Visual Processing Speed in the Aging Brain

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LMU Munich

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Submitted by **Adriana Lucía Ruiz Rizzo**

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Abstract

Either reading a text in the office or looking for an apple in the supermarket, we are continuously flooded with visual stimuli. But how does the human brain support the efficient processing of those stimuli? And, if pathological changes occur in the brain, how do these changes lead to reductions in such efficient processing? In the present dissertation, aging is used as a model to address these two questions. First, individual differences in visual processing speed are examined in association with the coherence of the brain's spontaneous activity and how this coherence is affected by normal aging. Second, individual differences in visual processing speed are studied in association with behavior in tasks that measure complex visual object perception in patients at risk of Alzheimer's dementia and healthy aging adults. Based on these two approaches, evidence will be presented for an association of a slowed visual processing with (a) decreased coherent activity of a frontoinsular network in healthy aging and (b) simultaneous object perception deficits in patients at risk of Alzheimer's dementia. This evidence provides critical insights into the particular link between visual processing speed and the coherence of the brain's spontaneous activity and reveals perceptual deficits in patients whose clinically most apparent impairments lie in memory.

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Overview

A traffic jam with cars, buses, trams, trucks, and all types of traffic signs; a crowd of people of different backgrounds walking at a different pace to get to many places; a colorful variety of fruits and vegetables in the supermarket—All these scenes are common environments of our daily life. But how can the human brain efficiently take up the visual information from such cluttered environments? One answer points to visual attention.

Visual processing speed is a central visual attention function that represents the rate of information uptake in a given instant. A reduction in visual processing speed is one of the best-described cognitive features of normal aging. Thus, aging can be used as a model to understand how the brain supports visual processing speed and, particularly, how specific changes in the brain can lead to reductions in visual processing speed.

In this Dissertation, individual differences in visual processing speed are examined in association with the spontaneous activity of the brain as well as with behavior in tasks that measure complex visual object perception. First, to determine brain correlates of visual processing speed, we analyzed intrinsic functional connectivity and how it is affected by normal aging. Second, to determine behavioral correlates of visual processing speed, we analyzed performance in tasks of complex object perception and how it differs between pathologically aging patients—known to suffer from slowing in visual processing—and healthy aging adults.

Visual processing speed has been traditionally measured by reaction time tasks. In such tasks, button presses are given in response to the appearance of a visual stimulus or the number of correct motor responses (e.g., writing numbers) in a limited time frame (e.g., 90 seconds) is counted. However, the performance in such tasks is affected by motor speed, which inherently introduces a confounding variable in aging individuals who show motor slowing.

Perceptual measures of visual processing speed (i.e., inspection time) require, instead, visual discrimination under variable presentation times, but without response time pressure. However, in inspection time measures, the individual perceptual threshold (i.e., the minimum effective exposure duration before stimulus processing starts) does additionally contribute to performance at a given exposure duration, and cannot be separated from visual processing speed.

Bundesen's theory of visual attention (TVA) offers an exceptional framework to study visual processing speed. First, TVA allows the mathematical estimation of a visual processing speed parameter obtained from verbal report accuracy—and not from a task requiring a speeded motor response. Second, the parameter visual processing speed is obtained independently from other visual parameters of visual processing, such as, e.g., visual perceptual threshold. Therefore, here the TVA framework is used to determine visual processing speed.

We determined brain correlates of visual processing speed in two studies. The first study assessed how visual processing speed is associated with functional connectivity in general, i.e., in a normal brain system that is neither in an advanced stage of aging nor affected by disease. Intrinsic functional connectivity captures the coherence of slow fluctuations in spontaneous brain activity—which reflects fluctuations in cortical excitability, critical for visual attention and visual processing speed in particular—and yields spatial patterns that involve different regions of the brain: 'intrinsic connectivity networks.' Visual processing speed was associated with the intrinsic functional organization within a brain network that includes medial and lateral frontal, insular, and thalamic regions: the so-called 'ventral attention,' 'cingulo-opercular,' or 'salience' network.

The second study on the brain correlates of visual processing speed focused on the critical network identified in the first study, i.e., the cingulo-opercular network, to evaluate whether age-related differences in its intrinsic functional organization are associated with individual differences in visual processing speed. We assessed healthy individuals from young to advanced ages and found that a decreased connectivity within the cingulo-opercular network mediates the reduction in visual processing speed that occurs with increasing age.

To determine behavioral correlates of visual processing speed, we assessed a group of aging patients that are known to have a slowing in visual processing that goes beyond that of normally aging individuals; these are patients with amnestic mild cognitive impairment at a high risk for developing Alzheimer's dementia. These patients showed deficits in simultaneous object perception and, crucially, the degree of these deficits was associated with the severity of the visual processing speed reduction.

Collectively, the present results indicate the association of visual processing speed in the aging brain with individual differences in both intrinsic functional connectivity and the perception of overlapping objects—shown in healthy and pathological aging,

respectively. Future directions based on these findings point to the association between changes in the intrinsic functional connectivity of the cingulo-opercular network and visual processing speed in early stages of Alzheimer's disease, such as mild cognitive impairment.

1. Outline

In the beginning, I present the general and specific objectives pursued during my Ph.D. in the section **Aims**. In the **Introduction**, I develop three topics. First, I define visual attention and visual processing speed. Moreover, I explain how to measure the resting brain with functional magnetic resonance imaging, yielding the so-called intrinsic brain networks. Finally, I present the main characteristics of the aging brain and, particularly, the main changes in visual processing speed on the one hand, and in the intrinsic functional organization of the brain, on the other, that occur during aging.

The core part of this Dissertation includes three **Studies** that address specific questions aimed at determining correlates of visual processing speed at the brain and at the behavioral level. The first two studies are manuscripts currently under review, and the third one is published.

Finally, in the **Summary and discussion** section, I combine the main insights obtained from the three studies as well as the future research paths they open.

2. Abbreviations

AD	-	Alzheimer's disease
aMCI	-	Amnestic mild cognitive impairment
BOLD	-	Blood oxygenation level dependent signal
BORB	-	Birmingham object recognition battery
fMRI	-	Functional magnetic resonance imaging
ICA	-	Independent component analysis
ICN	-	Intrinsic connectivity network
iFC	-	Intrinsic functional connectivity
MCI	-	Mild cognitive impairment
MRI	-	Magnetic resonance imaging
SPT	-	Simultaneous perception task
TVA	-	Theory of visual attention
TVA-WR	-	TVA-based whole-report task
VOSP	-	Visual object and space perception battery
VSTM	-	Visual short-term memory

3. Aims

The main goal of my Ph.D. was to examine individual differences in visual processing speed in association with the spontaneous activity of the brain as well as with behavior in tasks that measure complex visual object perception.

In particular, I aimed to determine:

a. Brain correlates of visual processing speed by analyzing intrinsic functional connectivity and how it is affected by normal aging. Potential network(s) related to visual processing speed that could serve as candidates for the analyses of brain correlates of age-related differences in visual processing speed were first identified in the young normal brain.

b. Behavioral correlates of visual processing speed by analyzing performance in tasks of complex object perception and how it differs between pathologically aging patients—known to suffer from slowing in visual processing—and healthy aging adults.

4. Introduction

4.1. Visual processing speed

4.1.1. Visual processing speed as a visual attention function

4.1.1.1. Definition of visual attention

Our visual world encompasses complex and rich environments; it is a crowded place full of visual stimuli, in which survival might depend on having the ability to apprehend information quickly. Visual attention is a neural and psychological phenomenon that can be operationalized and, consequently, scientifically approached. Visual attention has been defined as the neural property that allows the resolution of a competition among objects in the visual field through attentional selection (i.e., biased competition model; Desimone and Duncan 1995). Specifically, object features are coarsely coded into the neurons' visual receptive fields. Visual receptive fields increase in size along the ventral stream from posterior to anterior areas, including more objects at each successive level of the visual hierarchy. Therefore, the neural resources for processing become limited and, thus, individual objects must compete for them (Desimone and Duncan 1995). The theory of visual attention (TVA), proposed by Claus Bundesen in (1990), is a formalization of this so-called biased competition. TVA proposes a set of mathematical equations that permit the independent estimation of visual attention parameters (Bundesen 1990), with which we can reliably test hypotheses on biological or psychological phenomena.

4.1.1.2. Definition of visual processing speed

Visual attention represents a bias that can be oriented either to objects (i.e., visual pertinence or 'filtering') or features (i.e., visual bias or 'pigeonholing') (Bundesen, Vangkilde, and Petersen 2015). The 'pigeonholing' mechanism is purely feature-based, but also complementary to the 'filtering' mechanism, which, in turn, refers to the likelihood of perceiving and selecting the objects of a certain category—without affecting their belongingness as members of a particular category (Bundesen 1990). In particular, the 'pigeonholing' mechanism is the one that determines a visual processing speed capacity C at the individual level (Bundesen 1990).

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In neural terms, 'pigeonholing' represents a multiplicative scaling of the level of activation of the neurons that code for specific features in the visual system (Bundesen, Habekost, and Kyllingsbaek 2005). Such level indicates an increase in the firing rate (i.e., spikes per second) above the baseline rate of a neuron (Bundesen et al., 2005). Although the 'pigeonholing' mechanism affects the level of activation of feature-specific neurons within the visual system, it has been proposed to derive from frontal, parietal, or limbic areas (Bundesen et al., 2005).

Based on the conditional probabilities of making perceptual categorizations (i.e., 'pigeonholing'), visual processing speed C represents an individual capacity measure of the rate at which visual categorizations are encoded into visual short-term memory (VSTM) (Bundesen et al., 2005). Thus, visual processing speed C is operationalized as the number of letters that can be encoded in VSTM per second (Bundesen 1990).

4.1.2. Assessment and modeling of visual processing speed

The visual processing speed parameter of a subject can be estimated from report accuracy in a whole report task, where an array of unrelated letters is presented under variable exposure durations (Figure 1). Both masked and unmasked displays are used. In this task, subjects must report all letters seen, with a reasonable degree of certainty (i.e., not guessing).
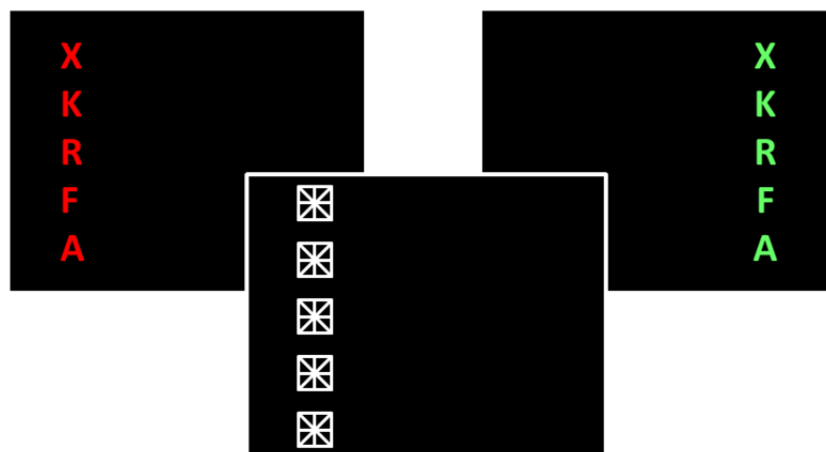
Figure 1. Example of a whole report task. An array of letters is briefly presented under different exposure durations. Some but not all trials are followed by post-display masks (see text). Participants must report all letters they are reasonably sure to have seen. Visual processing speed can be estimated from report accuracy across different exposure duration conditions. This image was created with illustrative purposes and does not reflect the paradigm used in the studies presented in this Dissertation.

According to TVA, the probability of correctly reporting a letter increases exponentially with longer exposure durations (Bundesen 1990). Correspondingly, the participant's report accuracy is modeled as an exponential growth function of the effective exposure duration, by a maximum-likelihood fitting algorithm (Figure 2) (Bundesen 1990; Dyrholm, Kyllingsbaek, Espeseth et al., 2011; Kyllingsbaek 2006). Three main parameters determine this function and the shape of its curve. First, the visual threshold for conscious perception $t0$ sets the start of visual processing and shifts its exponential distribution (Kyllingsbaek 2006). Second, the slope of the curve at $t0$ or parameter C indicates the rate of visual information uptake in a specific unit of time (i.e., letters encoded in VSTM per second). The third parameter, K, is the asymptote of the exponential function and illustrates the maximum number of elements that can be simultaneously represented in VSTM.

Reliable and valid TVA parameter fitting is given by the variability of effective exposure durations. Thus, both masked and unmasked trials (i.e., with and without post-display masks) are used in the whole report task. Unmasked trials, in particular, allow the additional component of iconic memory buffering (Sperling 1960). Accordingly, a parameter representing the effective exposure prolongation due to the visual after-image persistence (Sperling 1960) in unmasked trials, or parameter μ, is also estimated (in milliseconds). However, as μ only serves for the accurate estimation of the other, relevant parameters, this is not further considered.
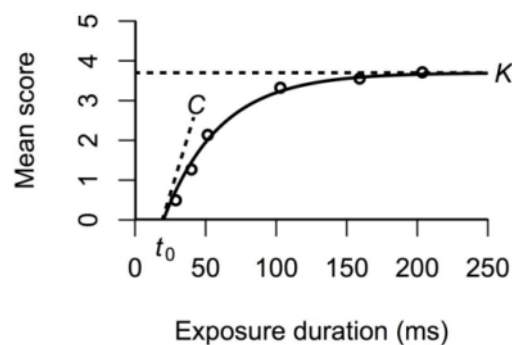
Figure 2. Illustration of the exponential growth function in TVA. Using the theory of visual attention (TVA), an individual participant's report accuracy in a whole report task (Figure 1) can be modeled as a function of exposure duration. Parameter $t0$ is the estimated visual perceptual threshold, parameter C or processing speed is the slope of the curve at x = t0, and parameter K or VSTM storage capacity is the asymptote of the curve. Figure taken from Asgeirsson, Nordfang, and Sorensen (2015). Licensed under CC BY 4.0.

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Theoretically, three factors can act in a multiplicative fashion to change visual processing speed C. These factors are (a) the probability of stimulus presentation, (b) the pertinence or relevance of the presented stimuli, and (c) the general level of alertness (Bundesen et al., 2015). In agreement with this proposal, empirical evidence has shown that C values linearly increase with the hazard rate (i.e., the conditional probability density) of the stimulus presentation (Vangkilde, Petersen, and Bundesen 2013). The increase in the hazard rate builds up the temporal expectation, and this, in turn, enhances the general level of alertness (Matthias, Bublak, Muller et al., 2010; Vangkilde et al., 2013). Moreover, exogenous increases in the degree of alertness through visual or auditory stimuli (i.e., phasic alertness) produce a direct positive, dose-dependent effect in visual processing speed C (Petersen, Petersen, Bundesen et al., 2017). Similarly, a pharmacological enhancement of tonic alertness with a single dose of psychostimulants has also shown to increase visual processing speed C up to a 30% in healthy young participants with relatively low baseline C (i.e., below the group median) (Finke, Dodds, Bublak et al., 2010). Thus, alertness has a major influence on visual processing speed.

4.1.3. Visual processing speed in the brain

Based on an individual difference approach, previous studies have investigated how visual processing speed is represented in the structure of the young healthy brain. For example, one study analyzed whether structural variability in specific frontoparietal and fronto-occipital white matter tracts mediates individual differences in visual processing speed (Chechlacz, Gillebert, Vangkilde et al., 2015). This study found that higher visual processing speed C is associated with stronger rightward asymmetry of the inferior fronto-occipital fasciculus (Chechlacz et al., 2015). Similarly, another study reported a significant association between visual processing speed C and the fractional anisotropy—a gross measure of microstructural white matter integrity—of the genu and body of the corpus callosum (Espeseth, Vangkilde, Petersen et al., 2014). Thus, these findings underscore the relevance of anterior areas, but also of their connectivity with posterior brain areas, for visual processing speed.

The association between the brain's electrical activity and visual processing speed has also been investigated in healthy young adults. In particular, neural correlates of visual processing speed have also been searched for in the temporal evolution of the brain's activity. Quantitative differences have been shown in event-related potentials

(ERP) derived from the electroencephalographic activity. Specifically, when healthy young participants are split according to their relatively high or relatively low visual processing speed, differences can be observed in the amplitude of the N1 ERP component – a negative-going component that peaks around 150-200 milliseconds post-stimulus (Wiegand, Tollner, Habekost et al., 2014).

4.1.4. Summary and knowledge gap

To sum up, visual processing speed is an individual measure of the efficiency for making perceptual categorizations. Using TVA, the visual processing speed C parameter can be estimated mathematically independently from the visual perceptual threshold, short-term memory storage capacity, or motor speed. One direct influence on visual processing speed comes from alertness, as shown by the effects of temporal expectation, exogenous stimulation, and psychostimulant medication. Finally, the neural substrates of visual processing speed have been studied using an individual differences approach, whereby the brain's white matter integrity and electroencephalographic activity have been shown relevant. However, **it has not been investigated yet whether and how visual processing speed is represented in the functional organization, i.e., in the intrinsic functional connectivity, of the healthy brain.**

4.2. The resting human brain

4.2.1. Visual processing speed in the resting brain

'Pigeonholing' (i.e., selection of categories) represents a multiplicative scaling of the level of activation of feature-specific neurons and determines visual processing speed C (Bundesen et al., 2005). Notably, fluctuations in the level of activation of cortical neurons occur *spontaneously* and continuously (Wu, Xiaoying, and Chuan 2008) and slowly propagate throughout the cortex by a nonlinear amplification of single neurons and an activity-dependent adaptation (Sanchez-Vives, Massimini, and Mattia 2017).

Co-activation of neuronal spiking activity (i.e., calcium signals) among particular cortical areas occur at different moments of slow "global propagating calcium waves" during light anesthesia in mice (Matsui, Murakami, and Ohki 2016). Such spontaneous co-activation, which starts at a local level, forms spatial patterns of neural activity at a whole-brain level.

Whole-brain spatial patterns of neural activity can be observed using resting-state hemodynamics (i.e., based on the dynamics of the blood flow in the blood vessels). These hemodynamic-based patterns spatiotemporally match those resulting from the spontaneous fluctuations in excitatory neural activity (Ma, Shaik, Kozberg et al., 2016; Matsui et al., 2016) and can even be predicted from local calcium events during slow wave activity (Schwalm, Schmid, Wachsmuth et al., 2017).

If resting-state hemodynamic-based co-activation among cortical areas does closely reflect the co-activation based on excitatory neural activity, we can reliably measure the hemodynamic-based co-activation in the human resting brain to understand visual processing speed at a neural level. Moreover, if the level of activation of cortical neurons fluctuates continuously forming whole-brain spatial patterns and, at the same time, determines an individual processing speed capacity C, we can test whether the degree of coherence in the spatial patterns relates to the level of visual processing speed of an individual. To measure the hemodynamic-based co-activation and the degree of coherence in the whole-brain spatial patterns, we can use the blood oxygenation level-dependent signal during functional magnetic resonance imaging and the analysis of the intrinsic functional connectivity (Figure 3).
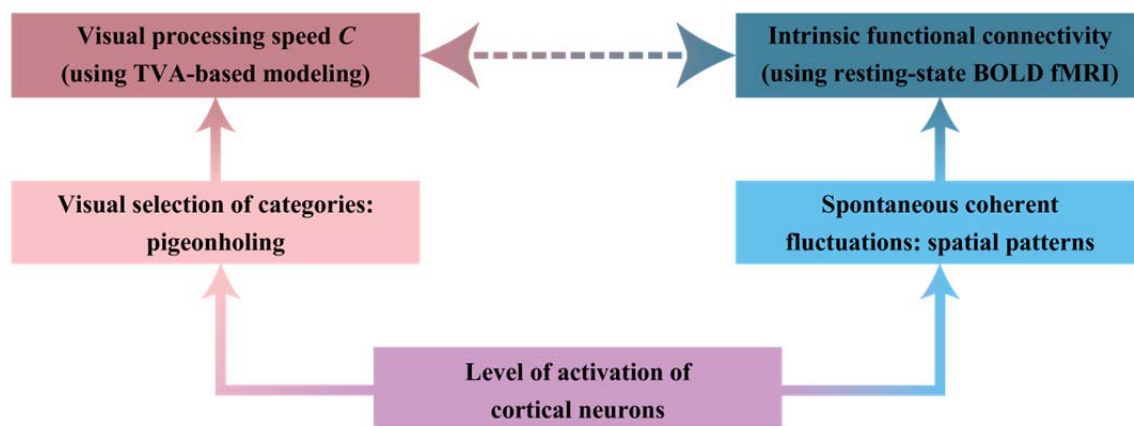
Figure 3. Rationale for studying visual processing speed in the resting brain. The level of activation of cortical neurons fluctuates continuously, which forms whole-brain spatial patterns that can be captured by analyzing intrinsic functional connectivity in the resting human brain using functional magnetic resonance imaging, fMRI (purple-blue track). Visual category selection (or 'pigeonholing') is represented by a multiplicative scaling of the level of activation of cortical neurons coding for a particular visual feature, thus determining the visual processing speed C capacity of an individual (purple-rose track). Therefore, we can test whether the degree of coherence in the spatial patterns (i.e., intrinsic functional connectivity) relates to the level of visual processing speed of an individual.

4.2.2. Intrinsic functional connectivity

4.2.2.1. The blood oxygenation level-dependent (BOLD) signal

With the help of positron emission tomography, it was revealed that induced increases in the neural activity of the normal human brain are accompanied by an escalation in regional blood flow, but not by a comparable increment in oxygen consumption (e.g., Blomqvist, Seitz, Sjogren et al., 1994; Fox, Raichle, Mintun et al., 1988) (Raichle and Mintun 2006). Such increase in regional blood flow is achieved through the so-called neurovascular coupling or the close interaction among the brain blood vessels, neurons, and glia (Girouard and Iadecola 2006; Hall, Howarth, Kurth-Nelson et al., 2016). Thus, given that all the oxygen brought (through the arteries) up to the brain tissue is not consumed—despite the increase in neuronal and metabolic activity—the 'level of blood oxygenation' in veins and capillaries will consequently be relatively heightened (Kim and Ogawa 2012; Raichle and Mintun 2006).

The blood 'level of oxygenation' indicates the relative addition of oxygen to hemoglobin, a protein in the red blood cells, and further determines hemoglobin's magnetic properties (Pauling and Coryell 1936). For example, the hemoglobin that carries

oxygen (i.e., oxygenated hemoglobin) is diamagnetic, whereas the hemoglobin that has delivered oxygen (i.e., deoxygenated hemoglobin) becomes paramagnetic owing to the oxygen-free iron ion. Being paramagnetic (i.e., with higher magnetic susceptibility) means that deoxygenated hemoglobin can disrupt a magnetic field (Pauling and Coryell 1936). Consequently, a local increase of oxygenated-to-deoxygenated hemoglobin ratio enhances the local signal that can be measured with magnetic resonance imaging (MRI) (Ogawa, Lee, Kay et al., 1990). This endogenously generated contrast was, therefore, named the blood oxygenation level-dependent, BOLD signal (Ogawa et al., 1990) (Figure 4).
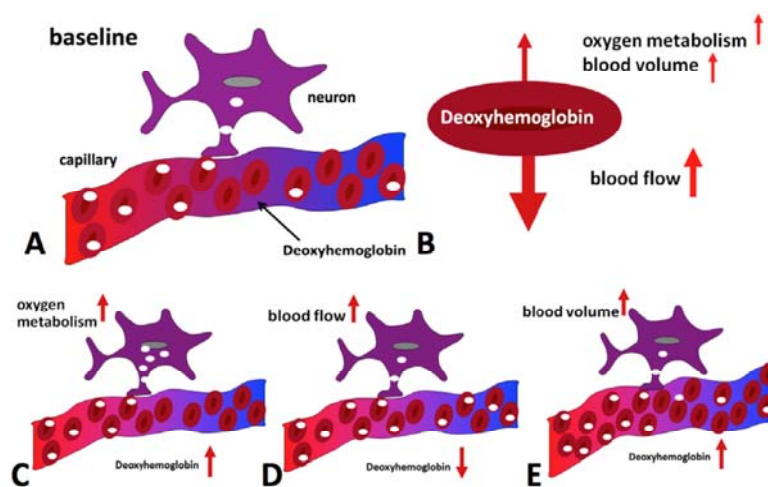
Figure 4. Origin of the "BOLD" signal. (A) During baseline, the amounts of deoxyhemoglobin and oxyhemoglobin are relatively similar, as shown in this schematic capillary. (B) When there is neural activity, the net level of deoxyhemoglobin is decreased due to increases in (C) oxygen metabolism, and blood (D) flow and (E) volume. The decreased deoxyhemoglobin (which distorts a magnetic field) relative to the increased oxyhemoglobin after neural activity creates an endogenous contrast, known as BOLD. Figure taken from Barth and Poser (2011). Licensed under CC BY 3.0.

The BOLD signal is, thus, based on the hemodynamic response to neural activity, and its response function is determined by changes in the cerebral blood flow, the cerebral metabolic oxygen rate, and the venous cerebral blood volume (Kim and Ogawa 2012). The BOLD signal has been proposed to arise from signaling processes mediated by both glutamate, locally, and amine and cholinergic neural systems, globally (Attwell and Iadecola 2002). The hemodynamic response has been shown to correlate with local field potentials; that is, with synaptic (input) rather than spiking (output) activity, which probably reflects the incoming input and local processing in a given area (Logothetis, Pauls, Augath et al., 2001).

4.2.2.2. Definition of intrinsic functional connectivity

Spontaneous fluctuations in the BOLD signal intensities measured with functional MRI (fMRI) (Figure 5) were initially regarded as noise in task-response studies (Fox and Raichle 2007). Therefore, the contribution of 'noise' was reduced through signal averaging (Fox and Raichle 2007). BOLD fluctuations are considered spontaneous because they occur during behavioral rest—i.e., where participants are not given any stimulus, or in which they are asked to refrain as much as possible from any cognitive, language, or motor response (Biswal, Yetkin, Haughton et al., 1995).
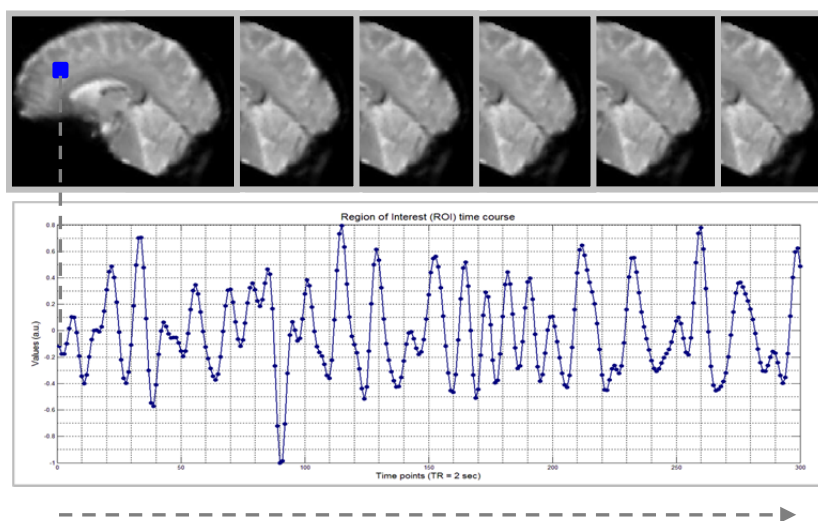
Figure 5. Example of the spontaneous fluctuations in the BOLD signal. BOLD signal intensity values are plotted as a function of time (600 seconds) with a sampling rate of 0.5 Hz (lower image), for a random voxel (blue square) in a T2*-weighted image of a human brain (upper image). This spatial information (i.e., brain voxels) across time, during resting, is the basis for intrinsic functional connectivity analysis. This image represents real data of a pilot participant and the time course of one random voxel.

Functional connectivity is defined as the *temporal correlation* of a neurophysiological index measured from different regions of the brain (Friston, Frith, Liddle et al., 1993; Friston 1994). In a pioneer study, the BOLD spontaneous fluctuations, given at a low frequency (0.01 - 0.1 Hz), were shown to correlate exclusively between left and right motor cortices when one or the other was used as a reference region (Biswal et al., 1995). Strikingly, the spatial map generated by such correlation resembled that of BOLD fMRI activation during a bilateral finger-tapping task, thus suggesting the presence of "functional connectivity" also during rest (Biswal et al., 1995).

There is an important distinction between 'activation' and 'connectivity.' During echo planar imaging (i.e., BOLD fMRI), brain volumes are rapidly acquired (e.g., every 2

seconds) to obtain spatial information on BOLD signal intensity changes throughout the entire brain (Cordes, Haughton, Arfanakis et al., 2000). In conventional task-related fMRI, such spatial information is used to study the increase in blood flow temporally locked to a stimulus or task (i.e., regional 'activation') (Cordes et al., 2000). In contrast, in functional connectivity fMRI, such spatial information allows examining spatial patterns that are based on the synchronicity of the fluctuations in the signal along time (i.e., 'connectivity') (Cordes et al., 2000). In the case of functional connectivity, moreover, the term 'intrinsic' is added because, during rest, the coherence of BOLD reveals different groups of brain regions that show 'positive' or 'negative' activation in task-related contexts (Fox, Snyder, Vincent et al., 2005).

Intrinsic functional connectivity (iFC) has repeatedly been shown in regions relevant for motor function, visual and auditory processing, executive functioning, memory (including the so-called default mode), and attention (a simplified description can be seen in the Table, and a further elaboration will be presented in the *section 4.2.3*) (Allen, Erhardt, Damaraju et al., 2011; Cordes et al., 2000; Damoiseaux, Rombouts, Barkhof et al., 2006; De Luca, Beckmann, De Stefano et al., 2006; Beckmann, DeLuca, Devlin et al., 2005; Smith, Fox, Miller et al., 2009; van den Heuvel and Hulshoff Pol 2010; Yeo, Krienen, Sepulcre et al., 2011). Although such a partition suggests a distinctive functional organization of the brain, it does not directly imply that those 'systems' are disconnected (Damoiseaux et al., 2006). Instead, a distinctive functional organization of the brain indicates a primary mode of interaction among specific brain regions (De Luca et al., 2006) that, in the face of a stimulus or a task, tend to work together (Laird, Fox, Eickhoff et al., 2011; Smith et al., 2009).

Table. Functional systems of the human brain obtained from intrinsic functional connectivity (iFC)

Systems	Brain regions typically included	First studies reporting these systems
"Motor"	Precentral gyri: motor cortex	Biswal et al., (1995)
"Sensorimotor"	Pre and postcentral gyri	Cordes et al., (2000)
"Auditory"	Primary and association auditory cortices in the superior temporal lobe	Cordes et al., (2000)
"Default mode"	Prefrontal, anterior and posterior cingulate cortices, superior parietal	Greicius, Krasnow, Reiss et al., (2003)
"Task-positive	Regions of the "dorsal attention" (Corbetta and	Fox et al., (2005)

network"	Shulman 2002) and dorsal-lateral and ventral prefrontal regions, insula, and supplementary motor area	
"Task-negative network"	Regions of the "default system" and cerebellum	Fox et al., (2005)
"Visual cortical"	Calcarine sulci, lingual gyri, occipitotemporal junction	Beckmann et al., (2005)
"Executive control"	Superior and middle prefrontal cortices, anterior cingulate and paracingulate gyri, ventrolateral prefrontal cortex, and thalamus	Beckmann et al., (2005)
"Dorsal attention"	Intraparietal sulcus, frontal eye fields	Fox, Corbetta, Snyder et al., (2006)
"Ventral attention"	Temporoparietal junction, ventral frontal cortex	Fox, Corbetta, et al., (2006)
"Lateralized components"	Respectively, left and right middle frontal and orbital, superior parietal, middle temporal gyrus, and posterior cingulate	Damoiseaux et al., (2006)
"Frontoparietal"	Dorsolateral prefrontal cortex, intraparietal sulcus, inferior parietal lobule, precuneus	Dosenbach, Fair, Miezin et al., (2007)
"Cingulo-opercular"	Dorsal anterior cingulate cortex, anterior insular, thalamus, frontal operculum, medial superior frontal cortex	Dosenbach et al., (2007)
"Salience network"	Anterior insula, dorsal anterior cingulate/paracingulate cortex, superior temporal lobe, dorsolateral prefrontal cortex, supplementary motor area, and frontal, temporal, and parietal opercula	Seeley, Menon, Schatzberg et al., (2007)
"Executive-control network"	Bilateral dorsolateral, ventrolateral, and dorsomedial prefrontal cortex, and lateral parietal cortices	Seeley et al., (2007)
"Frontoparietal control"	Lateral frontopolar, anterior prefrontal, dorsolateral prefrontal, anterior cingulate, and medial frontal cortices, lateral cerebellum, anterior insula, caudate, and anterior inferior parietal lobule.	Vincent, Kahn, Snyder et al., (2008)

4.2.2.3. Independent component analysis

Independent component analysis (ICA) is a method widely used to examine fMRI BOLD data. ICA is an iterative unsupervised neural-network learning algorithm (Bell and Sejnowski 1995) that performs blind separation of input data (McKeown, Makeig, Brown et al., 1998). More specifically, ICA models the signal observed at a given voxel as the sum of the contributions of latent independent components and Gaussian noise (Beckmann and Smith 2004).

ICA is based on three main assumptions: spatial sparsity, statistical independence, and linear summation. First, each component map, specified by a spatial distribution of values in each voxel, represents multifocal brain areas that share BOLD signal influence. Second, the components' distributions are spatially independent. Third, the observed BOLD signals are presumed to result from the linear sum of the individual components' contributions in each voxel (McKeown et al., 1998).

Each independent component has a particular spatial distribution of voxel values and an associated time course, and the number of components used to model the signal can be up to the number of time points in the data (i.e., fMRI volumes) (McKeown et al., 1998). At a first stage, a probabilistic component analysis is employed to find an appropriate linear subspace that contains the sources. At a second stage, the source signals (i.e., independent components) are estimated within the subspace obtained from the first stage using a fixed-point iteration scheme (Hyvarinen 1999). Finally, based on the estimated standard error of the residual noise, the extracted spatial maps are converted into Z-maps and assessed for significantly modulated voxels with a Gaussian Mixture Model for the distribution of intensity values (Beckmann and Smith 2004).

ICA can be performed in group resting-state data (see below). Group ICA is achieved by concatenating the data matrix (3D x time point) of each subject's dataset, one on top of each other. Subjects' functional data need to be co-registered into a standard space (e.g., with the help of their high-resolution anatomical images and a canonical template) and temporally normalized by estimated voxel-wise noise covariances (Beckmann and Smith 2005). Group independent component maps and their associated time courses are thereby obtained. However, an additional step is still needed to provide 'individual versions' of those group maps that allow performing group-level statistical analyses. This step is called 'dual regression.'

4.2.2.4. Dual-regression approach

For group-level analyses, data are temporally concatenated into one single large dataset (as mentioned above) (Beckmann et al., 2005; Calhoun, Adali, Pearlson et al., 2001). This method is referred to as 'temporal concatenation group ICA.' The independent components generated in the group ICA are the input for the dual-regression approach (Filippini, MacIntosh, Hough et al., 2009; Beckmann, Mackay, Filippini et al., 2009; Zuo, Kelly, Adelstein et al., 2010).

The dual-regression approach works in two stages: a spatial and a temporal regression (Zuo et al., 2010; Beckmann et al., 2009; Filippini et al., 2009; Smith, Utevsky, Bland et al., 2014). First, in the spatial regression, the un-thresholded independent components are used as predictors of the individual, preprocessed 4D datasets (i.e., 3D spatial dimensions across time or fMRI volumes). The spatial regression results in a time-point by number of components matrix, which contains the regression weights (i.e., beta coefficients) that characterize, in each subject, the temporal dynamics (i.e., time series) of each independent component. Next, in the temporal regression, the resulting matrix of temporal dynamics is used as a predictor, again, of the individual 4D datasets. The result of this spatial regression, for each individual, is a matrix of beta coefficients for each voxel and within each independent component. Importantly, dual regression characterizes the temporal and spatial dynamics of each component at the subject level, while also controlling for the influence of the remaining components (Smith et al., 2014).

Remarkably for the study of brain-behavior relationships, we can use the results of the temporal regression (i.e., individual spatial maps) to test hypotheses on the iFC within a specific network, and those of the spatial regression (i.e., individual time courses) to investigate iFC between particular networks.

Finally, the temporal concatenation group ICA and dual regression approaches have shown moderate to high short- and long-term test-retest reliability, thus representing an effective tool for the investigation of the resting brain and its functionally interconnected regions (Zuo et al., 2010).

4.2.3. Intrinsic connectivity networks

The analysis of the resting brain based on iFC – be it with ICA or with other analysis methods such as seed-based or graph-theory – yields robust spatial patterns that

reveal 'networks' of functional significance (Beckmann et al., 2005; Biswal, Mennes, Zuo et al., 2010; Yeo et al., 2011). The term 'network' suggests a gradual clustering, rather than a clear-cut set, of brain regions with a similar profile of activity (Sadaghiani, Hesselmann, Friston et al., 2010). Coherent spatial patterns have been shown in both primary sensory (e.g., visual, auditory, and somatomotor) and association (e.g., dorsal attention, default and executive control) regions (Allen et al., 2011; Beckmann et al., 2005; Smith et al., 2009; Yeo et al., 2011) (Figure 6). These patterns constitute the so-called intrinsic connectivity networks (ICNs) or 'resting-state networks.' ICNs may describe direct corticocortical axonal pathways, indirect polysynaptic connections, or shared feed-forward projections among cortical, subcortical, and cerebellar structures (Allen et al., 2011).
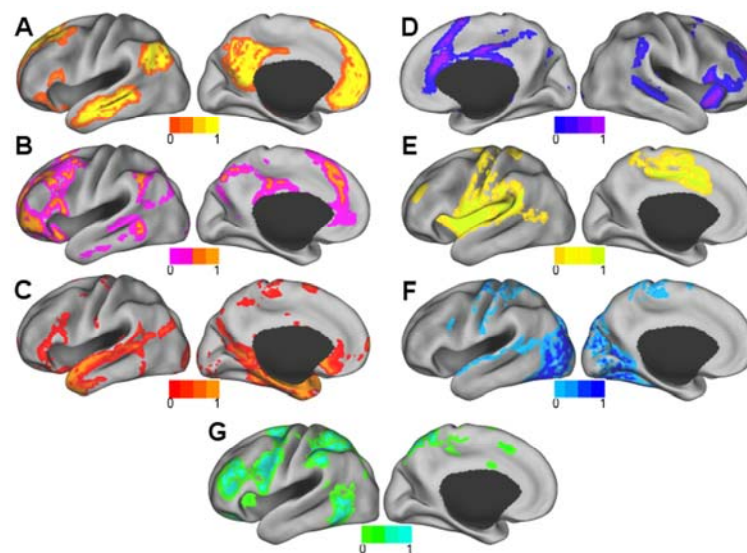
Figure 6. Canonical intrinsic connectivity networks in the human brain. These (and other) spatially defined networks emerge from the analysis of the spontaneous fluctuations of the BOLD signal during resting-state fMRI. Table 1 also shows examples of naming and regions comprised in these networks. (A-G) The default mode, frontoparietal control, language, ventral attention, sensorimotor, visual, and dorsal attention networks are shown. Figure taken from Lee, Hacker, Snyder et al., (2012). © 2012 Lee et al. Creative Commons Attribution License.

ICNs are highly consistent across species (Vincent, Patel, Fox et al., 2007), individuals (Beckmann et al., 2005; Damoiseaux et al., 2006), scanning sessions (Shehzad, Kelly, Reiss et al., 2009), development (Doria, Beckmann, Arichi et al., 2010), and states of consciousness such as sleep (Fukunaga, Horovitz, van Gelderen et al., 2006; Larson-Prior, Zempel, Nolan et al., 2009), anesthesia (Martuzzi, Ramani, Qiu et al., 2010), or active cognition (Smith et al., 2009). Moreover, ICNs reflect underlying

structural connectivity (Hagmann, Cammoun, Gigandet et al., 2008; Honey, Sporns, Cammoun et al., 2009; Segall, Allen, Jung et al., 2012). Critical for brain-behavior relationships, ICNs can predict how constituent brain regions will respond (Fox, Snyder, Zacks et al., 2006; Mennes, Kelly, Zuo et al., 2010) to a task and how an individual will perform (Fox, Snyder, Vincent et al., 2007) the task (Fox and Raichle 2007).

Although ICNs are given at a long-range, global scale, it is also acknowledged that multiple spatial and temporal scales of iFC are concurrently present in the brain and that ICNs indicate the integration of the information processing that occurs at more local levels (i.e., efficient topology) (Sadaghiani and Kleinschmidt 2013; van den Heuvel and Hulshoff Pol 2010).

4.2.4. Summary and knowledge gap

To sum up, the resting human brain can be assessed non-invasively with fMRI by measuring the relative changes in the blood oxygenation level or BOLD signal. When the coherence of this signal's spontaneous fluctuations is analyzed throughout the whole brain, an indicator of intrinsic functional connectivity can be obtained. Already for 20 years, studies have repeatedly and consistently shown that intrinsic functional connectivity occurs in sensory, motor, and association cortices, as well as subcortical regions, thus forming the so-called intrinsic connectivity networks. These networks constitute spatial patterns that can be predicted from the spontaneous fluctuations in the excitability of cortical neurons—as shown by studies in mice—, which could also influence visual attention functions and visual processing speed in particular.

