spatial maps contained Z-scores of every voxel within the according map. These Z-scores indicated the similarity of a particular voxel's time course to the time course of the respective component on the group-level while controlling for all other components. Therefore, the voxel-wise Z-scores were used as input for statistical tests to analyse whether the given component derived Z-scores do relate to behavioural variables. Importantly, the results of the statistical analyses are solely related to the specific output of the ICA, i.e. independent components. These components represent intrinsic brain networks but the precise brain regions included may vary[41]. In a last step, the randomise permutation-testing tool (5,000 permutations, FWE-corrected p = 0.05) within the FSL framework yielded one-sample *t*-test or 'group' spatial maps[39,40].

In order to identify typical intrinsic brain networks with our ICA-dual regression approach, we performed a spatial cross-correlation of our 30 independent components with intrinsic brain network templates derived from Allen *et al.*[15], using the *fslcc* command of FSL. Accordingly, we identified the component with the strongest correlation coefficient with the "salience network" (component IC55, $r = 0.35$) and right fronto-parietal network (component IC60, $r = 0.54$) of Allen *et al.*[15] as the CON and rFPN in the present study. These cross-correlations as well as a visual inspection of the brain areas included in the networks ensured that we identified the networks of interest for the present study. The CON comprises the cerebellum, amygdala, insula, basal ganglia, thalamus, paracingulate gyrus, anterior cingulate cortex, orbital gyrus, and frontal gyri (see Fig. 1a). The rFPN encompasses the cerebellum, prefrontal cortex, frontal gyri, intra-parietal sulcus, inferior parietal lobule, posterior cingulate cortex, and temporal gyri (middle and superior) (see Fig. 1b).

Statistical analyses. *Phasic alerting effects in healthy older participants.* Due to non-normal distributions of visual processing speed violating the assumptions of general linear models, we applied an equivalent robust model[42,43]. We used a robust method based on 20% trimmed means for a 2 × 2 repeated-measures design with the within subject factors cueing (cue vs. no-cue) and CTOA (short vs. long) for visual processing speed. These analyses were performed using the WRS package[44] in RStudio version 1.0.136[45].

Apart from orthodox statistics, we also ran the Bayesian counterpart of repeated-measures ANOVAs[46], using JASP version 0.8.5.1[47]. JASP calculates the Bayes factor which is a measure for the ratio of the likelihoods of two theories. By comparing those likelihood, the Bayes factor allows for a quantification of the evidence for each theory (e.g. null hypothesis and alternative, experimental hypothesis). Hence, if B_{10} is greater than 3 the present data substantially support the alternative hypothesis while values smaller than 1/3 are substantially favour the null hypothesis. B_{10} values between 1 and 3 (as well as 1 and 1/3 accordingly) solely yield anecdotal evidence for an hypothesis[48,49].

Associations between phasic alerting effects and iFC in healthy older participants. Cingulo-opercular and right fronto-parietal network. The individual spatial maps resulting from the described second step of the dual regression served as input for the intra-network analyses conducted in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). We performed two voxel-wise multiple regressions of the absolute cueing effect averaged over both CTOAs on iFC in the CON and rFPN. For the analyses of behaviour-iFC associations in a given network, we performed significance testing for significance threshold $p < 0.05$ together with family-wise error correction for multiple comparisons at the cluster level (FWE cluster-corrected). We added age, sex, education, and head motion as planned covariates. We controlled for head motion by adding mean volume-to-volume head motion, i.e. frame-wise displacement, as a covariate to the multiple regression. We chose the measure by Jenkinson *et al.*[50] as it considers voxel-wise differences in its derivation[51].

Auditory and visual networks. We also identified task-relevant, sensory networks by visual inspection and cross-correlation. Subsequently, we tested for a significant relation between alerting effects and iFC in two visual networks (IC39, $r = 0.37$; IC46, $r = 0.43$) and an auditory network (IC17, $r = 0.34$) as our behavioural task consisted of visual stimuli and contained an auditory cue.

Control analyses in other attention-relevant networks. In order to address the specificity of the relationship between phasic alerting effects and iFC, we additionally performed control analyses in other attention-relevant networks. We identified them by visual inspection and cross-correlation with templates by Allen *et al.* (2011) as we did with the two networks of interest. We chose to control for alerting associations with iFC in the executive control network (IC71, $r = 0.47$) and the left fronto-parietal network (IC52, $r = 0.42$) as both networks have been reported to be associated with attentional processes in fMRI task studies[1,52]. The executive control network is distinguishable from the left and right fronto-parietal networks as it contains bilateral temporal gyri, bilateral precuneus, and the right precentral gyrus[15]. It does neither include frontal structures nor is it restricted to one hemisphere.

Inter-network connectivity analyses in healthy older participants. Furthermore, we explored whether phasic alerting effects are significantly associated with inter-network functional connectivity pattern between the CON or rFPN and task-relevant (auditory and visual) networks. We also controlled for inter-network connectivity between the two networks of interest and other attention-relevant networks. We addressed these questions by entering the individual time courses of the mentioned intrinsic brain networks (yielded by the first step of dual regression) into an inter-network analysis (using custom code written in MATLAB; also see[53]). We correlated the time course of the CON and rFPN with the ones derived from the other five attention- and task-relevant networks of interest per participant. Subsequently, we performed Fisher r-to-Z transformation and correlation analyses to test whether the inter-network connectivity patterns were significantly correlated with the absolute cueing effect averaged over both CTOAs.

Age group comparison. Finally, to address whether previously analysed associations between phasic alerting effects and iFC in healthy older participants are, indeed, age group specific, we entered healthy older as well as younger participants into intra-network analyses in the CON and rFPN. For both networks, we performed voxel-wise multiple regressions of the absolute cueing effect in the long CTOA split by age group on iFC values ($p < 0.05$ FWE corrected for multiple comparisons at the cluster level). We compared a vector including values for the absolute cueing effect for younger participants and zeros for older participants with a vector containing absolute cueing effect values for older participants and zeros for younger participants. As we were interested in the interactive effect of phasic alerting and age group on iFC, we controlled for the main effects of both age group and absolute cueing effect. Additionally, we added sex, education, and head motion as planned covariates.

Data availability

The data and code used in this study are available upon request and data sharing complies with the institutional ethics approval.

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Author contributions

K.F. and C.S. conceived and designed the study. M.H. led and coordinated the data acquisition. M.H. and A.L.R.-R. analysed the fMRI data. M.H. analysed the behavioural data. K.F. and C.S. aided in the interpretation of the data. M.H. drafted the main manuscript. All authors repeatedly reviewed the drafts and revised the manuscript critically for important intellectual content.

Competing interests

The authors declare no competing interests.

Additional information

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Chapter 5

Project IV: Phasic alertness in amnestic mild cognitive impairment

The current chapter comprises the manuscript entitled "Phasic alerting increases visual processing speed in amnestic mild cognitive impairment" that has been submitted to Cortex and is available on the PsyArXiv preprint server. In this manuscript, we provide evidence for preserved phasic alerting effects on visual processing speed in patients with amnestic mild cognitive impairment.

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Contributions:

M.H. and K.F. conceived and designed the study. A.S., C.P., O. W. W., and K.F. organized the patient assessment, including medical examination, brain imaging, and neuropsychological assessment. N.N. programmed the behavioural paradigm. M.H., S.J., and A.S. conducted the experiment. M.H. analyzed the data. M.H. drafted the main manuscript. M.H., S.J., A.S., N.N., C.P., O.W.W., and K.F. critically revised the manuscript.

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Title

Phasic alerting increases visual processing speed in amnestic mild cognitive impairment

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Abbreviations

AD: Alzheimer's dementia
AED: adjusted exposure duration
aMCI: amnestic mild cognitive impairment
CTOA: cue target onset asynchrony
LOOIC: leave-one-out cross-validation information criterion
TVA: theory of visual attention
vSTM: visual short-term memory

Abstract

External warning cues temporarily increase the brain's sensitivity for upcoming events. Such increased levels of phasic alertness help individuals to flexibly adapt their reactions to the fast-changing requirements of highly complex visual environments. Previous studies reported that both healthy younger and older adults profit from phasic alerting cues. Arguably, such an intact phasic alerting mechanism could be even more relevant in pathologically aging individuals who are characterized by pronounced reductions of general processing capacity. The present study employed a theory of visual attention based whole report paradigm with auditory cues in order to investigate phasic alerting effects in amnestic mild cognitive impairment (aMCI) on a purely perceptual level. In addition, aMCI patients were compared to a previously reported sample of healthy older adults. The analysis in aMCI patients indicated that their visual processing speed was significantly higher in the cue compared to the no-cue condition. Across groups, auditory alerting cues significantly increased visual processing speed. Further, visual processing speed was reduced in aMCI patients compared to healthy older adults, replicating prior findings. Taken together, the results suggest that the processing system of aMCI patients exhibits general declines but can still flexibly integrate auditory warning signals. Phasic alerting cues facilitate a temporary increase in processing speed, enabling an efficient handling of upcoming sensory information.