Cognitively meaningful changes in the functional connectivity within intrinsic connectivity networks have been reported to occur during healthy aging. However, **it is not yet clear to what extent these changes in functional connectivity are associated with those in visual processing speed**.

4.3. The aging human brain

4.3.1. The aging brain during rest

4.3.1.1. Differences and changes in the aging brain

The differences (i.e., cross-sectional) or changes (i.e., longitudinal) in the human brain occurring with aging can be influenced by person-specific and environmental negative and positive factors (Lindenberger 2014) that occur along the entire lifespan (Raz and Rodrigue 2006). Therefore, the course and shape of these changes are best appreciated as a range of life 'trajectories' (Lindenberger 2014). Hypertension, metabolic markers (e.g., homocysteine level), cardiovascular risk, stress, aerobic fitness, or experience-dependent cognitive plasticity are factors that can modify the particular trajectory of the aging brain (Lindenberger 2014; Raz and Rodrigue 2006).

Increasing age has been associated with decreasing global gray matter volume (Good, Johnsrude, Ashburner et al., 2001) (Figure 7), density (Sowell, Peterson, Thompson et al., 2003), and thickness (Salat, Buckner, Snyder et al., 2004), and total cortical surface in both hemispheres (Salat et al., 2004). More specifically, gray matter volume loss has been reported in the central sulci, insula (Peelle, Cusack, and Henson 2012), superior parietal gyri, and cingulate sulci bilaterally, with a relative sparing of thalami, amygdalae, and hippocampi (Good et al., 2001). Cortical thinning has also been described for association cortices (e.g., inferior lateral frontal cortex), with a relative sparing of regions within the temporal lobe (Salat et al., 2004).

When examined from childhood, nonlinear effects of aging are observed in the gray matter density of dorsal areas of the frontal and parietal regions, both on lateral and medial surfaces and in the orbitofrontal cortex (Sowell et al., 2003). In particular, between the ages of 7 and 60 years, the loss of gray matter density in the superior frontal sulcus is of approximately 32%, but only of 5% between the ages of 40 and 87 years (Sowell et al., 2003). The respective values for the superior temporal sulcus are 12% (between 7 and 60 years old) and 24% (between 40 and 87 years old) decline (Sowell et al., 2003). Thus, this evidence collectively suggests a gray matter reduction that is more prominent in parietal and frontal regions, whereas the reduction in posterior temporal and primary cortices is relatively delayed or spared. Remarkably, this regional-specific reduction has been linked to poorer performance in cognitive domains that these regions

are thought to support; e.g., frontal volume has been associated with executive functions, and hippocampal volume with spatial memory (Raz and Rodrigue 2006). A regional-specific increase, in turn, has been related to protective factors that enhance cognitive reserve (such as higher education attainment) (Arenaza-Urquijo, Landeau, La Joie et al., 2013).
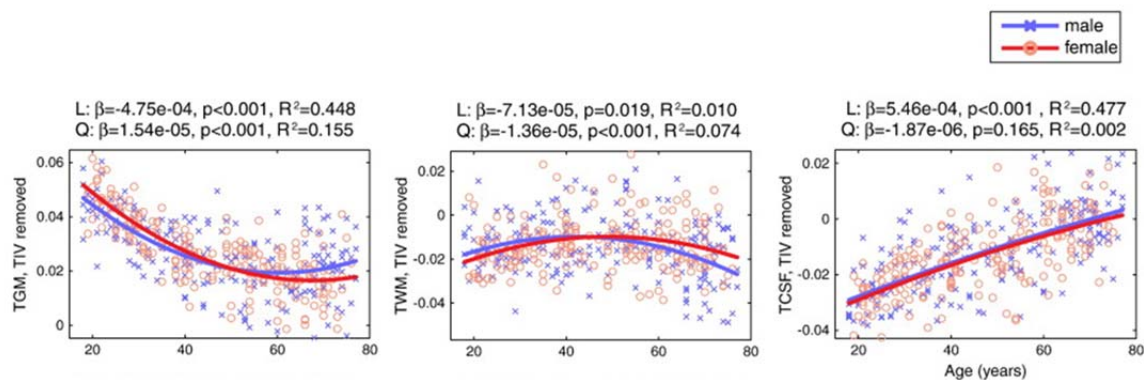
Figure 7. Differences in volume across age controlling for total intracranial volume (TIV). Total gray matter (TGM), white matter (TWM), and cerebrospinal fluid (TCSF) volumes as a function of age in a sample of 420 adults. Figure from Peelle et al., (2012). Only the right panel is reproduced from the original figure, further modified from vertical to horizontal arrangement. Licensed under CC BY 3.0.

The total volume of white matter was reported to increase with age until it reaches its peak in the mid-forties from where it starts to decrease (Sowell et al., 2003). However, global volumes of the white matter of the oldest are similar to those of the youngest (Sowell et al., 2003), which indicates no significant *global* decreases of white matter volume with age (Good et al., 2001) (Figure 7). In contrast, relative decreases of the white matter volume have been observed *locally* in the optic radiations, frontal white matter, and posterior limbs of internal capsule bilaterally, and areas of relative preservation in the posterior frontal lobes, cerebellum, and right temporal lobe (Good et al., 2001). Similarly, age effects on white matter microstructure (i.e., fractional anisotropy and mean diffusivity measures of white matter) have been reported in fibers such as the corpus callosum, corona radiata, cingulum, and superior longitudinal fasciculus (Espeseth et al., 2014).

A positive linear relationship between age and the volume of cerebrospinal fluid has been consistently reported (Sowell et al., 2003; Good et al., 2001; Raz and Rodrigue 2006) (Figure 7). The increase of cerebrospinal fluid includes its entire compartment in the ventricles and surface sulci, such as chiasmatic and supra cerebellar cisterns, cisterna magna, third ventricle, and the Sylvian and interhemispheric fissures (Good et al., 2001).

Given that aging is in itself a risk factor for diseases like Alzheimer's, Parkinson's, diabetes, hypertension, and arteriosclerosis, most elderly adults might experience some form of age-related neural pathology (Hedden and Gabrieli 2004). In particular, elderly adults with higher global amyloid burden—a pathological hallmark of Alzheimer's disease (see section 4.3.2)—but who are cognitively normal show gray matter reduction in frontal and parietal regions (Oh, Habeck, Madison et al., 2014). However, unlike in pathology, the volume reduction that occurs in normal aging does not necessarily reflect brain atrophy or neuronal death, but rather the loss of synaptic density (Hedden and Gabrieli 2004), as shown by studies of age-related differences in metabolic markers of neural integrity in vivo using magnetic resonance spectroscopy (Raz and Rodrigue 2006). Moreover, animal and human data suggest morphological alterations that are unique for aging and independent from neurodegenerative diseases. For example, loss of synaptic density in the prefrontal cortex and neuronal loss in the dentate gyrus, indicative of loss of synaptic input via the perforant pathway, would be characteristic of aging (Jagust 2013). In contrast, loss in both Cornus Ammonis subfield CA1 and entorhinal cortex would more likely reflect Alzheimer's pathology (Jagust 2013).

The decreased brain activity measured during task-related fMRI that older adults sometimes show, relative to younger adults, is seen as a manifestation of cognitive deficits (Grady 2012). When elderly show increased activity instead, this is interpreted as compensatory activity (if it results in better behavioral performance), as less efficient use of neural resources, or as a lack of selectivity in the brain response (Grady 2012). Whether showing decreased or increased activity, differences in brain activity in older adults are influenced by structural age changes, alterations in dopaminergic neurotransmission, or individual vulnerability to Alzheimer's disease pathology (Grady 2012).

4.3.1.2. IFC differences in the aging brain

Evidence based on various analysis methods has consistently shown significant differences in iFC in the aging brain both within and between intrinsic connectivity networks. Using ICA, age alone has been reported to account for 10 to 20% of the variance in iFC, with a general decrease within and across different networks and a specific iFC increase within the basal ganglia system (Allen et al., 2011). Machine learning based analyses have similarly revealed that decreased iFC between sensorimotor

and cingulo-opercular networks can correctly classify 'older' from 'younger' individuals (Meier, Desphande, Vergun et al., 2012).

Functional correlations between specific regions (seen in 'seed-based' analyses) within the default mode (e.g., anterior medial prefrontal and posterior cingulate/retrosplenial cortices) and dorsal attention networks (e.g., intraparietal sulcus and middle temporal area) have been shown to decrease with age (Andrews-Hanna, Snyder, Vincent et al., 2007). Importantly, such decrease is also observed in older adults with no signs of Alzheimer's disease pathology (i.e., in amyloid imaging) (Andrews-Hanna et al., 2007). Graph-theory based analyses have also revealed that, with increasing age, the average iFC density (i.e., the number of functional connections between a specific voxel and all the rest in the brain) is decreased for the default mode and dorsal attention networks, but increased for somatosensory, cerebellar, and thalamic networks (Tomasi and Volkow 2012). Beyond the default mode and dorsal attention networks, a decreased iFC has also been reported within the "salience" or cingulo-opercular network in healthy (Meier et al., 2012; He, Qin, Liu et al., 2014; Onoda, Ishihara, and Yamaguchi 2012) and pathological (He et al., 2014) aging.

Age-related changes in iFC are not just an epiphenomenon, but rather have a crucial functional relevance. For example, there is some evidence that the strength of iFC between the medial prefrontal cortex and the posterior cingulate/retrosplenial cortex contributes to cognitive decline not only in memory but also in executive function (Andrews-Hanna et al., 2007). Other studies have shown that, particularly in older (but not younger) adults, lower iFC within the anterior part of the default mode network correlates with lower performance on the Trail Making Test B (Damoiseaux, Beckmann, Arigita et al., 2008)—a speeded measure of executive control (Reitan and Wolfson 1985; Tombaugh 2004).

Positive associations between iFC of the salience network and visuospatial intelligence in the middle- and advanced-aged adults have also been reported (Onoda et al., 2012). Moreover, increased iFC between the anterior cingulate cortex and the hippocampus, posterior cingulate cortex, inferior frontal lobe, and angular gyrus has been reported for elderly with high cognitive reserve (i.e., higher education attainment) (Arenaza-Urquijo et al., 2013). Finally, encompassing the entire spectrum of (normal and pathological) aging, there is evidence of a significant association between iFC in the salience network and global cognitive state (He et al., 2014).

4.3.2. The aging brain under pathology

A clear demarcation between healthy and pathological aging is not straightforward. Mild cognitive impairment (MCI) constitutes a common example of pathological aging. Cognitive impairment, in general, is not a normal or expected effect of aging (Morris, Storandt, Miller et al., 2001; Morris and Price 2001). Therefore, when marked cognitive impairments (e.g., in memory) start to manifest, even despite functional independence, a prodromal stage of a neurodegenerative disease (e.g., Alzheimer's) could be occurring (Nestor, Scheltens, and Hodges 2004). However, MCI is heterogeneous and can either lead to dementia or remain stable until death (Mattsson, Zetterberg, Hansson et al., 2009). In particular, in the case of Alzheimer's disease (AD), MCI is regarded as a "symptomatic predementia phase" of AD (Albert, DeKosky, Dickson et al., 2011).

Studies have shown that patients with a diagnosis of MCI who later convert to AD dementia have abnormal levels of Amyloid-β (Aβ) and Tau protein in cerebrospinal fluid samples compared both with other MCI patients who are stable or convert to other dementias and with healthy controls (Mattsson et al., 2009). Senile or neuritic plaques (Aβ) and neurofibrillary tangles (Tau) (Figure 8), as well as degeneration of synapses and neurons, are the characteristic microscopic lesions in AD (Blennow, de Leon, and Zetterberg 2006). A widespread neocortical Aβ deposition (i.e., senile plaques) in the neocortex of a brain with AD has been proposed as the main distinction between pathological (e.g., MCI) and healthy aging (Morris and Price 2001). More specifically, whereas neurofibrillary tangles in structures of the medial temporal lobe accompany aging, the widespread presence of Aβ plaques indicates AD (Morris and Price 2001; Price, Davis, Morris et al., 1991).
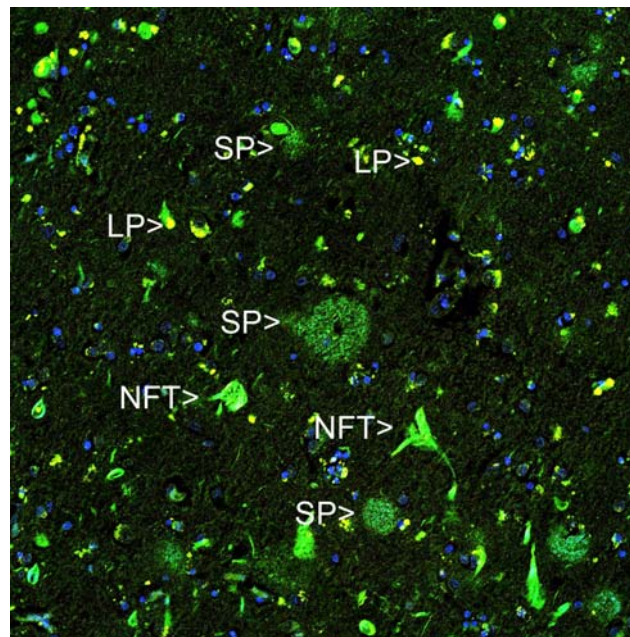
Figure 8. Senile plaques (SP) and neurofibrillary tangles. SP and NFT can be observed with Thioflavin stain (a fluorescent dye) on a section of the hippocampus of a patient with Alzheimer's disease. SP include a peptide derived from the amyloid precursor protein, the Amyloid β. LP: lipofuscin granules (lysosomes-derived autofluorescent inclusions that accumulate during normal aging). The Antibody and image courtesy of EnCor Biotechnology Inc. By Gerry P. J. Shaw (own work) via Wikimedia Commons CC BY-SA 3.0.

The so-called 'biomarkers' are biological *in vivo* or cognitive measures that can signal the start or progression of AD—i.e., the pathology and not necessarily the diagnostic entity of *AD dementia*. Biomarkers are necessary because AD has an insidious and slow onset and progression; for example, neurodegeneration has been estimated to start 20 to 30 years before clinical onset (Blennow et al., 2006). AD has been postulated as an extended period free of symptoms, but with pathophysiological processes going on (e.g., Sperling, Aisen, Beckett et al., 2011) with a particular temporal evolution (e.g., Jack, Knopman, Jagust et al., 2013). Thus, individuals with biomarker evidence of AD have a higher risk to develop symptoms congruent with AD dementia or predementia (Sperling et al., 2011). The most studied biomarkers in AD are Aβ (e.g., Aβ42 in cerebrospinal fluid or positron emission tomography [PET] amyloid imaging) and biomarkers of neuronal injury (e.g., Tau in cerebrospinal fluid, medial temporal lobe atrophy on MRI, and temporoparietal hypometabolism or hypoperfusion on PET or single-photon emission computed tomography) (Albert et al., 2011).

4.3.3. Visual processing speed differences in aging

In general, the speed of information processing has a major influence on cognition along development, as age-related differences in different cognitive variables are substantially attenuated when processing speed is accounted for (Kail and Salthouse 1994). For example, in healthy older adults (i.e., > 65 years), the processing speed can account for no less than 70% of the total age effect in cross-sectional (i.e., concurrent) measures of memory or verbal fluency (Sliwinski and Buschke 1999).

Traditionally measured with reaction times—i.e., with a motor response to a visual stimulus—visual processing speed shows an increase with age that is prominent, but also more variable intra-individually, after around the age of 50 (Der and Deary 2006). Other measures based on motor responses (e.g., writing numbers corresponding to symbols in a limited time or pressing a key that corresponds to a visually presented number) have also shown a significant decrease in visual processing speed both cross-sectional and longitudinally (Sliwinski and Buschke 1999). The motor component of these measures could, however, provide a confounding effect on visual processing speed assessment in aging. This confounding effect furthermore adds to the increased intra-individual performance variability (i.e., across tasks or at multiple occasions) that occurs with aging (Hultsch, MacDonald, and Dixon 2002). These potential shortcomings lead to difficulties in drawing specific inferences about individual differences in visual processing speed in aging.

Cross-sectional studies based on TVA modeling, which measure processing speed independent of motor speed, have also reported a significant reduction of visual processing speed in healthy aging (Espeseth et al., 2014; Habekost, Vogel, Rostrup et al., 2013; McAvinue, Habekost, Johnson et al., 2012). For example, one study documented that attention capacity parameters like speed and storage capacity show an increase from childhood to teenage years, but then a further linear decline through to older ages (McAvinue et al., 2012). Such decline was quantified in another study as from about 65 items/s at the age of 20 to about 40 items/s by the age of 80 (i.e., approx. 38%) in visual processing speed C estimates (Espeseth et al., 2014). Moreover, the decline of C has been shown still marked in advanced ages, with an average reduction to half as the age increased from 70 to 85 years (Habekost et al., 2013).

A more evident reduction of visual processing speed has been shown in pathological cases of aging, such as in acquired lesions (e.g., stroke) (e.g., Duncan,

Bundesen, Olson et al., 2003) or neurodegeneration (e.g., Huntington's disease or posterior cortical atrophy) (e.g., Finke, Schneider, Redel et al., 2007; Neitzel, Ortner, Haupt et al., 2016). In these cases, the marked reduction in visual processing speed has been shown to associate with simultanagnosia—or the deficit in perceiving more than one object at the same time (e.g., Bálint 1909; Friedman-Hill, Robertson, and Treisman 1995). Thus, cases of pathological aging have enriched the understanding of visual processing speed and shown the clinical implications of its severe reduction.

4.3.4. Summary and knowledge gap

To sum up, the aging human brain can follow a range of developmental trajectories that are influenced by both positive and negative individual and environmental factors. These trajectories can differentially affect the rate and degree of change in brain tissue. However, in general, gray matter decreases with age for most of the cortex, white matter increases until middle age and then starts to decrease, and cerebrospinal fluid follows a constant increase. The evoked activity of the brain also changes with aging, with both decreases and increases depending on the specific task or task demands. Both increases (mostly cortical) and decreases (mostly subcortical) are also shown in intrinsic functional connectivity with increasing age. Those changes are functionally relevant and not a mere epiphenomenon.

When compared to other age groups, individuals at older ages are characterized by a generalized reduction of higher-order cognition, in which visual processing speed appears to play a prominent role. Indeed, its prominent role is underscored by evidence from clinical cases of pathological aging, in which a reduction in visual processing speed is associated with a deficit in the simultaneous perception of objects. A staged decline of processing speed has been shown for patients with mild cognitive impairment, patients who are at high risk of a common age-related pathology, Alzheimer's dementia. However, **it has not yet been determined whether patients at risk of Alzheimer's dementia also manifest deficits in the simultaneous perception of objects.**

4.4. References

Albert, M. S., S. T. DeKosky, D. Dickson, B. Dubois, H. H. Feldman, N. C. Fox, et al. 2011. "The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." *Alzheimers Dement* 7 (3):270-9. doi: 10.1016/j.jalz.2011.03.008.

Allen, E. A., E. B. Erhardt, E. Damaraju, W. Gruner, J. M. Segall, R. F. Silva, et al. 2011. "A baseline for the multivariate comparison of resting-state networks." *Front Syst Neurosci* 5:2. doi: 10.3389/fnsys.2011.00002.

Andrews-Hanna, J. R., A. Z. Snyder, J. L. Vincent, C. Lustig, D. Head, M. E. Raichle, et al. 2007. "Disruption of large-scale brain systems in advanced aging." *Neuron* 56 (5):924-35. doi: 10.1016/j.neuron.2007.10.038.

Arenaza-Urquijo, E. M., B. Landeau, R. La Joie, K. Mevel, F. Mezenge, A. Perrotin, et al. 2013. "Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders." *Neuroimage* 83:450-7. doi: 10.1016/j.neuroimage.2013.06.053.

Asgeirsson, A. G., M. Nordfang, and T. A. Sorensen. 2015. "Components of Attention in Grapheme-Color Synesthesia: A Modeling Approach." *PLoS One* 10 (8):e0134456. doi: 10.1371/journal.pone.0134456.

Attwell, D., and C. Iadecola. 2002. "The neural basis of functional brain imaging signals." *Trends Neurosci* 25 (12):621-5.

Bálint, R. 1909. "Seelenlähmung des "Schauens,"optische Ataxie, räumliche Störung der Aufmerksamkeit." *Monatschr. Psychiat. Neurol.* 25:51-81.

Barth, M., and B. A. Poser. 2011. "Advances in High-Field BOLD fMRI." *Materials (Basel)* 4 (11):1941-1955. doi: 10.3390/ma4111941.

Beckmann, C. F., M. DeLuca, J. T. Devlin, and S. M. Smith. 2005. "Investigations into resting-state connectivity using independent component analysis." *Philos Trans R Soc Lond B Biol Sci* 360 (1457):1001-13. doi: 10.1098/rstb.2005.1634.

Beckmann, C. F., C. E. Mackay, N. Filippini, and S. Smith. 2009. "Group comparison of resting-state FMRI data using multi-subject ICA and dual regression." *Neuroimage* 47 (Suppl 1):S148.

Beckmann, C. F., and S. M. Smith. 2004. "Probabilistic independent component analysis for functional magnetic resonance imaging." *IEEE Trans Med Imaging* 23 (2):137-52. doi: 10.1109/TMI.2003.822821.

Beckmann, C. F., and S. M. Smith. 2005. "Tensorial extensions of independent component analysis for multisubject FMRI analysis." *Neuroimage* 25 (1):294-311. doi: 10.1016/j.neuroimage.2004.10.043.

Bell, A. J., and T. J. Sejnowski. 1995. "An information-maximization approach to blind separation and blind deconvolution." *Neural Comput* 7 (6):1129-59.

Biswal, B. B., M. Mennes, X. N. Zuo, S. Gohel, C. Kelly, S. M. Smith, et al. 2010. "Toward discovery science of human brain function." *Proc Natl Acad Sci U S A* 107 (10):4734-9. doi: 10.1073/pnas.0911855107.

Biswal, B., F. Z. Yetkin, V. M. Haughton, and J. S. Hyde. 1995. "Functional connectivity in the motor cortex of resting human brain using echo-planar MRI." *Magn Reson Med* 34 (4):537-41.

Blennow, K., M. J. de Leon, and H. Zetterberg. 2006. "Alzheimer's disease." *Lancet* 368 (9533):387-403. doi: 10.1016/S0140-6736(06)69113-7.

Blomqvist, G., R. J. Seitz, I. Sjogren, C. Halldin, S. Stone-Elander, L. Widen, et al. 1994. "Regional cerebral oxidative and total glucose consumption during rest and activation studied with positron emission tomography." *Acta Physiol Scand* 151 (1):29-43. doi: 10.1111/j.1748-1716.1994.tb09718.x.

Bundesen, C. 1990. "A theory of visual attention." *Psychol Rev* 97 (4):523-47.

Bundesen, C., T. Habekost, and S. Kyllingsbaek. 2005. "A neural theory of visual attention: bridging cognition and neurophysiology." *Psychol Rev* 112 (2):291-328. doi: 10.1037/0033-295X.112.2.291.

Bundesen, C., S. Vangkilde, and A. Petersen. 2015. "Recent developments in a computational theory of visual attention (TVA)." *Vision Res* 116 (Pt B):210-8. doi: 10.1016/j.visres.2014.11.005.

Calhoun, V. D., T. Adali, G. D. Pearlson, and J. J. Pekar. 2001. "A method for making group inferences from functional MRI data using independent component analysis." *Hum Brain Mapp* 14 (3):140-51.

Chechlacz, M., C. R. Gillebert, S. A. Vangkilde, A. Petersen, and G. W. Humphreys. 2015. "Structural Variability within Frontoparietal Networks and Individual Differences in Attentional Functions: An Approach Using the Theory of Visual Attention." *J Neurosci* 35 (30):10647-58. doi: 10.1523/JNEUROSCI.0210-15.2015.

Corbetta, M., and G. L. Shulman. 2002. "Control of goal-directed and stimulus-driven attention in the brain." *Nat Rev Neurosci* 3 (3):201-15. doi: 10.1038/nrn755.

Cordes, D., V. M. Haughton, K. Arfanakis, G. J. Wendt, P. A. Turski, C. H. Moritz, et al. 2000. "Mapping functionally related regions of brain with functional connectivity MR imaging." *AJNR Am J Neuroradiol* 21 (9):1636-44.

Damoiseaux, J. S., C. F. Beckmann, E. J. Arigita, F. Barkhof, P. Scheltens, C. J. Stam, et al. 2008. "Reduced resting-state brain activity in the "default network" in normal aging." *Cereb Cortex* 18 (8):1856-64. doi: 10.1093/cercor/bhm207.

Damoiseaux, J. S., S. A. Rombouts, F. Barkhof, P. Scheltens, C. J. Stam, S. M. Smith, et al. 2006. "Consistent resting-state networks across healthy subjects." *Proc Natl Acad Sci U S A* 103 (37):13848-53. doi: 10.1073/pnas.0601417103.

De Luca, M., C. F. Beckmann, N. De Stefano, P. M. Matthews, and S. M. Smith. 2006. "fMRI resting state networks define distinct modes of long-distance interactions in the human brain." *Neuroimage* 29 (4):1359-67. doi: 10.1016/j.neuroimage.2005.08.035.

Der, G., and I. J. Deary. 2006. "Age and sex differences in reaction time in adulthood: results from the United Kingdom Health and Lifestyle Survey." *Psychol Aging* 21 (1):62-73. doi: 10.1037/0882-7974.21.1.62.

Desimone, R., and J. Duncan. 1995. "Neural mechanisms of selective visual attention." *Annu Rev Neurosci* 18:193-222. doi: 10.1146/annurev.ne.18.030195.001205.

Doria, V., C. F. Beckmann, T. Arichi, N. Merchant, M. Groppo, F. E. Turkheimer, et al. 2010. "Emergence of resting state networks in the preterm human brain." *Proc Natl Acad Sci U S A* 107 (46):20015-20. doi: 10.1073/pnas.1007921107.

Dosenbach, N. U., D. A. Fair, F. M. Miezin, A. L. Cohen, K. K. Wenger, R. A. Dosenbach, et al. 2007. "Distinct brain networks for adaptive and stable task control in humans." *Proc Natl Acad Sci U S A* 104 (26):11073-8. doi: 10.1073/pnas.0704320104.

Duncan, J., C. Bundesen, A. Olson, G. Humphreys, R. Ward, S. Kyllingsbaek, et al. 2003. "Attentional functions in dorsal and ventral simultanagnosia." *Cogn Neuropsychol* 20 (8):675-701. doi: 10.1080/02643290342000041.

Dyrholm, M., S. Kyllingsbaek, T. Espeseth, and C. Bundesen. 2011. "Generalizing parametric models by introducing trial-by-trial parameter variability: The case of TVA." *Journal of Mathematical Psychology* 55 (6):416-429. doi: https://doi.org/10.1016/j.jmp.2011.08.005.

Espeseth, T., S. A. Vangkilde, A. Petersen, M. Dyrholm, and L. T. Westlye. 2014. "TVA-based assessment of attentional capacities-associations with age and indices of brain white matter microstructure." *Front Psychol* 5:1177. doi: 10.3389/fpsyg.2014.01177.

Filippini, N., B. J. MacIntosh, M. G. Hough, G. M. Goodwin, G. B. Frisoni, S. M. Smith, et al. 2009. "Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele." *Proc Natl Acad Sci U S A* 106 (17):7209-14. doi: 10.1073/pnas.0811879106.

Finke, K., C. M. Dodds, P. Bublak, R. Regenthal, F. Baumann, T. Manly, et al. 2010. "Effects of modafinil and methylphenidate on visual attention capacity: a TVA-based study." *Psychopharmacology (Berl)* 210 (3):317-29. doi: 10.1007/s00213-010-1823-x.

Finke, K., W. X. Schneider, P. Redel, M. Dose, G. Kerkhoff, H. J. Muller, et al. 2007. "The capacity of attention and simultaneous perception of objects: a group study of Huntington's disease patients." *Neuropsychologia* 45 (14):3272-84. doi: 10.1016/j.neuropsychologia.2007.06.006.

Fox, M. D., M. Corbetta, A. Z. Snyder, J. L. Vincent, and M. E. Raichle. 2006. "Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems." *Proc Natl Acad Sci U S A* 103 (26):10046-51. doi: 10.1073/pnas.0604187103.

Fox, M. D., and M. E. Raichle. 2007. "Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging." *Nat Rev Neurosci* 8 (9):700-11. doi: 10.1038/nrn2201.

Fox, M. D., A. Z. Snyder, J. L. Vincent, M. Corbetta, D. C. Van Essen, and M. E. Raichle. 2005. "The human brain is intrinsically organized into dynamic, anticorrelated functional networks." *Proc Natl Acad Sci U S A* 102 (27):9673-8. doi: 10.1073/pnas.0504136102.

Fox, M. D., A. Z. Snyder, J. L. Vincent, and M. E. Raichle. 2007. "Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior." *Neuron* 56 (1):171-84. doi: 10.1016/j.neuron.2007.08.023.

Fox, M. D., A. Z. Snyder, J. M. Zacks, and M. E. Raichle. 2006. "Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses." *Nat Neurosci* 9 (1):23-5. doi: 10.1038/nn1616.

Fox, P. T., M. E. Raichle, M. A. Mintun, and C. Dence. 1988. "Nonoxidative glucose consumption during focal physiologic neural activity." *Science* 241 (4864):462-4.

Friedman-Hill, S. R., L. C. Robertson, and A. Treisman. 1995. "Parietal contributions to visual feature binding: evidence from a patient with bilateral lesions." *Science* 269 (5225):853-5.

Friston, K. J. 1994. "Functional and effective connectivity in neuroimaging_a synthesis." *Hum Brain Mapp* 2 (1-2):56-78. doi: 10.1002/hbm.460020107.

Friston, K. J., C. D. Frith, P. F. Liddle, and R. S. Frackowiak. 1993. "Functional connectivity: the principal-component analysis of large (PET) data sets." *J Cereb Blood Flow Metab* 13 (1):5-14. doi: 10.1038/jcbfm.1993.4.

Fukunaga, M., S. G. Horovitz, P. van Gelderen, J. A. de Zwart, J. M. Jansma, V. N. Ikonomidou, et al. 2006. "Large-amplitude, spatially correlated fluctuations in BOLD fMRI signals during extended rest and early sleep stages." *Magn Reson Imaging* 24 (8):979-92. doi: 10.1016/j.mri.2006.04.018.

Girouard, H., and C. Iadecola. 2006. "Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease." *J Appl Physiol (1985)* 100 (1):328-35. doi: 10.1152/japplphysiol.00966.2005.

Good, C. D., I. S. Johnsrude, J. Ashburner, R. N. Henson, K. J. Friston, and R. S. Frackowiak. 2001. "A voxel-based morphometric study of ageing in 465 normal adult human brains." *Neuroimage* 14 (1 Pt 1):21-36. doi: 10.1006/nimg.2001.0786.

Grady, C. 2012. "The cognitive neuroscience of ageing." *Nat Rev Neurosci* 13 (7):491-505. doi: 10.1038/nrn3256.

Greicius, M. D., B. Krasnow, A. L. Reiss, and V. Menon. 2003. "Functional connectivity in the resting brain: a network analysis of the default mode hypothesis." *Proc Natl Acad Sci U S A* 100 (1):253-8. doi: 10.1073/pnas.0135058100.

Habekost, T., A. Vogel, E. Rostrup, C. Bundesen, S. Kyllingsbaek, E. Garde, et al. 2013. "Visual processing speed in old age." *Scand J Psychol* 54 (2):89-94. doi: 10.1111/sjop.12008.

Hagmann, P., L. Cammoun, X. Gigandet, R. Meuli, C. J. Honey, V. J. Wedeen, et al. 2008. "Mapping the structural core of human cerebral cortex." *PLoS Biol* 6 (7):e159. doi: 10.1371/journal.pbio.0060159.

Hall, C. N., C. Howarth, Z. Kurth-Nelson, and A. Mishra. 2016. "Interpreting BOLD: towards a dialogue between cognitive and cellular neuroscience." *Philos Trans R Soc Lond B Biol Sci* 371 (1705). doi: 10.1098/rstb.2015.0348.

He, X., W. Qin, Y. Liu, X. Zhang, Y. Duan, J. Song, et al. 2014. "Abnormal salience network in normal aging and in amnestic mild cognitive impairment and Alzheimer's disease." *Hum Brain Mapp* 35 (7):3446-64. doi: 10.1002/hbm.22414.

Hedden, T., and J. D. Gabrieli. 2004. "Insights into the ageing mind: a view from cognitive neuroscience." *Nat Rev Neurosci* 5 (2):87-96. doi: 10.1038/nrn1323.

Honey, C. J., O. Sporns, L. Cammoun, X. Gigandet, J. P. Thiran, R. Meuli, et al. 2009. "Predicting human resting-state functional connectivity from structural

connectivity." *Proc Natl Acad Sci U S A* 106 (6):2035-40. doi: 10.1073/pnas.0811168106.

Hultsch, D. F., S. W. MacDonald, and R. A. Dixon. 2002. "Variability in reaction time performance of younger and older adults." *J Gerontol B Psychol Sci Soc Sci* 57 (2):P101-15.

Hyvarinen, A. 1999. "Fast and robust fixed-point algorithms for independent component analysis." *IEEE Trans Neural Netw* 10 (3):626-34. doi: 10.1109/72.761722.

Jack, C. R., Jr., D. S. Knopman, W. J. Jagust, R. C. Petersen, M. W. Weiner, P. S. Aisen, et al. 2013. "Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers." *Lancet Neurol* 12 (2):207-16. doi: 10.1016/S1474-4422(12)70291-0.

Jagust, W. 2013. "Vulnerable neural systems and the borderland of brain aging and neurodegeneration." *Neuron* 77 (2):219-34. doi: 10.1016/j.neuron.2013.01.002.

Kail, R., and T. A. Salthouse. 1994. "Processing speed as a mental capacity." *Acta Psychol (Amst)* 86 (2-3):199-225.

Kim, S. G., and S. Ogawa. 2012. "Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals." *J Cereb Blood Flow Metab* 32 (7):1188-206. doi: 10.1038/jcbfm.2012.23.

Kyllingsbaek, S. 2006. "Modeling visual attention." *Behav Res Methods* 38 (1):123-33.

Laird, A. R., P. M. Fox, S. B. Eickhoff, J. A. Turner, K. L. Ray, D. R. McKay, et al. 2011. "Behavioral interpretations of intrinsic connectivity networks." *J Cogn Neurosci* 23 (12):4022-37. doi: 10.1162/jocn_a_00077.

Larson-Prior, L. J., J. M. Zempel, T. S. Nolan, F. W. Prior, A. Z. Snyder, and M. E. Raichle. 2009. "Cortical network functional connectivity in the descent to sleep." *Proc Natl Acad Sci U S A* 106 (11):4489-94. doi: 10.1073/pnas.0900924106.

Lee, M. H., C. D. Hacker, A. Z. Snyder, M. Corbetta, D. Zhang, E. C. Leuthardt, et al. 2012. "Clustering of resting state networks." *PLoS One* 7 (7):e40370. doi: 10.1371/journal.pone.0040370.

Lindenberger, U. 2014. "Human cognitive aging: corriger la fortune?" *Science* 346 (6209):572-8. doi: 10.1126/science.1254403.

Logothetis, N. K., J. Pauls, M. Augath, T. Trinath, and A. Oeltermann. 2001. "Neurophysiological investigation of the basis of the fMRI signal." *Nature* 412 (6843):150-7. doi: 10.1038/35084005.

Ma, Y., M. A. Shaik, M. G. Kozberg, S. H. Kim, J. P. Portes, D. Timerman, et al. 2016. "Resting-state hemodynamics are spatiotemporally coupled to synchronized and symmetric neural activity in excitatory neurons." *Proc Natl Acad Sci U S A* 113 (52):E8463-E8471. doi: 10.1073/pnas.1525369113.

Martuzzi, R., R. Ramani, M. Qiu, N. Rajeevan, and R. T. Constable. 2010. "Functional connectivity and alterations in baseline brain state in humans." *Neuroimage* 49 (1):823-34. doi: 10.1016/j.neuroimage.2009.07.028.

Matsui, T., T. Murakami, and K. Ohki. 2016. "Transient neuronal coactivations embedded in globally propagating waves underlie resting-state functional connectivity." *Proc Natl Acad Sci U S A* 113 (23):6556-61. doi: 10.1073/pnas.1521299113.

Matthias, E., P. Bublak, H. J. Muller, W. X. Schneider, J. Krummenacher, and K. Finke. 2010. "The influence of alertness on spatial and nonspatial components of visual attention." *J Exp Psychol Hum Percept Perform* 36 (1):38-56. doi: 10.1037/a0017602.

Mattsson, N., H. Zetterberg, O. Hansson, N. Andreasen, L. Parnetti, M. Jonsson, et al. 2009. "CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment." *JAMA* 302 (4):385-93. doi: 10.1001/jama.2009.1064.

McAvinue, L. P., T. Habekost, K. A. Johnson, S. Kyllingsbaek, S. Vangkilde, C. Bundesen, et al. 2012. "Sustained attention, attentional selectivity, and attentional capacity across the lifespan." *Atten Percept Psychophys* 74 (8):1570-82. doi: 10.3758/s13414-012-0352-6.

McKeown, M. J., S. Makeig, G. G. Brown, T. P. Jung, S. S. Kindermann, A. J. Bell, et al. 1998. "Analysis of fMRI data by blind separation into independent spatial components." *Hum Brain Mapp* 6 (3):160-88.

Meier, T. B., A. S. Desphande, S. Vergun, V. A. Nair, J. Song, B. B. Biswal, et al. 2012. "Support vector machine classification and characterization of age-related reorganization of functional brain networks." *Neuroimage* 60 (1):601-13. doi: 10.1016/j.neuroimage.2011.12.052.

Mennes, M., C. Kelly, X. N. Zuo, A. Di Martino, B. B. Biswal, F. X. Castellanos, et al. 2010. "Inter-individual differences in resting-state functional connectivity predict task-induced BOLD activity." *Neuroimage* 50 (4):1690-701. doi: 10.1016/j.neuroimage.2010.01.002.

Morris, J. C., and J. L. Price. 2001. "Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease." *J Mol Neurosci* 17 (2):101-18.

Morris, J. C., M. Storandt, J. P. Miller, D. W. McKeel, J. L. Price, E. H. Rubin, et al. 2001. "Mild cognitive impairment represents early-stage Alzheimer disease." *Arch Neurol* 58 (3):397-405.

Neitzel, J., M. Ortner, M. Haupt, P. Redel, T. Grimmer, I. Yakushev, et al. 2016. "Neurocognitive mechanisms of simultanagnosia in patients with posterior cortical atrophy." *Brain*. doi: 10.1093/brain/aww235.

Nestor, P. J., P. Scheltens, and J. R. Hodges. 2004. "Advances in the early detection of Alzheimer's disease." *Nat Med* 10 Suppl:S34-41. doi: 10.1038/nrn1433.

Ogawa, S., T. M. Lee, A. R. Kay, and D. W. Tank. 1990. "Brain magnetic resonance imaging with contrast dependent on blood oxygenation." *Proc Natl Acad Sci U S A* 87 (24):9868-72.

Oh, H., C. Habeck, C. Madison, and W. Jagust. 2014. "Covarying alterations in Abeta deposition, glucose metabolism, and gray matter volume in cognitively normal elderly." *Hum Brain Mapp* 35 (1):297-308. doi: 10.1002/hbm.22173.

Onoda, K., M. Ishihara, and S. Yamaguchi. 2012. "Decreased functional connectivity by aging is associated with cognitive decline." *J Cogn Neurosci* 24 (11):2186-98. doi: 10.1162/jocn_a_00269.

Pauling, L., and C. D. Coryell. 1936. "The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin." *Proc Natl Acad Sci U S A* 22 (4):210-6.

Peelle, J. E., R. Cusack, and R. N. Henson. 2012. "Adjusting for global effects in voxel-based morphometry: gray matter decline in normal aging." *Neuroimage* 60 (2):1503-16. doi: 10.1016/j.neuroimage.2011.12.086.

Petersen, A., A. H. Petersen, C. Bundesen, S. Vangkilde, and T. Habekost. 2017. "The effect of phasic auditory alerting on visual perception." *Cognition* 165:73-81. doi: 10.1016/j.cognition.2017.04.004.

Price, J. L., P. B. Davis, J. C. Morris, and D. L. White. 1991. "The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease." *Neurobiol Aging* 12 (4):295-312.

Raichle, M. E., and M. A. Mintun. 2006. "Brain work and brain imaging." *Annu Rev Neurosci* 29:449-76. doi: 10.1146/annurev.neuro.29.051605.112819.

Raz, N., and K. M. Rodrigue. 2006. "Differential aging of the brain: patterns, cognitive correlates and modifiers." *Neurosci Biobehav Rev* 30 (6):730-48. doi: 10.1016/j.neubiorev.2006.07.001.

Reitan, R. M., and D. Wolfson. 1985. *The Halstead-Reitan neuropsychological test battery: therapy and clinical interpretation.* Tucson, AZ: Neuropsychological Press.