Keywords

Phasic Alertness, Amnestic Mild Cognitive Impairment, Theory of Visual Attention, Dementia

1. Introduction

Warning cues increase the brain's sensitivity to the imminent appearance of targets (Oberlin, Alford, & Marrocco, 2005). These short-lived changes in the brain's readiness level are defined as phasic alertness (Sturm & Willmes, 2001). The ability to prepare for upcoming events is essential for optimally adapting behaviour to the fast-changing requirements in our highly complex visual environments. Arguably, such flexibility is of particular importance in older individuals, as it helps to compensate age-related declines in processing capacity (Espeseth, Vangkilde, Petersen, Dyrholm, & Westlye, 2014; McAvinue et al., 2012; Salthouse, 1996), allowing for temporarily improved processing in important situations. For *healthy* aging individuals, previous studies have demonstrated that they equally profit from phasic alerting cues compared to younger individuals (Fernandez-Duque & Black, 2006; Haupt, Sorg, Napiórkowski, & Finke, 2018; He, Heindel, Nassar, Siefert, & Festa, 2020; Karpouzian-Rogers, Heindel, Ott, Tremont, & Festa, 2019; Rabbitt, 1984). However, it is less clear whether this relevant mechanism is also preserved in *pathologically* aging individuals. During the development of Alzheimer’s disease, processing capacity is even further reduced compared to healthy aging individuals. Importantly, this decline is already evident in patients with amnestic Mild Cognitive Impairment (aMCI) (Bublak et al., 2011; Ruiz-Rizzo et al., 2017). Patients with aMCI show subtle cognitive impairments (including memory deficits) beyond what is expected in normal aging, but are not substantially impaired in their daily living activities (Roberts & Knopman, 2013). AMCI is regarded as an intermediate stage between healthy aging and dementia as patients with aMCI have a high risk for developing Alzheimer's dementia (AD) (Ward, Tardiff, Dye, & Arrighi, 2013). The present study sets out to systematically investigate phasic alertness in patients with aMCI. In more detail, we want to know whether the aMCI stage is characterized by a generally slowed and relatively rigid rate of information uptake or by a residual plasticity that allows a flexible enhancement of processing speed in alerting conditions.

Previous reaction-time based studies investigating phasic alerting effects in patients with aMCI and AD have yielded inconclusive results (Fernandez-Duque & Black, 2006; Festa-Martino, Ott, & Heindel, 2004; Karpouzian-Rogers et al., 2019; Martella et al., 2014; Tales, Muir, Bayer, Jones, & Snowden, 2002; Tales, Snowden, Brown, & Wilcock, 2006; Tales, Snowden, Haworth, & Wilcock, 2005; Tales et al., 2011). Studies in aMCI (Tales et al., 2005, 2011) and AD patients (Tales, Muir, Bayer, & Snowden, 2002) reported that visual alerting cues did not speed up reaction times in simple reaction tasks requiring target detection. Assessing alerting effects on target discrimination performance, one study did not observe reaction time benefits in aMCI patients (Festa-Martino et al., 2004), while other studies demonstrated such benefits in both aMCI (Tales et al., 2011) and AD patients

(Fernandez-Duque & Black, 2006; Tales et al., 2006). Finally, there is evidence that auditory alerting cues speed up reaction times in aMCI patients (Karpouzian-Rogers et al., 2019; Martella et al., 2014). Overall, auditory alerting cues might be more effective than visual alerting cues (Karpouzian-Rogers et al., 2019).

The classical theory underlying these reaction-time based studies is that phasic alertness leads to an enhanced readiness for responses and, thus, speeds up processes of preparation and execution of motor responses (Posner, 1978; Sturm & Willmes, 2001). However, recent studies have repeatedly demonstrated that phasic alerting already accelerates processing at the prior perceptual level (Haupt et al., 2018; Matthias et al., 2010; Petersen, Petersen, Bundesen, Vangkilde, & Habekost, 2017; Thiel, Zilles, & Fink, 2004). Arguably, such assessment of effects on the attentional level allows a more direct and pure estimation of the the brain's preparatory state. This is especially relevant in older adults, as reactions times are inevitably confounded by the overall slowing of motor processes in aging (Shalev, Humphreys, & Demeyere, 2016).

The theory of visual attention (TVA) (Bundesen, Vangkilde, & Habekost, 2015; Bundesen, 1990) offers a computational framework for the estimation and explanation of such perceptual effects. In short, TVA presumes that several visual objects are processed in parallel and compete for selection into a capacity-limited visual short term memory (vSTM) store. The processing speed of individual objects is the decisive selection criterion. Objects processed at greater rate compared to those at lower rate have a higher probability of being encoded into vSTM until its storage capacity is exceeded. The processing rate v is calculated as the product of the strength of sensory evidence that "x belongs to category *i*" and the visual bias of the observer towards category *i*.

$$v(x,i) = \eta\ (x,i)\ \beta_i. \tag{1}$$

Most importantly, the visual bias β_i is computed as a product of three factors:

$$\beta_i = A\ p_i u_i \tag{2}$$

A is the level of alertness, p_i reflects the prior probability of a certain feature, and u_i refers to the utility or subjective importance of this feature (Bundesen et al., 2015). Higher phasic alertness will result in a proportional increase in the observer's bias towards an object and, by that, to a proportional increase in the processing rate of the object. The overall visual processing speed *C* (in elements per second) is the sum of the processing speed *v* values of all presented objects (Habekost et al., 2013). When all objects have an equal prior probability and subjective importance, phasic alerting cues increasing the observer's alertness *A* will lead to a proportional increment in parameter *C* (Bundesen et al., 2015). Importantly, TVA-based modelling of verbal report of briefly presented letter arrays in a whole report task allows the parametric assessment of the latent parameters processing speed *C* and the phasic change in alertness *A* of a given participant (e.g. Haupt et al., 2018). The verbal report is given without speed stress and, thus, the resulting parameters are disentangled from potential motor slowing.

The present study takes advantage of the merits of the TVA-based whole report testing procedure, i.e. a theoretical integration of alertness effects and process-pure assessment, in order to investigate whether auditory phasic alerting cues induce phasic alertness effects on the perceptual level, i.e. increase visual processing speed, in aMCI patients.

2. Materials and Methods

2.1. Participants

Thirty-four patients with aMCI participated in the present study. Two patients had to be excluded due to extreme visual processing speed estimates (>2 SDs from the group mean in either cueing condition). The patients were compared to a previously reported sample of 32 healthy older adults (Haupt et al., 2018). The demographics of the final sample are reported in Table 1. All aMCI patients were recruited from the memory clinic of the department of neurology at the university hospital Jena. The study was reviewed and approved by the ethics committee of the university hospital Jena. All methods were performed in accordance with the ethics protocol's relevant guidelines and regulations as well as the Declaration of Helsinki. Written informed consent was obtained from all patients in agreement with the ethics protocol.

Patients underwent a standardized diagnostic assessment including medical history (both patient and informant interview), medical, neurological, and psychiatric examination, computer tomography or magnetic resonance imaging, blood tests, and neuropsychological assessment. The neuropsychological assessment comprised the German adaption of the Consortium to Establish a Registry for Alzheimer's Disease test battery (CERAD-Plus) (Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1988; Welsh, 1992). CERAD-Plus includes the Mini Mental Status Examination (MMSE) (Folstein, Folstein, McHugh, & Ingles, 1975).

In addition, patients completed the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) and the "Mehrfachwahl-Wortschatz-Intelligenztest" (MWT-B, a multiple choice German vocabulary test measuring crystallized intelligence) (Lehrl, Triebig, & Fischer, 1995).

Table 1.
Demographics of all aMCI patients and previously reported comparison sample of healthy older adults

aMCI patients (n=32)	N	Mean	SD	Range
age	32	72.41	7.65	55-84
sex (female/male)	14/18	-	-	-
handedness (right/left/ambidextrous)	29/2/1	-	-	-
years of school	32	9.97	1.45	8-13
MWTB score	26	31.46	3.59	21-36
MMSE score	32	27.75	1.08	25-30
CDR sum score	25	2.40	0.98	1-4.5
HADS anxiety score	31	6.29	3.08	1-12
HADS depression score	31	6.52	3.83	0-16

Healthy older adults (n=32)	N	Mean	SD	Range
age	32	71.2	4.7	60-77
sex (female/male)	11/21	-	-	-
handedness (right/left/ambidextrous)	30/0/2	-	-	-
years of school	32	11.8	1.8	8-14
MWTB score	30	32.7	2.2	26-36
MMSE score	32	28.8	1.1	27-30

Note. SD: standard deviation; MWTB: Mehrfachwahl-Wortschatz-Intelligenztest, maximum score = 37 points; MMSE: Mini-Mental State Examination, maximum score = 30 points with values < 24 points indicating probable dementia; CDR: Clinical Dementia Rating; HADS: Hospital Anxiety and Depression Scale

2.2. TVA-based whole report paradigm with alerting cues

AMCI was diagnosed based on four criteria: subjective and informant-reported memory deficits, cognitive impairments exceeding the age norms that affect at least the memory domain (subtest scores exceeding 1.5 standard deviations from the standardized mean score), informant-derived Clinical Dementia Rating (CDR) global score of 0.5 indicating questionable dementia (Morris, 1997), largely preserved activities of daily living measured with Bayer Activities of Daily Living (Hindmarch, Lehfeld, de Jongh, & Erzigkeit, 1998), and no dementia (excluded using ICD-10 criteria and CDR global score > 0.5). None of the patients showed predominant visual impairments typical of posterior cortical atrophy (McMonagle, Deering, Berliner, & Kertesz, 2006). Participants were excluded from the present study if they presented with persisting neurological or psychiatric diseases (e.g. strokes, tumors, alcoholism) or their brain scan indicated brain lesions altering cognitive functioning (e.g. stroke lesions).

All patients reported normal or corrected-to-normal vision and were able to follow verbal instructions without problems. Following this standardized diagnostic assessment, patients completed a TVA-based whole report paradigm, lasting approximately 30 minutes. The neuropsychological assessment and experimental paradigm took part on the same or different days.

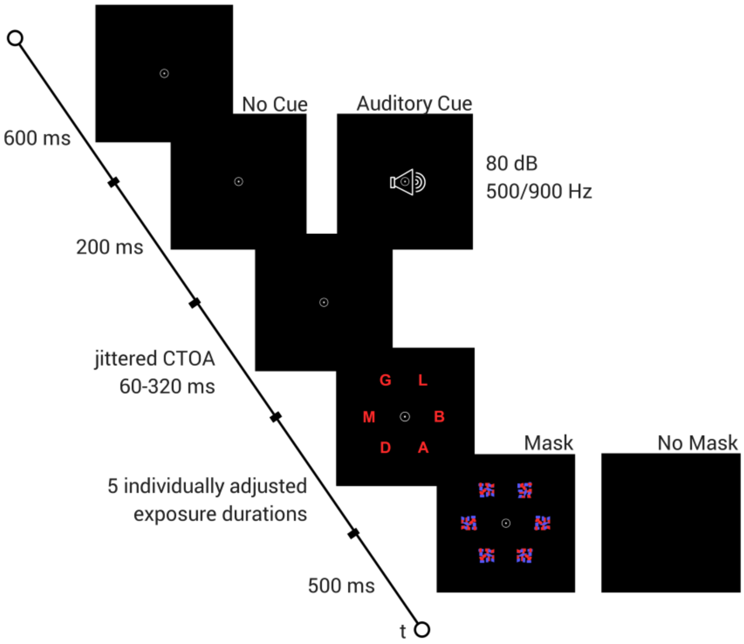

Figure 1. Exemplary trial sequence for TVA based verbal whole report paradigm with auditory alerting cues in aMCI patients. This image is licensed under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0).

The details of the TVA-based whole report procedure applied in the present study are comparable to the one used in healthy younger and older adults (Haupt et al., 2018). The whole report paradigm was conducted in a soundproof and darkened room. The paradigm was presented on a Asus 24 inch monitor (1920x1080 pixel screen resolution, 100 Hz refresh rate). Tones were presented using Logitech multimedia speakers. Patients had a constant viewing distance of 60 cm because their heads were located on a chin rest. An exemplary trial sequence is depicted in Figure 1. Patients fixated on a white circle (0.9x0.9cm) in the center of a black screen for 600 ms. In the cue condition, an 80 dB tone with a randomly chosen frequency of 500 or 900 Hz was presented for 200 ms with the screen remaining the same. In the no-cue condition, participants fixated on the screen for 200 ms without hearing a tone. The target displays consisted of six letters (1.3x1.1cm) that were randomly sampled from a set of 23 letters without replacement (ABCDEFGHJKLMNOPRSTUVWXZ) and presented on an imaginary circle. The exposure durations of the target displays were individually adjusted for each participant in a pre-test phase. Pre-test trials started with an exposure duration of 100 ms. Correct reports of at least 1 letter decreased the exposure duration by 10ms; incorrect reports increased the exposure duration by 10ms. The shortest exposure duration determined in these pre-test trials was used as the lowest adjusted exposure duration (AED) in the test phase. Based on the lowest AED, four additional AED were picked from a pre-defined list. Target displays with all 5 AED were followed by masks for 500ms (max. 1.8x1.8cm). In addition, 2 AED were also used for unmasked trials, prolonging the duration of effective exposure, i.e. allowing for after-images. Patients verbally reported the letters recognized with “fair certainty” without any importance of speed or order. The experimenter entered the letters on the keyboard before starting the next trials.

The whole report task allows for the estimation of visual processing speed *C*, visual short-term memory storage capacity *K*, and visual perceptual threshold *t0*. For detailed underlying estimation algorithms, please refer to Kyllingsbaek (2006). Figure 2 shows the mathematically modeled exponential growth function of a representative aMCI patient. It relates report accuracy (mean number of reported letters) to the different individually adjusted exposure durations. The slope of the exponential growth function in *t0* depicts the estimate of visual processing speed *C*. As the exposure durations were adjusted for the individual report accuracy and verbal responses were unspeeded, the estimates of visual processing speed are not confounded by individual differences in perceptual threshold or motor speed.

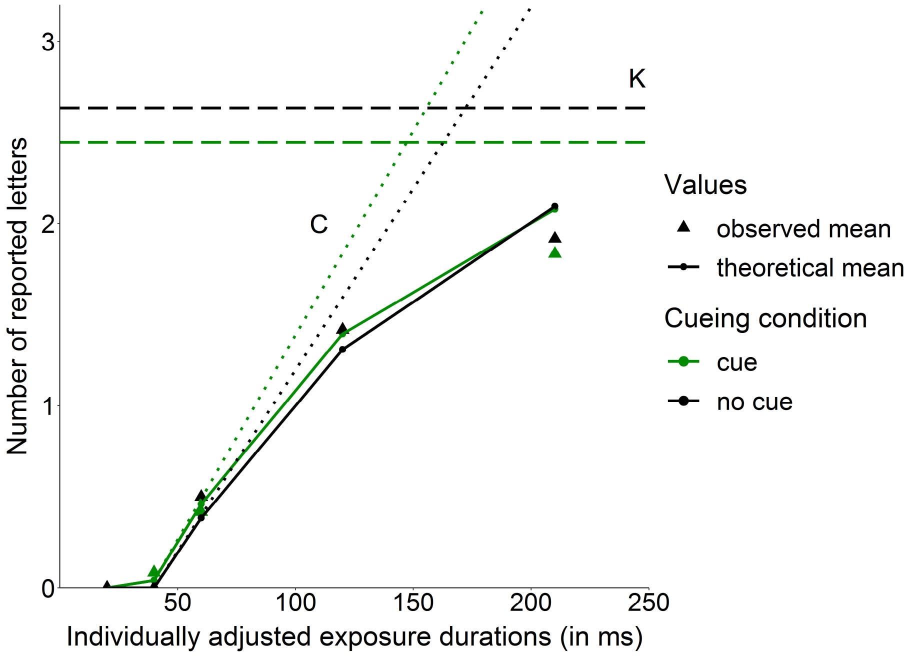

Figure 2. Whole report performance and TVA based modeling for a representative aMCI patient. This image is licensed under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0).