Sadaghiani, S., G. Hesselmann, K. J. Friston, and A. Kleinschmidt. 2010. "The relation of ongoing brain activity, evoked neural responses, and cognition." *Front Syst Neurosci* 4:20. doi: 10.3389/fnsys.2010.00020.

Sadaghiani, S., and A. Kleinschmidt. 2013. "Functional interactions between intrinsic brain activity and behavior." *Neuroimage* 80:379-86. doi: 10.1016/j.neuroimage.2013.04.100.

Salat, D. H., R. L. Buckner, A. Z. Snyder, D. N. Greve, R. S. Desikan, E. Busa, et al. 2004. "Thinning of the cerebral cortex in aging." *Cereb Cortex* 14 (7):721-30. doi: 10.1093/cercor/bhh032.

Sanchez-Vives, M. V., M. Massimini, and M. Mattia. 2017. "Shaping the Default Activity Pattern of the Cortical Network." *Neuron* 94 (5):993-1001. doi: 10.1016/j.neuron.2017.05.015.

Schwalm, M., F. Schmid, L. Wachsmuth, H. Backhaus, A. Kronfeld, F. Aedo Jury, et al. 2017. "Cortex-wide BOLD fMRI activity reflects locally-recorded slow oscillation-associated calcium waves." *Elife* 6. doi: 10.7554/eLife.27602.

Seeley, W. W., V. Menon, A. F. Schatzberg, J. Keller, G. H. Glover, H. Kenna, et al. 2007. "Dissociable intrinsic connectivity networks for salience processing and executive control." *J Neurosci* 27 (9):2349-56. doi: 10.1523/JNEUROSCI.5587-06.2007.

Segall, J. M., E. A. Allen, R. E. Jung, E. B. Erhardt, S. K. Arja, K. Kiehl, et al. 2012. "Correspondence between structure and function in the human brain at rest." *Front Neuroinform* 6:10. doi: 10.3389/fninf.2012.00010.

Shehzad, Z., A. M. Kelly, P. T. Reiss, D. G. Gee, K. Gotimer, L. Q. Uddin, et al. 2009. "The resting brain: unconstrained yet reliable." *Cereb Cortex* 19 (10):2209-29. doi: 10.1093/cercor/bhn256.

Sliwinski, M., and H. Buschke. 1999. "Cross-sectional and longitudinal relationships among age, cognition, and processing speed." *Psychol Aging* 14 (1):18-33.

Smith, D. V., A. V. Utevsky, A. R. Bland, N. Clement, J. A. Clithero, A. E. Harsch, et al. 2014. "Characterizing individual differences in functional connectivity using dual-regression and seed-based approaches." *Neuroimage* 95:1-12. doi: 10.1016/j.neuroimage.2014.03.042.

Smith, S. M., P. T. Fox, K. L. Miller, D. C. Glahn, P. M. Fox, C. E. Mackay, et al. 2009. "Correspondence of the brain's functional architecture during activation and rest." *Proc Natl Acad Sci U S A* 106 (31):13040-5. doi: 10.1073/pnas.0905267106.

Sowell, E. R., B. S. Peterson, P. M. Thompson, S. E. Welcome, A. L. Henkenius, and A. W. Toga. 2003. "Mapping cortical change across the human life span." *Nat Neurosci* 6 (3):309-15. doi: 10.1038/nn1008.

Sperling, G. 1960. "The information available in brief visual presentations." *Psychological monographs: General and applied* 74 (11):1-29. doi: http://dx.doi.org/10.1037/h0093759.

Sperling, R. A., P. S. Aisen, L. A. Beckett, D. A. Bennett, S. Craft, A. M. Fagan, et al. 2011. "Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." *Alzheimers Dement* 7 (3):280-92. doi: 10.1016/j.jalz.2011.03.003.

Tomasi, D., and N. D. Volkow. 2012. "Aging and functional brain networks." *Mol Psychiatry* 17 (5):471, 549-58. doi: 10.1038/mp.2011.81.

Tombaugh, T. N. 2004. "Trail Making Test A and B: normative data stratified by age and education." *Arch Clin Neuropsychol* 19 (2):203-14. doi: 10.1016/S0887-6177(03)00039-8.

van den Heuvel, M. P., and H. E. Hulshoff Pol. 2010. "Exploring the brain network: a review on resting-state fMRI functional connectivity." *Eur Neuropsychopharmacol* 20 (8):519-34. doi: 10.1016/j.euroneuro.2010.03.008.

Vangkilde, S., A. Petersen, and C. Bundesen. 2013. "Temporal expectancy in the context of a theory of visual attention." *Philos Trans R Soc Lond B Biol Sci* 368 (1628):20130054. doi: 10.1098/rstb.2013.0054.

Vincent, J. L., I. Kahn, A. Z. Snyder, M. E. Raichle, and R. L. Buckner. 2008. "Evidence for a frontoparietal control system revealed by intrinsic functional connectivity." *J Neurophysiol* 100 (6):3328-42. doi: 10.1152/jn.90355.2008.

Vincent, J. L., G. H. Patel, M. D. Fox, A. Z. Snyder, J. T. Baker, D. C. Van Essen, et al. 2007. "Intrinsic functional architecture in the anaesthetized monkey brain." *Nature* 447 (7140):83-6. doi: 10.1038/nature05758.

Wiegand, I., T. Tollner, T. Habekost, M. Dyrholm, H. J. Muller, and K. Finke. 2014. "Distinct neural markers of TVA-based visual processing speed and short-term storage capacity parameters." *Cereb Cortex* 24 (8):1967-78. doi: 10.1093/cercor/bht071.

Wu, J. Y., Huang Xiaoying, and Zhang Chuan. 2008. "Propagating waves of activity in the neocortex: what they are, what they do." *Neuroscientist* 14 (5):487-502. doi: 10.1177/1073858408317066.

Yeo, B. T., F. M. Krienen, J. Sepulcre, M. R. Sabuncu, D. Lashkari, M. Hollinshead, et al. 2011. "The organization of the human cerebral cortex estimated by intrinsic functional connectivity." *J Neurophysiol* 106 (3):1125-65. doi: 10.1152/jn.00338.2011.

Zuo, X. N., C. Kelly, J. S. Adelstein, D. F. Klein, F. X. Castellanos, and M. P. Milham. 2010. "Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach." *Neuroimage* 49 (3):2163-77. doi: 10.1016/j.neuroimage.2009.10.080.

5. Study 1: Visual processing speed in the resting human brain

Adriana L. Ruiz-Rizzo, Julia Neitzel, Hermann J. Müller, Christian Sorg, Kathrin Finke

Summary

In this manuscript titled **Distinctive Correspondence between Separable Visual Attention Functions and Intrinsic Brain Networks** and currently under second review in the journal *Frontiers in Human Neuroscience*, we present direct evidence for a distinctive network-based functional representation of independent visual attention functions in general and visual processing speed in particular. Based on visual processing speed *C* parameter estimates, we assigned healthy young adults to 'high' or 'low' (than the group median) performance subgroups. We tested whether these subgroups differ in the intra- and inter-network functional connectivity of functional networks that encompass brain areas relevant for visual attention: visual, executive control, right and left frontoparietal, and ventral and dorsal attention networks.

We found that higher visual processing speed was associated with lower intra-network functional connectivity of the right middle frontal gyrus within the ventral attention network only. Moreover, higher visual processing speed was associated with higher functional connectivity between the visual attention and right frontoparietal networks. Interestingly, the lower intra-network connectivity of the ventral attention network tended to relate to its higher connectivity with the right frontoparietal network. Importantly, these associations were distinct from those found for other visual attention parameters (e.g., top-down control).

The results of this study indicate that the ventral attention (also known as "salience" or "cingulo-opercular") and right frontoparietal networks are relevant for visual processing speed. These results complement previous evidence on structural connectivity in healthy young adults and further serve as a baseline to test specific hypotheses on the neural mechanisms of visual processing speed in healthy and pathological aging.

Graphic abstract

Intrinsic connectivity networks

Visual processing speed C

Authors' contributions

A.L.R.R., K.F., and C.S. designed the study. J.N. acquired the data. A.L.R.R. analyzed the imaging data and drafted the manuscript, the revised manuscript, and the response to reviewers. A.L.R.R., K.F., C.S., H.J.M., and J.N. wrote and revised critically the manuscript before submission as well as the response to reviewers and the revised version of the manuscript. K.F. and C.S. equally contributed as senior authors.

Manuscript: Distinctive correspondence between separable visual attention functions and intrinsic brain networks

Adriana L. Ruiz-Rizzo*[1,2], Julia Neitzel[1,3], Hermann J. Müller[1,5], Christian Sorg[2,3†], Kathrin Finke[1,2,5†]

[1] Department of General and Experimental Psychology, Ludwig-Maximilians-Universität München, Munich, Germany.

[2] Graduate School of Systemic Neurosciences, GSN LMU, Munich, Germany.

[3] Department of Neuroradiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany.

[4] Hans-Berger Department of Neurology, Friedrich Schiller University Jena, Jena, Germany

[5] School of Psychological Science, Birkbeck College, University of London, London, UK

[†] These authors equally contributed to this work

* Correspondence: Adriana L. Ruiz Rizzo. adriana.ruiz@lmu.de.

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Abstract

Separable visual attention functions are assumed to rely on distinct but interacting neural mechanisms. Bundesen's 'theory of visual attention' (TVA) allows the mathematical estimation of independent parameters that characterize individuals' attentional capacity (i.e., processing speed and short-term memory storage capacity) and selectivity (i.e., top-down control and spatial laterality). However, it is unclear whether these parameters for separable attention functions distinctively map onto different brain networks obtained from intrinsic functional connectivity, which organizes slowly fluctuating ongoing brain activity. Thirty-one demographically homogeneous healthy young participants performed whole- and partial-report tasks and underwent resting-state functional magnetic resonance imaging (rs-fMRI). Report accuracy was modeled using TVA to estimate, individually, four parameters: visual processing speed, visual short-term memory storage capacity, top-down control, and spatial laterality. Networks encompassing cortical areas relevant for visual attention were derived from independent component analysis of rs-fMRI data: visual, executive control, right and left frontoparietal, and ventral and dorsal attention networks. Two TVA parameters were mapped on particular functional networks. First, participants with higher (vs. lower) visual processing speed showed lower functional connectivity within the ventral attention network. Second, participants with more efficient (vs. less) efficient top-down control showed higher functional connectivity within the dorsal attention network and lower functional connectivity within the visual network. Additionally, high performance was associated with higher functional connectivity between networks, specifically, between the ventral attention and right frontoparietal networks for visual processing speed; and between the visual and executive control networks for top-down control. The higher inter-network functional connectivity was related to the lower intra-network connectivity. Thus, results demonstrate that separable visual attention functions correspond distinctively to the functional connectivity both within and between particular functional networks. Data suggest that individual differences in distinct functions of attentional selection are represented by differences in intrinsic connectivity of slowly fluctuating brain activity.

Introduction

Separable visual attention functions are assumed to rely on distinct but interacting neural mechanisms (Bundesen, Habekost, and Kyllingsbaek 2005; Desimone and Duncan 1995; Posner and Petersen 1990). The computational 'theory of visual attention' (TVA, Bundesen 1990) permits a set of independent parameters to be estimated that reflect attentional capacity (i.e., visual processing speed and short-term memory storage capacity) and selectivity (i.e., top-down control and spatial laterality). These TVA parameters have been suggested to constitute traits that characterize individuals' speed and efficiency of attentional selection processes (Finke, Bublak, Krummenacher et al., 2005). The relationship between these parameters and the basic organization of the brain has been addressed in local lesion (Kraft, Irlbacher, Finke et al., 2015; Neitzel, Ortner, Haupt et al., 2016; Peers, Ludwig, Rorden et al., 2005; Sorg, Myers, Redel et al., 2012) and structural connectivity studies (Chechlacz, Gillebert, Vangkilde et al., 2015). For example, reductions in visual processing speed have been associated with temporoparietal junction (Peers et al., 2005) and lateral thalamic non-traumatic lesions (Kraft et al., 2015), as well as with a parietal white-matter reduction in posterior cortical atrophy (Neitzel et al., 2016). A lateral spatial bias has been documented following medial thalamic lesions (Kraft et al., 2015) as well as asymmetric parietal hypometabolism induced by early Alzheimer's disease (Sorg et al., 2012). In healthy participants, visual short-term memory (VSTM) capacity has been associated with the organization of the superior longitudinal and inferior fronto-occipital fasciculi (Chechlacz et al., 2015), and top-down control has been related to task-related functional connectivity among parietal areas (Vossel, Weidner, Moos et al., 2016). Thus, these studies imply that TVA parameters closely reflect the integrity of attention-relevant brain areas and their connections, including their functional interactions. It is, however, unknown whether and how these parameters map onto functional networks overlapping those attention-relevant areas.

Functional networks that include regions relevant for visual attention have been identified based on their intrinsic functional connectivity (FC) (Allen, Erhardt, Damaraju et al., 2011; Fox, Corbetta, Snyder et al., 2006; Raichle 2015; Smith, Fox, Miller et al., 2009; Yeo, Krienen, Sepulcre et al., 2011). Intrinsic FC represents the correlation, among different brain regions, of infra-slowly (i.e., 0.01-0.1 Hz) ongoing blood oxygenation level dependent (BOLD) signal intensity fluctuations obtained from resting-state functional magnetic resonance imaging (fMRI) (Fox and Raichle 2007; Raichle 2011).

Such fluctuations reflect the dynamics of slowly propagating activity including cortical neuronal excitability (Matsui, Murakami, and Ohki 2016; Wu, Xiaoying, and Chuan 2008), linked with faster oscillatory activity by cross-frequency phase-amplitude coupling (Brookes, Woolrich, Luckhoo et al., 2011; He, Zempel, Snyder et al., 2010; Hipp, Hawellek, Corbetta et al., 2012; Mantini, Perrucci, Del Gratta et al., 2007). Intrinsic FC provides relevant information on both brain evoked activity (Mennes, Kelly, Zuo et al., 2010) and behavior (Markett, Reuter, Montag et al., 2014; Rosenberg, Finn, Scheinost et al., 2016; Rosenberg, Finn, Scheinost et al., 2017). Crucially, the brain networks identified through intrinsic FC are stable both within (Zuo, Kelly, Adelstein et al., 2010) and across subjects (Damoiseaux, Rombouts, Barkhof et al., 2006; De Luca, Beckmann, De Stefano et al., 2006), and largely correspond to structural connectivity (Honey, Sporns, Cammoun et al., 2009; Damoiseaux and Greicius 2009). These characteristics collectively suggest the possibility of a distinctive correspondence between specific, separable visual attention functions and particular intrinsic brain networks.

Here we examined whether and how independent visual attention parameters obtained from modeling using TVA are mapped onto distinct functional networks derived from intrinsic FC. Crucially, to avoid potential confounding from structural integrity or visual attention changes inherent in patient or developing populations, we assessed an age-homogeneous group of healthy participants. Moreover, following the neural interpretation of TVA (Bundesen et al., 2005), we focused on networks that comprise brain regions relevant for visual attention (for a review, see Parks and Madden 2013). White matter pathways could anatomically constrain functional network connectivity (Parks and Madden 2013), though not in a one-to-one fashion (Damoiseaux and Greicius 2009). Therefore, based on previous TVA-derived research on structural connectivity variability (e.g., Chechlacz et al., 2015), we expected a positive association between TVA parameter estimates and intrinsic FC.

Materials and Methods

Participants

Thirty-two healthy young subjects (25 to 27 years old) participated in this study. The 'Klinikum rechts der Isar's' Ethics Committee approved the study, which was conducted in agreement with the Declaration of Helsinki, and all participants gave written informed consent and were paid for their participation. All participants underwent BOLD-

fMRI during rest and TVA-based assessment in separate sessions conducted on the same day (though one participant did not perform the TVA partial-report task and thus had to be excluded from the analyses). And all had a normal or corrected-to-normal visual acuity and normal color vision. Before visual attention and MRI examination, participants were assessed for global cognitive functioning by trained psychologists using a short version of the German Wechsler Adult Intelligence scale-III (WAIS-III) (Von Aster, Neubauer, and Horn 2006), permitting computation of Full-Scale IQ. Demographic information is listed in Table 1. Males and females did not differ in any of the demographic variables.

Parametric assessment and estimation of visual attention functions

General procedure

The general TVA-based procedure for assessing visual attention functioning has been described in detail elsewhere (e.g., Finke, Neitzel, Bauml et al., 2015). Briefly, to assess visual attention functions, participants performed, in a balanced order, whole- and partial-report tasks that lasted approx. 0.5 h each. Within a trial, a central white cross (0.3° visual angle) appeared for 300 ms, followed by a 100-ms gap after which the task-relevant stimuli were presented (Figure 1). Stimuli comprised of red or green letters (0.5° high x 0.4° wide) randomly chosen from a pre-specified set ("ABEFHJKLMNPRSTWXYZ"). Letters were followed by masks (i.e., a box with a star inside) to allow overwriting the iconic memory store contents and accurately estimating visual short-term memory (see below). However, trials without post-display masks were introduced in the whole-report task to increase the variability of effective exposure times (by allowing for an additional component of iconic memory buffering; Sperling 1960) and thus ensure reliable and valid TVA parameter fitting. Stimuli were presented on a 17-inch monitor (1024 by 1280 pixel screen resolution, 60-Hz refresh rate), in a dimly lit room.

Visual attention capacity parameters

Capacity parameters were derived from report accuracy in the whole-report task (Figure 1, left panel), in which participants were instructed to report all letters they were fairly sure they had seen. First, in a pretest (24 trials), one individualized exposure duration was determined as the presentation time required to report one letter on average over several trials correctly. Shorter and longer exposure durations were then determined

based on that value. Next, the three durations were used to present stimuli either unmasked or immediately followed by masking stimuli, thus resulting in six effective exposure durations (for more details, see Finke et al., 2015). The average short, intermediate, and long exposure durations were, respectively, 45.17 (SD = 7.0), 82.23 (SD = 17.26), and 164.90 (SD = 33.40) ms. The task consisted of 192 trials presented in 4 blocks of 48 trials each. Within each block, trials were randomized and presented equally often under 12 conditions (2 masking conditions, 3 exposure durations, and 2 hemifields). Performance accuracy (i.e., the number of letters reported correctly) was measured as a function of effective exposure duration. Based on TVA, an exponential growth function was used to model the probability of selecting an object (Bundesen 1990; Kyllingsbaek 2006). The slope of the exponential curve at the minimum effective exposure duration $t0$ (for masked displays) reflects the processing rate C – or number of elements processed per second – and the asymptote indicates the VSTM storage capacity – or the maximum number of items that can be simultaneously represented in VSTM. The effective additional exposure duration in unmasked displays (mμ) – due to iconic memory buffering – was also determined to validly estimate parameters C and K. While mμ was of no further interest in our study, it was necessary to estimate because, in unmasked displays, storage of visual information in iconic memory leads to prolonged information processing (Finke et al., 2015).

Visual attention weighting parameters

Attentional weighting parameters were derived from report accuracy in the partial-report task (Figure 1, right panel), in which participants had to report targets (red letters) and ignore distractors (green letters). On each trial, (a) a single target, (b) a target and a distractor, or (c) two targets were presented horizontally or vertically at the corners of an imaginary square (for more details, see Finke et al., 2015). As in the whole-report task, the individual exposure duration was specified in a pretest (32 trials) as the duration at which the participant reported single targets with 80% accuracy. The average exposure duration was 91.50 ms (SD = 23.42). The task consisted of 6 blocks of 48 trials each (i.e., 288 trials in total). In contrast to the whole-report task, stimuli were always followed by a mask under 16 conditions (4 of target conditions, 8 target and distractor conditions, and 4 dual target conditions). From the probabilities of target report, attentional weights were separately derived for targets and distractors, and for each visual hemifield, based on TVA. More specifically, the selectivity of attentional weighting, or top-down control α,

was estimated as the ratio of the attentional weights allocated to targets to the weights assigned to distractors. Lower α values would then indicate high selectivity or preference for targets (i.e., more efficient top-down control), whereas higher values would indicate less selective processing. In turn, the spatial distribution of attention across visual hemifields, or spatial laterality w_{lat}, was defined as $w_{left}/ (w_{left} + w_{right})$, where w_{left} indicates the attentional weight allocated to the left visual hemifield and w_{right} the attentional weight allocated to the right visual hemifield. A value of 0.5 indicates balanced weighting, whereas values above or below 0.5 would be indicative of, respectively, left- or rightward spatial laterality (Finke et al., 2005).

Resting-state fMRI

Imaging data acquisition

Imaging data were acquired on a 3T MR scanner (Achieva TX, Philips, Netherlands) with an 8-channel phase-array head coil. Participants lay comfortably with their heads surrounded by soft foams to reduce head motion. Before starting the functional data acquisition, participants were instructed to close their eyes but avoid falling asleep (i.e., resting state), and we checked with them at the end of the sequence that they had not done so. Functional data were collected across 10 min 52 s during resting state, and comprised 250 T2*-weighted volumes using a gradient-echo echo-planar sequence: TR = 2,608 ms; TE = 35 ms; flip angle = 90°; FOV = 230 mm^2; matrix size = 64 x 63, 41 slices with 3.58 mm thickness and no interslice gap; reconstructed voxel size = 3.59 mm isotropic. Structural data were obtained from a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence: TR = 7.71 ms; TE = 3.93 ms; flip angle = 15°; field of view (FOV) = 256 mm^2; matrix = 256 x 256, 180 slices; voxel size = 1 mm^3.

Imaging data preprocessing

Imaging data were preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSF; Chao-Gan and Yu-Feng 2010), a toolbox in MATLAB (R2013a, version 8.1.0.604; The Mathworks Inc.; Natick, MA, USA). Briefly, the preprocessing included realignment, reorientation to the AC-PC axis of functional and structural images; segmentation of the structural T1-weighted image and co-registration of the segmented T1-weighted and the T2*-weighted functional images. No participant had to be excluded

based on excessive head motion, which was defined as cumulative translation or rotation larger than 3 mm or 3° or mean point-to-point translation or rotation greater than 0.15 mm or 0.1°. Six head motion parameters, as well as white-matter, CSF, and global signals were entered as nuisance covariates and regressed out from the functional data. Next, functional images were normalized into the Montreal Neurological Institute (MNI) space using unified segmentation of T1 image (Ashburner and Friston 2005), and resampled to 2 mm isotropic voxel size to keep the highest resolution possible. The normalized images were then smoothed using a 4 mm full-width-at-half-maximum (FWHM) Gaussian kernel.

Independent component and dual regression analyses

Preprocessed data were temporally concatenated and analyzed by probabilistic independent component analysis (ICA) as implemented in FSL (version 5.0.7) Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC version 3.14). In more detail, data were normalized for voxel-wise mean and variance, high-pass filtered (100 s cutoff), and then reduced into a 20-dimensional subspace by probabilistic principal component analysis. A low dimensionality was chosen to decompose the data into more spatially extended components reflecting intrinsic brain networks (Smith et al., 2009). Next, data were decomposed into time courses and spatial maps by optimizing for non-Gaussian spatial distributions using a fixed-point iteration technique (Hyvarinen 1999). Finally, estimated group-level component maps were divided by the standard deviation of the residual noise and thresholded by fitting a mixture model to the histogram of intensity (Beckmann and Smith 2004).

To obtain estimates of independent components for each participant, we performed dual regression analysis separately (Beckmann, Mackay, Filippini et al., 2009; Filippini, MacIntosh, Hough et al., 2009). The group independent components generated in the group ICA are the input for the dual regression analysis (Beckmann et al., 2009; Filippini et al., 2009; Zuo et al., 2010). Dual regression analysis allows quantifying, for each subject, the FC of each voxel with each group independent component while controlling for all other components – some of which represent artifacts (Smith, Utevsky, Bland et al., 2014). Crucially for our study, dual regression analysis has been shown to better detect individual variability in FC in comparison with traditional approaches such as seed-based analysis (Smith et al., 2014).

In the dual regression analysis, the group-average ICA-generated set of independent components was first regressed onto each participant's 4D preprocessed dataset. This regression yielded 20 time-courses – one per independent component – for each subject. Next, these time courses were regressed onto the same 4D datasets, which resulted in 20 spatial maps – one per independent component – for each subject (Filippini et al., 2009). Finally, group spatial maps were obtained using FSL's *randomise* permutation-testing tool, based on 500 permutations and a p-value of 0.05, corrected for multiple comparisons by threshold-free cluster enhancement (TFCE; Smith and Nichols 2009).

The individual networks for each participant included voxel-wise Z-scores or standardized parameter estimates (by the residual within-subject noise) obtained from the second regression. In other words, each map contained voxel-wise information on the particular contribution to an independent component while controlling for the influence of its contribution to all the other components (Filippini et al., 2009; Smith et al., 2014). Thus, each participant has 20 individual maps (one for each component); within each map, the Z-score of every voxel reflects how closely the voxel's time course resembles that group component's time course. These individual voxel-wise Z-maps were further used for group statistics, in which group differences could manifest in any brain region belonging to the independent component, irrespective of whether or not that region is *typically* included in the brain network that the independent component represents (Smith et al., 2014).

Selection of intrinsic brain networks for further statistical analysis

The particular choice of networks we focused our analyses on was based on both the neural interpretation of TVA (Bundesen et al., 2005) and the standard templates of intrinsic brain networks reported in the resting-state fMRI literature (e.g., Allen et al., 2011; Yeo et al., 2011). However, to find a distinctive correspondence between visual attention parameters and intrinsic brain networks, we first needed to ensure that the relative independence among networks was comparable to that among the different TVA parameters. Therefore, we chose ICA over, e.g., a seed-based approach. First, as a multivariate approach, ICA can yield a set of statistically independent sources or components (Beckmann and Smith 2004). Second, as a data-driven approach, it can extract noise from the signal (e.g., both physiological and scanner-related) (Zuo et al., 2010).

We selected the independent components that represent intrinsic brain networks relevant for visual attention. First, we identified relevant intrinsic networks by referring to typical networks described previously. In detail, to automatically select independent components reflecting intrinsic networks, we conducted multiple spatial cross-correlations with templates derived from FC based on resting-state fMRI of 1000 healthy subjects (Yeo et al., 2011), in which a 7-network parcellation of the cortex was found robust, including visual, dorsal and ventral attention, and frontoparietal networks. It should be noted that the labeling of these networks – though fitting in the context of attention research – is somewhat arbitrary, as these networks are also involved in other cognitive functions (Smith et al., 2009), i.e., there is no one-to-one mapping between intrinsic networks and function. After that, we chose the networks that best covered regions proposed by neural TVA to contribute to visual attention functions (i.e., frontal, parietal, limbic, and occipital; Bundesen et al., 2005), in particular: the visual, executive control, lateralized frontoparietal, and ventral and dorsal attention networks. To be independent of the special parcellation approach used by Yeo and colleagues for intrinsic networks (i.e., clustering), we considered reasonable to compare our spatial maps with network templates obtained using ICA. Thus, we conducted further spatial cross-correlations but with intrinsic brain network templates derived from an ICA approach based on the resting-state fMRI data of 603 healthy subjects (Allen et al., 2011). We found the chosen networks to exhibit the greatest overlap with frontoparietal and occipital-visual networks (i.e., IC60, IC72, IC55, IC34, IC64, and IC27 of Allen et al., 2011) that have been related with attention functions previously (e.g., Corbetta and Shulman 2002; Dosenbach, Fair, Miezin et al., 2007; Dosenbach, Fair, Cohen et al., 2008; Finke et al., 2015; Fox et al., 2006; Smith et al., 2009; Vincent, Kahn, Snyder et al., 2008), thus confirming our selection of attention-relevant brain networks. Please note that the extension of ICA-derived spatial maps can have a larger extension and include more regions than those classically associated with a specific network (Smith et al., 2014), without compromising the reliability of the method (Zuo et al., 2010).

Statistical analysis

Intra-network differences in functional connectivity between performance groups

Based on the individual TVA parameter estimates, the group median was calculated and used to split the sample into 'high' and 'low' performers (for parameters

visual processing speed C, visual short-term memory capacity K, and top-down control α) and left- and right- preference (for parameter spatial laterality w_{lat}). Next, we tested for differences in intrinsic FC in visual attention-relevant brain networks between the groups based on the median splits using Statistical Parametric Mapping, SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8/). Specifically, using a second-level (i.e., group) general linear model, we predicted each voxel's intra-network FC (within each visual attention-relevant network) from TVA performance (i.e., performance group of the variable of interest), controlling for the remaining three TVA parameters and for education and gender (i.e., variables of no interest).

Because our goal was to systematically examine whether and how TVA parameters are independently mapped onto distinct functional networks of the healthy brain, we performed six (i.e., one for each brain network) two-sample t-tests for each TVA parameter of interest. In the general linear model, intra-network FC was predicted from 7 parameters (i.e., 24 degrees of freedom). The two main parameters on which the contrasts were further tested corresponded to group (i.e., 'high' and low' performers). Within each group, the images included the individual network-specific Z-maps derived from dual regression; each voxel within each of these maps contained a value of how close its time course reflected the group component's time course. Results were corrected for multiple comparisons ($p < 0.05$ FWE-corrected at the cluster level, voxel-wise height threshold $p < 0.001$) and only results surviving the additional Bonferroni corrections at the network level (i.e., p_{corr} 0.05 / 6 networks = 0.0083) were considered further.

We chose a median split over a linear regression approach, for the following reasons. First, given the strong homogeneity of our sample regarding demographics, brain integrity, and behavior, we had no reasons to expect a linear relationship – or a particular direction of it – between intrinsic FC and TVA parameters. Second, as previous TVA-based studies on small healthy samples had revealed significant differences between performance groups in experimental manipulations (e.g., Finke, Dodds, Bublak et al., 2010) or brain measures (e.g., Wiegand, Tollner, Habekost et al., 2014), we wanted to keep our analyses and results comparable to these studies. Third, TVA parameters have been proposed to reflect latent traits of attentional capabilities (Finke et al., 2005), i.e., they can be taken to be relatively stable characteristics of a given individual. Given this, we can assume that our median split-defined groups are random samples of 'high' and 'low' performers from the population. Finally, the independence of TVA parameters is

given mathematically (Bundesen 1990) and empirically (Habekost, Petersen, and Vangkilde 2014), which reduces the probability (Iacobucci, Posavac, Kardes et al., 2015) of Type I errors (Maxwell and Delaney 1993). Note that, in our sample too, these parameters are statistically independent: p-values > 0.072.

Inter-network differences in functional connectivity between performance groups

We used the results of the first stage of the dual regression to implement inter-network connectivity analyses. For each subject, we correlated the time courses of the six independent components of interest and performed Fisher r-to-z transformation. Next, we tested whether the inter-network FC was significantly higher for 'high' than for 'low' performers. Finally, we examined whether intra-network FC correlated with inter-network FC.

Results

Visual attention parameters

Mean TVA parameter estimates for the entire sample, as well as separately for each performance and spatial laterality preference group are listed in Table 2. Note that for the spatial laterality parameter w_{lat}, the group mean did not differ from the value of 0.5, which indicates optimally balanced attention [$t(30) = -0.569$, $p = 0.573$]. Males and females did not differ significantly in any of the TVA parameter estimates (data not shown; all p-values > 0.179). The TVA parameters did not significantly correlate with each other (all p-values > 0.072; see Table 3 for pairwise correlations). Furthermore, except for a significant correlation between processing speed C and IQ (r = 0.37, p = 0.039), they also did not correlate with any of the demographic variables in the entire sample (all other p-values > 0.135). The group medians for the four TVA parameters used to split the sample are listed in Table 2. Importantly, the resulting groups differed exclusively in the TVA parameter of interest and not in any of the other TVA parameters, education, age, IQ, or gender [C: $t(18.8) = 5.382$, $p < 0.0001$, all other covariates: $p > 0.150$; K: $t(17) = 6.634$, $p < 0.00001$, all other covariates: $p > 0.108$; α: $t(29) = -9.308$, $p < 0.00001$, all other covariates: $p > 0.184$; w_{lat}: $t(29) = -6.764$, $p < 0.00001$, all other covariates: $p > 0.191$]. It is worth noting that only six participants (five males and one female) were always classified as 'high' (three) or 'low' (three) performers for C, K, and

α. These participants did not differ in any demographic or TVA variable from the rest of the sample ($p > 0.506$). Thus, our participants have a distinct profile in terms of the different parameters, instead of exhibiting a more general, either 'good' or 'poor' visual attention performance. Importantly, this corroborates the independence assumption maintained for the TVA parameters (e.g., Habekost et al., 2014) and indicates that the median split methodology can be validly applied here.

Selection of brain networks relevant for visual attention

Six components that comprised occipital, lateral frontal and parietal, and limbic regions were selected as relevant for visual attention out of 12 functionally relevant components (Figure 2). These components were cross-correlated with the templates of Yeo et al., (2011) as well as with the ICA-based 28 network templates of Allen et al., (2011), and those with the highest coefficients were selected as networks (e.g., IC3: r = 0.57 with IC60 of Allen et al.; IC4: r = 0.40 with IC72; IC6: r = 0.49 with IC55; IC7: r = 0.34 with IC34; IC11: r = 0.43 with IC64; and IC18: r = 0.45 with IC27).

The components shown in Figure 2 comprise the IC11 or 'visual' network, mainly encompassing occipital clusters on the lingual gyri and calcarine sulci, as well as clusters on the right middle frontal gyrus, and postcentral gyrus bilaterally. The IC18 or 'executive control' network included temporal and frontal clusters bilaterally on the superior and middle temporal gyrus, and the inferior frontal and precentral gyri, as well as on the precuneus and calcarine sulci. The IC3 or 'right frontoparietal' network comprised parietal clusters bilaterally on the inferior parietal lobule, superior and middle temporal gyrus, and inferior frontal gyrus, as well as on the left cerebellum and left calcarine sulcus. For IC7 or 'left frontoparietal' network, clusters were observed mainly in left frontal and parietal areas, including the inferior frontal gyrus, intraparietal sulcus, as well as in the right cerebellum, and left and inferior temporal gyri. The IC6 or 'ventral attention' network included bilateral frontoinsular regions such as the insula, anterior and middle cingulate cortex, middle frontal gyrus, as well as bilateral regions of the cerebellum, the thalamus, and the caudate nucleus, and of parieto-occipital areas. Finally, the IC4 or 'dorsal attention' network was formed by bilateral parietal clusters of the precuneus, superior and inferior parietal lobules, supramarginal gyrus, as well as middle and inferior temporal, superior frontal, precentral, and fusiform gyri, and cerebellum.

Intra-network differences in functional connectivity between performance groups

Based on our approach of median splits of a group of healthy participants, we observed voxel-wise intrinsic FC group differences in three particular attention-relevant brain networks (Table 4). With respect to capacity parameters, we found significant group differences for visual processing speed *C* in the ventral attention network, but no significant differences for VSTM capacity *K*. With regard to weighting parameters, we found significant group differences for top-down control α in the dorsal attention and visual networks. In addition, for spatial laterality w_{lat}, we found significant differences in the right frontoparietal network – though this result did not survive Bonferroni correction at the network level (Table 4). In more detail, the group with relatively higher visual processing speed showed lower intrinsic FC of the right middle frontal gyrus in the ventral attention network (Figure 3). Moreover, more efficient top-down control was associated with higher FC of the right precuneus in the dorsal attention network, but also with lower FC of the right calcarine sulcus in the visual network.

To account for possible differences in e.g., noise levels between groups we calculated the temporal signal-to-noise ratio of the realigned fMRI time series and repeated the analyses including it as a covariate in the model. In the case of the ventral attention and visual networks, the results remained the same [$t(23) = 4.74$, $p = 0.008$, $k = 60$ voxels for the ventral attention network, and $t(23) = 6.49$, $p = 0.001$, $k = 129$ voxels for the visual network; same cluster peaks for both as in Table 4]. In the case of the dorsal attention network, the results were slightly reduced, but still significant [$t(23) = 6.26$, $p = 0.013$, $k = 33$ voxels]. Thus, group differences were not explained by systematic differences in signal quality.

Directionality of functional connectivity differences

Although we had no strong expectations regarding the directionality of the results, we decided to explore *inter*-network FC (i.e., among brain networks) to better understand the finding of a relatively lower intra-network FC (i.e., among brain regions within one network) in 'high' compared to 'low' performers. More specifically, we wanted to ascertain whether or not a higher *inter*-network FC is observed for the visual and ventral attention networks (i.e., those with lower *intra*-network FC) in high performers. Inter-network FC has been shown to vary among individuals, and this variation is associated with attention performance (Kelly, Uddin, Biswal et al., 2008). Thus, we expected to find

a difference also in inter-network FC between high and low performers. Moreover, the strength of the negative relationship between 'task-positive' and 'task-negative' networks has been associated with more consistent behavioral performance (Kelly et al., 2008). Thus, we hypothesized a *positive* relationship among 'task-positive' networks for high performers. Finally, we determined whether a *high* inter-network FC is related to the *low* intra-network FC of the visual and ventral attention networks.

Inter-network differences in functional connectivity between performance groups

We tested whether the inter-network FC was significantly higher for 'high' than for 'low' performers in the visual and ventral attention networks. Finally, we examined whether a lower intra-network FC correlated significantly with higher inter-network FC.

To start with, the correlation matrix of the Z values (i.e., r-to-z transformation), averaged across the entire sample, is presented in Figure 4 to illustrate the inter-network FC. Next, Figure 5 depicts a group matrix for both visual processing speed C (left) and top-down control α (right), summarizing significant differences in inter-network FC between high and low performers. We only tested differences in the ventral attention network for visual processing speed, and in the visual network for top-down control (vector framed by white) – because, in both cases, the respective intra-network FC was lower for high compared to low performers. We found only the inter-network FC of the ventral attention network with the right frontoparietal network to be significantly increased for the group with higher visual processing speed C estimates (mean Z value for high performers, 0.269 vs. 0.116 for low performers, $t(29) = 1.685$, $p = 0.051$, 1-tailed). For top-down control, only the inter-network FC of the visual network with the executive control network was significantly increased for the group with better (i.e., lower) top-down control α estimates (mean Z value for better, 0.020 vs. -0.111 for poorer, $t(29) = 1.895$, $p = 0.030$, 1-tailed). These results, however, do not survive Bonferroni correction (i.e., $p = 0.01$).

The observed high inter-network FC in high performers could explain the low intra-network FC. To test for this possibility, we computed the correlation between intra-network FC in the ventral attention and visual networks and inter-network FC with the right frontoparietal and executive control networks, respectively. We controlled for the intra-network FC of the right frontoparietal and executive control networks, respectively. Marginally ($r = -0.28$, $p = 0.069$) and significantly negative (r = -0.31, p = 0.045)

correlations were found for the ventral attention and visual networks, respectively. This pattern indicates that high inter-network FC could indeed explain the observed low intra-network FC in high performers.

Discussion

We examined whether and how visual attention parameters derived from TVA-based model fitting that are assumed to represent latent traits underlying the individual efficiency of the visual selection process are mapped onto distinct brain networks obtained from intrinsic functional connectivity (FC). We divided the sample into groups of high and low performers for each relevant TVA parameter and compared their FC of networks that encompass cortical regions relevant for visual attention.

First, we found significant intra-network FC group differences for two TVA parameters. Participants with higher, compared to those with lower, visual processing speed exhibited lower FC of the right middle frontal gyrus within the ventral attention network. Furthermore, participants with more efficient, compared to those with less efficient, top-down control exhibited higher FC of the right precuneus within the dorsal attention network and lower FC of the right calcarine sulcus within the visual network.

Second, we found that for those networks where participants with superior attentional performance showed lower *intra*-network FC than those with inferior performance, the same participants also showed higher *inter*-network FC. More precisely, significantly higher inter-network FC was found for the ventral attention network with the right frontoparietal network in the group with higher compared to that with lower processing speed. For top-down control, significantly higher inter-network FC was found for the visual network with the executive control network in the group with more efficient compared to that with less efficient top-down control. Our results demonstrate for the first time a distinctive correspondence between particular visual attention parameters and FC of different brain networks.

Visual attention capacity parameters

Visual processing speed *C* and the ventral attention network

Our finding of a linkage between visual processing speed and FC within the ventral attention network, and particularly in the right middle frontal gyrus, points to a role of this frontoparietal, limbic network for the rate of visual information uptake. As the

ventral attention network has been previously documented to be relevant for tonic alertness (e.g., Coste and Kleinschmidt 2016; Sadaghiani, Scheeringa, Lehongre et al., 2010; Sestieri, Corbetta, Spadone et al., 2014), our current result shows agreement with theoretical proposals (Bundesen, Vangkilde, and Petersen 2015) and empirical evidence (Finke et al., 2010; Matthias, Bublak, Costa et al., 2009; Petersen, Petersen, Bundesen et al., 2017; Wiegand, Petersen, Finke et al., 2017; Vangkilde, Coull, and Bundesen 2012) for a close link between alertness and visual processing speed.