The original whole report paradigm designed for healthy younger and older adults consisted of 8 blocks with 84 trials each. Half of the trials were preceded by an auditory alerting cue while the other half of trials were uncued (Haupt et al., 2018). In addition to the alerting cue manipulation, the paradigm included two jittered cue target onset asynchrony (CTOA) spectrums (average of 120ms versus average of 260ms). As the effects induced by the auditory alerting cue were comparable across the short and long CTOA spectrums in older participants (Haupt et al., 2018) and we aimed to shorten the paradigm significantly for the use in patient populations, we decided to combine both CTOA spectrums and refrain from analyzing them separately. Furthermore, based on a simulation of when the TVA-based model fitting yielded reliable attention parameters in healthy older participants, we reduced the number of trials to 336 (168 cued and 168 uncued trials; 4 blocks with 84 trials each). Due to time limitations in the clinical setting, 7 patients were tested with only 168 trials. We reassured that these data could nevertheless be validly used by refitting the data of the remaining 26 patients with originally 336 trials by only including the first half of their trials (168 trials). The visual processing speed estimates based on 336 or 168 trials of the same patients yielded a correlation coefficient of rho = .89 and did not significantly differ from each other (see Supplementary Material). Hence, we included the visual processing speed estimates based on 168 test trials for the 7 mentioned patients in all analyses.

2.3. Statistical analyses

Behavioural data were analyzed with Bayesian multilevel models by using the brms package version 2.9.0 (Bürkner, 2017, 2018) in R version 3.5.1 (R Core Team, 2018), an interface to the probabilistic programming language Stan (rstan version 2.19.2) (Carpenter et al., 2017). First, we analyzed phasic alerting effects on visual processing speed in aMCI patients. For this, we used a minimal model with cueing condition as fixed effect (cue vs. no-cue) and subject-level intercepts as a random effect. We added subjects as a random effect because we want to incorporate that aMCI patients might differ in their baseline performance, i.e. random intercepts in our statistical model. Models including random slopes did not converge successfully. As the distributions of visual processing speed in both cueing conditions deviated from normality and were characterized by heavy tails, we used a Student's t likelihood for our model, which can be thought of as a Bayesian robust regression method. We compared the fit statistics of this model to a model using a Gaussian likelihood by applying the leave-one-out cross-validation information criterion (LOOIC) for model-selection (Vehtari, Gelman, & Gabry, 2017). For all models, default (flat) priors were used. Second, we compared phasic alerting effects in aMCI patients to those in a previously reported sample of healthy older adults (Haupt et al., 2018). We used a model with cueing condition and group as fixed effects and intercepts by subject as a random effect. We then added an interaction term to the model in order to assess whether the cueing x group interaction is significant. All models were fit using brms' default four chains, each with 2000 iterations and a warm-up period of 1000 samples. R-hat values for all parameters in all models equalled 1.0 and the minimum effective sample size across all parameters was 634. Taken together, these measures indicate that all models converged successfully.

Compared to traditional null-hypothesis significance testing, i.e. repeated-measures ANOVAs, multilevel models do not only address the potential significance of a difference between conditions but estimate the difference itself (for more information about multilevel modelling see Alday, Schlesewsky, & Bornkessel-Schlesewsky, 2017; for general information regarding estimation see Cumming, 2014)(Alday et al., 2017). Parameters estimates can be interpreted as statistically significant (in line with traditional null-hypothesis significance testing) if their credible intervals do not contain zero.

3. Results

First, we analyzed the effect of cueing condition (cue vs. no-cue) on visual processing speed *C* in the aMCI patient sample by using the Bayesian multilevel model defined in Methods. We used sum coding for the cueing contrast [0.5 -0.5] so that the estimates reflect the difference between both conditions. Means, i.e. fixed-effect parameter estimates, and standard deviations of the posterior distribution as well as the corresponding two-sided 95% credible intervals are presented in Table 3. LOOIC values indicated that the Student's t likelihood model and the Gaussian likelihood model have comparable model fits. The mean of the posterior distribution indicates that visual processing speed *C* is 2.3 items per second higher in the cue compared to no-cue condition. As the credible intervals do not contain zero, the effect of cueing condition is distinguishable from random noise in this experiment.

Table 2. *Summary of model fits and fixed effect estimates for aMCI patients*

Fixed effect	Mean	SD	l-95% CI	u-95% CI	LOOIC
C ~ 1+Cueing+(1|Subject); Student's t likelihood					391.6
Cueing	2.29	0.94	0.49	4.16	
C ~ 1+Cueing+(1|Subject); Gaussian likelihood					390.1
Cueing	2.34	0.97	0.44	4.25	

Note. Parameter estimates can be interpreted as statistically significant if their credible intervals do not contain zero. Smaller LOOIC values indicate better model fit.

Second, we repeated the described analysis including the two formerly excluded outliers to check that the results are robust. The analysis with 34 participants also shows that the effect of cueing is distinguishable from random noise (see Supplements).

Table 4. *Summary of model fits and fixed effect estimates for comparison of healthy older adults and aMCI patients*

Fixed effect	Mean	SD	l-95% CI	u-95% CI	LOOIC
C ~ 1+Cueing+Group+(1|Subject); Student's t likelihood					737.8
Cueing	2.01	0.59	0.88	3.16	
Group	-6.53	1.69	-9.88	-3.26	
C ~ 1+Cueing+Group+(1|Subject); Gaussian likelihood					737.3
Cueing	2.06	0.58	0.92	3.21	
Group	-6.34	1.72	-9.71	-3.00	
C ~ 1+Cueing+Group+Cueing:Group+(1|Subject); Student's t likelihood					740.0
Cueing	2.01	0.57	0.88	3.12	
Group	-6.60	1.73	-9.80	-3.11	
Cueing:Group	0.44	1.16	-1.85	2.68	
C ~ 1+Cueing+Group+Cueing:Group+(1|Subject); Gaussian likelihood					741.6
Cueing	2.06	0.59	0.95	3.22	
Group	-6.41	1.72	-9.77	-2.96	
Cueing:Group	0.59	1.11	-1.62	2.79	

Note. Parameters estimates can be interpreted as statistically significant if their credible intervals do not contain zero. Smaller LOOIC values indicate better model fit.

Third, we compared phasic alerting effects on visual processing speed in aMCI patients and a previously reported sample of healthy older adults (Haupt et al., 2018) by adding group as a fixed effect (see Table 4). We used sum coding for cueing and group contrasts [0.5 -0.5] so that the according estimates reflect the difference between both conditions. LOOIC values indicated that the fits for the models with a Student's t likelihood and a Gaussian likelihood are comparable. The means of the posterior distribution demonstrate that visual processing speed *C* is 2 items per second higher in the cue compared to no-cue condition and reduced by 6.5 items per second in aMCI patients compared to healthy older controls. Both the main effects of cueing condition and group are distinguishable from random noise. Adding the interaction of cueing condition and group to the model does not improve model fit and the credible intervals for this interaction term contain and are nearly centred around zero. Hence, the present results indicate that the interaction effect of cueing and group was indistinguishable from random noise in this experiment.

Table 4 shows visual processing speed estimates in the cue and no-cue condition for aMCI patients and healthy older adults. These two conditions only differed in the level of alertness; all other test parameters were kept constant throughout the experiment. According to TVA, the cue-induced increase in alertness proportionally increases visual processing speed. Therefore, the relative difference of visual processing speed (C_{Cue} - C_{Nocue}/ C_{NoCue}) reflects the phasic change in alertness *A*. Auditory alerting cues increased visual processing speed and, thus, the alertness level *A* by around 16% in aMCI patients and 9% in healthy older adults.

Table 4. *Visual processing speed estimates per cueing condition and group*

	Cue condition mean (SD)	No-cue condition mean (SD)	Relative cueing effect
Healthy older participants	26.7 (6.5)	24.9 (6.8)	0.09 (0.17)
aMCI patients	20.6 (7.8)	18.2 (7.2)	0.16 (0.29)

Note. SD: standard deviation

4. Discussion

Aging individuals face a general decline in visual processing capacities (Espeseth et al., 2014; Habekost et al., 2013; McAvinue et al., 2012). Declines in visual processing speed are even more pronounced in patients with aMCI who are at risk for developing dementia (Ruiz-Rizzo et al., 2017). Auditory cues can temporarily increase the speed of visual processing in healthy older adults (Haupt et al., 2018). Arguably, such an intact phasic alerting mechanism could be even more relevant in aMCI patients in order for them to overcome their pronounced general slowing when faced with important upcoming events. The present study set out to investigate whether aMCI patients profit from auditory alerting cues. We applied a TVA-based whole report paradigm with auditory alerting cues in aMCI patients. In order to compare the size of such phasic alerting effects on visual processing speed to the one observed in healthy aging, we compared the results of aMCI patients to those of a previously reported sample of healthy older adults (Haupt et al., 2018).