Although uncorrected for multiple comparisons, our further finding on higher inter-network FC between the ventral attention and the right frontoparietal network further supports the close link between alertness and visual processing speed. Right-sided brain regions have generally been implicated in the maintenance of an alert state under conditions without external warning cues (i.e., tonic alertness) and with increased time on task (i.e., vigilance) (e.g., Pardo, Fox, and Raichle 1991; Sturm and Willmes 2001). In healthy individuals, the right middle frontal gyrus has been shown to exhibit higher activity during maintenance of an alert state (Sturm, de Simone, Krause et al., 1999), as well as higher spontaneous activity during high degrees of tonic alertness, as measured by pupil size changes (Schneider, Hathway, Leuchs et al., 2016). Moreover, in patients with tonic alertness deficits following right-sided ventral lesions, tonic alertness training leads to an increase in the activity of the right middle frontal gyrus (Thimm, Fink, Kust et al., 2006). Similarly, stroke damage to areas in the right mid-frontal lobe, often involved in the neglect syndrome, can also produce deficits in sustained attention (Husain and Rorden 2003). Finally, evidence from structural connectivity has also shown that the degree of right-side lateralization of the inferior fronto-occipital fasciculus is positively associated with visual processing speed in healthy young subjects (Chechlacz et al., 2015). In sum, in young healthy adults who process visual information faster, these frontoinsular and parietal networks that are important for tonic and phasic alertness, respectively, appear to be functionally well coupled.

According to TVA, visual processing speed represents the number of visual elements that can be categorized in a given unit of time (e.g., one second; Bundesen 1990). This rate of encoding into VSTM depends on the strength of the sensory evidence, a perceptual decision bias, and on the relative attentional weight of a specific object. In the neural interpretation of TVA, NTVA (Bundesen et al., 2005), the encoding speed is suggested to depend on both the number of cortical neurons representing the categorization and the firing rates of those neurons. More specifically, a perceptual

decision bias determines how an object is categorized by changing the firing rate of the cortical neurons that code a particular feature (i.e., 'pigeonholing'). The individual overall visual processing speed, parameter C, has been related, both theoretically and empirically, to alertness functions. For example, stimulant medication with methylphenidate and modafinil (Finke et al., 2010) as well as experimental manipulations enhancing phasic alertness (Matthias et al., 2009) have been shown to lead to an increase in this attentional capacity parameter. Recently, the effects of phasic alertness and temporal expectancy of upcoming stimuli were more formally integrated into the theory. More specifically, an enhancement of overall visual processing speed C was suggested, which would be given by a multiplicative upscaling of the activation, i.e., of the firing rates of all neurons coding the presented stimulus array by changes in perceptual bias (Vangkilde et al., 2012; Wiegand et al., 2017). Bias values have been proposed to derive from higher order areas (e.g., in frontal cortex) and, directly or indirectly, from the limbic system (Bundesen et al., 2005).

VSTM storage capacity K

One reason for our non-significant findings regarding this parameter might be the low variability in its estimates and, thus, the lack of statistical power at the present sample size. Another reason might be the reliance of VSTM capacity on spatially organized sustained activity implemented via recurrent thalamocortical feedback loops (Bundesen et al., 2005), as supported by studies on the connectivity of thalamocortical fibers (Menegaux, Meng, Neitzel et al., 2017). Thus, future studies could examine inter-network thalamocortical FC in samples with greater variance in this parameter (e.g., in aging).

Visual attention weighting parameters

Top-down control α and dorsal attention and visual networks

From a mechanistic perspective, the neural TVA suggests that top-down control is a selection bias, whereby higher 'attentional weights' are assigned to objects that belong to a currently relevant category (e.g., red letters) (Bundesen et al., 2005). In the present study, we found that more efficient top-down control was linked with higher FC within the dorsal attention network, particularly in the precuneus. This result is in agreement with task-based neuroimaging studies (e.g., Giesbrecht, Woldorff, Song et al., 2003; Hopfinger, Buonocore, and Mangun 2000; Vossel et al., 2016; Weissman, Mangun, and

Woldorff 2002; Wojciulik and Kanwisher 1999), which have also revealed a general role of dorsal parietal regions in the control of selective attention. Importantly, however, our results add to the existing evidence for a role of the precuneus in attentional top-down controlled, task-based selection that is *independent* of individual capabilities in spatial attentional selection or processing speed.

We found that more efficient, compared to less efficient, top-down control was associated with lower FC within the visual network, particularly in the calcarine sulcus. Moreover, more efficient control was related to higher FC between the visual and the executive control networks, though this result did not survive Bonferroni correction. Importantly, lower FC within the visual network was significantly associated with higher FC of the visual with the executive control network. Thus, it appears that it is the degree of functional coupling of the visual network with the executive control network that might be relevant for the individual degree of efficiency of top-down control. This finding accords with the assumption of a critical role of the executive control network in the adaptive control of goal-directed selection (Dosenbach et al., 2007; Dosenbach et al., 2008). Collectively, ours and previous findings suggest, in agreement with theoretical accounts on visual attentional processing, that the efficiency of top-down control is related to the degree of interaction between the executive control network generating attentional control signals and sensory structures that process visual information (Bressler, Tang, Sylvester et al., 2008; Bundesen et al., 2005; Corbetta and Shulman 2002; Desimone and Duncan 1995; Posner and Petersen 1990).

Although we failed to find a significant inter-network FC between the visual and the dorsal attention networks, our results do not imply a lack of functional interaction between them. Instead, our results only allow us to suggest that higher intra-network FC in the dorsal attention network is by itself relevant for more efficient top-down control. In consequence, the relevant role of the intra-network FC in top-down control would then be additional to that of the inter-network FC between the visual and the executive control networks. This interpretation would fit a view in which multiple cortical and non-cortical sources can be involved in top-down control as long as they can carry information on task-related top-down control (Gilbert and Li 2013). In this regard, our finding of a significant inter-network FC of the visual network with the executive control network is not entirely surprising. In particular, the prefrontal cortex – a central component of the executive control network – has been revealed as a source of biasing signals in object-based attention (Baldauf and Desimone 2014). Thus, from our perspective, rather than

directly implying a lack of interaction between the visual and the dorsal attention networks—or an exclusivity of the executive control network for top-down control over the visual network—our results highlight the relevance of all three networks.

Spatial laterality w_{lat}

The lack of significant (Bonferroni corrected) group differences in any network for this parameter is not surprising in this sample of healthy young participants, given that no significant deviation from 0.5 in their w_{lat} values was present. In neurologically impaired samples, by contrast, parameter w_{lat} does exhibit high variance, such as in patients with mild cognitive impairment and mild Alzheimer's disease, in which significant spatial biases have been revealed (Redel, Bublak, Sorg et al., 2012; Sorg et al., 2012). Accordingly, studies on groups with more evident lateralized attentional performance might well reveal a relationship of parameter w_{lat} with FC.

Visual attention functions in the "resting brain"

In mice, infra-slowly spontaneous neuronal fluctuations (i.e., $0.01 - 0.1$ Hz) have been shown to underlie the intrinsic FC obtained from BOLD fMRI (Matsui et al., 2016). In humans, spontaneous slow cortical potentials (< 0.5 Hz) measured with intracranial EEG have also been shown to be associated with intrinsic FC, where both have been proposed to reflect fluctuations of cortical excitability (He, Snyder, Zempel et al., 2008; Raichle 2011). These fluctuations indicate spontaneous subthreshold depolarizations of the cortical neuronal membranes, which influences the level of activation of cortical neurons (Wu et al., 2008). If spontaneous fluctuations of cortical excitability do indeed influence attention continuously, their spatial patterns of coherence among brain regions and networks could be captured by intrinsic FC. In consequence, the differential spatial patterns obtained by FC could, then, distinguish among separable attention traits.

In support of such links, previous findings have suggested that particular functional interactions within (Markett et al., 2014; Rosenberg et al., 2016) and between (Kelly et al., 2008) spontaneously active functional networks relate to individual differences in performance in attention tasks. In agreement with these findings, here we also identified particular functional networks whose intra- and inter-network FC corresponds to specific, separable visual attention functions represented by individual parameters or latent traits (Finke et al., 2005).

Functional implications and further issues

Collectively, our results offer an array of possibilities, based on the analysis of the brain's intrinsic activity, to trace the loss or gain in specific visual attention functions under pathological or cognitively-enhancing conditions. Visual attention functions can be impaired to varying degrees and further interact in a particular neurological or psychiatric disorder. Therefore, identifying the correspondence between those functions and the multiple functional organization of the healthy brain can help to understand the different attentional syndromes they cause. For example, it is clear from previous work that the severity of the spatial deficits in neglect – a neurological syndrome mainly with rightward attentional bias – also depends on the integrity of functional networks that support non-spatial functions (Corbetta, Kincade, Lewis et al., 2005; He, Snyder, Vincent et al., 2007; Husain and Rorden 2003).

Some neurological disorders, however, can present with less evident visual attention deficits. For example, as our group has previously reported, amnestic mild cognitive impairment and incipient Alzheimer's disease can present with both top-down control deficits (Redel et al., 2012) and a staged slowing of visual processing (Bublak, Redel, Sorg et al., 2011). Particularly – though not exclusively – in these cases, our results set a ground to focus on a functional network when investigating the interaction among visual attention deficits and with other cognitive or behavioral symptoms, or their change with disease progression. The advantage of our approach lies on its feasibility for patient populations, as information on multiple visual attention traits and functional networks can be obtained with two simple psychophysical tasks and one short, easy fMRI session.

Our results mainly highlight the relevance of particular functional networks for both visual attention capacity and weighting parameters. As a voxel-wise approach was used to identify those functional networks, differences were observed in specific regions within those networks. However, we do not see those regions as respectively 'responsible for' visual processing speed or top-down control: The voxels conforming those regions have values that indicate their connectivity with a particular network (Beckmann et al., 2009; Smith et al., 2014) and not values indicating their levels of activity. Rather, we see them simply as clusters whose voxels reached statistical significance in this particular sample; at best, they allowed us to identify the relevant networks for visual attention

functions. Furthermore, given that we relied on the group median to divide this sample, we cannot make strong claims about an 'increased' or 'decreased' FC in healthy young adults. We think it would be more useful to elucidate whether the directionality of FC holds practical significance in terms of, for example, predicting the level of BOLD activity or connectivity during the whole- and partial-report tasks. Previous task-related fMRI studies have shown that individual differences in visual attention functions might not be reflected in differences in BOLD evoked amplitudes (Gillebert, Dyrholm, Vangkilde et al., 2012) but in differential connectivity between regions (Vossel et al., 2016). Thus, future studies could assess the associations between 'offline' (i.e., during rest) and 'online' (i.e., during task) measures of FC in the context of separate visual attention functions to establish the practical relevance of the directionality of FC.

Limitations

Our results must be interpreted considering several limitations. First, although eye movements were not monitored throughout the tasks, systematic eye movements are unlikely because of the short exposure durations in both whole- and partial-report tasks. Second, previous work has shown that frame-to-frame motion can impact resting-state FC (Power, Barnes, Snyder et al., 2012). Although we relied on the power of ICA to extract noise from the signal corresponding to functional networks (Beckmann and Smith 2004; Zuo et al., 2010), it could still be possible that low-scale noise could influence FC measures. Thus, future studies should consider applying more stringent methods of head motion control, such as head motion scrubbing regressors, even in samples of young adults.

Finally, we checked that our participants had not fallen asleep during the resting-state fMRI sequence, but we cannot entirely exclude that they had done so without being aware of it. However, we are confident that possible micro sleep did not affect our intrinsic functional connectivity measure for two reasons. First, previous research has shown that functional connectivity of both higher order and primary sensory networks can be maintained during the transition from wake to sleep (e.g., Larson-Prior et al., 2009). And second, spatial changes within functional networks (i.e., decoupling of the default mode network) have been reported during deep sleep (e.g., Horovitz et al., 2009). However, it is unlikely that our participants had reached deep sleep within the ~ 11

minutes of the resting-state fMRI sequence as they were not sleep-deprived and reaching deep sleep in an unknown and unusual environment is not easy.

Summary and conclusion

In sum, here we showed that visual attention functions correspond distinctively to the functional connectivity both within and between particular functional networks. Within networks, (i) higher visual processing speed was associated with lower functional connectivity in the ventral attention network; and (ii) more efficient top-down control was associated with higher functional connectivity within the dorsal attention network and lower functional connectivity within the visual network. Between networks, higher functional connectivity was observed between (i) the visual attention and right frontoparietal networks for higher visual processing speed; and (ii) the visual and executive control networks for more efficient top-down control. Finally, lower functional connectivity within a network might be explained by the higher functional connectivity between networks. To conclude, our results point to a distinctive network-based functional representation of separable visual attention functions, which can further serve to test specific hypotheses about the neural mechanisms of visual attention functions in aging or pathology.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

Tables

Table 1. Demographic variables

Demographic variable	Entire sample (n = 31)	Females (n = 14)	Males (n = 17)	*p*-value
Age [years]	26.56 ± 0.55	26.61 ± 0.55	26.52 ± 0.56	0.680
Education [years]	11.55 ± 1.59	11.50 ± 1.56	11.59 ± 1.66	0.881
Intelligence [IQ]	99.94 ± 11.64	100.57 ± 8.55	99.41 ± 13.93	0.788

Mean ± standard deviations are shown.

Table 2. TVA parameter estimates

TVA parameter	Entire sample (n = 31)	High performance (n = 16)	Low performance (n = 15)
Processing speed C (Md = 24.30)	25.89 ± 7.34	30.76 ± 7.05	20.70 ± 2.45
VSTM capacity K (Md = 2.83)	3.03 ± 0.47	3.37 ± 0.41	2.66 ± 0.10
Top-down control α (Md = 0.49)	0.52 ± 0.21	0.34 ± 0.12	0.71 ± 0.10
		Right preference (n = 16)	Left preference (n = 15)
Spatial laterality wlat (Md = 0.49)	0.49 ± 0.06	0.45 ± 0.04	0.54 ± 0.03

Mean ± standard deviation are shown. *Md* = Median value used to split the groups.

Table 3. Pairwise correlations among TVA parameters

TVA parameters	C	K	α
C			
K	.18 (p = .328)		
α	.18 (p = .343)	.20 (p = .284)	
w_{lat}	-.09 (p = .636)	-.03 (p = .873)	.33 (p = .073)

TVA parameters: C: visual processing speed; K: visual short-term memory storage capacity; α: top-down control; w_{lat}: spatial laterality

Table 4. Group differences in intrinsic FC between subgroups defined according to TVA parameters

TVA parameter	Brain network	Peak brain area	Cluster size (voxels)	MNI coordinates (x, y, z) in mm	t value	p value
C	Ventral attention	R middle frontal	60	36, 54, 20	4.79	0.008*
K	-	-	-	-	-	-
α	Dorsal attention	R precuneus	36	12, -62, 60	6.38	0.008*
	Visual	R calcarine sulcus	126	8, -76, 10	6.52	0.001*
w_{lat}	Right frontoparietal	R Angular	55	34, -70, 50	5.08	0.038

L: Left; R: Right. All p values are corrected for Family-Wise Error (FWE). *Survive additional Bonferroni correction ($p = 0.05 / 6 = 0.0083$) at the network level.

Figures
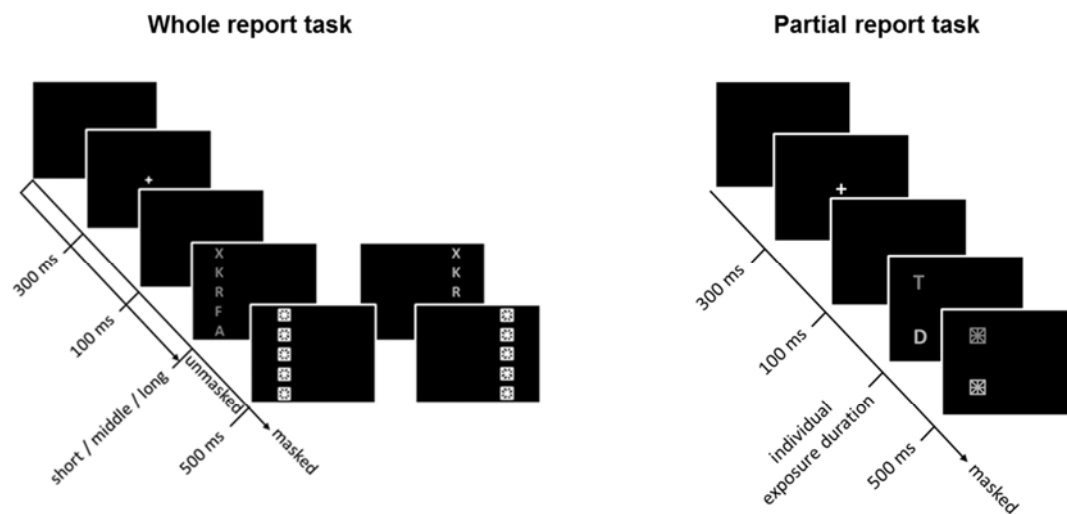
Figure 1. Whole- (left) and partial-report (right) tasks used to assess and estimate visual attention functions. In the partial-report task, targets (T) are presented in red and distracters (D) in green.
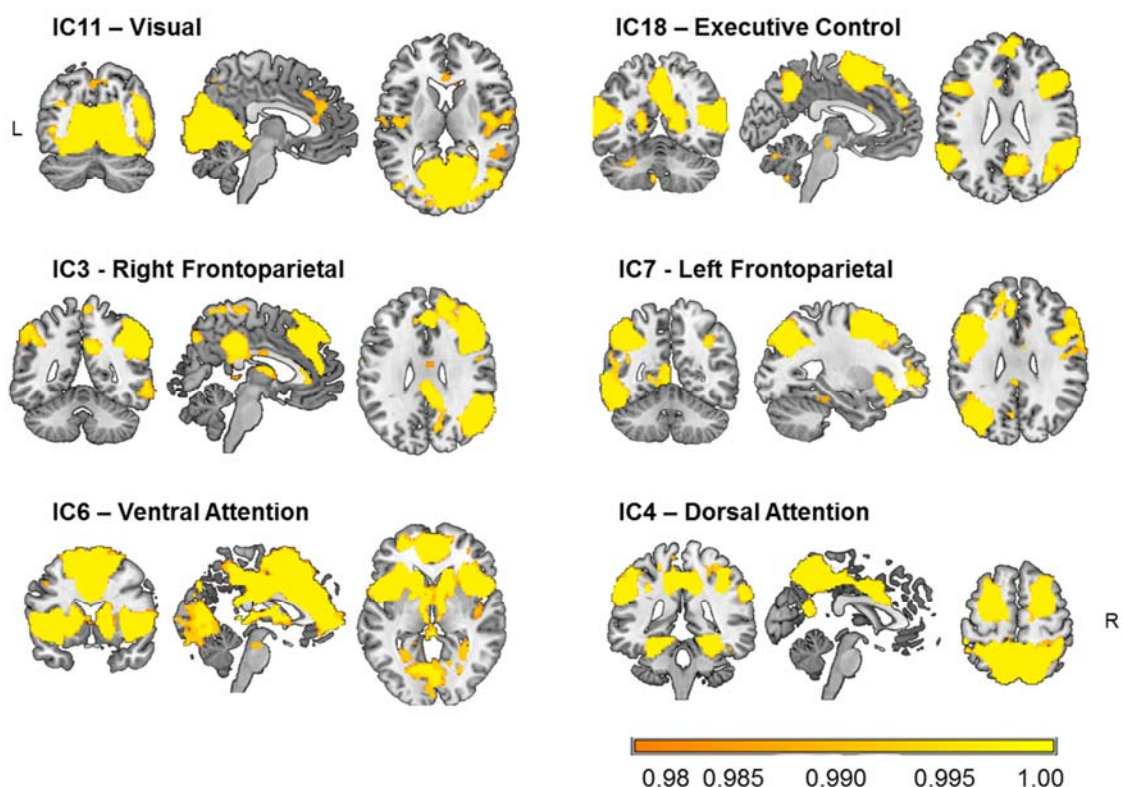
Figure 2. Visual attention-relevant brain networks selected from 20 components obtained from independent component (IC) analysis and dual regression of resting-state BOLD-fMRI data of 31 healthy young participants. The spatial maps represent voxels significantly belonging to each network ($p < 0.05$, FWE-corrected) and are overlaid onto an anatomical high-resolution brain-extracted template in MNI space (MRIcron; Holmes, Hoge, Collins et al., 1998; Rorden and Brett 2000). The labels just serve to identify them and follow conventional names given in the literature.
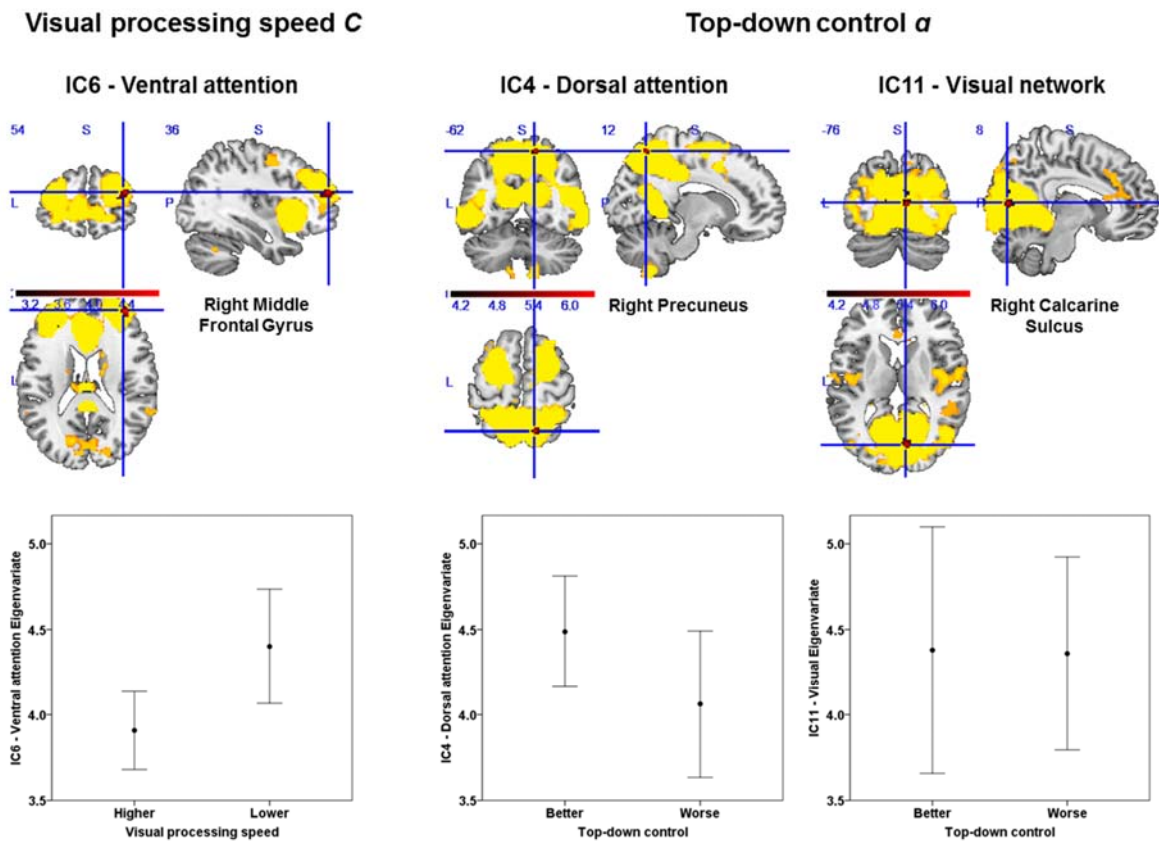
Figure 3. Group differences in intrinsic functional connectivity (FC). The group with higher visual processing speed *C* estimates showed lower FC of the right middle frontal gyrus within a ventral attention network (left part). The group with better top-down control *α* estimates showed both higher FC of the right precuneus within a dorsal attention (middle part) and lower connectivity of the right calcarine sulcus within a visual network (right part). Significant clusters (in red) are overlaid onto the respective group spatial maps of Figure 2 (in yellow). Below these maps, respective group differences can be observed with respect to the Eigenvariate or average FC of the networks. Error bars indicate standard error of the mean. Significant clusters have FWE-corrected *p*-values < 0.0083. Red bars show *t*-values (see also Table 4).
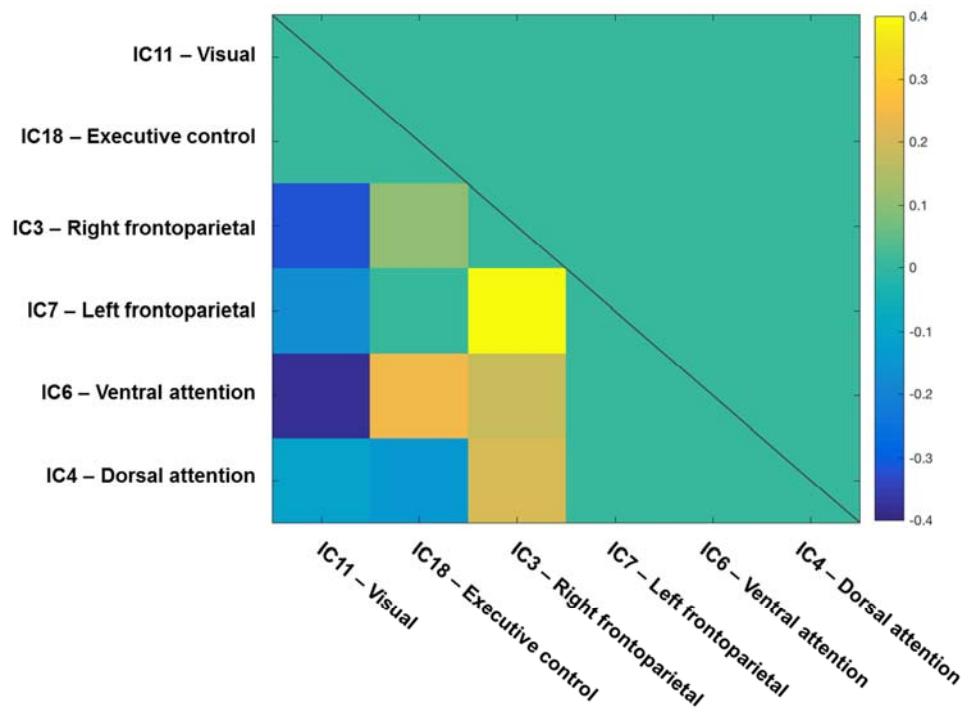
Figure 4. Inter-network functional connectivity (FC) among visual-attention relevant networks. One-sample *t*-test results (q < 0.05 FDR corrected for multiple comparisons) of the correlations among components on one side of a symmetrical matrix (below the diagonal line). Significant correlations are color-coded in warm (positive) and cool (negative) colors, whereas non-significant correlations are coded in turquoise. Spatial maps of components are depicted in Figure 2. The color bar shows mean Fisher r-to-z transformed values.
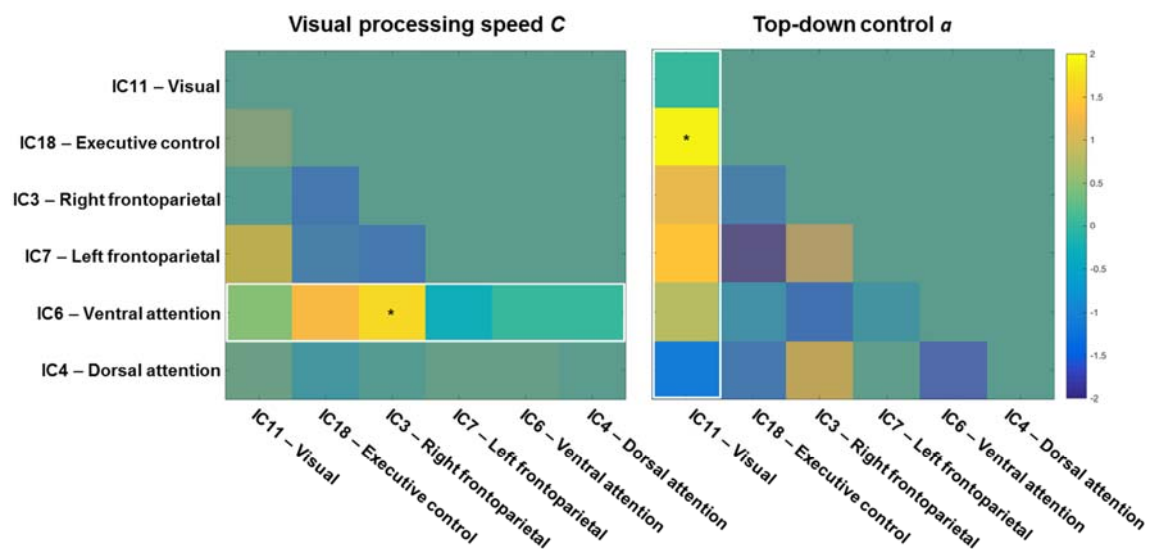
Figure 5. Visual processing speed (left) and top-down control (right) matrices showing t-values of high vs. low performance group differences. Higher inter-network functional connectivity (FC) values of the ventral attention (left) and visual (right) networks with the other networks were tested for the high performance group of speed and top-down control, respectively. The inter-network FC of the ventral attention network with the right frontoparietal network was significantly higher for the group with higher visual processing speed *C*. The inter-network FC of the visual network with the executive control network

was significantly higher for the group with better top-down control α. The color bar shows *t* values (*df* = 29, high vs. low, *p* < 0.05).

References

Allen, E. A., E. B. Erhardt, E. Damaraju, W. Gruner, J. M. Segall, R. F. Silva, et al. 2011. "A baseline for the multivariate comparison of resting-state networks." *Front Syst Neurosci* 5:2. doi: 10.3389/fnsys.2011.00002.

Ashburner, J., and K. J. Friston. 2005. "Unified segmentation." *Neuroimage* 26 (3):839-51. doi: 10.1016/j.neuroimage.2005.02.018.

Baldauf, D., and R. Desimone. 2014. "Neural mechanisms of object-based attention." *Science* 344 (6182):424-7. doi: 10.1126/science.1247003.

Beckmann, C. F., C. E. Mackay, N. Filippini, and S. Smith. 2009. "Group comparison of resting-state FMRI data using multi-subject ICA and dual regression." *Neuroimage* 47 (Suppl 1):S148.

Beckmann, C. F., and S. M. Smith. 2004. "Probabilistic independent component analysis for functional magnetic resonance imaging." *IEEE Trans Med Imaging* 23 (2):137-52. doi: 10.1109/TMI.2003.822821.

Bressler, S. L., W. Tang, C. M. Sylvester, G. L. Shulman, and M. Corbetta. 2008. "Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention." *J Neurosci* 28 (40):10056-61. doi: 10.1523/JNEUROSCI.1776-08.2008.

Brookes, M. J., M. Woolrich, H. Luckhoo, D. Price, J. R. Hale, M. C. Stephenson, et al. 2011. "Investigating the electrophysiological basis of resting state networks using magnetoencephalography." *Proc Natl Acad Sci U S A* 108 (40):16783-8. doi: 10.1073/pnas.1112685108.

Bublak, P., P. Redel, C. Sorg, A. Kurz, H. Forstl, H. J. Muller, et al. 2011. "Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease." *Neurobiol Aging* 32 (7):1219-30. doi: 10.1016/j.neurobiolaging.2009.07.012.

Bundesen, C. 1990. "A theory of visual attention." *Psychol Rev* 97 (4):523-47.

Bundesen, C., T. Habekost, and S. Kyllingsbaek. 2005. "A neural theory of visual attention: bridging cognition and neurophysiology." *Psychol Rev* 112 (2):291-328. doi: 10.1037/0033-295X.112.2.291.

Bundesen, C., S. Vangkilde, and A. Petersen. 2015. "Recent developments in a computational theory of visual attention (TVA)." *Vision Res* 116 (Pt B):210-8. doi: 10.1016/j.visres.2014.11.005.

Chao-Gan, Y., and Z. Yu-Feng. 2010. "DPARSF: A MATLAB Toolbox for "Pipeline" Data Analysis of Resting-State fMRI." *Front Syst Neurosci* 4:13. doi: 10.3389/fnsys.2010.00013.

Chechlacz, M., C. R. Gillebert, S. A. Vangkilde, A. Petersen, and G. W. Humphreys. 2015. "Structural Variability within Frontoparietal Networks and Individual Differences in Attentional Functions: An Approach Using the Theory of Visual Attention." *J Neurosci* 35 (30):10647-58. doi: 10.1523/JNEUROSCI.0210-15.2015.

Corbetta, M., M. J. Kincade, C. Lewis, A. Z. Snyder, and A. Sapir. 2005. "Neural basis and recovery of spatial attention deficits in spatial neglect." *Nat Neurosci* 8 (11):1603-10. doi: 10.1038/nn1574.

Corbetta, M., and G. L. Shulman. 2002. "Control of goal-directed and stimulus-driven attention in the brain." *Nat Rev Neurosci* 3 (3):201-15. doi: 10.1038/nrn755.

Coste, C. P., and A. Kleinschmidt. 2016. "Cingulo-opercular network activity maintains alertness." *Neuroimage* 128:264-72. doi: 10.1016/j.neuroimage.2016.01.026.

Damoiseaux, J. S., and M. D. Greicius. 2009. "Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity." *Brain Struct Funct* 213 (6):525-33. doi: 10.1007/s00429-009-0208-6.

Damoiseaux, J. S., S. A. Rombouts, F. Barkhof, P. Scheltens, C. J. Stam, S. M. Smith, et al. 2006. "Consistent resting-state networks across healthy subjects." *Proc Natl Acad Sci U S A* 103 (37):13848-53. doi: 10.1073/pnas.0601417103.

De Luca, M., C. F. Beckmann, N. De Stefano, P. M. Matthews, and S. M. Smith. 2006. "fMRI resting state networks define distinct modes of long-distance interactions in the human brain." *Neuroimage* 29 (4):1359-67. doi: 10.1016/j.neuroimage.2005.08.035.

Desimone, R., and J. Duncan. 1995. "Neural mechanisms of selective visual attention." *Annu Rev Neurosci* 18:193-222. doi: 10.1146/annurev.ne.18.030195.001205.

Dosenbach, N. U., D. A. Fair, A. L. Cohen, B. L. Schlaggar, and S. E. Petersen. 2008. "A dual-networks architecture of top-down control." *Trends Cogn Sci* 12 (3):99-105. doi: 10.1016/j.tics.2008.01.001.

Dosenbach, N. U., D. A. Fair, F. M. Miezin, A. L. Cohen, K. K. Wenger, R. A. Dosenbach, et al. 2007. "Distinct brain networks for adaptive and stable task

control in humans." *Proc Natl Acad Sci U S A* 104 (26):11073-8. doi: 10.1073/pnas.0704320104.

Filippini, N., B. J. MacIntosh, M. G. Hough, G. M. Goodwin, G. B. Frisoni, S. M. Smith, et al. 2009. "Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele." *Proc Natl Acad Sci U S A* 106 (17):7209-14. doi: 10.1073/pnas.0811879106.

Finke, K., P. Bublak, J. Krummenacher, S. Kyllingsbaek, H. J. Muller, and W. X. Schneider. 2005. "Usability of a theory of visual attention (TVA) for parameter-based measurement of attention I: evidence from normal subjects." *J Int Neuropsychol Soc* 11 (7):832-42.

Finke, K., C. M. Dodds, P. Bublak, R. Regenthal, F. Baumann, T. Manly, et al. 2010. "Effects of modafinil and methylphenidate on visual attention capacity: a TVA-based study." *Psychopharmacology (Berl)* 210 (3):317-29. doi: 10.1007/s00213-010-1823-x.

Finke, K., J. Neitzel, J. G. Bauml, P. Redel, H. J. Muller, C. Meng, et al. 2015. "Visual attention in preterm born adults: specifically impaired attentional sub-mechanisms that link with altered intrinsic brain networks in a compensation-like mode." *Neuroimage* 107:95-106. doi: 10.1016/j.neuroimage.2014.11.062.

Fox, M. D., M. Corbetta, A. Z. Snyder, J. L. Vincent, and M. E. Raichle. 2006. "Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems." *Proc Natl Acad Sci U S A* 103 (26):10046-51. doi: 10.1073/pnas.0604187103.

Fox, M. D., and M. E. Raichle. 2007. "Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging." *Nat Rev Neurosci* 8 (9):700-11. doi: 10.1038/nrn2201.

Giesbrecht, B., M. G. Woldorff, A. W. Song, and G. R. Mangun. 2003. "Neural mechanisms of top-down control during spatial and feature attention." *Neuroimage* 19 (3):496-512.

Gilbert, C. D., and W. Li. 2013. "Top-down influences on visual processing." *Nat Rev Neurosci* 14 (5):350-63. doi: 10.1038/nrn3476.

Gillebert, C. R., M. Dyrholm, S. Vangkilde, S. Kyllingsbaek, R. Peeters, and R. Vandenberghe. 2012. "Attentional priorities and access to short-term memory: parietal interactions." *Neuroimage* 62 (3):1551-62. doi: 10.1016/j.neuroimage.2012.05.038.

Habekost, T., A. Petersen, and S. Vangkilde. 2014. "Testing attention: comparing the ANT with TVA-based assessment." *Behav Res Methods* 46 (1):81-94. doi: 10.3758/s13428-013-0341-2.

He, B. J., A. Z. Snyder, J. L. Vincent, A. Epstein, G. L. Shulman, and M. Corbetta. 2007. "Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect." *Neuron* 53 (6):905-18. doi: 10.1016/j.neuron.2007.02.013.

He, B. J., A. Z. Snyder, J. M. Zempel, M. D. Smyth, and M. E. Raichle. 2008. "Electrophysiological correlates of the brain's intrinsic large-scale functional architecture." *Proc Natl Acad Sci U S A* 105 (41):16039-44. doi: 10.1073/pnas.0807010105.

He, B. J., J. M. Zempel, A. Z. Snyder, and M. E. Raichle. 2010. "The temporal structures and functional significance of scale-free brain activity." *Neuron* 66 (3):353-69. doi: 10.1016/j.neuron.2010.04.020.

Hipp, J. F., D. J. Hawellek, M. Corbetta, M. Siegel, and A. K. Engel. 2012. "Large-scale cortical correlation structure of spontaneous oscillatory activity." *Nat Neurosci* 15 (6):884-90. doi: 10.1038/nn.3101.

Holmes, C. J., R. Hoge, L. Collins, R. Woods, A. W. Toga, and A. C. Evans. 1998. "Enhancement of MR images using registration for signal averaging." *J Comput Assist Tomogr* 22 (2):324-33.

Honey, C. J., O. Sporns, L. Cammoun, X. Gigandet, J. P. Thiran, R. Meuli, et al. 2009. "Predicting human resting-state functional connectivity from structural connectivity." *Proc Natl Acad Sci U S A* 106 (6):2035-40. doi: 10.1073/pnas.0811168106.

Hopfinger, J. B., M. H. Buonocore, and G. R. Mangun. 2000. "The neural mechanisms of top-down attentional control." *Nat Neurosci* 3 (3):284-91. doi: 10.1038/72999.

Husain, M., and C. Rorden. 2003. "Non-spatially lateralized mechanisms in hemispatial neglect." *Nat Rev Neurosci* 4 (1):26-36. doi: 10.1038/nrn1005.

Hyvarinen, A. 1999. "Fast and robust fixed-point algorithms for independent component analysis." *IEEE Trans Neural Netw* 10 (3):626-34. doi: 10.1109/72.761722.

Iacobucci, D., S. D. Posavac, F. R. Kardes, M. J. Schneider, and D. L. Popovich. 2015. "The median split: Robust, refined, and revived." *Journal of Consumer Psychology* 25 (4):690-704. doi: doi.org/10.1016/j.jcps.2015.06.014.

Kelly, A. M., L. Q. Uddin, B. B. Biswal, F. X. Castellanos, and M. P. Milham. 2008. "Competition between functional brain networks mediates behavioral variability." *Neuroimage* 39 (1):527-37. doi: 10.1016/j.neuroimage.2007.08.008.

Kraft, A., K. Irlbacher, K. Finke, C. Kaufmann, S. Kehrer, D. Liebermann, et al. 2015. "Dissociable spatial and non-spatial attentional deficits after circumscribed thalamic stroke." *Cortex* 64:327-42. doi: 10.1016/j.cortex.2014.12.005.

Kyllingsbaek, S. 2006. "Modeling visual attention." *Behav Res Methods* 38 (1):123-33.

Mantini, D., M. G. Perrucci, C. Del Gratta, G. L. Romani, and M. Corbetta. 2007. "Electrophysiological signatures of resting state networks in the human brain." *Proc Natl Acad Sci U S A* 104 (32):13170-5. doi: 10.1073/pnas.0700668104.

Markett, S., M. Reuter, C. Montag, G. Voigt, B. Lachmann, S. Rudorf, et al. 2014. "Assessing the function of the fronto-parietal attention network: insights from resting-state fMRI and the attentional network test." *Hum Brain Mapp* 35 (4):1700-9. doi: 10.1002/hbm.22285.

Matsui, T., T. Murakami, and K. Ohki. 2016. "Transient neuronal coactivations embedded in globally propagating waves underlie resting-state functional connectivity." *Proc Natl Acad Sci U S A* 113 (23):6556-61. doi: 10.1073/pnas.1521299113.

Matthias, E., P. Bublak, A. Costa, H. J. Muller, W. X. Schneider, and K. Finke. 2009. "Attentional and sensory effects of lowered levels of intrinsic alertness." *Neuropsychologia* 47 (14):3255-64. doi: 10.1016/j.neuropsychologia.2009.08.004.

Maxwell, S. E., and H. D. Delaney. 1993. "Bivariate Median Splits and Spurious Statistical Significance." *Psychological Bulletin* 113 (1):181-190. doi: dx.doi.org/10.1037/0033-2909.113.1.181.

Menegaux, A., C. Meng, J. Neitzel, J. G. Bauml, H. J. Muller, P. Bartmann, et al. 2017. "Impaired visual short-term memory capacity is distinctively associated with structural connectivity of the posterior thalamic radiation and the splenium of the corpus callosum in preterm-born adults." *Neuroimage* 150:68-76. doi: 10.1016/j.neuroimage.2017.02.017.

Mennes, M., C. Kelly, X. N. Zuo, A. Di Martino, B. B. Biswal, F. X. Castellanos, et al. 2010. "Inter-individual differences in resting-state functional connectivity predict task-induced BOLD activity." *Neuroimage* 50 (4):1690-701. doi: 10.1016/j.neuroimage.2010.01.002.

Neitzel, J., M. Ortner, M. Haupt, P. Redel, T. Grimmer, I. Yakushev, et al. 2016. "Neuro-cognitive mechanisms of simultanagnosia in patients with posterior cortical atrophy." *Brain*. doi: 10.1093/brain/aww235.

Pardo, J. V., P. T. Fox, and M. E. Raichle. 1991. "Localization of a human system for sustained attention by positron emission tomography." *Nature* 349 (6304):61-4. doi: 10.1038/349061a0.

Parks, E. L., and D. J. Madden. 2013. "Brain connectivity and visual attention." *Brain Connect* 3 (4):317-38. doi: 10.1089/brain.2012.0139.

Peers, P. V., C. J. Ludwig, C. Rorden, R. Cusack, C. Bonfiglioli, C. Bundesen, et al. 2005. "Attentional functions of parietal and frontal cortex." *Cereb Cortex* 15 (10):1469-84. doi: 10.1093/cercor/bhi029.

Petersen, A., A. H. Petersen, C. Bundesen, S. Vangkilde, and T. Habekost. 2017. "The effect of phasic auditory alerting on visual perception." *Cognition* 165:73-81. doi: 10.1016/j.cognition.2017.04.004.

Posner, M. I., and S. E. Petersen. 1990. "The attention system of the human brain." *Annu Rev Neurosci* 13:25-42. doi: 10.1146/annurev.ne.13.030190.000325.

Power, J. D., K. A. Barnes, A. Z. Snyder, B. L. Schlaggar, and S. E. Petersen. 2012. "Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion." *Neuroimage* 59 (3):2142-54. doi: 10.1016/j.neuroimage.2011.10.018.

Raichle, M. E. 2011. "The restless brain." *Brain Connect* 1 (1):3-12. doi: 10.1089/brain.2011.0019.

Raichle, M. E. 2015. "The restless brain: how intrinsic activity organizes brain function." *Philos Trans R Soc Lond B Biol Sci* 370 (1668). doi: 10.1098/rstb.2014.0172.

Redel, P., P. Bublak, C. Sorg, A. Kurz, H. Forstl, H. J. Muller, et al. 2012. "Deficits of spatial and task-related attentional selection in mild cognitive impairment and Alzheimer's disease." *Neurobiol Aging* 33 (1):195 e27-42. doi: 10.1016/j.neurobiolaging.2010.05.014.

Rorden, C., and M. Brett. 2000. "Stereotaxic display of brain lesions." *Behav Neurol* 12 (4):191-200.

Rosenberg, M. D., E. S. Finn, D. Scheinost, R. T. Constable, and M. M. Chun. 2017. "Characterizing Attention with Predictive Network Models." *Trends Cogn Sci* 21 (4):290-302. doi: 10.1016/j.tics.2017.01.011.

Rosenberg, M. D., E. S. Finn, D. Scheinost, X. Papademetris, X. Shen, R. T. Constable, et al. 2016. "A neuromarker of sustained attention from whole-brain functional connectivity." *Nat Neurosci* 19 (1):165-71. doi: 10.1038/nn.4179.

Sadaghiani, S., R. Scheeringa, K. Lehongre, B. Morillon, A. L. Giraud, and A. Kleinschmidt. 2010. "Intrinsic connectivity networks, alpha oscillations, and tonic alertness: a simultaneous electroencephalography/functional magnetic resonance imaging study." *J Neurosci* 30 (30):10243-50. doi: 10.1523/JNEUROSCI.1004-10.2010.

Schneider, M., P. Hathway, L. Leuchs, P. G. Samann, M. Czisch, and V. I. Spoormaker. 2016. "Spontaneous pupil dilations during the resting state are associated with

activation of the salience network." *Neuroimage* 139:189-201. doi: 10.1016/j.neuroimage.2016.06.011.

Sestieri, C., M. Corbetta, S. Spadone, G. L. Romani, and G. L. Shulman. 2014. "Domain-general signals in the cingulo-opercular network for visuospatial attention and episodic memory." *J Cogn Neurosci* 26 (3):551-68. doi: 10.1162/jocn_a_00504.

Smith, D. V., A. V. Utevsky, A. R. Bland, N. Clement, J. A. Clithero, A. E. Harsch, et al. 2014. "Characterizing individual differences in functional connectivity using dual-regression and seed-based approaches." *Neuroimage* 95:1-12. doi: 10.1016/j.neuroimage.2014.03.042.

Smith, S. M., P. T. Fox, K. L. Miller, D. C. Glahn, P. M. Fox, C. E. Mackay, et al. 2009. "Correspondence of the brain's functional architecture during activation and rest." *Proc Natl Acad Sci U S A* 106 (31):13040-5. doi: 10.1073/pnas.0905267106.

Smith, S. M., and T. E. Nichols. 2009. "Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference." *Neuroimage* 44 (1):83-98. doi: 10.1016/j.neuroimage.2008.03.061.

Sorg, C., N. Myers, P. Redel, P. Bublak, V. Riedl, A. Manoliu, et al. 2012. "Asymmetric loss of parietal activity causes spatial bias in prodromal and mild Alzheimer's disease." *Biol Psychiatry* 71 (9):798-804. doi: 10.1016/j.biopsych.2011.09.027.

Sperling, G. 1960. "The information available in brief visual presentations." *Psychological monographs: General and applied* 74 (11):1-29. doi: http://dx.doi.org/10.1037/h0093759.

Sturm, W., A. de Simone, B. J. Krause, K. Specht, V. Hesselmann, I. Radermacher, et al. 1999. "Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere." *Neuropsychologia* 37 (7):797-805.

Sturm, W., and K. Willmes. 2001. "On the functional neuroanatomy of intrinsic and phasic alertness." *Neuroimage* 14 (1 Pt 2):S76-84. doi: 10.1006/nimg.2001.0839.

Thimm, M., G. R. Fink, J. Kust, H. Karbe, and W. Sturm. 2006. "Impact of alertness training on spatial neglect: a behavioural and fMRI study." *Neuropsychologia* 44 (7):1230-46. doi: 10.1016/j.neuropsychologia.2005.09.008.

Vangkilde, S., J. T. Coull, and C. Bundesen. 2012. "Great expectations: temporal expectation modulates perceptual processing speed." *J Exp Psychol Hum Percept Perform* 38 (5):1183-91. doi: 10.1037/a0026343.

Vincent, J. L., I. Kahn, A. Z. Snyder, M. E. Raichle, and R. L. Buckner. 2008. "Evidence for a frontoparietal control system revealed by intrinsic functional connectivity." *J Neurophysiol* 100 (6):3328-42. doi: 10.1152/jn.90355.2008.

Von Aster, M. , A. Neubauer, and R. Horn. 2006. *Wechsler Intelligenztest für Erwachsene (WIE). Deutschsprachige Bearbeitung und Adaptation des WAIS-III von David Wechsler, Frankfurt Main Ger Harcourt Test Serv*. Frankfurt, Germany: Pearson Assessment.

Vossel, S., R. Weidner, K. Moos, and G. R. Fink. 2016. "Individual attentional selection capacities are reflected in interhemispheric connectivity of the parietal cortex." *Neuroimage* 129:148-58. doi: 10.1016/j.neuroimage.2016.01.054.

Weissman, D. H., G. R. Mangun, and M. G. Woldorff. 2002. "A role for top-down attentional orienting during interference between global and local aspects of hierarchical stimuli." *Neuroimage* 17 (3):1266-76.

Wiegand, I., A. Petersen, K. Finke, C. Bundesen, J. Lansner, and T. Habekost. 2017. "Behavioral and Brain Measures of Phasic Alerting Effects on Visual Attention." *Front Hum Neurosci* 11:176. doi: 10.3389/fnhum.2017.00176.

Wiegand, I., T. Tollner, T. Habekost, M. Dyrholm, H. J. Muller, and K. Finke. 2014. "Distinct neural markers of TVA-based visual processing speed and short-term storage capacity parameters." *Cereb Cortex* 24 (8):1967-78. doi: 10.1093/cercor/bht071.

Wojciulik, E., and N. Kanwisher. 1999. "The generality of parietal involvement in visual attention." *Neuron* 23 (4):747-64.

Wu, J. Y., Huang Xiaoying, and Zhang Chuan. 2008. "Propagating waves of activity in the neocortex: what they are, what they do." *Neuroscientist* 14 (5):487-502. doi: 10.1177/1073858408317066.

Yeo, B. T., F. M. Krienen, J. Sepulcre, M. R. Sabuncu, D. Lashkari, M. Hollinshead, et al. 2011. "The organization of the human cerebral cortex estimated by intrinsic functional connectivity." *J Neurophysiol* 106 (3):1125-65. doi: 10.1152/jn.00338.2011.

Zuo, X. N., C. Kelly, J. S. Adelstein, D. F. Klein, F. X. Castellanos, and M. P. Milham. 2010. "Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach." *Neuroimage* 49 (3):2163-77. doi: 10.1016/j.neuroimage.2009.10.080.

6. Study 2: Visual processing speed and the resting human brain in healthy aging

Adriana L. Ruiz-Rizzo, Hermann J. Müller, Signe Vangkilde, Christian Sorg, Kathrin Finke

Summary

In this manuscript titled **Decreased Cingulo-Opercular Network Functional Connectivity Mediates the Impact of Aging on Visual Processing Speed**, <u>currently under review in the journal *NeuroImage*</u>, we provide evidence for the specific mediator role of the intrinsic functional connectivity (iFC) within the cingulo-opercular network in the effect that aging has on visual processing. A reduction in visual processing speed is one of the best-established changes that occur during aging, but the neural factors that account for it are incompletely understood.

Based on previous evidence, here we test the hypothesis that a decrease in the iFC within the cingulo-opercular network accounts for the reduction in visual processing speed during aging. We used a whole report task and modeling based on Bundesen's computational theory of visual attention to assess visual processing speed in 91 healthy participants from 20 to 77 years old. IFC was estimated using independent component and dual regression analyses of resting-state functional magnetic resonance imaging data.

We found that decreased insular iFC was significantly associated with visual processing speed reduction. This association was not explained by gender, education, anxiety, or brain volume. Decreased insular iFC was further not associated with visual short-term memory capacity or visual perceptual threshold. Moreover, the iFC of the left insula was found to mediate the association between age and visual processing speed. Such mediation was not observed for the dorsal attention or default mode networks. These results, thus, consistently point to a decreased iFC of the cingulo-opercular network as an exclusive mediator between age and visual processing speed.

The mediation of iFC of the cingulo-opercular network between age and visual processing speed suggests that it is not aging on its own what, in a deterministic manner, would lead to the well-established visual processing speed decrements. Instead, such mediation indicates that individuals at an advanced age could have "normal" visual

processing speed—or comparable to that of younger individuals—given a "normal" iFC of the cingulo-opercular network. Accordingly, this result suggests TVA parameter visual processing speed C as a testable neuro-cognitive marker for the efficacy of processing speed training as well as for brain-behavior analyses in pathological aging.

Graphic abstract
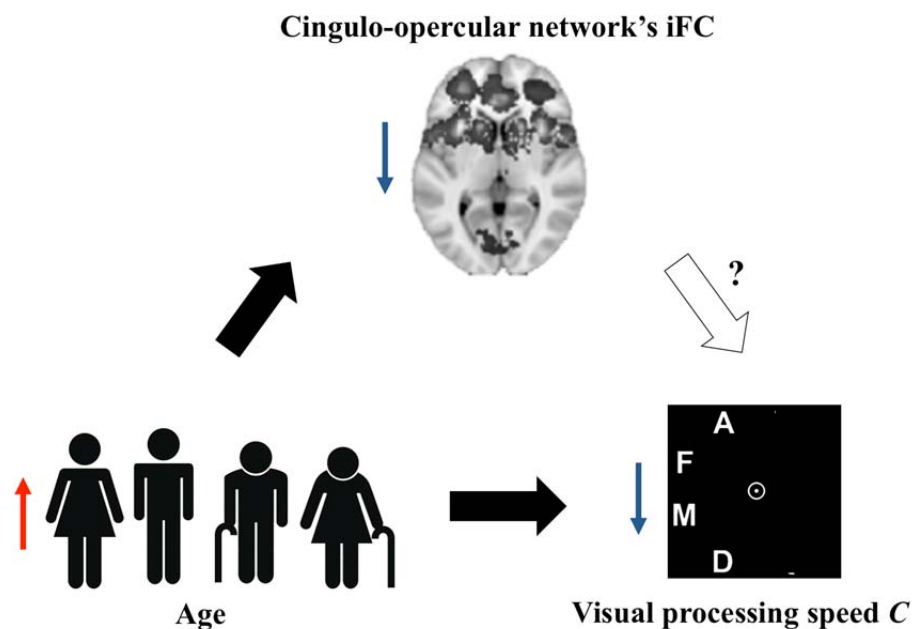
Authors' contributions

A.L.R.R., K.F., and C.S. designed the study. A.L.R.R. acquired and analyzed the data, and drafted the manuscript. A.L.R.R., K.F., C.S., H.J.M., and S.V. wrote and critically revised the manuscript before submission.

Manuscript: Decreased cingulo-opercular network functional connectivity mediates the impact of aging on visual processing speed

Authors and affiliations:

Adriana L. Ruiz-Rizzo[1,2], Christian Sorg[1,3], Hermann J. Müller[1,2], Signe Vangkilde[4], Kathrin Finke[1,5]

[1]Graduate School of Systemic Neurosciences, GSN LMU Munich, Munich (Germany)

[2]Department of General and Experimental Psychology, Ludwig-Maximilans-Universität München, Munich

[3]TUM-Neuroimaging Center, TUM-NIC, Technische Universität München, Munich

[4]Department of Psychology, Center for Visual Cognition, University of Copenhagen, Copenhagen (Denmark)

[5]Hans Berger Department of Neurology, Jena University Hospital, Jena (Germany)

Corresponding author:

Adriana L. Ruiz Rizzo. Department of General and Experimental Psychology, Ludwig-Maximilans-Universität München, Leopoldstraße 13, 80802 Munich, Germany. Phone: +49 89 2180 72569, email: adriana.ruiz@lmu.de.

Running title: Cingulo-opercular network and processing speed in aging

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Abstract

A reduction in visual processing speed is one of the well-established changes that occur during aging. The neural factors that account for this reduction are, however, incompletely understood. The cingulo-opercular network plays a crucial role in tonic alertness, one of the major determinants of visual processing speed. Based on previous reports of age-related decreases in the intrinsic functional connectivity (iFC) within the cingulo-opercular network, we hypothesized that these decreases account for the reduction in visual processing speed during aging. We used a whole-report task and modeling based on Bundesen's computational 'theory of visual attention' to assess visual processing speed independent from other visual attention functions and motor speed in 91 healthy participants from 20 to 77 years old. IFC was estimated using independent component and dual regression analyses of resting-state functional magnetic resonance imaging data. We found a significant age-related decrease in the iFC of the anterior and middle cingulate cortex, middle frontal gyri, bilateral insula, and left cerebellum. In particular, decreased insular iFC was significantly associated with the visual processing speed reduction. Moreover, the iFC of the left insula was found to mediate the association between age and visual processing speed. Importantly, this mediation was exclusive for visual processing speed and the iFC of the cingulo-opercular network, and was not explained by gender, education, or brain volume. Our results thus provide evidence for a specific mediator role of cingulo-opercular network iFC decrease in the effect that aging exerts on visual processing speed.

Introduction

A decline of processing speed represents a major cognitive change during aging (Salthouse 1996). In particular, a reduction of visual processing speed, or rate of information encoding into visual short-term memory (VSTM), has previously been established in both healthy (Espeseth, Vangkilde, Petersen et al., 2014; Habekost, Vogel, Rostrup et al., 2013; McAvinue, Habekost, Johnson et al., 2012) and, more severely, pathological aging (Bublak, Redel, Sorg et al., 2011; Ruiz-Rizzo, Bublak, Redel et al., 2017) – using computational approach based on Bundesen's (1990) 'theory of visual attention' (TVA). TVA permits the contribution of processing speed to the efficiency of visual selection and recognition to be quantitatively estimated, independently of motor speed or other visual attention functions, including VSTM capacity, the perceptual threshold, or attentional top-down control (Bundesen 1990; Habekost, Petersen, and Vangkilde 2014). Of note, a major influence on visual processing speed has been demonstrated for tonic alertness (Matthias, Bublak, Muller et al., 2010), an 'intensity' aspect of attention related to the ability to maintain an appropriate level of arousal (Posner and Petersen 1990; Sturm and Willmes 2001). Increasing tonic alertness via psycho-stimulant medication has also been shown to enhance visual processing speed (Finke, Dodds, Bublak et al., 2010). At a neural level, tonic alertness has been identified as a function of a cingulo-opercular network's spontaneous (Sadaghiani, Scheeringa, Lehongre et al., 2010; Schneider, Hathway, Leuchs et al., 2016) and sustained activity (Coste and Kleinschmidt 2016; Sadaghiani and D'Esposito 2015; Sestieri, Corbetta, Spadone et al., 2014) during task performance. This network – also referred to as a 'salience' (e.g., Seeley, Menon, Schatzberg et al., 2007) or 'ventral attention' (e.g., Yeo, Krienen, Sepulcre et al., 2011) network – is centered on the anterior insula and the anterior cingulate cortex (Dosenbach, Fair, Miezin et al., 2007; Dosenbach, Fair, Cohen et al., 2008; Menon and Uddin 2010; Seeley et al., 2007). Given that the cingulo-opercular network plays a crucial role for tonic alertness, its relevance for visual processing speed would appear plausible.

Age-related changes of the cingulo-opercular network have previously been described particularly as regards its intrinsic functional connectivity (iFC) (He, Qin, Liu et al., 2014; Onoda, Ishihara, and Yamaguchi 2012). IFC refers to the coherence of the infra-slow (i.e., 0.01 – 0.1 Hz) spontaneous neural activity, typically measured with BOLD- (blood-oxygenation-level-dependent-) functional magnetic resonance imaging

(fMRI) during resting state (De Luca, Beckmann, De Stefano et al., 2006; Fox and Raichle 2007; Raichle 2015). Specifically, age-related decreases of the cingulo-opercular network's iFC have been reported for bilateral frontoinsular, dorsal anterior cingulate, and left dorsolateral prefrontal cortices (He et al., 2014), with these changes being related to reductions in global cognitive state (He et al., 2014), visuospatial intelligence, and executive functions (Onoda et al., 2012). The present study was based on the assumption that quantitative measures with higher cognitive specificity might reveal whether a more basic function − namely, visual processing speed − is at the core of these relations. A prime role of visual processing speed is plausible given that it accounts for a significant amount of variance in diverse cognitive tasks (e.g., fluid intelligence), especially in old age (e.g., Deary and Stough 1996).

Specifically, we investigated whether and how changes in the iFC of the cingulo-opercular network may account for the age-related decline of visual processing speed. A cross-sectional cohort of healthy adults performed a whole-report attentional task and underwent resting-state fMRI. Using a TVA-based approach, visual processing speed was estimated, and its association with age-related changes in the iFC of the cingulo-opercular network was examined. In addition, to assess the concurrent criterion validity of such an association, we examined whether the results would generalize to a conventional neuropsychological measure of speed, the Trail Making Test (TMT; Tombaugh 2004). We also performed a series of control analyses. First, we controlled for the potential influence of anxiety on the relation between iFC and visual processing speed, using it as a covariate, given its previous association with the iFC of the cingulo-opercular network (e.g., Seeley et al., 2007). Second, we investigated for respective potential influences on visual processing speed of the iFC of default mode and dorsal attention networks, documented to decrease with aging (Andrews-Hanna, Snyder, Vincent et al., 2007; Damoiseaux, Beckmann, Arigita et al., 2008; Ferreira and Busatto 2013). Finally, we examined the relationship of the cingulo-opercular network's iFC with other visual attention functions, including the perceptual threshold and VSTM storage capacity, which are also known to be affected by aging (McAvinue et al., 2012).

Materials and Methods

Participants

The present study includes 91 healthy adults, in the age range from 20 to 77 years (mean age: 48.8 ± 19.2 years; 46 females; mean education: 12.0 ± 1.6 years; 4 left-handed). The study was approved by the LMU Munich ethics committee, and written informed consent was obtained from all participants. Initially, 108 adults (19 to 78 years old) of the Munich INDIREA aging cohort[1] had taken part in this study. However, 17 participants had to be excluded owing to incomplete or unreliable data (n = 12), uncorrected visual acuity decreases (n = 2), or moderate symptoms of depression (n = 3) [i.e., BDI (Beck, Steer, and Brown 1996) scores above 19]. The MiniMental State Examination (MMSE; Folstein, Folstein, and McHugh 1975) was applied for dementia screening in participants from 60 years onwards. Participants in the elderly group had no indication of cognitive impairment (mean MMSE score: 29 ± 0.9). All 91 participants included in this study were free of previous or current psychiatric or neurological disorders, psychiatric or neurological medication, diabetes, color blindness, and current symptoms of depression (mean BDI score: 5.2 ± 4.8). In one session, participants underwent resting-state functional magnetic resonance imaging (fMRI) at the Department of Neuroradiology, Klinikum rechts der Isar, Munich (Germany). In a separate, psychophysical testing session, visual attention functioning was assessed using a whole-report task. Session order depended on individual participants' convenience. The average time between sessions was 2.6 months.

Assessment and estimation of visual processing speed C

A whole-report task, based on TVA (Bundesen 1990), was used to estimate visual processing speed *C*. On each trial, four red letters were briefly presented to participants, who were instructed to verbally report, in any order, all letters they were fairly certain they had seen. Stimuli were randomly chosen from a set of letters (A, B, D, E, F, G, H, J, K, L, M, N, O, P, R, S, T, V, X, Z). Letters appeared on an imaginary semicircle, with a radius of 5.27° of visual angle, on either the right or the left of a fixation point (Figure 1). To ensure balanced visual stimulation in both hemifields, targets were accompanied by four blue symbols (composed of random letter parts; see Figure 1 for an example) of the same luminance displayed on the symmetrical semicircle on the other side of fixation.

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[1] INDIREA: 'Individualised Diagnostics and Rehabilitation of Attentional Disorders' project. All participants underwent extensive behavioral assessment (i.e., memory, attention, and intelligence) and neuroimaging (i.e., functional and structural MRI, and electroencephalography).

Visual stimuli were 1.3° of visual angle in diameter, and both letters and symbols appeared only once in a particular trial.

The task included 10 blocks of 40 trials each (400 trials in total), with targets presented in the left and, respectively, the right hemifield in half of the blocks. The stimulus exposure durations were individually adjusted in a short pre-test and determined as follows. To start with, the participant was presented with one trial (adjustment) display for 80 ms, with stimulus exposure terminated by post-display masks (see below). If s/he reported at least one letter correctly, the exposure duration was decreased by 10 ms, and this procedure continued for the next 15 adjustment trials (divided into 4 blocks, and accompanied for 4 trials always presented unmasked for 200 ms and 4 trials always masked for 250 ms, i.e., 12 trials in total in each block). The exposure duration was decreased until the lowest duration was established at which the participant could no longer report one letter. If this point was reached before the last of the 16 adjustment trials, the exposure duration was kept constant for the remaining adjustment trials. Setting the lowest exposure duration so low was meant to ensure that we would obtain a valid estimate of the visual threshold parameter. Then, based on that lowest exposure duration, four longer values were additionally chosen to allow for variability in letter report performance across the whole range from near-floor to near-ceiling, and thus render the TVA-based parameter estimation more precise. The five exposure durations thus determined were then introduced in the subsequent whole-report task. Note that, on *masked* trials, the displays were shown for one of the five durations and immediately followed by masks (a scattered patch of red and blue squares, 1.3° in size) presented for 900 ms at each stimulus location, so as to avoid visual persistence effects. In addition to trials with masked display exposure, we introduced *unmasked* trials (without post-display masks), to increase the variability of *effective* exposure times (by allowing for an additional component of iconic memory buffering; Sperling 1960) and thus ensure reliable and valid TVA parameter fitting. Specifically, on unmasked trials, displays were presented at one of two exposure durations: one was the same as the second shortest masked duration and the other one was 200 ms. The latter (200-ms unmasked) duration was used for the purposes of simultaneous electroencephalographic measurement for the analysis of event-related potentials, which will not be reported here. Thus, overall, trials displays were presented for seven *effective* exposure durations, five masked and two unmasked. A block of 40 trials (with hemifield blocked) thus consisted of 15 masked trials, with 3 trials for each of the 5 set exposure durations; 3 unmasked trials with the

second shortest duration; and 22 unmasked trials with 200-ms duration. Trials were presented in random order within each block.

Participants were tested in a sound-attenuated chamber (Industrial Acoustics Company) with a dim light placed behind them. Stimuli were presented on a 24" LED screen with an 800px x 600px resolution and a 100-Hz refresh rate. The viewing distance was kept constant at about 65 cm. At the beginning of each block, a black screen with a white arrow appeared pointing towards the side where the stimuli would appear for that specific block. In each trial, the experimenter entered the reported letters in the reported order and manually started the next trial. After stimulus presentation, a white question mark appeared in the center of the screen prompting the start of the verbal report. The measure of interest was pure report accuracy (at a given effective exposure duration), disregarding the speed and the order of the participant's letter report. At the end of each block, the participant received visual feedback in the form of the percentage of correctly reported (out of all reported) letters, displayed in the form of an accuracy bar. To avoid too liberal or too conservative responding, participants were instructed to keep their report accuracy in the range between 70% and 90% correct, which was shown in green on the accuracy bar. The whole-report task lasted 45 minutes approximately, after which participants completed other behavioral tasks and questionnaires.

Visual processing speed C was estimated by modeling the participant's report accuracy as function of the effective exposure duration, using a maximum likelihood-fitting algorithm (Bundesen 1990; Dyrholm, Kyllingsbaek, Espeseth et al., 2011; Kyllingsbaek 2006). The TVA-based fitting procedure models the probability of correct letter report in terms of an exponential growth function with increasing (effective) exposure duration. The slope of the function at its origin represents processing speed or parameter C, i.e., the rate of visual information uptake (in elements per second). Additionally, two other parameters were estimated: parameter t_0, indicating the visual perceptual threshold, i.e., the longest ineffective exposure duration (in ms) below which information uptake is effectively zero; and parameter K, indicating the maximum number of elements that can be simultaneously represented in visual short-term memory (VSTM). With aging, t_0 exhibits an increase whereas K shows a decrease (Espeseth et al., 2014). An additional parameter, parameter μ, representing the prolongation of the effective exposure duration (in ms) on unmasked trials, was also estimated in the TVA fitting process. However, as μ only serves for the valid estimation of the relevant parameters C, K, and t_0, this parameter is of no further relevance in the present study. In summary, the

computational model used had 6 degrees of freedom (df): C, 1 df; t_0, 1 df; K, 3 df (the reported K value is the expected K given a particular distribution of the probability that on a given trial $K = 1, 2, 3$, or 4); and μ, 1 df. For those participants whose t_0 was estimated to be below 0, we re-fitted the data fixing t_0 at 0.

Other behavioral tasks and questionnaires

Trail Making Test (TMT) A

The TMT-A measures visual scanning speed in terms of the time required to connect circles with numbers in ascending order (Reitan and Wolfson 1985; Tombaugh 2004). If participants made errors in this task, they were asked to correct them, thus increasing the total time of task performance (Spreen and Strauss 1998). Only seven participants made an error (with the maximum number of errors made being 1). We examined the association of the time to complete the TMT-A with the iFC of the cingulo-opercular network.

State-Trait Anxiety Inventory (STAI)

The STAI Form X (Laux, Glanzmann, Schaffner et al., 1981; Spielberger, Gorsuch, and Lushene 1970) consists of two reliable (Barnes, Harp, and Jung 2002) self-report scales of 20 items each that measure state anxiety (i.e., how a person feels at a particular moment regarding circumstances that are perceived as threatening) and trait anxiety (i.e., how a person generally experiences apprehension, tension, and increased autonomic nervous system activity). Thus, trait anxiety refers to individual differences in the frequency and intensity of anxiety, whereas state anxiety can fluctuate as a function of stressors (Spielberger 1972). All items are rated on a 4-point scale ("not at all" to "a lot" for State Anxiety, and "almost never" to "almost always" for Trait Anxiety).

MRI data acquisition

MRI data were acquired on a Philips Ingenia 3T system (Netherlands), using a 32-channel SENSE head coil. Functional MRI T2*-weighted data were collected for 12.5 min while participants' rested with their eyes closed, after having been told not to fall asleep. We checked that participants had not fallen asleep by directly asking them immediately after finishing the sequence. Foam padding was used to constrain

participants' head motion while scanning, and earplugs and headphones were provided to reduce adverse effects of scanner noise. Six hundred volumes of BOLD-fMRI signal were acquired from each individual, using a multiband (Feinberg and Setsompop 2013) echo-planar imaging (EPI) sequence, with a 2-fold in-plane SENSE acceleration (SENSE factor, S = 2) and an M-factor of 2 (Preibisch, Castrillon, Buhrer et al., 2015). Other fMRI acquisition parameters were: repetition time, TR = 1250 ms; time to echo, TE = 30 ms; phase encoding, PE direction: anterior-posterior; flip angle = 70º; field of view, FOV = 192 mm^2; matrix size = 64 x 64 mm, 40 slices; slice thickness = 3.0 mm; interslice gap 0.3 mm; reconstructed voxel size = 3 x 3 x 3.29 mm. A high-resolution T1-weighted anatomical volume was acquired using a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: TR = 9 ms; TE = 4 ms; inversion time, TI = 0 ms; flip angle = 8 º; 170 sagittal slices; FOV = 240 x 240 x 170 mm; reconstruction matrix = 240 x 240; reconstructed voxel size = 1 mm isotropic.

MRI Data Analysis

Resting-state fMRI data preprocessing

Six hundred resting-state fMRI volumes per individual were preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSF; Chao-Gan and Yu-Feng 2010), a toolbox for data analysis of resting-state fMRI based on MATLAB (R2016b; MathWorks Inc.; Natick, MA, USA). To start with, the first five volumes were discarded to compensate for T1 saturation effects. Next, the data were slice timing corrected, realigned, reoriented to the AC-PC axis, and co-registered to the individual structural images. Nuisance variables (i.e., six head motion parameters, white matter, CSF, and global signals) were regressed out from the functional data. Data were normalized to MNI (Montreal Neurological Institute) space, with a 2-mm isotropic voxel size and smoothed using a 4-mm full-width-at-half-maximum (FWHM) Gaussian kernel. No excessive head motion was identified across subjects (i.e., cumulative translation or rotation 3 mm or 3° and mean point-to-point translation or rotation 0.15 mm or 0.1°). Frame-wise displacement was not correlated with age (p > 0.30) (Power, Barnes, Snyder et al., 2012). To further ensure the independence of our findings from movement-induced artifacts, we repeated our analysis on 'scrubbed' fMRI data, in which movement-induced artifacts had been censored by the identification and exclusion of volumes possibly contaminated by movement (Power et al., 2012). To this end, volumes whose root mean square of

translational and rotational head movement parameters exceeded a predefined threshold of the root mean square of such parameters (0.25 mm + 2 standard deviations of all subjects) were excluded from further analyses (Satterthwaite, Elliott, Gerraty et al., 2013). To foreshadow the results, findings based on censored data were almost identical with those based on not-censored data, indicating the independence of our findings from movement-induced artifacts. Finally, given the relevance of controlling the signal-to-noise ratio (SNR) in studies of aging (D'Esposito, Deouell, and Gazzaley 2003), we examined the temporal SNR of the fMRI time series (Murphy, Bodurka, and Bandettini 2007) in relation to age, but found no significant association $(r(89) = -0.09, p = 0.394)$.

Independent component analysis and dual regression

The preprocessed resting-state fMRI data were analyzed by employing probabilistic independent component analysis (ICA) with 20 dimensions in FSL MELODIC (Beckmann and Smith 2004; Smith, Jenkinson, Woolrich et al., 2004). The preprocessed data were normalized for voxel-wise mean and variance and then reduced to a 20-dimensional subspace by probabilistic principal component analysis. Subsequently, data were decomposed into time courses and spatial maps by optimizing for non-Gaussian spatial distributions using a fixed-point iteration technique (Hyvarinen 1999). The resulting group-level independent components were divided by the standard deviation of the residual noise and thresholded by fitting a mixture model to the histogram of intensity (Beckmann and Smith 2004). To further conduct statistical group analyses on the independent component corresponding to the cingulo-opercular network, we performed dual regression (Beckmann, Mackay, Filippini et al., 2009; Filippini, MacIntosh, Hough et al., 2009), which permitted us to obtain individual spatial maps with associated time courses. Dual regression is a multivariate approach that works in two stages, namely, a spatial and a temporal regression. First, the group independent component maps are regressed onto the participant's 4D preprocessed dataset, resulting in subject-specific time courses (one for each independent component per fMRI volume). Second, those time courses are regressed onto the same 4D dataset, resulting in subject-specific spatial maps (one for each independent component). To select the component of interest, we performed a spatial cross-correlation between the 20 independent components and the 7-networks parcellation reported by Yeo et al. (2011). We identified as the cingulo-opercular network the component with the highest spatial correlation coefficient with the 'ventral attention' network of Yeo et al. (2011) (component 7, $r = 0.23$; see Introduction for different

naming). By visual inspection, we confirmed that this component included the key structures of the cingulo-opercular network, namely, insula and anterior cingulate cortex (Dosenbach et al., 2007; Dosenbach et al., 2008; Menon and Uddin 2010; Seeley et al., 2007).

Estimation of total brain volume

We estimated the total brain volume for each participant, normalized for their head size, based on the T1-weighted high-resolution anatomical volume using SIENAX in FSL (Smith, Zhang, Jenkinson et al., 2002; Smith et al., 2004). Briefly, SIENAX works by first removing non-brain tissue; performing affine registration to MNI152 space (Jenkinson and Smith 2001; Jenkinson, Bannister, Brady et al., 2002) using the skull images to determine registration scaling; and segmenting into tissue types using partial volume estimation (Zhang, Brady, and Smith 2001) to calculate the total volume of brain tissue. This value is then multiplied by the estimated volumetric scaling factor – obtained from the skull image – to reduce variability due to between-subject differences in head size. We used these values of normalized brain volume as a control variable for the correlation analyses between behavioral measures and iFC, and thus always report partial correlation coefficients, unless otherwise specified.

Statistical analyses

Multiple regression analysis

We performed a voxel-wise multiple regression of age on iFC while controlling for education and gender for the cingulo-opercular network ($p < 0.05$ FWE corrected for multiple comparisons at the cluster level, voxel-wise height threshold $p < 0.001$) using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Next, the Eigenvariates (i.e., individual average iFC values) of each of the significant age-related clusters were extracted and further examined in relation to the visual processing speed parameter *C*. To assess the specificity of our results, we performed similar voxel-wise analyses using the default mode and dorsal attention networks. The significant clusters of the cingulo-opercular network were additionally examined in relation to the other visual attention parameters (i.e., VSTM storage capacity, *K*, and perceptual threshold, t_0) and to the TMT-A scores. Partial correlation analyses were used to determine whether the variance in each significant iFC cluster contributed above and beyond age to the variance in visual

processing speed. If so, a further mediation analysis (*see below*) was conducted on the clusters that fulfilled this criterion. All reported p values are based on one-tailed tests, unless otherwise specified, given the previous reports on the associations between age and visual processing speed (e.g., McAvinue et al., 2012), and among age, iFC of the cingulo-opercular network, and cognitive functions (e.g., He et al., 2014; Onoda et al., 2012).

Mediation analysis

After determining via partial correlations the potential mediator(s) of the association between age and visual processing speed (following Baron and Kenny's criteria) (Baron and Kenny 1986), we computed how much of this association the potential mediator could explain. In our proposed mediation model, the total effect of age on visual processing speed was estimated with a simple linear regression. Second, this total effect was deconstructed into an indirect and a direct effect. Third, the indirect effect, reflecting the significance of the mediation (i.e., $p < 0.05$, two-tailed), was evaluated using bootstrapping (Hayes 2012; Mackinnon and Fairchild 2009; Preacher and Hayes 2004) with 5000 replication samples. The indirect effect represents an estimate of the amount of change in visual processing speed per year of age.

Results

Visual processing speed in aging

Means and standard deviations in TVA parameters obtained from the whole-report task as well as scores from the TMT and STAI are listed in Table 1. Males and females did not differ in any of these behavioral measures (all p-values > 0.124). As expected (e.g., McAvinue et al., 2012), visual processing speed C estimates were significantly negatively correlated with age. Similarly, VSTM storage capacity (K) and, marginally, perceptual threshold (t_0) parameters as well as performance in the TMT-A were significantly associated with age (Table 1). None of the anxiety measures showed a consistent relationship with age.

Functional connectivity of the cingulo-opercular network in aging

The cingulo-opercular network encompassed frontal regions such as the inferior frontal and middle frontal gyri bilaterally, anterior and middle cingulate cortex; insular regions; the superior temporal gyrus; parietal regions such as supramarginal gyrus, inferior parietal lobule, and precuneus; and subcortical regions such as the basal ganglia, thalamus, amygdala, brain stem, and cerebellum (one-sample t-test, controlled for gender and education, $p < 0.05$ FWE-corrected at the cluster level; Figure 2).

In a voxel-wise multiple regression analysis, we found significantly reduced iFC in the right anterior and middle cingulate cortices, bilateral insula, bilateral middle frontal gyrus, and left cerebellum, with increasing age (controlled for gender and education, $p < 0.05$ FWE-corrected at the cluster level; Figure 3 and Table 2).

A decrease in the iFC of the cingulo-opercular network mediates the age-related reduction in visual processing speed

IFC values of bilateral insula clusters were significantly positively associated with visual processing speed *C* (left insula: $r(89) = 0.34$, $p = 0.001$; right insula: $r(89) = 0.26$, $p = 0.005$; Figure 4). The right anterior cingulate cluster's iFC values as well as those of the left middle frontal gyrus also correlated significantly with visual processing speed *C* ($r(89) = 0.21$, $p = 0.023$ and $r(89) = .20$, $p = 0.028$, respectively), though these correlations were no longer significant when normalized brain volume was controlled for ($p > 0.080$). In contrast, the associations between each insula cluster and processing speed *C* were still significant after controlling for normalized brain volume (left insula: $r(88) = 0.30$, $p = 0.002$; right insula: $r(88) = 0.22$, $p = 0.017$). Next, we examined whether the iFC values of the insula clusters are potential mediators of the age-related reduction of visual processing speed (Baron and Kenny 1986). When the correlation between age and *C* was controlled for iFC, this was no longer significant (left insula: $r(88) = -0.02$, $p = 0.870$; right insula: $r(88) = -.09$, $p = .205$). In contrast, when the correlation between iFC and *C* was controlled for age, it did remain significant for both the left ($r(88) = 0.27$, $p = 0.004$) and the right insula ($r(88) = 0.19$, $p = 0.036$). Statistical tests based on normal theory (e.g., Sobel 1982) confirmed this result (left insula: effect = -0.075, SE = 0.0307, Z = -2.46, $p = 0.014$; right insula, effect = -0.0439, SE = 0.0257, Z = -1.71, $p = 0.088$). Unstandardized coefficients (and their respective standard errors and significance values) of the different effects are shown in Figure 5.