The analysis in aMCI patients revealed that visual processing speed is significantly higher in the cue compared to the no-cue condition. The comparison of aMCI patients and healthy older adults replicated the prior finding that visual processing speed in aMCI patients is further reduced compared to healthy aging individuals (Ruiz-Rizzo et al., 2017). Most importantly, higher visual processing speed values in the cue compared to the no-cue condition and the absence of a significant interaction between cueing condition and group indicated that, across groups, auditory alerting cues significantly increase visual processing speed. These results in aMCI patients suggest that their processing system can flexibly integrate external warning signals. Auditory alerting cues can be utilized to temporarily adapt to situational demands by increasing the speed of processing for upcoming information.

In line with the findings in healthy aging, the cue-induced increase in visual processing in aMCI patients demonstrates that the effect of external warning signals is already found on the perceptual processing level (and not restricted to later stages of motor preparation and response). Thus, despite patients' overall slowing of visual processing, their capability to flexibly adjust and mobilize additional processing capacities in important situations seems to be preserved.

As processing speed is closely linked to general cognitive abilities and functional independence (Ritchie, Tucker-Drob, & Deary, 2014), our findings have important clinical implications. If it is possible to temporarily enhance visual processing speed in patients at risk for dementia, such obvious residual plasticity could be targeted in future intervention studies. For example, computerized processing speed trainings have been reported to be effective in healthy older adults, improving their everyday functioning as well as ratings of health and quality of life (Ball, Edwards, & Ross, 2007; Wolinsky et al., 2010). It appears that especially individuals with low baseline speed show pronounced individual gain from such interventions (Ball et al., 2007; Edwards et al., 2005). Potentially, cue-induced phasic alerting benefits can serve as biomarkers of individual gain, i.e. indicate the degree to which a more durable benefit could be gained from a rather long-term intervention.

Decisively, the observation of preserved phasic alerting effects in aMCI patients does not necessarily imply that the phasic alerting system is not affected by the underlying neurodegeneration. Alternatively, the brain mechanisms underlying the alertness effect in aMCI patients might differ to some degree to those in healthy older individuals. In fact, a previous study pointed out that aMCI patients might be characterized by a functioning but qualitatively different alerting system (Karpouzian-Rogers et al., 2019). The authors found that, while demonstrating significant alerting benefits, aMCI patients did not show the more pronounced spatial cueing effects that were found in healthy older adults under cued compared to uncued conditions. Thus, while cueing leads to increased phasic arousal in the brain's alertness system and to faster visual processing in aMCI patients, the degree to which further systems, e.g. spatial attention or memory, can use the provided "boost" might be limited. Further studies could address the question how alerting cue-induced visual processing speed benefits translate into other cognitive processes or behaviour. Brain imaging studies could contribute to an improved understanding of neural mechanisms and brain networks underlying phasic alertness in aMCI patients and could help to address whether these differ between healthy aging individuals and those at risk for cognitive decline. Finally, it would be relevant to assess whether the conversion from aMCI to AD is accompanied by a decline in phasic alertness effects. Future studies are needed to investigate whether the loss of independent functioning in every-day life situations is related to a potential inability to prepare for upcoming events.

5. Conclusion

The present study set to investigate phasic alertness in aMCI patients using a TVA based verbal whole report paradigm with auditory alerting cues. The analysis in aMCI patients indicated that their visual processing speed was significantly higher in the cue compared to the no-cue condition. The cue-induced phasic alerting effects on the perceptual level were comparable between healthy older adults and aMCI patients. However, baseline visual processing speed was reduced in aMCI patients compared to healthy older adults. Taken together, the present study suggests that the processing system of aMCI patients exhibits general declines but can still flexibly integrate auditory warning signals in order to temporarily speed up the processing of upcoming sensory information.

Disclosure statement

The authors declare no financial or non-financial competing interests.

Author contributions

Marleen Haupt: Conceptualization, Formal Analysis, Investigation Writing-Original Draft, Visualization **Steffen Jödecke:** Investigation, Writing-Review & Editing **Annie Srowig:** Investigation, Writing-Review & Editing **Natan Napiórkowski:** Software **Christoph Preul:** Resources, Writing-Review & Editing **Otto W. Witte:** Resources **Kathrin Finke:** Conceptualization, Writing-Review & Editing, Supervision, Funding acquisition

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Chapter 6

General Discussion

The goal of this thesis was to systematically link phasic alerting effects on visual processing speed to underlying iFC patterns in healthy and pathological aging. The first section of the General Discussion offers an overview of the main findings and presents the conclusions drawn from these findings for each project. The second section consolidates the findings of all projects and discusses overarching implications. The third section critically evaluates methodological limitations and the fourth section outlines potential directions for future studies. A summary of the main scientific advances proposed in this thesis concludes the General Discussion.

6.1 Main findings of each project

6.1.1 Project I

In the first research project, we investigated phasic alerting effects on visual processing in healthy younger and older adults (Haupt et al., 2018). Both healthy younger (n=34) and older (n=32) participants completed a TVA-based whole report paradigm with auditory alerting cues.

First, we replicated former research in younger adults by demonstrating that their visual processing speed was, overall, higher in the cue compared to no-cue condition. In addition to the cueing manipulation, we also varied the time window between the presentation of the cue and target display, i.e. cue-target onset asynchrony (CTOA). Interestingly, the results revealed a statistically significant phasic alerting effect in the longer CTOA while there was no significant effect in the shorter CTOA. In a follow-up analysis exploring individual performance patterns in the short CTOA, we could identify two rather equally distributed subgroups: participants demonstrating cue-induced performance benefits or cue-induced performance detriments. The subgroup exhibiting decreased visual processing speed following the alerting cue in the short CTOA was characterized by significantly higher baseline processing speed than the subgroup that benefited. Accordingly, we suggested that participants with high intrinsic alertness levels are potentially over-aroused by additional phasic alerting cues resulting in detrimental effects on their performance.

Second, we investigated phasic alerting effects on visual processing speed in healthy older participants. This study for the first time demonstrated that phasic alerting cues significantly increase TVA-based estimates of visual processing speed in healthy older adults. The varying CTOAs did not significantly alter the phasic alerting effect as seen in the healthy younger group. These results demonstrated that external cues, indicating the imminent appearance of a relevant stimulus, can momentarily enhance the perceptual processing speed of healthy older participants.

Third, in order to address age group specific differences in phasic alerting effects on visual processing speed, we directly compared the performance of healthy younger and older participants. We replicated an overall reduction of visual processing speed in older compared to younger adults (Espeseth et al., 2014; Habekost et al., 2013; McAvinue et al., 2012; Ruiz-Rizzo et al., 2019). Most importantly, the analysis revealed phasic alerting effects of comparable magnitude in both age groups. This result contravened previous studies reporting significant decreases in phasic alerting effects in healthy older participants (Festa-Martino et al., 2004; Gamboz et al., 2010; Jennings et al., 2007; Zhou et al., 2011). We proposed that differences in cueing modality can account for these seemingly contradictory results. The abovementioned studies providing evidence for age-related decreases in phasic alerting used visual cues. In contrast, auditory alerting cues have been reported to elicit phasic alerting in effects in both healthy younger and older participants (He et al., 2020; Karpouzian-Rogers et al., 2019). Our results tied in with the auditory alerting studies, supporting the notion that auditory phasic alerting effects are preserved in healthy aging. However, the key difference to all former studies is that we used a TVA-based verbal whole report paradigm with auditory alerting cues to measure phasic alerting effects on a purely perceptual level. Therefore, our study suggested that auditory alerting cues do not only speed up motor responses but also increase the speed of visual processing on the perceptual level.