The cingulo-opercular network specifically mediates the visual processing speed age-related reduction

Given the well-known age-related decrease in other intrinsic brain networks, such as the default mode and dorsal attention networks (Damoiseaux et al., 2008; Ferreira and Busatto 2013; Tomasi and Volkow 2012), it might be possible that the reduction in visual processing speed was associated with a general age-related decrease of iFC (rather than exclusively with that of the cingulo-opercular network). Accordingly, from the ICA and dual regression analyses, we selected the default mode and the dorsal attention networks (Yeo et al., 2011). For the default mode network, on one hand, age-related decreased iFC was found in the middle temporal gyri bilaterally as well as in the right cuneus and left precuneus. Only the iFC values of the clusters localized on the left middle temporal gyrus (peak MNI coordinates, x, y, z: -60, -58, 8; k = 107 voxels) were marginally related to C values, while controlling for normalized brain volume (r(88) = 0.20, p = 0.026). On the other hand, for the dorsal attention network, clusters significantly reduced with aging were, in turn, found in the left superior, middle, and inferior (pars triangularis) frontal gyri, left orbitofrontal cortex, left superior parietal lobule, left precuneus, right posterior middle temporal gyrus, and right postcentral gyrus. Only the iFC values of the cluster localized on the left orbitofrontal cortex (MNI peak coordinates: -26, 58, -2; 239 voxels; r(88) = 0.20, p = 0.029) and those of the cluster on the right supramarginal gyrus (MNI peak coordinates: 68, -20, 36; 157 voxels; r(88) = 0.175, p = 0.049) were marginally correlated with C. To further test whether the iFC of these regions could still mediate the association between age and visual processing speed, we computed the respective partial correlations controlling for age. For both the default mode and dorsal attention network clusters, these correlations were no longer significant (p > 0.060 and p > 0.075, respectively), indicating that their iFC cannot explain the variance in visual processing speed values above and beyond age.

Control analyses

Trail Making Test. To assess the concurrent criterion validity of the association between processing speed and the iFC of the insula clusters, we used the performance on the TMT-A, shown to decrease with aging (Tombaugh 2004). As expected, TVA estimates of visual processing speed C were significantly associated with the time needed

to complete the TMT-A (r(88) = -0.28, p = 0.004, one young participant lacked TMT-A data), with higher visual processing speed being associated with lower time to complete the task. Moreover, higher performance in the TMT-A was associated with higher iFC of the insula clusters. Specifically, less time needed to complete the TMT-A significantly correlated with higher iFC, for both the left (r(87) = -0.34, p = 0.001) and the right (r(87) = -0.20, p = 0.030) insula controlling for normalized brain volume. Finally, unlike with visual processing speed C estimates, the iFC of the insula clusters did not explain the variance in TMT-A performance above and beyond age (both p-values > 0.145).

Visual attention functions. Other visual attention parameters have been shown to decrease with age (e.g., Espeseth et al., 2014). Thus, to test whether the iFC of the insula clusters was associated specifically with visual processing speed C (and not generally with visual attention), we also examined the correlation with VSTM capacity K and perceptual threshold t_0, controlling for normalized brain volume. The left insular iFC correlated only marginally with VSTM capacity K (r(88) = 0.17, p = 0.054). The right insular iFC did not correlate with K (p > 0.335), and none of the insular clusters correlated with t_0 estimates (both p-values > 0.150).

Anxiety. Additionally, we inspected whether the iFC of the insula clusters correlated with the anxiety scores derived from both STAI scales. The correlation was not significant (all p-values > 0.130). However, previous reports have pointed to a role of the dorsal anterior cingulate cortex (Seeley et al., 2007), for which we indeed found a significant, though modest, correlation with the State Anxiety scores (r(89) = 0.20, p = 0.030). Moreover, the iFC of the left middle frontal gyrus (r(89) = 0.23, p = 0.014) and that of the left cerebellum (r(89) = 0.18, p = 0.042) also correlated with these scores. No further significant correlations were observed. Importantly, controlling for anxiety scores did not affect the association between visual processing speed C and the iFC of the insula clusters (all p-values < 0.007).

Gray matter. Post-hoc, we performed a voxel-based morphometry analysis (Ashburner and Friston 2000) on the individual T1-weighted anatomical image to establish whether the mediation of the relation between aging and visual processing speed – observed for the iFC of the insula – was due to a reduction of the insular gray matter. Age was voxel-wise regressed on the segmented, normalized, modulated, and smoothed (4-mm isotropic Gaussian kernel) gray matter images, while controlling for gender and education (see *Statistical analyses*). This regression was restricted to a binary mask of the insula taken from the Harvard-Oxford probabilistic cortical atlas (with a 50% probability

threshold;   see   Supplementary   Figure   S1   white   mask fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Next, we extracted the Eigenvariate of the multiple regression results to use it as a control variable for the correlation between the iFC of the insula clusters and the visual processing speed C estimates. The association with visual processing speed was still significant for both the iFC of the left insula cluster while controlling for the left insula gray matter (r(88) = 0.30, p = 0.002; x, y, z MNI coordinates of the peak: -40, -8, 8; k = 497) and the iFC of the right insula cluster while controlling for its respective gray matter (r(88) = 0.23, p = 0.016; MNI coordinates: 42, -4, 6; k = 495). However, as the cluster size (i.e., k) of these anatomical probabilistic masks were almost two times larger than the respective iFC clusters, and given the functional and structural heterogeneity of the insular cortex (Chang, Yarkoni, Khaw et al., 2013), it remains possible that non-relevant parts had been included. To address this, we also restricted the analyses to binary masks of the iFC results (i.e., k = 226 voxels for the left insula and k = 77 voxels for the right insula; see red masks in Figure S1). As with the probabilistic anatomical masks, we found that the relationship between iFC and visual processing speed held significant while respectively controlling for the gray matter of the left (r(88) = 0.30, p = 0.002) and the right (r(88) = 0.24, p = 0.010) insula.

Vascular risk. Twelve out of our 33 elderly participants (i.e., > 60 years) were at risk for vascular events and, thus, took hypertensive (n = 9), lipid-lowering (n = 2), or antiplatelet (n = 1) medication. Mann-Whitney U tests showed no significant differences in either visual processing speed or the insular iFC between the presumed high- and low-risk subgroups (all p-values > 0.162). Moreover, when the possible vascular risk was used as a control variable in the correlation between visual processing speed and the iFC of each insula cluster, it did still remain significant (r(30) = 0.41, p = 0.009 and r(30) = 0.45, p = 0.005 for the left and the right insular iFC, respectively).

Discussion

We modeled visual processing speed independently of other visual attention functions and motor speed (using a TVA-based approach) and tested its association with the iFC of the cingulo-opercular network in aging. We did confirm such an association, which could, moreover, not be accounted for by individual variability in gender, education, brain volume, anxiety, or gray matter changes. Additionally, this association was specific to visual processing speed (and not general to visual attention) and not

evident with other intrinsic brain networks whose iFC decreases with aging (i.e., the default mode and dorsal attention networks). Our results thus demonstrate, for the first time, a mediator role of the insular iFC of the cingulo-opercular network in the relation between increasing age and the slowing of visual processing. We conclude that the iFC of the cingulo-opercular network is central for visual processing speed reductions in healthy aging.

Mediator role of the iFC of the cingulo-opercular network in the visual processing speed reduction in aging

Our results (Table 1) replicate previous findings on decreases in both visual processing speed (Espeseth et al., 2014; Habekost et al., 2013; McAvinue et al., 2012; Salthouse 1996; Tombaugh 2004) and the iFC of the cingulo-opercular network (Figure 3) (He et al., 2014; Onoda et al., 2012; Meier, Desphande, Vergun et al., 2012) over the course of normal aging. More importantly, however, our results demonstrate that a decreased iFC of the cingulo-opercular network is associated with the age-related reduction in visual processing speed (Figure 4). Specifically, the insular iFC was significantly related to visual processing speed, and the iFC of the *left* insula, in particular, was found to mediate the association between age and speed (Figure 5). Visual processing speed has long been known to explain a significant part of the variability in different, speed-dependent cognitive tasks and fluid intelligence especially in the elderly (e.g., Deary and Stough 1996; Deary, Der, and Ford 2001; Deary, Johnson, and Starr 2010). Moreover, the TVA visual processing speed parameter C has been suggested to represent a quantitative measure of an individual, latent parameter (Finke, Bublak, Krummenacher et al., 2005) with substantial influence on cognitive capabilities. Our results thus argue that the previously established links between the iFC of the left insula in the cingulo-opercular network and general cognitive measures in elderly individuals (e.g., He et al., 2014; Onoda et al., 2012) are mediated by a reduction in this more specific, basic function.

The mediation of iFC of the cingulo-opercular network between age and visual processing speed (Figure 5) suggests that it is not simply aging per se that, in a deterministic manner, would give rise to the well-established decrements in visual processing speed. Instead, it implies that, even at an advanced age, individuals might exhibit relatively 'normal' visual processing speed (comparable to that of younger

individuals) – given 'normal' (i.e., youth-like) iFC of the cingulo-opercular network. Accordingly, the TVA parameter visual processing speed *C* may provide a testable neuro-cognitive marker for the efficacy of processing speed training (e.g., Ball, Edwards, and Ross 2007) as well as for brain-behavior analyses in pathological aging (e.g., Bublak et al., 2011; Ruiz-Rizzo et al., 2017). Note, however, that this result is based on cross-sectional and correlational data, which do not allow firm inferences to be drawn regarding the directional relationship(s) among aging, iFC, and speed.

Also of note, the iFC of the cingulo-opercular network did not mediate the association between age and performance in the TMT-A, which is readily explained by this standard measure's high reliance on motor speed (i.e., the speed of connecting the circles on the paper form). Arguably therefore, because our TVA-based measure does not hinge on the speed of motor responding (Habekost et al., 2014), we were able to establish the relationship between iFC and visual processing speed more directly, without potential confound of age-induced motor slowing.

Previous studies have revealed significant associations between task-evoked (Coste and Kleinschmidt 2016; Sadaghiani and D'Esposito 2015) and spontaneous (Schneider et al., 2016; Sadaghiani et al., 2010) fMRI BOLD activity of the cingulo-opercular network and the level of tonic alertness. Our results are in agreement with these studies, as alertness in general (Bundesen, Vangkilde, and Petersen 2015; Matthias et al., 2010; Petersen, Petersen, Bundesen et al., 2017), and *tonic* alertness in particular (Finke et al., 2010; Matthias et al., 2010; Vangkilde, Petersen, and Bundesen 2013), has been shown to exert a direct influence on visual processing speed. In addition to these prior studies, we now provide direct evidence for the crucial role of the cingulo-opercular network for visual processing speed across individuals over a wide range of ages.

Finally, the convergence of the results regarding the *left* insula within the cingulo-opercular network raises a question as to the cause of this lateralized iFC effect on visual processing speed. On the one hand, as our stimuli were letters, this effect could reflect the functional dominance of the left hemisphere for processing verbal stimuli (i.e., briefly presented letters). On the other hand, differential interhemispheric iFC has been reported for the insula, specifically: preferential iFC of the left insula with frontal regions vs. preferential iFC of the right insula with parietal regions (Kann, Zhang, Manza et al., 2016). Thus, there might indeed be a functional hemispheric dominance of the *left* insula in visual processing speed.

Specificity of the association between the iFC of the cingulo-opercular network and visual processing speed

In line with previous reports (e.g., Seeley et al., 2007), anxiety was also associated with the iFC of the anterior cingulate cortex in our sample. Previous fMRI evidence has pointed to activity of cingulo-opercular network regions as a neural correlate of interoceptive awareness (i.e., the perception of visceral signals like the heart beat) (Critchley, Wiens, Rotshtein et al., 2004), a core factor in the pathophysiology of anxiety disorders. In the current study, however, anxiety did not explain the age-related reduction in the insular iFC. Moreover, according to a previous study, there is no significant relationship between the individual degree of interoceptive awareness and the level of alertness in healthy subjects (Matthias, Schandry, Duschek et al., 2009). Collectively, these results suggest that different patterns of brain activity or connectivity within the cingulo-opercular network might, independently, underlie both anxiety-related symptoms and visual processing speed.

Our findings of an age-related reduction of iFC in the default mode and dorsal attention networks are in agreement with previous reports (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Ferreira and Busatto 2013). Moreover, the marginally significant relationships that we observed between iFC in the default mode and dorsal attention networks and visual processing speed would, in principle, also be in line with previously-reported significant associations (e.g., Andrews-Hanna et al., 2007). However, in contrast to the iFC in the cingulo-opercular network, we found no evidence for the iFC in these two networks to contribute above and beyond age to the variance in visual processing speed. Rather than supporting a *general* relationship between age-related decreases in iFC across diverse networks and visual processing speed decrements, our results indicate that the iFC of the cingulo-opercular network plays a special mediator role.

We replicated previous findings that visual attention functions other than processing speed (i.e., VSTM capacity and perceptual threshold) are also significantly affected by aging (Espeseth et al., 2014; McAvinue et al., 2012). However, our results do show that the iFC of the cingulo-opercular network was exclusively associated with visual processing speed. Of theoretical importance, this is in line with a central assumption of the neural interpretation of TVA (NTVA, Bundesen, Habekost, and Kyllingsbaek 2005), namely, that the different visual attention parameters reflect distinct

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neural processes that contribute independently to the individual attentional performance. Thus, it is likely that the brain mechanisms underlying changes in VSTM capacity and perceptual threshold are distinct from those in visual processing speed.

Possible biological factors of iFC changes in aging

Both vascular (e.g., reactivity or pathology of the blood vessels; D'Esposito et al., 2003) and structural (e.g., changes in gray matter; Lu, Lee, Tishler et al., 2013) changes might potentially induce the age-related decrease in the iFC of the cingulo-opercular network. However, controlling for either vascular risk or gray matter volume (i.e., as measured by voxel-based morphometry) did not change the significance of the association between speed and iFC. Thus, our results do point to variations in the intrinsic *functional* organization of the cingulo-opercular network as critical for reductions in visual processing speed. It remains to be determined whether structural connectivity changes (e.g., as measured by tractography) within the cingulo-opercular network or with other networks underlie the changes in iFC.

Conclusion

In summary, our results demonstrate a specific mediator role of the cingulo-opercular network's iFC in the impact of aging on visual processing speed. Future longitudinal studies could attempt to identify whether, among older individuals, changes in iFC and visual processing speed occur at similar or different time points. To conclude, the evidence presented here, for the first time, points to a significant role of the iFC of the cingulo-opercular network in the attentional processing capacity of healthy aging individuals.

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Acknowledgments

Tables

Table 1. Behavioral results and their correlation with age

Behavioral measure	Mean ± SD	Range	Correlation with age
WR TVA estimates			
Processing speed *C*	22.52 ± 7.76	9.71 - 47.00	r = -0.21 (p = 0.025)
VSTM capacity *K*	3.17 ± 0.41	1.95 - 3.88	r = -0.25 (p = 0.009)
Perceptual threshold t_0	13.54 ± 13.76	0.00 - 67.13	r = 0.19 (p = 0.032)
Trail Making Test			
TMT-A (s)	32.52 ± 12.99	13.44 - 74.98	r = 0.65 (p < 0.001)
STAI			
STAI-State	33.46 ± 8.69	0 - 59	r = -0.19 (p = 0.074)
STAI-Trait	33.56 ± 9.93	0 - 67	r = -0.09 (p = 0.375)

Abbreviations. STAI: State-Trait Anxiety Inventory; WR: Whole-report task based on the theory of visual attention (TVA). In bold: Significant at p < 0.05, one-tailed. The p values for both STAI scales are two-tailed.

Table 2. Brain regions (local maxima) of the cingulo-opercular network whose iFC significantly decreased with age.

Brain region (AAL)	MNI coordinates in mm (x, y, z)	Cluster size (voxels)	*Z* value of peak coordinate	*p* value
R ACC	2, 28, 22	747	5.85	< 0.001
L MFG	-26, 40, 40	440	5.50	< 0.001
L cerebellum	-50, -60, -36	167	5.48	0.001
L insula	-44, 12, -10	226	4.98	< 0.001
R MCC	14, -32, 38	347	4.54	< 0.001
R MFG	34, 40, 36	312	4.54	< 0.001
R insula	44, 12, -10	77	4.27	< 0.001

Abbreviations. AAL: Anatomical Automatic Labeling; ACC: anterior cingulate cortex; L: left; MCC: middle cingulate cortex; MFG: middle frontal gyrus; MNI: Montreal Neurological Institute; R: right. Multiple-regression controlled for gender and education, p < 0.05 FWE corrected at the cluster level.

Figures
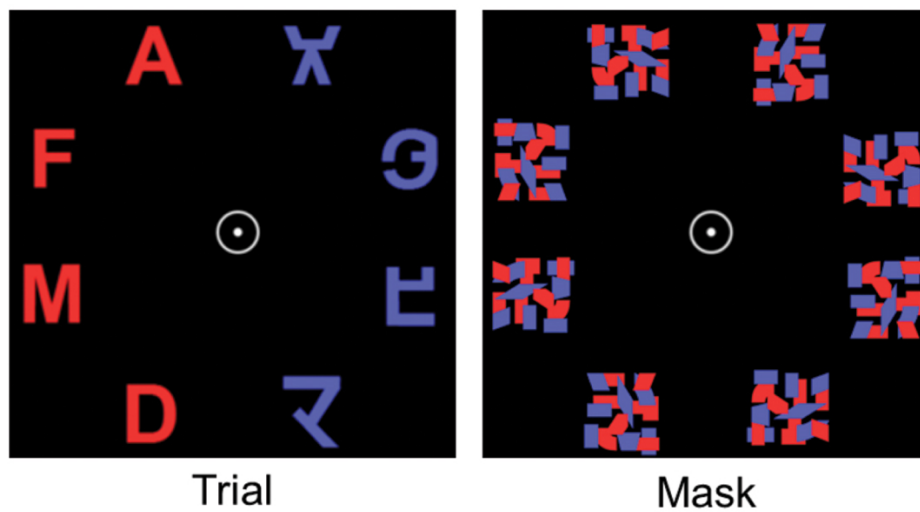
Figure 1. Example of a trial and the mask used for whole report task. Symbols were symmetrically presented contralateral to the target stimuli to ensure balanced physical stimulation. Stimuli diameters were equal to 1.3° visual angle.
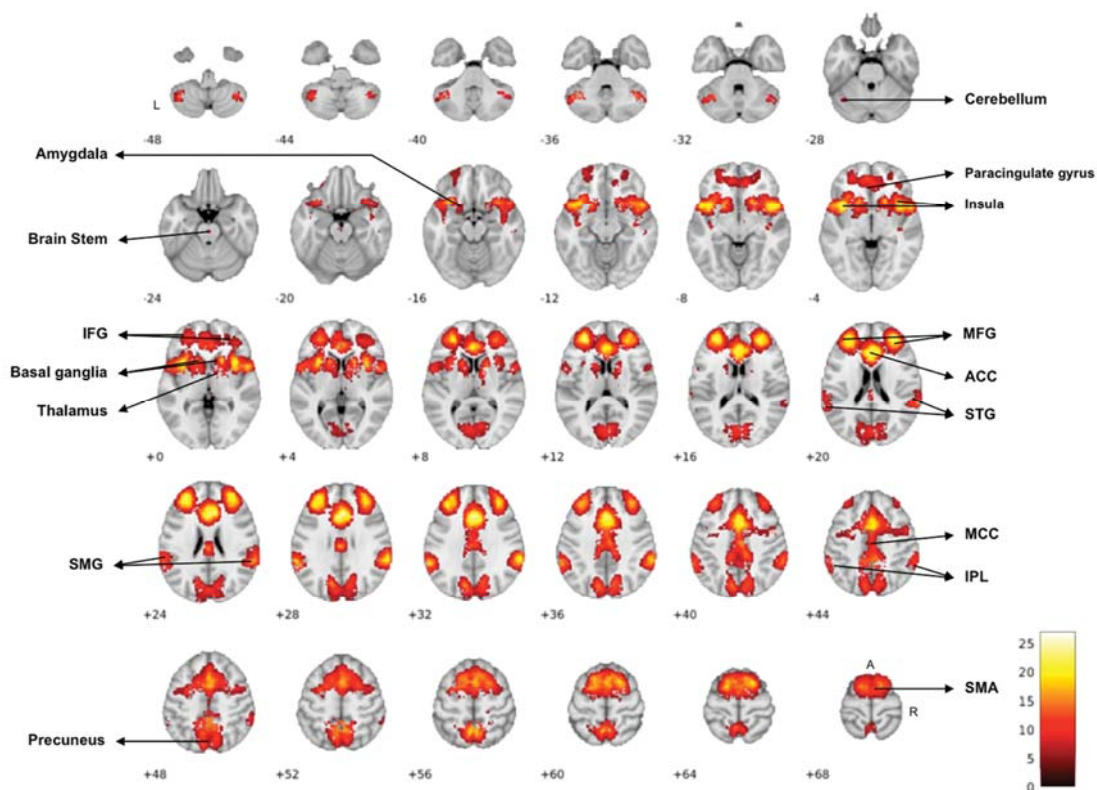
Figure 2. Statistical parametric mapping of the cingulo-opercular network obtained with independent component analysis of resting-state fMRI data and one-sample t-test. Significant voxels (p < 0.05 FWE-corrected at the cluster level) are overlaid onto an anatomical standard MNI152 template. ACC: anterior cingulate cortex; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; MCC: middle cingulate cortex; MFG: middle frontal gyrus; SMA: supplementary motor area; SMG: supramarginal gyrus; STG: superior temporal gyrus. The color bar indicates *t* values.
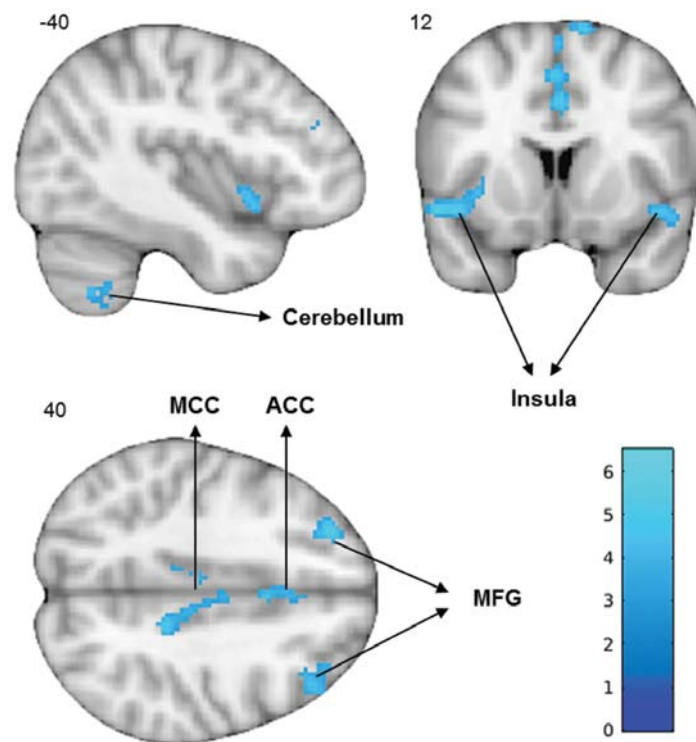
Figure 3. SPM of voxel-wise multiple regression of age on functional connectivity of the cingulo-opercular network (see Figure 2), while controlling for gender and education (p < 0.05 FWE-corrected at the cluster level). Overlaid onto a standard MNI152 template are the voxels with decreased functional connectivity with increasing age. Clusters were found in the anterior and middle cingulate cortex (ACC and MCC), middle frontal gyrus (MFG) bilaterally, insula bilaterally, and left cerebellum. The color bar indicates *t* values.
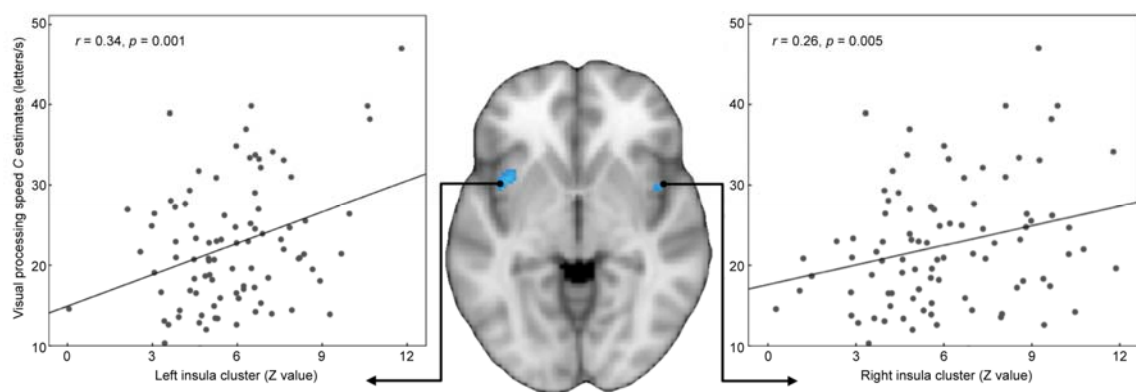
Figure 4. Scatter plots illustrating processing speed C as a function of the iFC of two insular clusters (left: -44, 12, -10, 226 voxels; right: 44, 12, -10, 77 voxels) within the cingulo-opercular network (see Figure 2). The insular clusters are derived from SPM of Figure 3, reflecting the association between iFC and age. Partial coefficients controlling for normalized brain volume: left insula, r(88) = 0.30, p = 0.002; right insula, r(88) = 0.22, p = 0.017.
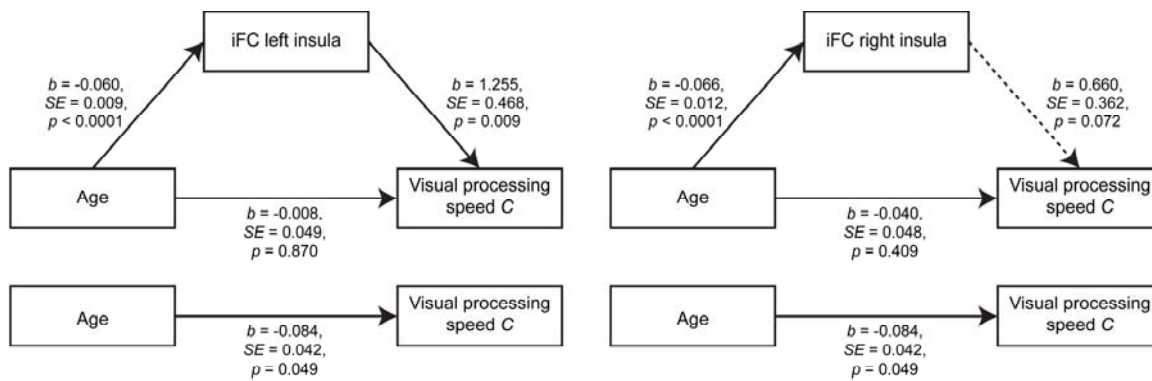
Figure 5. Unstandardized coefficients (*b*) and their respective standard errors (SE) and *p* values (two-tailed) for each path of the mediation model. Thicker lines indicate significant paths, dashed lines marginally significant paths, and thinner lines no significant paths.
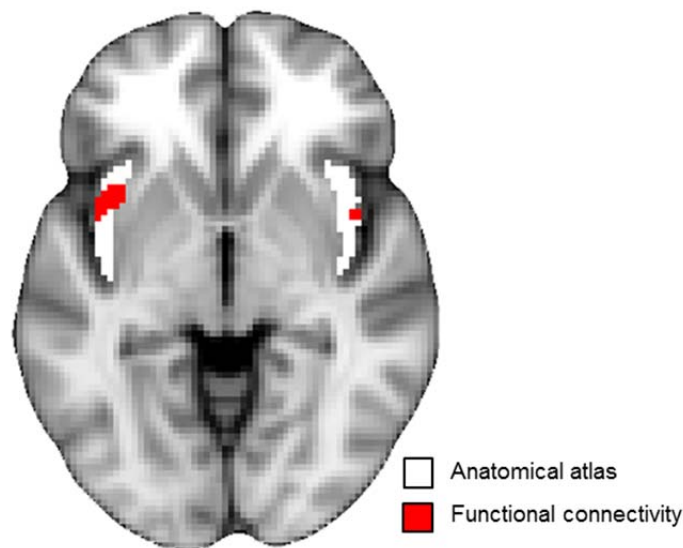
Supplementary Figure. Insular masks based on the Harvard-Oxford cortical atlas (white) and on the functional connectivity results (Figure 3) used to restrict multiple regression analyses of aging onto gray matter.

References

Andrews-Hanna, J. R., A. Z. Snyder, J. L. Vincent, C. Lustig, D. Head, M. E. Raichle, et al. 2007. "Disruption of large-scale brain systems in advanced aging." *Neuron* 56 (5):924-35. doi: 10.1016/j.neuron.2007.10.038.

Ashburner, J., and K. J. Friston. 2000. "Voxel-based morphometry--the methods." *Neuroimage* 11 (6 Pt 1):805-21. doi: 10.1006/nimg.2000.0582.

Ball, K., J. D. Edwards, and L. A. Ross. 2007. "The impact of speed of processing training on cognitive and everyday functions." *J Gerontol B Psychol Sci Soc Sci* 62 Spec No 1:19-31.

Barnes, L. L., D. Harp, and W. S. Jung. 2002. "Reliability generalization of scores on the Spielberger state-trait anxiety inventory." *Educational and Psychological Measurement* 62 (4):603-618.

Baron, R. M., and D. A. Kenny. 1986. "The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations." *J Pers Soc Psychol* 51 (6):1173-82.

Beck, A. T., R. A. Steer, and G. K. Brown. 1996. *Manual for the Beck Depression Inventory-II*. Second Edition ed. San Antonio, TX: The Psychological Corporation.

Beckmann, C. F., C. E. Mackay, N. Filippini, and S. Smith. 2009. "Group comparison of resting-state FMRI data using multi-subject ICA and dual regression." *Neuroimage* 47 (Suppl 1):S148.

Beckmann, C. F., and S. M. Smith. 2004. "Probabilistic independent component analysis for functional magnetic resonance imaging." *IEEE Trans Med Imaging* 23 (2):137-52. doi: 10.1109/TMI.2003.822821.

Bublak, P., P. Redel, C. Sorg, A. Kurz, H. Forstl, H. J. Muller, et al. 2011. "Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease." *Neurobiol Aging* 32 (7):1219-30. doi: 10.1016/j.neurobiolaging.2009.07.012.

Bundesen, C. 1990. "A theory of visual attention." *Psychol Rev* 97 (4):523-47.

Bundesen, C., T. Habekost, and S. Kyllingsbaek. 2005. "A neural theory of visual attention: bridging cognition and neurophysiology." *Psychol Rev* 112 (2):291-328. doi: 10.1037/0033-295X.112.2.291.

Bundesen, C., S. Vangkilde, and A. Petersen. 2015. "Recent developments in a computational theory of visual attention (TVA)." *Vision Res* 116 (Pt B):210-8. doi: 10.1016/j.visres.2014.11.005.

Chang, L. J., T. Yarkoni, M. W. Khaw, and A. G. Sanfey. 2013. "Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference." *Cereb Cortex* 23 (3):739-49. doi: 10.1093/cercor/bhs065.

Chao-Gan, Y., and Z. Yu-Feng. 2010. "DPARSF: A MATLAB Toolbox for "Pipeline" Data Analysis of Resting-State fMRI." *Front Syst Neurosci* 4:13. doi: 10.3389/fnsys.2010.00013.

Coste, C. P., and A. Kleinschmidt. 2016. "Cingulo-opercular network activity maintains alertness." *Neuroimage* 128:264-72. doi: 10.1016/j.neuroimage.2016.01.026.

Critchley, H. D., S. Wiens, P. Rotshtein, A. Ohman, and R. J. Dolan. 2004. "Neural systems supporting interoceptive awareness." *Nat Neurosci* 7 (2):189-95. doi: 10.1038/nn1176.

D'Esposito, M., L. Y. Deouell, and A. Gazzaley. 2003. "Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging." *Nat Rev Neurosci* 4 (11):863-72. doi: 10.1038/nrn1246.

Damoiseaux, J. S., C. F. Beckmann, E. J. Arigita, F. Barkhof, P. Scheltens, C. J. Stam, et al. 2008. "Reduced resting-state brain activity in the "default network" in normal aging." *Cereb Cortex* 18 (8):1856-64. doi: 10.1093/cercor/bhm207.

De Luca, M., C. F. Beckmann, N. De Stefano, P. M. Matthews, and S. M. Smith. 2006. "fMRI resting state networks define distinct modes of long-distance interactions in the human brain." *Neuroimage* 29 (4):1359-67. doi: 10.1016/j.neuroimage.2005.08.035.

Deary, I. J., G. Der, and G. Ford. 2001. "Reaction times and intelligence differences: A population-based cohort study." *Intelligence* 29 (5):389-399. doi: https://doi.org/10.1016/S0160-2896(01)00062-9.

Deary, I. J., W. Johnson, and J. M. Starr. 2010. "Are processing speed tasks biomarkers of cognitive aging?" *Psychol Aging* 25 (1):219-28. doi: 10.1037/a0017750.

Deary, I. J., and C. Stough. 1996. " Intelligence and inspection time: Achievements, prospects, and problems." *American Psychologist* 51 (6):599-608. doi: http://dx.doi.org/10.1037/0003-066X.51.6.599.

Dosenbach, N. U., D. A. Fair, A. L. Cohen, B. L. Schlaggar, and S. E. Petersen. 2008. "A dual-networks architecture of top-down control." *Trends Cogn Sci* 12 (3):99-105. doi: 10.1016/j.tics.2008.01.001.

Dosenbach, N. U., D. A. Fair, F. M. Miezin, A. L. Cohen, K. K. Wenger, R. A. Dosenbach, et al. 2007. "Distinct brain networks for adaptive and stable task control in humans." *Proc Natl Acad Sci U S A* 104 (26):11073-8. doi: 10.1073/pnas.0704320104.

Dyrholm, M., S. Kyllingsbaek, T. Espeseth, and C. Bundesen. 2011. "Generalizing parametric models by introducing trial-by-trial parameter variability: The case of TVA." *Journal of Mathematical Psychology* 55 (6):416-429. doi: https://doi.org/10.1016/j.jmp.2011.08.005.

Espeseth, T., S. A. Vangkilde, A. Petersen, M. Dyrholm, and L. T. Westlye. 2014. "TVA-based assessment of attentional capacities-associations with age and indices of

brain white matter microstructure." *Front Psychol* 5:1177. doi: 10.3389/fpsyg.2014.01177.

Feinberg, D. A., and K. Setsompop. 2013. "Ultra-fast MRI of the human brain with simultaneous multi-slice imaging." *J Magn Reson* 229:90-100. doi: 10.1016/j.jmr.2013.02.002.

Ferreira, L. K., and G. F. Busatto. 2013. "Resting-state functional connectivity in normal brain aging." *Neurosci Biobehav Rev* 37 (3):384-400. doi: 10.1016/j.neubiorev.2013.01.017.

Filippini, N., B. J. MacIntosh, M. G. Hough, G. M. Goodwin, G. B. Frisoni, S. M. Smith, et al. 2009. "Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele." *Proc Natl Acad Sci U S A* 106 (17):7209-14. doi: 10.1073/pnas.0811879106.

Finke, K., P. Bublak, J. Krummenacher, S. Kyllingsbaek, H. J. Muller, and W. X. Schneider. 2005. "Usability of a theory of visual attention (TVA) for parameter-based measurement of attention I: evidence from normal subjects." *J Int Neuropsychol Soc* 11 (7):832-42.

Finke, K., C. M. Dodds, P. Bublak, R. Regenthal, F. Baumann, T. Manly, et al. 2010. "Effects of modafinil and methylphenidate on visual attention capacity: a TVA-based study." *Psychopharmacology (Berl)* 210 (3):317-29. doi: 10.1007/s00213-010-1823-x.

Folstein, M. F., S. E. Folstein, and P. R. McHugh. 1975. ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician." *J Psychiatr Res* 12 (3):189-98.

Fox, M. D., and M. E. Raichle. 2007. "Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging." *Nat Rev Neurosci* 8 (9):700-11. doi: 10.1038/nrn2201.

Habekost, T., A. Petersen, and S. Vangkilde. 2014. "Testing attention: comparing the ANT with TVA-based assessment." *Behav Res Methods* 46 (1):81-94. doi: 10.3758/s13428-013-0341-2.

Habekost, T., A. Vogel, E. Rostrup, C. Bundesen, S. Kyllingsbaek, E. Garde, et al. 2013. "Visual processing speed in old age." *Scand J Psychol* 54 (2):89-94. doi: 10.1111/sjop.12008.

Hayes, A. F. 2012. "PROCESS: A versatile computational tool for observed variable mediation, moderation, and conditional process modeling." accessed May 5th.

He, X., W. Qin, Y. Liu, X. Zhang, Y. Duan, J. Song, et al. 2014. "Abnormal salience network in normal aging and in amnestic mild cognitive impairment and Alzheimer's disease." *Hum Brain Mapp* 35 (7):3446-64. doi: 10.1002/hbm.22414.

Hyvarinen, A. 1999. "Fast and robust fixed-point algorithms for independent component analysis." *IEEE Trans Neural Netw* 10 (3):626-34. doi: 10.1109/72.761722.

Jenkinson, M., P. Bannister, M. Brady, and S. Smith. 2002. "Improved optimization for the robust and accurate linear registration and motion correction of brain images." *Neuroimage* 17 (2):825-41.

Jenkinson, M., and S. Smith. 2001. "A global optimisation method for robust affine registration of brain images." *Med Image Anal* 5 (2):143-56.

Kann, S., S. Zhang, P. Manza, H. C. Leung, and C. R. Li. 2016. "Hemispheric Lateralization of Resting-State Functional Connectivity of the Anterior Insula: Association with Age, Gender, and a Novelty-Seeking Trait." *Brain Connect* 6 (9):724-734. doi: 10.1089/brain.2016.0443.

Kyllingsbaek, S. 2006. "Modeling visual attention." *Behav Res Methods* 38 (1):123-33.

Laux, L., P. Glanzmann, P. Schaffner, and C. D. Spielberger. 1981. *Das State-Trait-Angstinventar (Testmappe mit Handanweisung, Fragebogen STAI-G Form X 1 und Fragebogen STAI-G Form X 2)*. Weinheim: Beltz.

Lu, P. H., G. J. Lee, T. A. Tishler, M. Meghpara, P. M. Thompson, and G. Bartzokis. 2013. "Myelin breakdown mediates age-related slowing in cognitive processing speed in healthy elderly men." *Brain Cogn* 81 (1):131-8. doi: 10.1016/j.bandc.2012.09.006.

Mackinnon, D. P., and A. J. Fairchild. 2009. "Current Directions in Mediation Analysis." *Curr Dir Psychol Sci* 18 (1):16. doi: 10.1111/j.1467-8721.2009.01598.x.

Matthias, E., P. Bublak, H. J. Muller, W. X. Schneider, J. Krummenacher, and K. Finke. 2010. "The influence of alertness on spatial and nonspatial components of visual attention." *J Exp Psychol Hum Percept Perform* 36 (1):38-56. doi: 10.1037/a0017602.

Matthias, E., R. Schandry, S. Duschek, and O. Pollatos. 2009. "On the relationship between interoceptive awareness and the attentional processing of visual stimuli." *Int J Psychophysiol* 72 (2):154-9. doi: 10.1016/j.ijpsycho.2008.12.001.

McAvinue, L. P., T. Habekost, K. A. Johnson, S. Kyllingsbaek, S. Vangkilde, C. Bundesen, et al. 2012. "Sustained attention, attentional selectivity, and attentional capacity across the lifespan." *Atten Percept Psychophys* 74 (8):1570-82. doi: 10.3758/s13414-012-0352-6.

Meier, T. B., A. S. Desphande, S. Vergun, V. A. Nair, J. Song, B. B. Biswal, et al. 2012. "Support vector machine classification and characterization of age-related reorganization of functional brain networks." *Neuroimage* 60 (1):601-13. doi: 10.1016/j.neuroimage.2011.12.052.

Menon, V., and L. Q. Uddin. 2010. "Saliency, switching, attention and control: a network model of insula function." *Brain Struct Funct* 214 (5-6):655-67. doi: 10.1007/s00429-010-0262-0.

Murphy, K., J. Bodurka, and P. A. Bandettini. 2007. "How long to scan? The relationship between fMRI temporal signal to noise ratio and necessary scan duration." *Neuroimage* 34 (2):565-74. doi: 10.1016/j.neuroimage.2006.09.032.

Onoda, K., M. Ishihara, and S. Yamaguchi. 2012. "Decreased functional connectivity by aging is associated with cognitive decline." *J Cogn Neurosci* 24 (11):2186-98. doi: 10.1162/jocn_a_00269.

Petersen, A., A. H. Petersen, C. Bundesen, S. Vangkilde, and T. Habekost. 2017. "The effect of phasic auditory alerting on visual perception." *Cognition* 165:73-81. doi: 10.1016/j.cognition.2017.04.004.

Posner, M. I., and S. E. Petersen. 1990. "The attention system of the human brain." *Annu Rev Neurosci* 13:25-42. doi: 10.1146/annurev.ne.13.030190.000325.

Power, J. D., K. A. Barnes, A. Z. Snyder, B. L. Schlaggar, and S. E. Petersen. 2012. "Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion." *Neuroimage* 59 (3):2142-54. doi: 10.1016/j.neuroimage.2011.10.018.

Preacher, K. J., and A. F. Hayes. 2004. "SPSS and SAS procedures for estimating indirect effects in simple mediation models." *Behav Res Methods Instrum Comput* 36 (4):717-31.

Preibisch, C., G. Jg Castrillon, M. Buhrer, and V. Riedl. 2015. "Evaluation of Multiband EPI Acquisitions for Resting State fMRI." *PLoS One* 10 (9):e0136961. doi: 10.1371/journal.pone.0136961.

Raichle, M. E. 2015. "The restless brain: how intrinsic activity organizes brain function." *Philos Trans R Soc Lond B Biol Sci* 370 (1668). doi: 10.1098/rstb.2014.0172.