6.1.2 Project II

The aim of the second research project was to identify iFC patterns underlying phasic alerting effects on visual processing speed in healthy younger participants (Haupt et al., 2019). We related phasic alerting effects in the long CTOA (assessed in the previously described project I) to intra- as well as inter-network connectivity in the CON and other RSN relevant for attention or sensory processing. We used a combined group-level ICA and dual regression approach to extract individual spatial maps, representing RSN, and used them as inputs for voxel-wise multiple regressions. We controlled for influences of age, sex, education, head motion, and baseline visual processing speed by including these variables as covariates in the model. The voxel-wise multiple regressions revealed that higher visual processing speed in the auditory alerting condition was significantly associated with lower iFC in the CON. We neither identified significant behaviour-iFC relationships in other RSN nor inter-network connectivity patterns accounting for phasic alerting effects. Taken together, the results suggested that phasic alerting effects on visual processing speed in healthy younger adults are primarily associated with iFC in the CON.

The highlighted role of the CON for phasic alertness extended former findings regarding the CON's relevance for tonic alertness (Coste & Kleinschmidt, 2016; Ruiz-Rizzo et al., 2018; Sadaghiani et al., 2010; Sadaghiani & D'Esposito, 2015; Schneider et al., 2016). Coste and Kleinschmidt (2016) observed that pre-stimulus activations in brain areas forming the CON were significantly higher in fast response trials versus slow response trials. Based on this event-related analysis of speeded button presses following target appearance, the authors proposed that activity in the CON plays a decisive role for maintaining tonic alertness (Coste & Kleinschmidt, 2016). Sadaghiani and D'Esposito (2015) reported both increased activity and increased functional connectivity in the CON in conditions with high tonic alertness demands, i.e. jittered time intervals between target appearances, as compared to low demands, i.e. fixed intervals. Ruiz-Rizzo et al. (2018) demonstrated that higher TVA-based estimates of basic visual processing speed, reflecting an individual's intrinsic processing capacities, were related to lower iFC in the CON. Furthermore, spontaneous fluctuations in the CON at rest were significantly correlated with other markers of tonic alertness, such as global field power of alpha oscillations (Sadaghiani et al., 2010) and spontaneous pupil dilations (Schneider et al., 2016). Importantly, the present study gave reason to assume that the CON does not solely play an important role for tonic but also phasic alertness in healthy younger participants. Such a common network of particular importance to both tonic and phasic alertness was corroborated by a review of fMRI and PET data. Sturm and Willmes (2001) concluded that phasic and tonic alertness tasks activate identical brain areas, merely differing in the extent of these activation patterns.

To the best of our knowledge, the present study for the first time identified the CON as the primary iFC correlate of phasic alerting effects, measured as cue-induced visual processing speed increments in a TVA-based whole report paradigm, in healthy younger adults.

6.1.3 Project III

The third research project set out to determine whether phasic alertness in healthy aging can be linked to the same iFC pattern that underlies phasic alertness in younger participants or primarily relates to other RSN (Haupt et al., 2020). The two main RSN candidates were the CON and the right fronto-parietal network (rFPN). The CON played a crucial role for phasic alertness in healthy younger participants (Haupt et al., 2019) and the rFPN was proposed to be essential for the maintenance of alertness functions in healthy aging (Robertson, 2013, 2014). Following an analysis pipeline comparable to the one used in the sample of younger adults, we related individual spatial maps resulting from a combined ICA and dual regression approach to phasic alerting effects on visual processing speed, measured in a TVA-based whole report paradigm. In contrast to the results in healthy younger adults, a voxel-wise multiple regression in the CON did not yield significant associations between phasic alerting effects and iFC in healthy older participants. However, in the rFPN, higher phasic alerting effects were significantly related to lower iFC. In addition, we conducted the same analysis in auditory and visual networks as our behavioural tasks included visual stimuli and auditory cues. Higher phasic alerting effects were significantly related to lower iFC in these sensory networks. Inter-network connectivity patterns between these sensory networks and the rFPN were not significantly linked to phasic alerting effects. We proposed that our method is not sensitive enough to reflect the communication between these RSN but that, most probably, the rFPN and sensory networks are in bi-directional exchange of information. In sum, the results indicated that the rFPN plays a particular role for phasic alerting effects in healthy older adults, supporting the previously suggested importance of this network. Robertson (2014) hypothesized that the integrity and functional connectivity of right-hemispheric fronto-parietal brain structures are essential for attentional functions mediated by noradrenaline (NA), e.g. alertness. Moreover, enhancing the activity of the noradrenergic system (by using a handgrip exercise) increased the functional connectivity between the locus coeruleus (LC), the primary source of NA, and the fronto-parietal network in healthy older women (Mather et al., 2020). The present results extented these previous findings by associating inter-individual differences in the ability to utilize auditory alerting cues to increase visual processing speed with iFC in the rFPN.

Furthermore, we compared healthy older participants to the previously reported sample of healthy younger adults (Haupt et al., 2019). In the rFPN, behaviour-iFC associations did not significantly differ between age groups. The association of phasic alerting effects and iFC in the CON was significantly lower in the healthy older adults than in the younger adults. This finding tied in with a recent resting-state like fMRI study reporting reduced functional connectivity between the LC and salience network in healthy older compared to younger adults (Lee et al., 2020). Taken together, the results of the present study indicated that the rFPN plays an important role for phasic alertness in healthy aging. Further, the study provided first evidence for age group specific associations between phasic alerting effects on visual processing speed and iFC.

6.1.4 Project IV

The fourth research project explored the effect of auditory alerting cues on visual processing speed in aMCI patients. Patients completed a shortened TVA-based whole report paradigm with auditory alerting cues. We refrained from analyzing separate CTOA spectrums in order to minimize the number of trials needed to study phasic alertness in a patient population. The results in aMCI patients indicated that visual processing speed estimates are significantly higher in the cue condition than in the no-cue condition. We additionally compared aMCI patients to a previously reported sample of healthy older adults (Haupt et al., 2018) and replicated that visual processing speed is further reduced in aMCI patients (Ruiz-Rizzo et al., 2017). Importantly, auditory alerting cues significantly increased the speed of visual processing across both groups. According to a TVA extension, changes in the level of alertness proportionally increases visual processing speed if the prior probability and utility of all features is kept constant (Bundesen et al., 2015). Conversely, the relative cue-induced difference in visual processing speed reflects changes in the level of alertness. The results of the present study suggested that auditory alerting cues increase the level of alertness by approximately 16 percent in aMCI patients and 9 percent in healthy older individuals. Taken together, the present study provided evidence for preserved phasic alerting effects on visual processing speed in an early stage of pathological aging. The processing system of aMCI patients appeared to be able to flexibly adjust its capability to situational demands and mobilize additional processing capacities for important upcoming sensory inputs in response to external warning cues. We argue that this intact phasic alerting mechanism could help patients to temporarily overcome their pronounced reductions in processing speed.

6.2 Key implications across projects

6.2.1 Theory of visual attention based assessment of phasic alertness

Employing a TVA-based verbal whole report paradigm with auditory alerting cues demonstrated that auditory alerting cues increase visual processing speed in healthy younger adults, healthy older adults, and aMCI patients. Hence, the perceptual processing of all three assessed populations benefited from external auditory warning signals. The results also illustrated a step-wise decline of baseline visual processing speed across the aging spectrum, replicating previous studies (Espeseth et al., 2014; Habekost et al., 2013; McAvinue et al., 2012; Ruiz-Rizzo et al., 2019).

Overall, the presented research projects emphasize the advantages of using the TVA framework to study phasic alertness in healthy and pathological aging. First, TVA-based whole report paradigms allow for the estimation of separate attention parameters, i.e. perceptual threshold, visual short term memory capacity, and visual processing speed (Bundesen, 1990). This parameterized approach excels at detecting specific attentional deficits in aging and clinical populations (for a review on clinical TVA-bases studies see Habekost, 2015). Second, individual phasic alerting effects can be quantified by holding the prior probability and subjective importance of all features in a whole report constant and adding an alerting cue (Bundesen et al., 2015). Due to the multiplicative nature of the perceptual bias, higher alertness levels will result in a proportional increase in visual processing speed. Accordingly, the difference of visual processing speed estimates in a cue and no-cue condition reflect the individual phasic alerting effect (Bundesen et al., 2015). Third, TVA-based paradigms do not require speeded motor responses as the participants are asked to verbally report remembered letters without any time limit. Therefore, TVA-based whole report paradigms enable researchers to investigate phasic alerting effects on a purely perceptual level. This is especially beneficial when assessing populations characterized by a general slowing of motor processes. Besides, TVA-based paradigms individually adjust the exposure duration of target displays. These adjustments account for inter-individual and between-group differences in perceptual threshold and, by that, ensuring an appropriate comparison level.