Reitan, R. M., and D. Wolfson. 1985. *The Halstead-Reitan neuropsychological test battery: therapy and clinical interpretation.* Tucson, AZ: Neuropsychological Press.

Ruiz-Rizzo, A. L., P. Bublak, P. Redel, T. Grimmer, H. J. Muller, C. Sorg, et al. 2017. "Simultaneous object perception deficits are related to reduced visual processing

speed in amnestic mild cognitive impairment." *Neurobiol Aging* 55:132-142. doi: 10.1016/j.neurobiolaging.2017.03.029.

Sadaghiani, S., and M. D'Esposito. 2015. "Functional Characterization of the Cingulo-Opercular Network in the Maintenance of Tonic Alertness." *Cereb Cortex* 25 (9):2763-73. doi: 10.1093/cercor/bhu072.

Sadaghiani, S., R. Scheeringa, K. Lehongre, B. Morillon, A. L. Giraud, and A. Kleinschmidt. 2010. "Intrinsic connectivity networks, alpha oscillations, and tonic alertness: a simultaneous electroencephalography/functional magnetic resonance imaging study." *J Neurosci* 30 (30):10243-50. doi: 10.1523/JNEUROSCI.1004-10.2010.

Salthouse, T. A. 1996. "The processing-speed theory of adult age differences in cognition." *Psychol Rev* 103 (3):403-28.

Satterthwaite, T. D., M. A. Elliott, R. T. Gerraty, K. Ruparel, J. Loughead, M. E. Calkins, et al. 2013. "An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data." *Neuroimage* 64:240-56. doi: 10.1016/j.neuroimage.2012.08.052.

Schneider, M., P. Hathway, L. Leuchs, P. G. Samann, M. Czisch, and V. I. Spoormaker. 2016. "Spontaneous pupil dilations during the resting state are associated with activation of the salience network." *Neuroimage* 139:189-201. doi: 10.1016/j.neuroimage.2016.06.011.

Seeley, W. W., V. Menon, A. F. Schatzberg, J. Keller, G. H. Glover, H. Kenna, et al. 2007. "Dissociable intrinsic connectivity networks for salience processing and executive control." *J Neurosci* 27 (9):2349-56. doi: 10.1523/JNEUROSCI.5587-06.2007.

Sestieri, C., M. Corbetta, S. Spadone, G. L. Romani, and G. L. Shulman. 2014. "Domain-general signals in the cingulo-opercular network for visuospatial attention and episodic memory." *J Cogn Neurosci* 26 (3):551-68. doi: 10.1162/jocn_a_00504.

Smith, S. M., M. Jenkinson, M. W. Woolrich, C. F. Beckmann, T. E. Behrens, H. Johansen-Berg, et al. 2004. "Advances in functional and structural MR image analysis and implementation as FSL." *Neuroimage* 23 Suppl 1:S208-19. doi: 10.1016/j.neuroimage.2004.07.051.

Smith, S. M., Y. Zhang, M. Jenkinson, J. Chen, P. M. Matthews, A. Federico, et al. 2002. "Accurate, robust, and automated longitudinal and cross-sectional brain change analysis." *Neuroimage* 17 (1):479-89.

Sobel, M. E. 1982. "Asymptotic Confidence Intervals for Indirect Effects in Structural Equation Models." *Sociological Methodology* 13:290-312. doi: 10.2307/270723.

Sperling, G. 1960. "The information available in brief visual presentations." *Psychological monographs: General and applied* 74 (11):1-29. doi: http://dx.doi.org/10.1037/h0093759.

Spielberger, C. D. 1972. *Anxiety: Current trends in research*. London: Academic Press.

Spielberger, C. D., R. L. Gorsuch, and R. E. Lushene. 1970. *State-Trait Anxiety Inventory, Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologist Press.

Spreen, O., and E. Strauss. 1998. *A compendium of neuropsychological tests: Administration, norms and commentary*. Second Edition ed. New York: Oxford University Press.

Sturm, W., and K. Willmes. 2001. "On the functional neuroanatomy of intrinsic and phasic alertness." *Neuroimage* 14 (1 Pt 2):S76-84. doi: 10.1006/nimg.2001.0839.

Tomasi, D., and N. D. Volkow. 2012. "Aging and functional brain networks." *Mol Psychiatry* 17 (5):471, 549-58. doi: 10.1038/mp.2011.81.

Tombaugh, T. N. 2004. "Trail Making Test A and B: normative data stratified by age and education." *Arch Clin Neuropsychol* 19 (2):203-14. doi: 10.1016/S0887-6177(03)00039-8.

Vangkilde, S., A. Petersen, and C. Bundesen. 2013. "Temporal expectancy in the context of a theory of visual attention." *Philos Trans R Soc Lond B Biol Sci* 368 (1628):20130054. doi: 10.1098/rstb.2013.0054.

Yeo, B. T., F. M. Krienen, J. Sepulcre, M. R. Sabuncu, D. Lashkari, M. Hollinshead, et al. 2011. "The organization of the human cerebral cortex estimated by intrinsic functional connectivity." *J Neurophysiol* 106 (3):1125-65. doi: 10.1152/jn.00338.2011.

Zhang, Y., M. Brady, and S. Smith. 2001. "Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm." *IEEE Trans Med Imaging* 20 (1):45-57. doi: 10.1109/42.906424.

7. Study 3: Visual processing speed and complex object perception in pathological aging

Adriana L. Ruiz-Rizzo, Peter Bublak, Petra Redel, Timo Grimmer, Hermann J. Müller, Christian Sorg, Kathrin Finke

Summary

In this paper titled **Simultaneous Object Perception Deficits and Reduced Visual Processing Speed in Amnestic Mild Cognitive Impairment**, we highlight the relevance of visual processing speed assessment for disclosing non-memory impairments in patients with single-domain amnestic mild cognitive impairment (aMCI).

Specifically, in a group of patients diagnosed with single-domain aMCI due to Alzheimer's disease (AD), we observed simultaneous object perception deficits. Notably, the deficits observed were not related to their global cognitive state as assessed by the Mini-Mental State Examination, or to their verbal memory, visual short-term memory, perceptual sensitivity, or visual object agnosia. Rather, these deficits were significantly associated with a reduction in visual processing speed as previously reported in patients with stroke, Huntington's disease, or posterior cortical atrophy.

The results of this study can have at least three crucial implications for the early detection of subjects at risk for developing AD dementia. First, the results underscore the presence of non-memory deficits even in single-domain aMCI, i.e., a reduction of visual processing speed. Second, simultaneous object perception assessment can become a novel tool for the early detection of AD that can be applied easily by assistant personnel. Finally, our results suggest an account for the high sensitivity of visual memory deficits as well as spatial navigation deficits in disclosing AD-related cognitive decline.

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Graphic abstract

Authors' contributions

K.F. and P.B. designed the study. P.R. and T.G. recruited the patients and healthy controls and further assessed them. A.L.R.R. analyzed the data and drafted the manuscript. A.L.R.R., K.F., P.B., C.S., H.J.M., P.R., and T.G. wrote and critically revised the manuscript before submission.

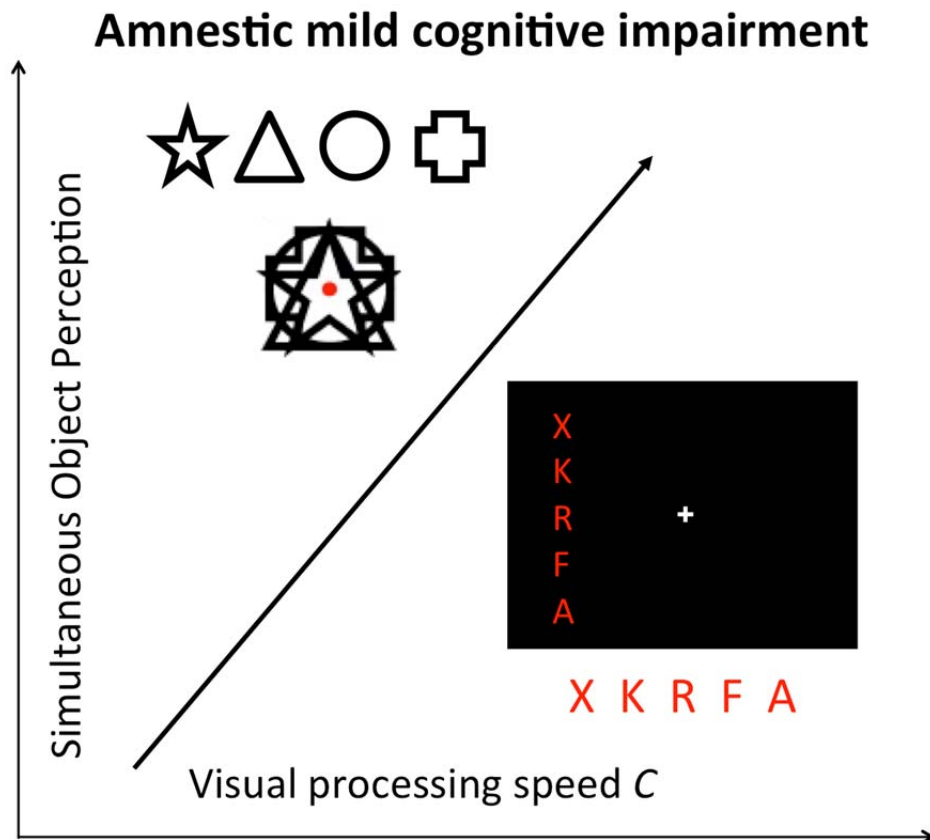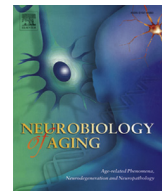**Paper: Simultaneous Object Perception Deficits and Reduced Visual Processing Speed in Amnestic Mild Cognitive Impairment**

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Simultaneous object perception deficits are related to reduced visual processing speed in amnestic mild cognitive impairment

Adriana L. Ruiz-Rizzo [a,b], Peter Bublak [c], Petra Redel [a], Timo Grimmer [d],
Hermann J. Müller [a,b], Christian Sorg [d,e,f], Kathrin Finke [a,b,c,*]

[a] Department of General and Experimental Psychology, Ludwig-Maximilians-Universität München, Munich, Germany
[b] Graduate School of Systemic Neurosciences, LMU, Munich, Germany
[c] Hans Berger Department of Neurology, Jena University Hospital, Jena, Germany
[d] Klinikum rechts der Isar, Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany
[e] Klinikum rechts der Isar, TUM-NIC Neuroimaging Center, Technische Universität München, Munich, Germany
[f] Klinikum rechts der Isar, Department of Neuroradiology, Technische Universität München, Munich, Germany

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ABSTRACT

Simultanagnosia, an impairment in simultaneous object perception, has been attributed to deficits in visual attention and, specifically, to processing speed. Increasing visual attention deficits manifest over the course of Alzheimer's disease (AD), where the first changes are present already in its symptomatic predementia phase: amnestic mild cognitive impairment (aMCI). In this study, we examined whether patients with aMCI due to AD show simultaneous object perception deficits and whether and how these deficits relate to visual attention. Sixteen AD patients with aMCI and 16 age-, gender-, and education-matched healthy controls were assessed with a simultaneous perception task, with shapes presented in an adjacent, embedded, or overlapping manner, under free viewing without temporal constraints. We used a parametric assessment of visual attention based on the Theory of Visual Attention. Results show that patients make significantly more errors than controls when identifying overlapping shapes, which correlate with reduced processing speed. Our findings suggest simultaneous object perception deficits in very early AD, and a visual processing speed reduction underlying these deficits.

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1. Introduction

Deficient memory is considered the hallmark of Alzheimer's disease (AD), already manifesting in mild dementia and amnestic mild cognitive impairment (aMCI) as a symptomatic predementia phase of AD (Albert et al., 2011; Morris et al., 2001; Petersen, 2004). However, growing evidence suggests the presence of visual attentional impairments early in the course of AD (Alescio-Lautier et al., 2007; Bonney et al., 2006; Bublak et al., 2011; Finke et al., 2013; Perry and Hodges, 1999; Perry et al., 2000; Rapp and Reischies, 2005; Redel et al., 2012; Rizzo et al., 2000). Significant relationships of such impairments to hypometabolism and functional connectivity changes in frontoparietal attention systems have been documented (Neufang et al., 2011, 2014; Sorg et al., 2007, 2012). Of note, frontoparietal hypometabolism and atrophy overlapping with

β-amyloid accumulation at the aMCI stage have been revealed even to precede similar changes in memory-relevant temporal structures (Drzezga et al., 2011; Engler et al., 2006; Kemppainen et al., 2007; Mattsson et al., 2014; Mintun et al., 2006; Sorg et al., 2012). Among the affected attention functions, for example, visual processing speed shows a staged decline (Bublak et al., 2011), implying that individual cases suffer from more or less severe slowing. Critically, for diverse patient groups, it has been suggested that reduced visual processing speed can lead to impairments in the ability to perceive several objects at the same time, that is, to perceive symptoms of simultanagnosia (Chechlacz et al., 2012; Duncan et al., 2003; Finke et al., 2007). Thus, in the present study, we asked whether patients with aMCI show deficits in simultaneous object perception and, if so, whether these deficits are associated with a reduction of processing speed.

Patients with simultanagnosia are not able to integrate the objects within a visual scene to achieve a meaningful interpretation, although recognition of single objects is usually preserved (Bálint, 1909; Coslett and Saffran, 1991; Holmes, 1918; Wolpert, 1924). In patients with full-blown simultanagnosia, perception

* Corresponding author at: Ludwig-Maximilians-Universität München, Department of General and Experimental Psychology/Neuro-Cognitive Psychology, Leopoldstr. 13, 80802 Munich, Germany. Tel.: +49 (0) 89/2180 72520; fax: +49 (0) 89/2180 5211.

E-mail address: finke@psy.lmu.de (K. Finke).

appears to stick to a single object at a time in the scene, resulting in the acquisition of visual information in a piecemeal fashion (Rizzo and Vecera, 2002). Particular severe problems occur if 2 or more objects are presented in an overlapping manner (e.g., Bálint and Harvey, 1995; Luria, 1959). For example, Luria reported that patients with simultanagnosia were not able to identify 2 overlapping triangles of different colors that formed the "star of David"; rather, they reported only one of them (Luria, 1959). Interestingly, the neural damage in cases with simultanagnosia due to acquired lesions typically involves extensive bilateral frontoparietal areas (Chechlacz et al., 2012; Ptak, 2012), including the same regions (e.g., Corbetta, 1998) that are affected in predementia phases of AD (Perry and Hodges, 1999). Thus, some degree of simultanagnosia can be expected to be present in aMCI patients, too.

A crucial step towards a systematic analysis of processing speed and visual short-term memory (VSTM) as putative causes of simultaneous object perception deficits was taken by applying parametric measurement of attention based on the "Theory of Visual Attention" (TVA; Bundesen, 1990) to patients with simultanagnosia. TVA is a unified computational account for visual single-stimulus recognition and attentional selection from multielement displays (Bundesen, 1990), essentially implementing a mathematical formalization of the biased competition model (Desimone and Duncan, 1995). Within TVA, both visual recognition and attentional selection consist in making perceptual categorizations (Bundesen, 1998). There are 2 fundamental capacity parameters that can be independently estimated based on the TVA formalization: visual processing speed C and VSTM storage capacity K. Parameter C is a quantitative estimate of the number of objects that can be processed in parallel per second; parameter K, in turn, is the estimate of the maximum number of objects that can be maintained simultaneously in the VSTM store. Both C and K parameters can be derived from an individual's performance in a whole-report task, where observers' ability to perceive and report multiple letter stimuli is assessed as a function of the effective array exposure duration (Bundesen, 1990) (for application in clinical samples, see Bublak et al., 2011; Finke et al., 2005; McAvinue et al., 2015). Using TVA assessment, Duncan et al. (2003) found severely reduced visual processing speed, even with single-item presentation, in 2 patients with both dorsal and ventral simultanagnosia, while VSTM storage capacity appeared to be preserved (Duncan et al., 2003). Furthermore, Finke et al. (2007) conducted a first group analysis based on TVA: an assessment of patients with Huntington's disease, who typically suffer from increasingly severe visual processing speed deficits (Finke et al., 2006). Finke et al. (2007) found that patients with more pronounced slowing displayed greater impairments in simultaneous object perception. They concluded that a slowing of the rate of visual information uptake gives rise to impaired perception of multiple overlapping stimuli in Huntington's disease (Finke et al., 2007). These results were also replicated in a recent study in patients with posterior cortical dementia (Neitzel et al., 2016). Of note, a staged decline of visual processing speed was also found in the amnestic form of Alzheimer's disease (Bublak et al., 2011). Thus, given the relevance of deficient visual processing speed in diverse patient groups, in the present study we, too, focused on the role of this specific attentional (dys)function with regard to potential deficits in simultaneous object perception in aMCI patients.

In particular, we aimed to ascertain whether there are deficits in simultaneous object perception in aMCI due to AD, and, if so, whether these deficits are associated with a reduction of visual processing speed. To this end, we compared aMCI patients and healthy control (HC) participants on several simultanagnosia tests and a TVA-based whole-report paradigm.

2. Materials and methods

2.1. Participants

Sixteen patients with a diagnosis of aMCI due to AD (9 females; mean age 70.9 ± 7.8 years; 11.6 mean years of education) and 16 age-, gender-, and education-matched HCs (9 females; 69.9 ± 7.4 years old, 11.6 mean years of education) participated in our study. Patients were diagnosed at, and recruited from, the Memory Clinic of the Department of Psychiatry, Technische Universität München, Germany, and controls were recruited from the general community through flyers and word-of-mouth recommendation. All participants gave written informed consent to take part in this study according to the Declaration of Helsinki II, and the study had local ethical committee approval.

Participants underwent a standardized diagnostic process that included medical, psychiatric, and neurological examinations. Patients had additionally brain-imaging diagnostics including structural magnetic resonance imaging and fluorodeoxyglucose positron emission tomography. All participants had undergone an informant-derived Clinical Dementia Rating (Morris, 1993), with patients having values of 0.5 and controls of 0, and neuropsychological assessment using the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; German version; Berres et al., 2000), including the Mini–Mental State Examination (MMSE; Folstein et al., 1975) and the clock-drawing test (Shulman et al., 1993). Based on this assessment, aMCI patients fulfilled cognitive impairment criteria according to Petersen (Petersen et al., 1999, 2001), along with largely preserved activities of daily living (Bayer ADL scale; Hindmarch et al., 1998), and no dementia according to the International Classification of Diseases, Tenth Revision criteria (WHO, 2010). Furthermore, all aMCI patients of this study met the criteria for MCI due to AD (Albert et al., 2011). Beyond patients' MCI, they had biological signs of AD in terms of bilateral temporoparietal hypometabolism as shown in fluorodeoxyglucose positron emission tomography (Albert et al., 2011). Criteria for exclusion from the study were history of other neurological diseases and imaging evidence of marked brain lesions that affected cognition (e.g., stroke lesions). Three of the 16 patients were under antidepressant medication ($n = 1$ with selective serotonin reuptake inhibitors, $n = 1$ with tricyclic, and $n = 1$ with noradrenergic and specific serotonergic antidepressants). Concerning genotyping, 11 patients had either 1 ($n = 9$) or 2 ($n = 2$) alleles of the APOE ε4 allele.

HCs were free of any current, or history of, psychiatric or neurological condition. Patients and controls did not differ in age, gender, or education (see Table 1). As expected from the diagnosis, aMCI patients had significantly lower MMSE scores, that is, a lower global cognitive state, than controls [$t(30) = -4.025$, $p < 0.001$] (Table 1 for all demographic details). All aMCI patients were able to follow verbal instructions and to concentrate sufficiently during the tasks. All participants had normal or corrected-to-normal vision and were not color-blind.

2.2. Procedure

After their routine clinical assessment, aMCI patients and controls underwent testing of simultanagnosia and visual attention, specific for the present study. This testing was conducted in 2–3 one-hour sessions. Well-established clinical test batteries known to be sensitive to simultanagnosia symptoms were administered to most of our study participants ($n = 13$ aMCI and $n = 10$ HC). Moreover, the simultaneous perception task (SPT), a time-unlimited experimental task that allows for different levels of

Table 1
Demographic variables of both groups

Variable	aMCI patients, $n = 16$	Control participants, $n = 16$	t (30)	p-value
Sex (female [%]/male [%])	7/9 (43.8)/(56.3)	7/9 (43.8)/(56.3)	—	—
Age (y)	70.86 (7.81)	69.95 (7.39)	0.34	0.369
Education (y)	11.63 (1.86)	11.63 (1.02)	0.00	0.500
MMSE/30	26.69 (1.49)	28.44 (0.89)	**−4.02**[a]	**<0.001**
Handedness (right/left/ambidextrous)	15/1/0	12/2/2	—	—

Bold value indicates statistical significance at $p = 0.0004$.
Key: MMSE, Mini−Mental State Examination; aMCI, amnestic mild cognitive impairment.
[a] Statistically significant at $p < .05$, 1-tailed. Means (standard deviation, SD) are shown if not otherwise stated (Folstein et al., 1975).

difficulty and has proved useful to reveal simultanagnosia symptoms in neurodegenerative samples, such as Huntington's disease (Finke et al., 2007), was applied in all participants. To assess visual attention, TVA-based whole and partial reports were applied in all participants, but we only focus on the whole-report results here. In both the SPT and the TVA whole-report (TVA-WR), stimuli were shown on a 17-inch monitor (1024 × 768 pixels screen resolution). The viewing distance was approximately 50 cm.

2.3. Assessment of simultanagnosia symptoms

2.3.1. Neuropsychological assessment of simultanagnosia—BORB and VOSP

Specific tasks were taken from 2 standardized and widely used neuropsychological batteries that are employed to assess impairments in the simultaneous perception of visual objects and spatial locations in patient populations. More specifically, the overlapping figures−line drawings subtest of the Birmingham Object Recognition Battery (BORB) (Riddoch and Humphreys, 1993) and the subtests Dot Counting, Position Discrimination, and Number Location of the Visual Object and Space Perception Battery (VOSP) (Warrington and James, 1991) were used. For the BORB, we obtained the time (in seconds) per sheet in paired nonoverlapping and overlapping line drawing condition and a ratio between the 2 (i.e., overlapping time divided by nonoverlapping time). For the VOSP, we used the total score of correct responses in each subtest.

2.3.2. Experimental assessment of simultaneous object perception—SPT

The SPT (Finke et al., 2007) is an experimental task that assesses simultaneous object perception deficits. We consider the SPT as complementary to the standard neuropsychological simultanagnosia batteries because it is time-unconstrained (i.e., it sets no time limit for participants to respond to stimuli), uses basic geometric shapes for which no elaborated semantic knowledge is needed, and delivers more detailed information on the pattern of deficits in simultaneous

object perception because set sizes and condition types vary. In short, the SPT consists of the digital presentation of 9 different black line drawings of shapes on a white background without time limit. These 9 line drawings correspond to basic shapes including square, triangle, heart-shape, pentagon, hexagon, moon, cross, star, and circle (see Fig. 1). The participant's task is to identify them in each of 16 trials under 4 conditions that increase in the complexity of simultaneous object perception. The first condition, single stimulus, is a control condition in which each of these open shapes is separately presented twice; this condition permits ensuring that the participant can correctly perceive, identify, and name all the stimuli. In the 3 following conditions, adjacent, embedded, and overlapping, the shapes are simultaneously presented in trial displays with 2 to 5 items presented in an adjacent, embedded, or overlapping manner (Fig. 1). After the participant indicates that the answer is complete, the next trial starts. A trial counts as an error if the participant is not able to identify at least one of the shapes presented on that trial. The percentage of error trials is computed for each of the conditions that include simultaneously presented shapes. Importantly, we made sure that all participants were able to correctly name all shapes presented in whatever size, small or large, in a pretest. Moreover, to reduce the influence of potential changes in verbal recall ability, or of variability of verbal productions, in patients, the verbal labels they assigned to displayed objects were scored as "correct" even if these labels were "uncommon", as long as they indicated correct visual identification.

2.4. Assessment of visual attention

TVA is a computational model that permits mathematical estimation of relevant, independent attentional capacity parameters such as visual processing speed, C, and VSTM storage capacity, K (Bundesen, 1990). The participant's task is to report verbally as many letters as possible from briefly presented arrays of letters on a black background. Only "fair certainty" of recognition, rather than the order or speed of reporting, is emphasized in the instruction. The duration of the arrays is individually adjusted in a short pretest.

Fig. 1. Example-items: (A) adjacent (B) embedded, and (C) overlapping shapes condition of the simultaneous perception task (SPT; see (Finke et al., 2007) for a presentation of all trial displays). Each condition has 4 trials of 2−5 different geometrical shapes that are presented to the participant without time limit. A trial counts as an error trial if the participant fails to identify at least one of the shapes. Before the adjacent condition, there is a control condition, in which each shape is presented alone to ensure that the participant can identify and name them all.

Table 2
BORB and VOSP results for both groups

Subtest	aMCI patients ($n = 13$)		Healthy controls ($n = 10$)		$t(21)$	p-value	95% CI	Cohen's d
	M	SD	M	SD				
BORB								
Paired nonoverlapping (seconds per sheet)	25.78	7.89	21.95	4.57	1.36	0.093	[−2.01 to 9.67]	0.59
Paired overlapping (seconds per sheet)	38.82	23.71	25.13	3.80	**1.80**	0.043	[−2.14 to 29.52]	0.79
Ratio (overlapping/nonoverlapping)	1.48	0.50	1.16	0.14	**1.92**	0.034	[−0.02 to 0.65]	0.84
VOSP								
Dot counting/10	9.31	1.11	9.70	0.67	−0.98	0.168	[−1.22 to 0.44]	−0.43
Position discrimination/20	17.92	2.46	19.50	0.85	**−2.15**	0.024	[−3.14 to −0.01]	−0.94
Number location/10	8.38	1.56	8.70	1.16	−0.53	0.299	[−1.54 to 0.91]	−0.23

In bold are statistically significant at $p < 0.05$, 1-tailed.
Key: aMCI, amnestic mild cognitive impairment; BORB, Birmingham Object Recognition Battery (Riddoch and Humphreys, 1993); line drawings condition; CI, confidence interval of the difference; M, mean; SD, standard deviation; VOSP, Visual Object and Space Perception Battery (Warrington and James, 1991).

The experimenter enters the reported letters in the reported order and starts the next trial with a button press.

To estimate TVA parameters, an exponential growth function models the participant's letter report accuracy as a function of the effective exposure duration, according to a maximum likelihood method. The threshold for visual perception, parameter $t0$, expressed in milliseconds, is the estimated minimal exposure duration below which information uptake is assumed to be zero. The other 2 parameters estimated from TVA-WR accuracy are processing speed C, that is, the number of items that can be processed in parallel per second, and VSTM storage capacity K, that is, the number of items that can be held in a VSTM store.

2.5. Statistical analysis

The SPSS v.22 statistical package was used to perform statistical analyses. Two-sample t-tests were used to evaluate the differences between aMCI patients and controls in all demographic variables as well as in TVA-WR parameter estimates, and BORB, and VOSP results. A mixed ANOVA was conducted on SPT performance (i.e., percentage of errors) with group (aMCI, HC) as between-subjects factor, and condition type (adjacent, embedded, and overlapping) and set size (2, 3, 4, and 5) as within-subjects factors, to compare group performance in multiple object perception. Finally, a Spearman-rho analysis was performed to evaluate the association between SPT performance in the overlapping condition and TVA-WR parameter estimates (processing speed C, and VSTM storage capacity K) in the group of aMCI patients.

3. Results

3.1. Patients show simultaneous object perception deficits in clinical neuropsychological and experimental tasks

3.1.1. Simultanagnosia symptoms in standard neuropsychological tests

Participants' performance in the BORB and VOSP is presented in Table 2. In the BORB, aMCI patients needed roughly the same time as controls to name nonoverlapping pairs of line drawings [patients: M = 25.78, SD = 7.89 seconds vs. controls: M = 21.95, SD = 4.57 seconds, $t(21) = 1.36$, $p = 0.093$, Cohen's d = 0.59], but significantly more time than controls to name pairs of overlapping line drawings [M = 38.82, SD = 23.71 seconds vs. M = 25.13, SD = 3.80 seconds, $t(21) = 1.80$, $p = 0.043$, Cohen's d = 0.79]. Thus, we found higher overlapping to nonoverlapping figure ratios for aMCI patients than for controls [M = 1.48, SD = 0.50 versus M = 1.16, SD = 0.14, $t(21) = 1.92$, $p = 0.034$, Cohen's d = 0.84]. Analyzing the aMCI patients' performance based on the BORB test

norm data [i.e., M = 21.5 seconds per sheet (0.9 per item) for overlapping line drawings, and M = 23.9 per sheet (1.0 per item) for nonoverlapping drawings] revealed that they were significantly impaired in their identification (i.e., naming) time for both nonoverlapping and overlapping line drawings (Riddoch and Humphreys, 1993). At the individual level, all but one aMCI patients exhibited longer identification times and higher overlapping to nonoverlapping ratios than the average values reported in the test's norms (i.e., 1.0/1.1; Riddoch and Humphreys, 1993). Of note, general performance in the BORB did not correlate with the CERAD delayed verbal recall (p-value >0.1), and only the overlapping to nonoverlapping ratio significantly correlated with the CERAD delayed visual recall (rho = −0.786, $p = 0.001$), so that longer times to identify overlapping, compared to nonoverlapping, figures were associated with lower scores in visual recall.

In the space perception battery of the VOSP, aMCI patients exhibited significantly lower performance than controls in the Position Discrimination subtest only [patients: M = 17.92, SD = 2.46 vs. controls: M = 19.50, SD = 0.85, $t(21) = −2.15$, $p = 0.024$, Cohen's d = −0.94; other subtests' p-values >0.1]. An additional comparison of aMCI patient data to the tests' norm data revealed that in Position Discrimination, aMCI patients scored on average below the 5% cutoff score (i.e., 18) for healthy participants and their numerical average was even below that of the clinical norm group with right-hemisphere damage (i.e., M = 18.7) (Warrington and James, 1991). At the individual level, almost half (46%) of the patients failed this subtest. We did not find significant differences between the groups in the Dot Counting and Number Location subtests, with the patients too performing within the norms in these tests. Unlike the BORB, the VOSP Position Discrimination scores correlated significantly negatively with the CERAD delayed verbal recall (rho = −0.724, $p = 0.003$), but not with the visual recall (rho = −0.081, $p = 0.396$). However, when the association between Position Discrimination and delayed verbal recall was assessed in the only 6 patients who failed the subtest, the correlation was no longer significant (rho = 0.088, $p = 0.434$).

In sum, aMCI patients showed deficits in simultaneous object perception in standard neuropsychological tests. These deficits were revealed chiefly in the BORB overlapping figures—line drawings subtest, sensitive to simultanagnosia symptoms. Additionally, significant deficits in position discrimination appear to indicate a deficit in simultaneous perception of spatial locations. However, normal performance in dot counting and location of numbers indicates that spatial perception was basically spared in the aMCI patients. Importantly, the deficits observed in aMCI were not related to low global cognitive state as measured by the MMSE (all p's > 0.2). Only the deficit in simultaneous perception of spatial locations was related to verbal memory performance, and only the
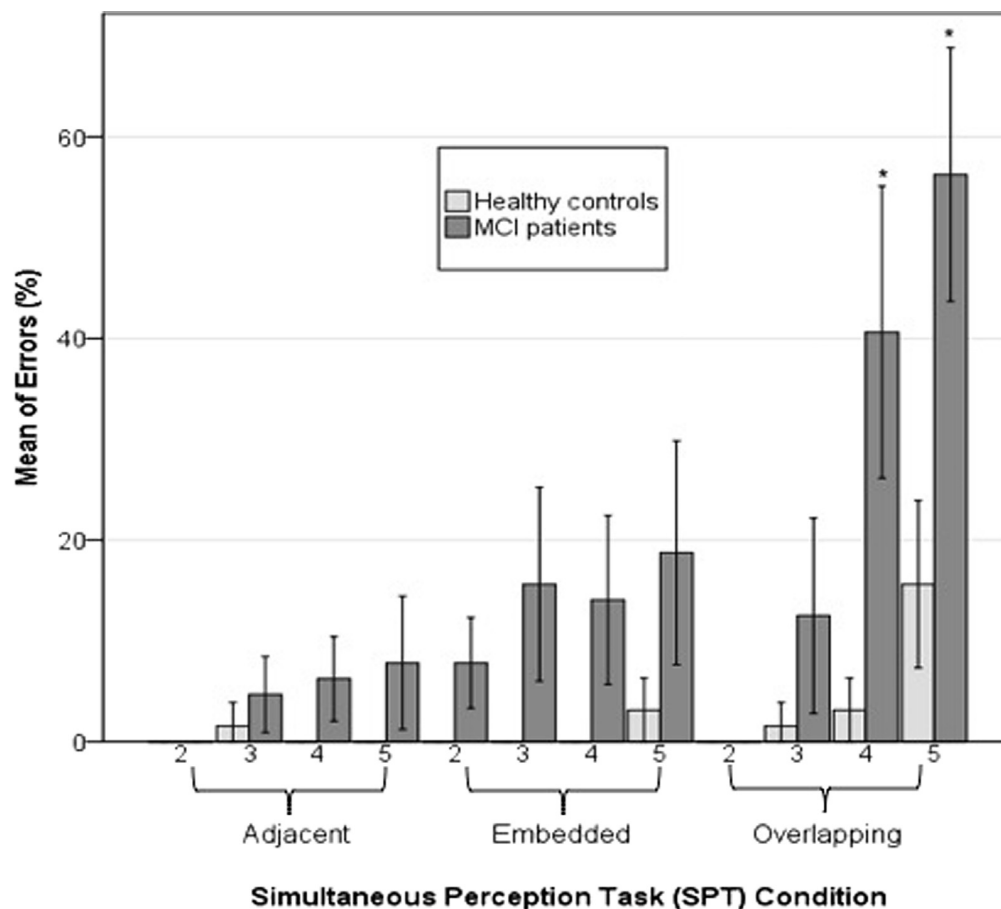
Fig. 2. Mean error percentages in the simultaneous perception task (SPT) per set size and condition type are depicted for the MCI patients group (dark gray) and the age-, gender-, and education-matched healthy control participants group (light gray). Note that aMCI patients did not make errors in the 2-shapes trials in both the adjacent and overlapping conditions of the SPT. Error bars indicate standard error of the mean. *Significantly different at $p < 0.005$, 2-tailed. Abbreviations: aMCI, amnestic mild cognitive impairment; MCI, mild cognitive impairment.

overlapping to nonoverlapping ratio was associated with visual memory performance.

3.1.2. Simultaneous object perception deficits in experimental SPT task

Average error percentages in the SPT are depicted in Fig. 2 separately for each group, condition, and set size. The mixed ANOVA, with main terms for group, condition, and set size, revealed all main effects to be significant (group: $F_{1, 30} = 18.482$, $p < 0.001$; condition: $F_{1.79, 53.66} = 20.173$, $p < 0.001$; and set size: $F_{2.93, 87.93} = 19.909$, $p < 0.001$). Three 2-way interactions among the factors were also observed (group by condition: $F_{1.79, 53.66} = 8.481$, $p = 0.001$; group by set size: $F_{2.93, 87.93} = 8.434$, $p < 0.001$; and condition by set size: $F_{3.47, 103.98} = 10.868$, $p < 0.001$). Finally, there was also a significant group by condition by set size interaction ($F_{3.47, 103.98} = 4.003$, $p = 0.007$). To analyze this 3-way interaction in more detail, we computed mixed ANOVAs with the factors group and set size separately for each condition (i.e., adjacent, embedded, and overlapping). In all conditions, significant main effects of group (adjacent: $F_{1, 30} = 5.171$, $p = 0.030$; embedded: $F_{1, 30} = 11.942$, $p = 0.002$; overlapping: $F_{1, 30} = 16.904$, $p < 0.001$) indicated that aMCI patients generally made more errors than controls. A significant main effect of set size was found only in the overlapping condition ($F_{2.652, 79.56} = 24.513$, $p < 0.001$; adjacent and embedded p's > 0.188). Similarly, the group by set size interaction was only

significant in the overlapping condition ($F_{2.652, 79.56} = 9.518$, $p < 0.001$; adjacent and embedded p's > 0.188). Post hoc t-tests showed that aMCI patients were significantly worse than HCs when more than 3 shapes were simultaneously presented [Fig. 2; 4 shapes, mean: 40.62 vs. 3.12, aMCI patients and controls, respectively, $t(30) = 3.795$, $p = 0.001$, Cohen's d = 1.38; 5 shapes: 56.25 vs. 15.62, respectively, $t(30) = 4.044$, $p < 0.001$, Cohen's d = 1.48; both p's 1-tailed]. These results indicate that aMCI patients were in general worse than controls in identifying simultaneously presented shapes. However, only when these shapes were presented in an overlapping manner did aMCI patients show particularly severe difficulties with larger set sizes (i.e., >3 items).

3.2. Visual attention deficits

As listed in Table 3, aMCI patients exhibited significantly lower processing speed C estimates and significantly higher perceptual thresholds $t0$ than HC participants in the TVA-WR. In other words, aMCI patients required relatively longer stimulus durations and were able to process fewer elements simultaneously compared to control participants. However, we did not find a significant difference in VSTM storage capacity K estimates between groups. Neither processing speed C (rho $= -0.242$, $p = 0.183$) nor $t0$ estimates (rho $= -0.372$, $p = 0.130$) significantly correlated with global cognitive state as assessed by the MMSE.

Table 3
Whole-report TVA (TVA-WR) estimates for aMCI patients and healthy controls

TVA-WR parameters	aMCI patients (n = 16)		Healthy controls (n = 16)		t(30)	p-value	95% CI	Cohen's d
	M	SD	M	SD				
Processing speed C	13.82	5.37	17.55	5.36	**−1.97**	0.029	[−7.60 to 0.25]	−0.72
Storage capacity K	2.63	0.39	2.69	0.44	−0.37	0.358	[−0.35 to 0.25]	−0.13
Visual threshold t0	112	60.39	35.17	46.91	**4.02**[*]	<0.001	[37.78 to 115.87]	1.47

Bold values are statistically significant at $p < 0.05$ and at $p < 0.001$ (*), 1-tailed.
Key: aMCI, amnestic mild cognitive impairment; CI, confidence interval of the difference; M, mean; SD, standard deviation; TVA, Theory of Visual Attention (Bundesen, 1990).

3.3. Overlapping figure perception deficits are associated with reduced processing speed in aMCI

To determine whether simultaneous object perception deficits in patients with aMCI are associated with a slowing in visual information uptake (i.e., a reduction in visual processing speed C), we correlated the percentage of errors in the SPT overlapping condition, collapsed across set size (i.e., the measure that was assumed to be most sensitive for subtle changes in simultaneous object perception and that turned out to be most affected), with processing speed C in patients with aMCI. As expected, higher error percentages in identifying simultaneously presented, overlapping objects were associated with lower estimates of processing speed C (Fig. 3; rho = −0.497, p = 0.025, 1-tailed), but not with VSTM capacity K (rho = 0.034, p = 0.450) or t0 (rho = 0.148, p = 0.292) estimates. To examine whether the relationship between simultaneous perception deficits and processing speed would be confirmed when using clinically established tasks for the assessment of simultanagnosia, we calculated the correlations between visual processing speed and performance on those tasks on which patients performed worse than HCs. Note that complete data were available only for a subgroup of patients (n = 13). We found a tendency towards a negative relationship between the latencies to name pairs of overlapping objects in the BORB and processing speed

C (rho = −0.426, p = 0.073). However, the correlation between errors in the Position Discrimination condition of the VOSP and processing speed C was nonsignificant (rho = 0.128, p = 0.339). The correlation between the percentage of errors in the SPT and processing speed C did not change for patients with at least one risk e4 allele of ApoE (n = 11) compared to the whole sample of patients (n = 16) and became nonsignificant (closed circles in Fig. 3; rho = −0.372, p = 0.130). Importantly, these deficits in simultaneous object perception did not relate to the relatively low global cognitive state in aMCI patients as assessed by the MMSE (rho = −0.301, p = 0.128), or to verbal memory as assessed in the CERAD delayed verbal recall (rho = 0.111, p = 0.341). However, similar to the BORB results, simultaneous object perception deficits in aMCI patients did also relate to visual memory recall (rho = −0.532, p = 0.017) and were, thus, not solely impaired by the patients' relatively low global cognitive state or general memory impairments.