6.2.2 Age group specific behaviour-iFC relationships

In the research projects forming this thesis, we wanted to investigate whether phasic alerting effects on visual processing speed are associated with spatial patterns of coherent BOLD activity, a measure also known as iFC. We employed a combined multi-subject ICA and dual regression approach as the resulting individual spatial maps allowed us to test specific hypotheses about the associations between phasic alerting effects and iFC in RSN of interest (Beckmann et al., 2009). We applied this analysis approach in both healthy younger and older participants. In healthy younger adults, phasic alerting effects were primarily linked to iFC in the CON. In healthy older adults, phasic alerting effects were principally related to iFC in the rFPN. A direct comparison of both age groups revealed that the association between phasic alertness and iFC in the CON is significantly higher in younger adults compared to older adults. These results provided first evidence for different iFC patterns underlying phasic alertness in younger and older adults. While the behavioural results indicated that phasic alerting effects on visual processing speed are preserved in healthy aging, aging individuals appeared to be characterized by a distinct underlying brain network. The projects emphasize that a combined ICA and dual regression approach provides the opportunity to link phasic alerting effects to iFC patterns. Importantly, we cannot measure intrinsic brain activity at the level of subthreshold depolarizations of neurons in the human cortex. But as the onset of slow calcium waves is specifically linked to BOLD signals (Schwalm et al., 2017), we can capture intrinsic brain activity by measuring BOLD signal fluctuations in fMRI. The established behaviour-iFC associations extend our knowledge about brain processes underlying phasic alertness in healthy younger and older adults. Moreover, the described projects illustrate that this approach could be instrumental in analyzing brain correlates of phasic alertness in aMCI patients.

6.2.3 Clinical implications

This thesis highlighted that aMCI, an early stage of Alzheimer's disease, is not only characterized by memory deficits but also by reductions in visual processing speed. Most importantly though, patients at the aMCI stage were not only characterized by a general slowing of their rate of information uptake, but their processing system also exhibited a residual plasticity allowing it to flexibly enhance visual processing speed in response to external auditory warning signals. This finding has important clinical implications.

Due to the high prevalence of Alzheimer's disease as well as the high progression rate from aMCI to AD, methods for early disease detection are needed. Computerised cognitive tests are non-invasive, comparably inexpensive, and require less time than imaging approaches. The combination of reduced visual processing speed and preserved phasic alerting effects compared to age-matched healthy older controls could serve as an additional indicator for early stages of Alzheimer's disease. We hypothesize that the conversion from the aMCI to AD stage could be accompanied by further visual processing speed reductions and the absence of phasic alerting effects. If evidence from future studies would support this hypothesis, TVA-based whole reports with auditory alerting cues could potentially also be used for monitoring disease progression.

Furthermore, the observed residual plasticity of the processing system of patients at risk for developing dementia could be targeted in intervention studies. Such interventions could benefit patients' general cognitive abilities and functional independence as processing speed is closely related to age-related declines in these domains (Ritchie et al., 2014). Previous studies reported that computerized processing speed trainings improve everyday functioning as well subjective ratings of health and quality of life in healthy older adults (Ball et al., 2007; Wolinsky et al., 2010).

6.3 Methodological considerations

This thesis tapped the full potential of combining a TVA-based whole report paradigm including auditory alerting cues with resting-state fMRI acquisition. While this approach excelled at specifying iFC patterns underlying phasic alerting effects, it also has its limitations. This section discusses the most relevant methodological considerations regarding the TVA-based assessment of phasic alerting effects and the analysis of iFC. It also addresses the limitations of a cross-sectional study design.

6.3.1 Theory of visual attention based assessment

The TVA-based assessment of visual attention functions in healthy elderly or patient populations is limited by several aspects. First, TVA-based experiments require specific test conditions. The described paradigms are conducted in a soundproof and darkened testing room with dim lighting and a computer set-up allowing for a refreshing rate of 100Hz. An experimenter is required to be present throughout the experiment in order to enter the verbally reported letters and start the next trial. Further, participants have to be seated with their chin located on a chin rest, ensuring a constant viewing distance and fixation. Accordingly, TVA-based tests cannot be used as bedside tests but require both a specific testing room and patient mobility. This renders a TVA-based assessment of phasic alertness in patients with physical impairments impossible. As more severe stages of pathological aging are also characterized by the worsening of patients' physical condition, TVA-based paradigms cannot be used to monitor attention functions in these patients. Second, a certain number of trials is needed as input to the parameter fitting procedure in order for the TVA model to yield reliable estimates. Equally high numbers of trials are needed per experimental condition of interest, limiting the number of experimental manipulations. Studies investigating the effects of continuous independent variables or independent variables with several factor levels would result in infeasible test durations. Moreover, the high number of trials required is disadvantageous when trying to shorten testing procedures as much as possible for aging and patient populations. While healthy younger participants might be able to endure long testing sessions, aging individuals who are no longer able to sit or focus for such a prolonged duration, cannot be examined with rather complex designs. Third, the TVA-based fitting procedure estimates attention parameters as summary measures that rely on participants' performance over the course of the whole experiment. TVA-based paradigms are not a straight-forward suitable approach to examine trial-to-trial variability in performance. Therefore, TVA-based paradigms do not allow for analysing time courses of phasic alerting effects on visual processing speed. For example, TVA-based paradigms do not offer the possibility to assess whether phasic alerting effects ramp up or decay differently in healthy younger adults, healthy older adults, and aMCI patients. Despite these limitations, TVA-based verbal whole report paradigms with auditory alerting cues are a suitable approach to compare visual processing speed estimates in a cue and no-cue condition. This approach, as presented in this thesis, allows quantifying phasic alerting effects on a purely perceptual level in healthy aging individuals and patients whose physical and cognitive conditions allow them to perform the task.

6.3.2 Intrinsic functional connectivity

BOLD imaging

BOLD imaging is not a direct measure of neuronal activity. However, previous studies provide consistent evidence for a direct correlation between BOLD signal responses as well as fluctuations and neuronal activity (e.g. He et al., 2008; Logothetis et al., 2001; Matsui et al., 2016; Schwalm et al., 2017).

Voxel-wise analysis approach

The dual regression we used in our analyses yields individual spatial maps which we used as the input for voxel-wise multiple regressions in order to test which specific iFC patterns were associated with phasic alerting effects in healthy younger and older participants. These individual spatial maps contain Z-scores indicating the similarity of the time course of voxel A to the time course of the whole spatial map while controlling for the influence of all other spatial maps (Smith et al., 2014b). The use of such relative values has two important implications. First, the cluster peak of a significant behaviour-iFC association does not imply that the according brain region is responsible or decisive for the associated behaviour. The analysis merely allows for the conclusion that the association between behaviour, i.e. phasic alerting effects, and iFC in this particular network is best represented in the voxels forming the significant cluster. Accordingly, this approach is not suitable when the goal of the study is to investigate brain regions which are involved in or decisive for performing a certain task. Instead, a voxel-wise analysis approach is appropriate when aiming at identifying RSN underlying a specific behavioural variable of interest, i.e. phasic alerting effects in the research projects forming this thesis. Second, we do not obtain one value that meaningfully represents iFC in a particular network when using a voxel-wise analysis approach. As a result, we can neither correlate one behavioural and one iFC score per network and participant nor directly compare behaviour-iFC relationships between networks. Considering this limitation, the results of our analyses suggest that phasic alerting effects are primarily but not exclusively associated with iFC in the CON in healthy younger adults and with iFC in the rFPN in healthy older adults.

Behaviour-iFC associations

The results of our behavioural analysis showed that auditory cues increase visual processing to a comparable extent in healthy younger and older adults. However, the analysis of resting-state fMRI data demonstrated that different iFC patterns underlie phasic alerting effects in healthy younger and older adults. It is still an open question which mechanisms can explain the reorganization of iFC patterns underlying phasic alertness in aging. Importantly, the brain reorganization processes are highly complex and healthy aging cannot be simply characterized by an overall decreased iFC. Depending on the precise network or subsystem, iFC has been reported to be constant, to increase, or to decrease with older age (e.g. Campbell et al., 2013; Zonneveld et al., 2019). The interpretation of age-related changes in behaviour-iFC associations is even more complex. For example, age-related increases in iFC could be the result of compensation for decreased iFC in other RSN or with other brain structures, age-related structural grey or white matter changes, certain neurotransmitter declines, or changes of cerebral vasculature (Ferreira & Busatto, 2013). The wide variety of potential reasons for increased iFC in a certain network emphasize that higher iFC does not, by default, imply better behavioural performance. Our age group comparison of iFC patterns underlying phasic alertness yielded that the association between phasic alerting effects and iFC in the CON is significantly lower in healthy older adults compared to healthy younger adults. However, we cannot answer the question as to why the association between phasic alerting effects and iFC in the CON is decreased in healthy aging because we did not measure other aspects of brain architecture and connectivity. Accordingly, we cannot relate iFC reductions in the CON to other brain processes but can only hypothesize that changes in iFC patterns are in complex interplay with age-related changes in neurovasculature, neurotransmitters, and grey as well as white matter changes. When discussing future directions in the subsequent section, we address age-related changes in the activity and functional connectivity of the locus coeruleus as one factor that could potentially contribute to a decreased association between iFC in the CON and phasic alerting effects in healthy aging.

6.3.3 Cross-sectional study design

Due to the cross-sectional design of our studies, we can neither assess intra-individual changes across the lifespan nor infer the directionality of associations between phasic alertness, iFC, and age groups. Longitudinal studies would allow for the investigation of intra-individual age-related changes in behaviour and iFC patterns. Such a trajectory approach could also aid in clarifying whether changes in iFC and behaviour occur simultaneously or which process sets in first. In addition, longitudinal samples could ideally reflect a continuous aging spectrum rather than discrete age groups.

6.4 Future directions

The four projects presented in this thesis pave the way for future studies extending the findings on iFC correlates underlying phasic alertness in healthy and pathological aging. Future projects could relate behaviour-iFC associations to the locus coeruleus-noradrenaline system and include AD patients.

6.4.1 Locus coeruleus-noradrenaline system

The described projects did not directly link phasic alertness or iFC patterns to the locus coeruleus-noradrenaline system. However, measures of LC activity and connectivity could aid in specifying the neuronal processes underlying alertness in healthy and pathological aging. The LC is a small nucleus located in the brain stem and the brain's main source of NA. NA regulates a variety of memory and attention processes, most notably alertness. Previous studies emphasize the importance of the LC for cognitive abilities in healthy and pathological aging (for a review see Mather & Harley, 2016). On the one hand, cognitive decline in late life is significantly correlated with neuronal density in the LC quantified in post-mortem brain autopsies (Wilson et al., 2013). On the other hand, the LC-NA system indirectly contributes to cognitive processes in healthy aging by playing a decisive role for cognitive reserve (Clewett et al., 2016; Robertson, 2013). Cognitive reserve describes inter-individual differences in cognitive processing in aging. Individuals with high cognitive reserve are considered to be able to maintain efficient levels of cognitive functioning even when faced with age-related or pathologic brain changes (Stern, 2012). Accordingly, it would be interesting to investigate whether LC integrity can account for inter-individual differences in phasic alerting effects. Are individual differences in the integrity of the LC related to individual differences in the flexibility to speed up visual processing in response to an auditory cue? Future studies are needed to answer this question. The LC does not only play an important role in healthy aging but also in the development of AD. It depicts one of the first brain regions exhibiting a tau pathology before the pathology spreads further to the transentorhinal region and, later, the whole neocortex (Braak et al., 2011). LC tau pathology already manifests in early adulthood, i.e. pretangle stage, and increases with age (Braak et al., 2011). Furthermore, post-mortem LC volume is significantly correlated with the progression of AD (Theofilas et al., 2017). In line with this finding, future studies could address the question whether LC volume is indicative of intact or absent phasic alerting effects in different stages of pathological aging.

Due to advances in neuroimaging techniques, the LC integrity cannot only be assessed post-mortem, but it can also be measured reliably using neuromelanin-sensitive MRI sequences (Clewett et al., 2016; Dahl et al., 2019; Liu et al., 2017; Sasaki et al., 2006; Shibata et al., 2006; Takahashi et al., 2015). Higher LC signal intensity is correlated with higher verbal intelligence, cognitive reserve, and memory performance in healthy older adults (Clewett et al., 2016; Dahl et al., 2019). Task-related LC activity is also directly linked to LC signal intensity (Clewett et al., 2018). Further, LC signal intensity is significantly decreased in aMCI and AD patients compared to healthy older adults (Takahashi et al., 2015). In combination with other biomarkers, in vivo LC imaging can contribute to the differential diagnosis and progress monitoring of AD (Betts et al., 2019a; Betts et al., 2019b). Taken together, this imaging method offers new insights into age- and pathology-related cognitive changes. Analysing neuromelanin-sensitive MRI sequences could, therefore, be a promising approach for relating phasic alerting effects on visual processing speed to LC signal intensity.

In addition, pupillometry provides a window into LC activity (Betts et al., 2019b; Mather & Harley, 2016). Pupil diameter covaries with continuous BOLD signal changes in the LC, measured using neuromelanin-sensitive MRI sequences, during an oddball task and at rest (Murphy et al., 2014). In younger participants, pupil dilations are also associated with spontaneous BOLD fluctuations, i.e. iFC, in the salience network (Schneider et al., 2016). According to animal models, pupillometry is a marker for fluctuations in neuronal excitability, i.e. intrinsic changes in membrane potentials (Schwalm & Jubal, 2017). These findings underline that spontaneous fluctuations of neuronal excitability, BOLD signal fluctuations, and pupil diameter fluctuations are all closely linked to the LC-NA system. Furthermore, phasic alerting effects in both healthy younger and older participants can be measured on the level of behavioural responses as well as pupillary responses (He et al., 2020). Therefore, pupillometry might be a useful tool for measuring phasic alerting effects with minimal task and response demands in healthy and pathological aging.

In sum, measures of locus coeruleus activity can aid in specifying the neuronal processes underlying alertness in healthy and pathological aging. Moreover, future studies measuring the connectivity between the LC and RSN could potentially explain the age-related changes in the associations between phasic alerting effects and iFC in the CON. A recent study analyzing resting-state-like fMRI data provides first evidence for this account. Lee et al. (2020) demonstrate that, in comparison to younger adults, healthy older adults are characterized by reduced functional connectivity between the LC and the salience network. Hence, not only iFC within and between RSN but also their functional connections with the LC might be a potential brain mechanism underlying phasic alerting effects in healthy and pathological aging. Future studies analysing age-related changes of functional connections between the LC and different RSN could potentially help in understanding why phasic alerting effects are significantly related to the CON in younger adults while they are primarily associated with the rFPN in healthy older adults.

6.4.2 Phasic alertness in AD patients

The described projects address phasic alerting effects on visual processing speed in healthy aging and aMCI patients. In order to improve our understanding regarding the trajectory of phasic alerting abilities, future studies could assess patients at different stages of AD. Future studies first have to test whether AD patients are able to complete TVA-based whole report paradigms with auditory alerting cues. If AD patients are in the position to participate in a comparable study design, future projects could investigate whether auditory alerting cues increase visual processing speed in these patients. Are progressions in pathological aging, i.e. aMCI versus AD patients, characterized by stepwise reductions of basic visual processing speed and phasic alerting effects? Overall, future research is needed to establish whether TVA-based paradigms depict a non-invasive and inexpensive tool to trace the progression of alertness deficits in Alzheimer’s disease.

6.5 Conclusion

This thesis identified systematic associations between phasic alerting effects on visual processing speed and intrinsic functional connectivity in healthy and pathological aging. We showed that auditory phasic alerting cues increase visual processing speed in younger adults, healthy aging individuals, and patients with amnestic mild cognitive impairment. In younger adults, we demonstrated that phasic alerting effects are significantly related to intrinsic functional connectivity in the cingulo-opercular network. In healthy older adults, we found that phasic alerting effects are primarily associated with intrinsic functional connectivity in the right fronto-parietal network. Overall, this thesis complements research on phasic alertness in healthy and pathological aging by reliably measuring phasic alerting effects on a perceptual level and deepening the understanding of underlying brain mechanisms. Adopting whole report paradigms based on the theory of visual attention and relating the estimated phasic alerting effects on visual processing speed to intrinsic functional connectivity patterns depicts a promising approach for investigating neuro-cognitive mechanisms of phasic alertness at different stages of pathological aging.

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