We also examined whether a more low-level visual impairment, that is, the elevated visual threshold that was documented, might alternatively, or additionally, explain the deficits in SPT performance. Importantly, the significant association between visual processing speed C and percentage of errors in the SPT overlapping condition was replicated when controlling for t0 (rho = −0.492, p = 0.031). Accordingly, the simultaneous object perception deficits displayed by aMCI patients are not so much related to a more basic
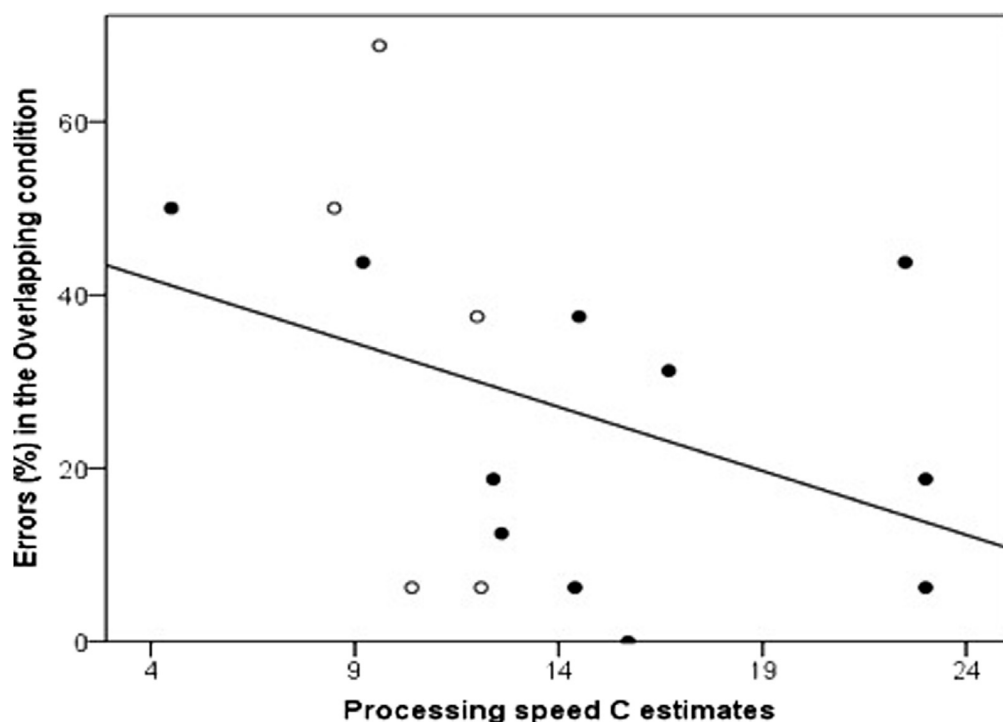
Fig. 3. Scatterplot relating aMCI patients' individual parameter estimates of visual processing speed C and their percentage of errors in the overlapping condition of the simultaneous perception task (SPT). C estimates are significantly negatively correlated with errors; rho = −0.497, p = 0.025, 1-tailed. Closed circles are aMCI patients with at least one risk allele (4 allele) and open circles are aMCI patients with the 3 allele or 2 allele. Abbreviation: aMCI, amnestic mild cognitive impairment.

elevation of the visual threshold than to a reduction of visual processing speed per se.

Finally, we examined for a more general association between the rate of visual information uptake and simultaneous object perception also in our normal observers. The respective correlation between the percentage of errors in the SPT overlapping condition and visual processing speed *C* was not significant in the HC group (rho = −0.162, *p* = 0.274, 1-tailed). However, the difference between the respective correlation coefficients of the patient and healthy groups was not significant either (Z = 0.97, *p* = 0.166, 1-tailed).

4. Discussion

The present study investigated whether aMCI patients show a deficit of simultaneous object perception and whether such a deficit is attributable to a reduced visual processing rate. We provide direct evidence for (1) simultaneous object perception deficits in aMCI as an early symptomatic predementia phase of AD and (2) reduced visual processing speed underlying simultaneous object perception deficits. Three main findings support this evidence. First, aMCI patients show deficits in simultaneous object perception. More specifically, when aMCI patients had to identify each one of a set of overlapping shapes in the BORB, they needed significantly more time than age-, education-, and gender-matched HCs, resulting in significantly higher overlapping to nonoverlapping time ratios. Second, compared to HCs, aMCI patients showed significantly lower processing speed *C* in a TVA-based whole-report paradigm. Finally, specifically the individual severity of the processing speed reduction was significantly related to—and would, thus, appear to underlie—the simultaneous object perception deficits in aMCI.

4.1. Simultaneous object perception deficits in aMCI

We found that patients with aMCI had significant difficulties compared to HCs in 2 tasks of simultaneous object perception, the BORB and the SPT. In both tasks, deficits occurred in particular when objects were presented in an overlapping manner, that is, under conditions that are conducive for simultanagnosia symptoms to become manifest (Bálint and Harvey, 1995; Laeng et al., 1999; Luria, 1959; Riddoch and Humphreys, 2004; Valenza et al., 2004). More precisely, in the BORB, aMCI patients were slow particularly in the overlapping condition, as indexed by a higher overlapping to nonoverlapping time ratio; in the SPT, they exhibited an increasing number of errors with increasing set size particularly in the overlapping condition. Importantly, aMCI patients showed relatively normal speed in identifying nonoverlapping drawings in the BORB, and all patients were able to name the single shapes presented at all (large and small) sizes in the screening part of the SPT, as well as in the adjacent condition. Thus, importantly, the deficit in identifying overlapping shapes does not relate to reduced visual acuity, semantic memory deficits, or visual object agnosia. Remarkably, although simultaneous object perception deficits as reported here are characteristic of posterior cortical atrophy (Neitzel et al., 2016; Tang-Wai et al., 2004) and quite common in AD dementia (Mendez et al., 1990; Rizzo et al., 2000), whether they are also present in individuals with aMCI at a symptomatic predementia phase of the more typical form of AD had, to the best of our knowledge, not been systematically tested before.

The use of the experimental SPT delivered fine-grained information on the nature of the multiple object perception deficits in aMCI. Specifically, we observed that only when stimuli were presented in an overlapping manner did aMCI patients show increased set size effects compared to HCs. Of note, the simultaneous object perception deficits were not only evident in our experimental task, but were also revealed in the BORB. As the diagnosis of aMCI

focuses on memory impairments, simultaneous object perception is usually not evaluated in routine neuropsychological assessment; thus, it is unsurprising that such deficits in an established standard neuropsychological test for simultanagnosia had not been reported before. Furthermore, it is worth noting that both tasks use free viewing conditions without any time restrictions, and yet performance was particularly compromised in conditions with multiple overlapping shapes. In most previous studies, the duration of stimulus exposition to patients with simultanagnosia had been limited (Coslett and Saffran, 1991; Duncan et al., 2003; Huberle and Karnath, 2006; Pavese et al., 2002). In the present study, by contrast, we used the nonspeeded SPT to enable us to examine separately processing speed and simultaneous object perception. In other words, we used the SPT to determine whether indications of slowing of visual processing in a whole-report task using briefly presented letter arrays (Duncan et al., 2003; Finke et al., 2007) can make valid predictions regarding deficits under unconstrained viewing conditions.

Furthermore, the present study revealed a positive association between the degree of simultaneous object perception deficits and the degree of visual memory impairment in aMCI patients. In the BORB, higher overlapping to nonoverlapping time ratios related to lower scores in visual recall. In the SPT, more errors in the overlapping condition related to lower scores in visual recall. Thus, our results shed light on the question as to why especially visual memory tests using complex visual material such as the Rey−Osterrieth and the Benton tests are exceptionally sensitive for the earliest AD-related decline even in the preclinical phase (Kawas et al., 2003). Difficulties in these tasks might result from basic impairments in the encoding of multiple visual stimuli or stimuli containing multiple parts. Thus, while appropriate for cognitive screening, conclusions about the deficits underlying low performance in these tests should be drawn with caution.

Unlike with visual memory impairments, simultaneous object perception deficits were not associated with relatively low global cognitive state or verbal memory impairments in aMCI. This lack of association strongly suggests that simultaneous object perception deficits constitute an independent aspect in their own right in aMCI, which might, in turn, underlie low performance in visual memory tasks. In the context of evidence suggesting that aMCI is a heterogeneous entity in its clinical progression (Li and Zhang, 2015), assessing simultaneous object perception might help disclose multidimensionality in aMCI patients who, at first glance, present as a single-domain aMCI individuals. The simultaneous object perception deficits displayed by aMCI patients are, however, not comparable to those shown by the classical cases reported by Bálint (1909); rather, they would be classified only as "mild" (Hecaen and De Ajuriaguerra, 1954).

Concerning daily-life functioning, we usually do not perceive and handle objects in an isolated manner. Thus, arguably, increasing deficits in the simultaneous perception of objects likely contribute to the incipient problems of daily living during aMCI, including impairments in spatial navigation (Laczo et al., 2009), such as in way-finding (Allison et al., 2016), which might signal the clinical start of AD dementia.

4.2. Visual processing speed reduction leads to simultaneous perception deficits in aMCI

In the present study, we followed the group study−based approach to neurodegenerative diseases advocated by Rizzo and Vecera (2002) and first applied by Finke et al. (2007) in research on simultanagnosia and its underlying attentional deficits. Based on a staged decline in visual attention functions and in particular processing speed in individual cases of aMCI (Bublak et al., 2011),

and on previous reports that visual processing speed reduction can lead to symptoms of simultanagnosia (Chechlacz et al., 2012; Duncan et al., 2003; Finke et al., 2007; Neitzel et al., 2016), we hypothesized that reduced visual processing speed underlies simultaneous object perception deficits in aMCI. In agreement with the results in patients with stroke (Duncan et al., 2003) and Huntington's disease (Finke et al., 2007), we observed a significant association between visual processing speed and simultaneous object perception in aMCI patients. Taken together, these results indicate that aMCI patients' reductions in visual processing speed underlie their simultaneous object perception deficits. Moreover, our results complement the previous findings in indicating that, despite heterogeneous causes, the relationship between a reduced speed of visual information uptake and deficient simultaneous objects perception constitutes a general principle across patients with symptoms of simultanagnosia. Likewise, our results add to the existing evidence that sufficient visual processing speed provides the necessary basis for identifying, integrating, and making sense of the components of complex visual scenes. Accordingly, the association between processing speed (reductions) and simultaneous object perception (errors) would not be exclusive to aMCI patients, but may hold for healthy participants too. In the present study, such an association may simply have been obscured by healthy participants performing near ceiling on the simultaneous object perception task. Consistent with a general association, we did not find a significant difference in the correlation coefficients between the aMCI patients and the control participants. However, further studies using experimental conditions best suited to assess simultaneous object perception in healthy samples are required to settle the generalizability of this association.

At a first glance, it might seem astonishing that reduced visual processing speed would affect the identification of overlapping shapes only, leaving the speed and accuracy of identifying multiple shapes presented in an embedded or adjacent fashion relatively unaffected. As similarly argued before (Duncan et al., 2003; Finke et al., 2007), patients with slow visual processing might use a strategy of serial selection. Consistent with the piecemeal perception known from patients with simultanagnosia (Paterson and Zangwill, 1944; Rizzo and Vecera, 2002), such a strategy would engender the selection of one stimulus after the other. For example, with adjacent stimuli, adaptive concentration of the available, reduced processing resources on a given stimulus location at a time will increase the likelihood of successful encoding, though the overall time taken for the whole set of stimuli will be increased and patients will appear to perform slower. Embedded stimuli, too, might be processed and reported in series, starting with the outer- or inner-most object and reporting them in a sequential manner, ordered by stimulus size. When objects are overlapping, as they typically are in multielement complex daily scenes, according to biased competition models (Bundesen, 1990; Bundesen et al., 2005; Desimone and Duncan, 1995), objects would compete for selection and access to VSTM. Moreover, the amount of processing capacity that is distributed among objects is limited, and, thus, only those objects that are processed fastest are selected and stored in VSTM (Bundesen, 1990). If processing capacity is overall reduced—as in patients with simultaneous perception deficits—only the most salient object can be selected; the others, by contrast, will not gain access to VSTM and will thus not be consciously represented (Duncan et al., 2003).

One might expect that processing speed would also be related to performance in the adjacent and embedded conditions, given that multiple objects must be perceived and categorized across all SPT conditions. In nonoverlapping conditions, however, the receptive fields are not shared, as a result of which the neural competition is not as severe as in the overlapping condition (Bundesen et al., 2005;

Desimone and Duncan, 1995). In our overlapping condition, the stimulus array contained multiple objects that were superimposed at the same location, that is, they were segmented into shape parts, or fragments, with overlapping contours. In this situation, a serial selection strategy cannot be successful. Due to the concentration of processing resources on one single location, 2 or more objects that share the same position will also have to share processing capacity. Thus, when patients with slowed visual processing are forced (to attempt) to divide their limited processing resources among multiple objects, their capacity will be exhausted (Humphreys and Price, 1994; Riddoch and Humphreys, 2004). Consequently, the likelihood of making errors or omitting some objects will be high, because patients cannot muster the resources necessary to reach the depth of discrimination required for successful (whole-) object identification. Thus, all but the most salient objects will have only a low probability of being identified.

The association with visual processing speed C was only borderline significant with performance in the paired overlapping condition of the BORB, and not reliable for the Position Discrimination condition of the VOSP. These results differ from a previous report of significant correlations in patients with posterior cortical atrophy (Neitzel et al., 2016). As clinical neuropsychological batteries designed to assess severe symptoms, the BORB and VOSP may not be sensitive to more subtle deficits in simultaneous object perception, as displayed by aMCI patients. In the BORB, only pairs of overlapping objects are presented, while in the SPT aMCI patients showed a significantly increased error rate only at higher set sizes in the overlapping condition (see Fig. 2 and Table 2). Thus, the more complex SPT, with up to 5 overlapping stimuli, yielded a greater variation of responses, permitting a significant relationship between simultaneous object perception deficits and reduced processing speed to be successfully established in aMCI.

Since the first analyses of patients with simultanagnosia, the precise underlying cognitive deficit has been a matter of debate. For example, a "general weakening" of visual traces (Luria, 1959) or visual representations (Bálint, 1909) was suggested to slow even the perception of single objects, thereby disproportionately affecting the perception of multiple objects. This view received support from evidence that single-item processing too is slowed in patients with simultanagnosia (Friedman and Alexander, 1984; Kinsbourne and Warrington, 1962; Levine and Calvanio, 1978). Other authors (Coslett and Saffran, 1991; Friedman-Hill et al., 1995; Pavese et al., 2002) proposed that a deficit in VSTM storage gives rise to an inability to bind shape and position properties of more than 1 object and, as a result, in storing multiple objects. Accordingly, Rizzo and Vecera (2002) proposed to take attentional functions and specifically VSTM into consideration to gain a clearer understanding of simultanagnosia. However, research examining whether VSTM or processing speed deficits underlie symptoms of simultanagnosia has found that the latter are primarily related to visual processing speed, rather than to VSTM storage capacity, reductions (Duncan et al., 2003; Finke et al., 2007; Neitzel et al., 2016).

It is well known that with increasing encoding time, more items can be encoded into VSTM (Vogel et al., 2006). Thus, appropriate methodological procedures are required for validly measuring (individual) VSTM capacity in participants with reduced visual processing speed. In the TVA-based whole-report paradigm, exposure durations are adjusted individually so as to ensure that even participants displaying severely reduced processing speeds and/or an elevated visual threshold can fill their VSTM store up to its limit (Bundesen, 1990; Finke et al., 2005). Following this approach (which permits processing speed and storage capacity to measured independently), we were able to demonstrate that VSTM storage capacity is actually relatively spared in aMCI patients. For subsequent stages of the disease—that is, AD dementia—, by

contrast, previous reports have already documented reduced VSTM capacity (Bublak et al., 2011; Vecera and Rizzo, 2004).

4.3. Possible neural mechanisms underlying simultaneous object perception deficits in aMCI

According to the neural TVA, processing capacity is directly related to the number and activation of cortical neurons that are devoted to the processing of a visual object, so that (potentially) important objects are represented by more cells than less important ones (Bundesen et al., 2005, 2015). Consequently, any disease process that hampers neuronal function can reduce processing capacity.

In the typical aMCI, structural and functional changes of a frontoparietal network are well documented (Mattsson et al., 2014; Perry and Hodges, 1999; Sorg et al., 2007, 2012). Frontoparietal regions, as well as the white-matter tracts connecting them, are considered relevant for attentional processing (Coull et al., 1996; Ptak, 2012; Thiebaut de Schotten et al., 2011). Early in the process of AD, at the aMCI stage, frontal and posterior parietal regions show hypometabolism even without signs of gray matter atrophy (Kljajevic et al., 2014) and decreased functional connectivity (Sorg et al., 2007), and amyloid deposition, metabolic changes, and atrophy when AD is already established (Buckner et al., 2005).

Another factor that might contribute to reduced processing speed is the dysfunction of the cholinergic system, like that occurring in AD (Coyle et al., 1983), as cholinergic neurotransmission is known to be relevant for fast perceptual processing (Schliebs and Arendt, 2011). The cholinergic system is assumed to play a decisive role in the attentional processing of sensory stimuli (e.g., Rizzo, et al., 2000) due to its innervation of attention-related (i.e., frontal and parietal) areas (Lawrence and Sahakian, 1995). In sum, the simultaneous object perception deficits that we observed in patients with aMCI find an explanation in the reduction of visual processing speed, which, in turn, might be attributable to the neural changes in a frontoparietal attention network.

4.4. Limitations

Visual crowding due to contour interactions (Hess et al., 2000; Huurneman et al., 2012) might, conceivably, also explain simultaneous object perception deficits in aMCI patients. If so, the deficits would be indicative of a low-level visual, rather than a higher level cognitive, limitation. Indeed, in our sample of aMCI patients, the perceptual threshold $t0$ was significantly increased (see Table 3). However, the association between visual processing speed C and SPT performance remained unaffected even when we controlled for this low-level factor. Future studies might more systematically vary contour interactions to examine for possible effects of visual crowding on simultaneous object perception in aMCI patients. Further, as deficits in attentional selection parameters have previously been described in aMCI (Redel et al., 2012), follow-on studies might also profitably investigate the association between TVA partial-report and SPT performance. Moreover, further research would be necessary in order to determine whether visual processing speed is a basic mechanism underlying simultaneous object perception in healthy observers generally.

4.5. Outlook

The findings of significant simultaneous object deficits have clinical implications and demonstrate the relevance of analyzing cognitive domains beyond memory in aMCI patients in both clinical and research settings. Investigating in a longitudinal manner the neural mechanisms of reduced visual processing speed in aMCI and their relation to the spread of AD pathology and brain connectivity measures could help us better understand when and how these deficits start to appear.

5. Conclusion

In this study, we report simultaneous object perception deficits in patients with aMCI and show that these deficits are particularly severe in patients with reduced visual processing speed. Collectively, our results and those of previous studies allow us to conclude that visual processing speed reduction is a crucial process that underlies deficits in simultaneous object perception.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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References

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 270—279.

Alescio-Lautier, B., Michel, B.F., Herrera, C., Elahmadi, A., Chambon, C., Touzet, C., Paban, V., 2007. Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: role of attention. Neuropsychologia 45, 1948—1960.

Allison, S.L., Fagan, A.M., Morris, J.C., Head, D., 2016. Spatial navigation in preclinical Alzheimer's disease. J. Alzheimers Dis. 52, 77—90.

Bálint, R., 1909. Seelenlähmung des "Schauens,"optische Ataxie, räumliche Störung der Aufmerksamkeit. Monatschr. Psychiat. Neurol. 25, 51—81.

Bálint, R., Harvey, M., 1995. Psychic paralysis of gaze, optic ataxia, and spatial disorder of attention. Cogn. Neuropsychol. 12, 265—281.

Berres, M., Monsch, A.U., Bernasconi, F., Thalmann, B., Stahelin, H.B., 2000. Normal ranges of neuropsychological tests for the diagnosis of Alzheimer's disease. Stud. Health Technol. Inform. 77, 195—199.

Bonney, K.R., Almeida, O.P., Flicker, L., Davies, S., Clarnette, R., Anderson, M., Lautenschlager, N.T., 2006. Inspection time in non-demented older adults with mild cognitive impairment. Neuropsychologia 44, 1452—1456.

Bublak, P., Redel, P., Sorg, C., Kurz, A., Forstl, H., Muller, H.J., Schneider, W.X., Finke, K., 2011. Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease. Neurobiol. Aging 32, 1219—1230.

Buckner, R.L., Snyder, A.Z., Shannon, B.J., LaRossa, G., Sachs, R., Fotenos, A.F., Sheline, Y.I., Klunk, W.E., Mathis, C.A., Morris, J.C., Mintun, M.A., 2005. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J. Neurosci. 25, 7709—7717.

Bundesen, C., 1990. A theory of visual attention. Psychol. Rev. 97, 523—547.

Bundesen, C., 1998. A computational theory of visual attention. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 353, 1271—1281.

Bundesen, C., Habekost, T., Kyllingsbaek, S., 2005. A neural theory of visual attention: bridging cognition and neurophysiology. Psychol. Rev. 112, 291—328.

Bundesen, C., Vangkilde, S., Petersen, A., 2015. Recent developments in a computational theory of visual attention (TVA). Vis. Res. 116, 210—218.

Chechlacz, M., Rotshtein, P., Hansen, P.C., Riddoch, J.M., Deb, S., Humphreys, G.W., 2012. The neural underpinings of simultanagnosia: disconnecting the visuospatial attention network. J. Cogn. Neurosci. 24, 718—735.

Corbetta, M., 1998. Frontoparietal cortical networks for directing attention and the eye to visual locations: identical, independent, or overlapping neural systems? Proc. Natl. Acad. Sci. U. S. A. 95, 831—838.

Coslett, H.B., Saffran, E., 1991. Simultanagnosia. To see but not two see. Brain 114 (Pt 4), 1523—1545.

Coull, J.T., Frith, C.D., Frackowiak, R.S., Grasby, P.M., 1996. A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. Neuropsychologia 34, 1085—1095.

Coyle, J.T., Price, D.L., DeLong, M.R., 1983. Alzheimer's disease: a disorder of cortical cholinergic innervation. Science 219, 1184—1190.

Desimone, R., Duncan, J., 1995. Neural mechanisms of selective visual attention. Annu. Rev. Neurosci. 18, 193—222.

Drzezga, A., Becker, J.A., Van Dijk, K.R., Sreenivasan, A., Talukdar, T., Sullivan, C., Schultz, A.P., Sepulcre, J., Putcha, D., Greve, D., Johnson, K.A., Sperling, R.A., 2011. Neuronal dysfunction and disconnection of cortical hubs in non-demented subjects with elevated amyloid burden. Brain 134 (Pt 6), 1635—1646.

Duncan, J., Bundesen, C., Olson, A., Humphreys, G., Ward, R., Kyllingsbaek, S., van Raamsdonk, M., Rorden, C., Chavda, S., 2003. Attentional functions in dorsal and ventral simultanagnosia. Cogn. Neuropsychol. 20, 675—701.

Engler, H., Forsberg, A., Almkvist, O., Blomquist, G., Larsson, E., Savitcheva, I., Wall, A., Ringheim, A., Langstrom, B., Nordberg, A., 2006. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain 129 (Pt 11), 2856—2866.

Finke, K., Bublak, P., Dose, M., Muller, H.J., Schneider, W.X., 2006. Parameter-based assessment of spatial and non-spatial attentional deficits in Huntington's disease. Brain 129 (Pt 5), 1137—1151.

Finke, K., Bublak, P., Krummenacher, J., Kyllingsbaek, S., Muller, H.J., Schneider, W.X., 2005. Usability of a theory of visual attention (TVA) for parameter-based measurement of attention I: evidence from normal subjects. J. Int. Neuropsychol. Soc. 11, 832—842.

Finke, K., Myers, N., Bublak, P., Sorg, C., 2013. A biased competition account of attention and memory in Alzheimer's disease. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 368, 20130062.

Finke, K., Schneider, W.X., Redel, P., Dose, M., Kerkhoff, G., Muller, H.J., Bublak, P., 2007. The capacity of attention and simultaneous perception of objects: a group study of Huntington's disease patients. Neuropsychologia 45, 3272—3284.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189—198.

Friedman, R.B., Alexander, M.P., 1984. Pictures, images, and pure alexia: a case study. Cogn. Neuropsychol. 1, 9—23.

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

Hecaen, H., De Ajuriaguerra, J., 1954. Balint's syndrome (psychic paralysis of visual fixation) and its minor forms. Brain 77, 373—400.

Hess, R.F., Dakin, S.C., Kapoor, N., 2000. The foveal 'crowding' effect: physics or physiology? Vis. Res 40, 365—370.

Hindmarch, I., Lehfeld, H., de Jongh, P., Erzigkeit, H., 1998. The Bayer Activities of Daily Living Scale (B-ADL). Dement. Geriatr. Cogn. Disord. 9 (Suppl 2), 20—26.

Holmes, G., 1918. Disturbances of visual orientation. Br. J. Ophthalmol. 2, 449—468.

Huberle, E., Karnath, H.O., 2006. Global shape recognition is modulated by the spatial distance of local elements—evidence from simultanagnosia. Neuropsychologia 44, 905—911.

Humphreys, G.W., Price, C.J., 1994. Visual feature discrimination in simultanagnosia: a study of two cases. Cogn. Neuropsychol. 11, 393—434.

Huurneman, B., Boonstra, F.N., Cox, R.F., Cillessen, A.H., van Rens, G., 2012. A systematic review on 'Foveal Crowding' in visually impaired children and perceptual learning as a method to reduce Crowding. BMC Ophthalmol. 12, 27.

Kawas, C.H., Corrada, M.M., Brookmeyer, R., Morrison, A., Resnick, S.M., Zonderman, A.B., Arenberg, D., 2003. Visual memory predicts Alzheimer's disease more than a decade before diagnosis. Neurology 60, 1089—1093.

Kemppainen, N.M., Aalto, S., Wilson, I.A., Nagren, K., Helin, S., Bruck, A., Oikonen, V., Kailajarvi, M., Scheinin, M., Viitanen, M., Parkkola, R., Rinne, J.O., 2007. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. Neurology 68, 1603—1606.

Kinsbourne, M., Warrington, E.K., 1962. A disorder of simultaneous form perception. Brain 85, 461—486.

Kljajevic, V., Grothe, M.J., Ewers, M., Teipel, S. Alzheimer's Disease Neuroimaging Initiative, 2014. Distinct pattern of hypometabolism and atrophy in preclinical and predementia Alzheimer's disease. Neurobiol. Aging 35, 1973—1981.

Laczo, J., Vlcek, K., Vyhnalek, M., Vajnerova, O., Ort, M., Holmerova, I., Tolar, M., Andel, R., Bojar, M., Hort, J., 2009. Spatial navigation testing discriminates two types of amnestic mild cognitive impairment. Behav. Brain Res. 202, 252—259.

Laeng, B., Kosslyn, S.M., Caviness, V.S., Bates, J., 1999. Can deficits in spatial indexing contribute to simultanagnosia? Cogn. Neuropsychol. 16, 81—114.

Lawrence, A.D., Sahakian, B.J., 1995. Alzheimer disease, attention, and the cholinergic system. Alzheimer Dis. Assoc. Disord. 9 (Suppl 2), 43—49.

Levine, D.N., Calvanio, R., 1978. A study of the visual defect in verbal alexia-simultanagnosia. Brain 101, 65—81.

Li, X., Zhang, Z.J., 2015. Neuropsychological and neuroimaging characteristics of amnestic mild cognitive impairment subtypes: a selective overview. CNS Neurosci. Ther. 21, 776—783.

Luria, A.R., 1959. Disorders of "simultaneous perception" in a case of bilateral occipito-parietal brain injury. Brain 82, 437—449.

Mattsson, N., Tosun, D., Insel, P.S., Simonson, A., Jack Jr., C.R., Beckett, L.A., Donohue, M., Jagust, W., Schuff, N., Weiner, M.W. Alzheimer's Disease Neuroimaging Initiative, 2014. Association of brain amyloid-beta with cerebral perfusion and structure in Alzheimer's disease and mild cognitive impairment. Brain 137 (Pt 5), 1550—1561.

McAvinue, L.P., Vangkilde, S., Johnson, K.A., Habekost, T., Kyllingsbaek, S., Bundesen, C., Robertson, I.H., 2015. A componential analysis of visual attention in children with ADHD. J. Atten. Disord. 19, 882—894.

Mendez, M.F., Turner, J., Gilmore, G.C., Remler, B., Tomsak, R.L., 1990. Balint's syndrome in Alzheimer's disease: visuospatial functions. Int. J. Neurosci. 54, 339—346.

Mintun, M.A., Larossa, G.N., Sheline, Y.I., Dence, C.S., Lee, S.Y., Mach, R.H., Klunk, W.E., Mathis, C.A., DeKosky, S.T., Morris, J.C., 2006. [11C]PIB in a non-demented population: potential antecedent marker of Alzheimer disease. Neurology 67, 446—452.

Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43, 2412—2414.

Morris, J.C., Storandt, M., Miller, J.P., McKeel, D.W., Price, J.L., Rubin, E.H., Berg, L., 2001. Mild cognitive impairment represents early-stage Alzheimer disease. Arch. Neurol. 58, 397—405.

Neitzel, J., Ortner, M., Haupt, M., Redel, P., Grimmer, T., Yakushev, I., Drzezga, A., Bublak, P., Preul, C., Sorg, C., Finke, K., 2016. Neuro-cognitive mechanisms of simultanagnosia in patients with posterior cortical atrophy. Brain 139 (Pt 12), 3267—3280.

Neufang, S., Akhrif, A., Riedl, V., Forstl, H., Kurz, A., Zimmer, C., Sorg, C., Wohlschlager, A.M., 2011. Disconnection of frontal and parietal areas contributes to impaired attention in very early Alzheimer's disease. J. Alzheimers Dis. 25, 309—321.

Neufang, S., Akhrif, A., Riedl, V., Forstl, H., Kurz, A., Zimmer, C., Sorg, C., Wohlschlager, A.M., 2014. Predicting effective connectivity from resting-state networks in healthy elderly and patients with prodromal Alzheimer's disease. Hum. Brain Mapp. 35, 954—963.

Paterson, A., Zangwill, O.L., 1944. Disorders of visual space perception associated with lesions of the right cerebral hemisphere. Brain 67, 331—358.

Pavese, A., Coslett, H.B., Saffran, E., Buxbaum, L., 2002. Limitations of attentional orienting. Effects of abrupt visual onsets and offsets on naming two objects in a patient with simultanagnosia. Neuropsychologia 40, 1097—1103.

Perry, R.J., Hodges, J.R., 1999. Attention and executive deficits in Alzheimer's disease. A critical review. Brain 122 (Pt 3), 383—404.

Perry, R.J., Watson, P., Hodges, J.R., 2000. The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. Neuropsychologia 38, 252—271.

Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J. Intern. Med. 256, 183—194.

Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., Ritchie, K., Rossor, M., Thal, L., Winblad, B., 2001. Current concepts in mild cognitive impairment. Arch. Neurol. 58, 1985—1992.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 56, 303—308.

Ptak, R., 2012. The frontoparietal attention network of the human brain: action, saliency, and a priority map of the environment. Neuroscientist 18, 502—515.

Rapp, M.A., Reischies, F.M., 2005. Attention and executive control predict Alzheimer disease in late life: results from the Berlin Aging Study (BASE). Am. J. Geriatr. Psychiatry 13, 134—141.

Redel, P., Bublak, P., Sorg, C., Kurz, A., Forstl, H., Muller, H.J., Schneider, W.X., Perneczky, R., Finke, K., 2012. Deficits of spatial and task-related attentional selection in mild cognitive impairment and Alzheimer's disease. Neurobiol. Aging 33, 195.e27—195.e42.

Riddoch, M.J., Humphreys, G.W., 1993. BORB: Birmingham Object Recognition Battery. Lawrence Erlbaum Associates, LEA, East Sussex.

Riddoch, M.J., Humphreys, G.W., 2004. Object identification in simultanagnosia: when wholes are not the sum of their parts. Cogn. Neuropsychol. 21, 423—441.

Rizzo, M., Anderson, S.W., Dawson, J., Myers, R., Ball, K., 2000. Visual attention impairments in Alzheimer's disease. Neurology 54, 1954—1959.

Rizzo, M., Vecera, S.P., 2002. Psychoanatomical substrates of Balint's syndrome. J. Neurol. Neurosurg. Psychiatry 72, 162—178.

Schliebs, R., Arendt, T., 2011. The cholinergic system in aging and neuronal degeneration. Behav. Brain Res. 221, 555—563.

Shulman, K.I., Gold, D.P., Cohen, C.A., Zucchero, C.A., 1993. Clock-drawing and dementia in the community: a longitudinal study. Int. J. Geriatr. Psychiatry 8, 487—496.

Sorg, C., Myers, N., Redel, P., Bublak, P., Riedl, V., Manoliu, A., Perneczky, R., Grimmer, T., Kurz, A., Forstl, H., Drzezga, A., Muller, H.J., Wohlschlager, A.M., Finke, K., 2012. Asymmetric loss of parietal activity causes spatial bias in prodromal and mild Alzheimer's disease. Biol. Psychiatry 71, 798—804.

Sorg, C., Riedl, V., Muhlau, M., Calhoun, V.D., Eichele, T., Laer, L., Drzezga, A., Forstl, H., Kurz, A., Zimmer, C., Wohlschlager, A.M., 2007. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 104, 18760—18765.

Tang-Wai, D.F., Graff-Radford, N.R., Boeve, B.F., Dickson, D.W., Parisi, J.E., Crook, R., Caselli, R.J., Knopman, D.S., Petersen, R.C., 2004. Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. Neurology 63, 1168—1174.

Thiebaut de Schotten, M., Dell'Acqua, F., Forkel, S.J., Simmons, A., Vergani, F., Murphy, D.G., Catani, M., 2011. A lateralized brain network for visuospatial attention. Nat. Neurosci. 14, 1245—1246.

Valenza, N., Murray, M.M., Ptak, R., Vuilleumier, P., 2004. The space of senses: impaired crossmodal interactions in a patient with Balint syndrome after bilateral parietal damage. Neuropsychologia 42, 1737—1748.

Vecera, S.P., Rizzo, M., 2004. Visual attention and visual short-term memory in Alzheimer's disease. In: Cronin-Golomb, A., Hof, P.R. (Eds.), Vision in Alzheimer's Disease Interdisciplinary Topics in Gerontology. Karger, Basel, pp. 248–270.

Vogel, E.K., Woodman, G.F., Luck, S.J., 2006. The time course of consolidation in visual working memory. J. Exp. Psychol. Hum. Percept. Perform. 32, 1436–1451.

Warrington, E.K., James, M., 1991. The Visual Object and Space Perception Battery. Thames Valley Test Company, Bury St Edmunds.

WHO, 2010. International Statistical Classification of Diseases and Related Health Problems, ICD-10. WHO Press.

Wolpert, I., 1924. Die simultanagnosie — störung der gesamtauffassung. Z. für die gesamte Neurologie Psychiatrie 93, 397–415.

8. Summary and Discussion

8.1. Correlates of visual processing speed in the human brain: spontaneous activity during rest

8.1.1. Visual processing speed in association with the spontaneous activity of the young healthy brain

Using an individual differences approach, we investigated whether visual processing speed is reflected in the intrinsic functional organization of the human brain. We identified one network for visual processing speed: the "ventral attention" (also known as "salience" or "cingulo-opercular") network[2]. We followed two assumptions: (a) studying the healthy young brain precludes any aging-related or pathological (confounding) influence; (b) network(s) where intrinsic functional connectivity (iFC) differences are observed are relevant for visual processing speed. Based on these assumptions, we conducted this study in a homogeneous sample of healthy young participants.

Three aspects of our analysis approach are worth considering before putting our findings into a theoretical context. First, we performed a voxel-wise analysis of six different frontoparietal, frontolimbic, and occipital networks estimated using independent component analysis and that included brain regions relevant for visual attention. We did not purportedly limit our 'search space' a priori, because no previous TVA-based study had so far directly assessed visual processing speed and iFC. Moreover, evaluating iFC differences in different intrinsic connectivity networks, instead of focusing on only one, could also provide us with a specificity measure for our findings. However, given the resultant multiple comparisons and the increased likelihood of type I, or alpha, errors, we adjusted the significance thresholds at both the cluster and network levels.

Second, our result was based on a median split—instead of a linear regression—approach because our sample was demographically homogeneous and, thus, we could not expect high variance in estimates of both brain and behavior. Although a sample median is somewhat arbitrarily defined, it was a preferable method in our case because it allows

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[2] From now on, referred to as "ventral attention/cingulo-opercular network"

an easier interpretation. Our results are based on differences in visual processing speed relative to other individuals of their age and education group.

The final aspect to consider is that the general linear model was used to find differences at the brain level. In this model, we included the other three TVA parameters, also estimated for each participant, education, and sex as covariates. Controlling for these variables in the statistical parametric mapping would ensure that our iFC results were exclusively due to group differences in visual processing speed.

The subgroup with relatively *higher* visual processing speed *C* estimates showed *lower* iFC within the ventral attention network, particularly in a cluster localized in the right middle frontal gyrus. No significant differences were found for the five other networks. The direction of the difference (i.e., lower iFC in higher speed) for the ventral attention/cingulo-opercular network was somewhat counterintuitive. Therefore, we explored the possibility that although the iFC *within* the ventral attention/cingulo-opercular network was lower, its iFC *with other* brain networks would be higher. We also reasoned that the higher iFC of the ventral attention/cingulo-opercular network with other attention networks could be related to its lower intra-iFC. We found that the iFC of the ventral attention/cingulo-opercular network was higher with the right frontoparietal network in the subgroup with higher visual processing speed. No other differences were found with other networks. Additionally, for the ventral attention/cingulo-opercular network, its higher iFC with the right frontoparietal network tended to be associated with its lower intra-network iFC.

Within the field of human cognitive neuroscience, the ventral attention/cingulo-opercular network has been proposed as a "human task-set system" (Dosenbach, Visscher, Palmer et al., 2006). This proposal is founded on the finding that dorsal anterior cingulate cortex, medial superior frontal cortex, and bilateral anterior insula/frontal operculum show start-cue and sustained activation across different visual and auditory tasks during fMRI (Dosenbach et al., 2006). More broadly, this network has been proposed to serve the maintenance of tonic alertness: Positive correlations have been observed between the BOLD fMRI slow activity and the global field power of oscillations in the upper alpha band (i.e., 10-12 Hz, an electroencephalographic marker of vigilance fluctuations) during simultaneous measurement (Sadaghiani, Scheeringa, Lehongre et al., 2010). Such positive correlations are prominent in the dorsal anterior cingulate cortex, the right anterior insula, the right anterior prefrontal cortex, the thalamus, and the basal ganglia (Sadaghiani et al., 2010).

A full task profile (i.e., within and across tasks) of the ventral attention/cingulo-opercular network has been characterized in a task-based fMRI study in healthy young participants (Sestieri, Corbetta, Spadone et al., 2014). This study investigated whether regions of this network exhibit sustained activity during and across perceptual (i.e., attending to environmental stimuli) or memory (i.e., retrieval of relevant episodic information) search tasks. For both tasks, results showed sustained activity in all processing stages within each task of the dorsal anterior cingulate /pre-supplementary cortex and anterior insula/frontal operculum regions (Sestieri et al., 2014). Thus, these results support a general involvement of the ventral attention/cingulo-opercular network in sustained attention (i.e., tonic alertness), directed to either external or internal stimuli (Sestieri et al., 2014).

More recent evidence from task-based fMRI activation studies has confirmed the role of the ventral attention/cingulo-opercular network in 'tonic alertness' and 'task-set.' For example, in both visual and auditory tasks, higher BOLD fMRI activity in the anterior insula/frontal operculum, anterior cingulate cortex, and thalamus was shown to precede faster correct responses (i.e., trials with high alertness) to unpredictable, un-cued stimuli, compared to the activity before slower responses (i.e., trials with low alertness) (Coste and Kleinschmidt 2016). Notably, this evidence is based on reaction times, a traditional measure of processing speed.

Our inter-network iFC findings point to the coupling between the ventral attention/cingulo-opercular network and the right frontoparietal network as relevant for the individual level of visual processing speed. Right hemisphere cortical and subcortical regions have been implicated in the maintenance of an alert state under unwarned conditions and during extended time periods (Sturm, de Simone, Krause et al., 1999; Sturm and Willmes 2001). Evidence from structural connectivity has also shown that the degree of right-sided lateralization of the inferior fronto-occipital fasciculus is positively associated with visual processing speed in young subjects (Chechlacz, Gillebert, Vangkilde et al., 2015). Moreover, both ventral attention/cingulo-opercular network regions and frontoparietal regions overlapping the right frontoparietal network have been reported to correlate with increases in pupil size—a physiological index of cortical arousal (Schneider, Hathway, Leuchs et al., 2016).

A direct relationship between alertness and visual processing speed has been demonstrated both theoretically (Bundesen, Vangkilde, and Petersen 2015) and empirically (Finke, Dodds, Bublak et al., 2010; Matthias, Schandry, Duschek et al., 2009;

Vangkilde, Coull, and Bundesen 2012; Wiegand, Petersen, Finke et al., 2017). A neural mechanism that could support such relationship is the multiplicative scaling of the firing rates of the neurons coding a particular category (Vangkilde, Petersen, and Bundesen 2013), or 'perceptual bias' (Bundesen, Habekost, and Kyllingsbaek 2005). Frontal, parietal, and limbic areas—such as those comprising the networks here shown relevant for visual processing speed—had been previously proposed as a possible neural source of perceptual bias (Bundesen et al., 2005).

In sum, we used an individual differences approach in a homogeneous sample of healthy young participants. This approach allowed us to find a representation of visual processing speed in the functional organization of the brain. Such 'representation' pertains to two features of the ventral attention/cingulo-opercular network's intrinsic functional connectivity: its intra-network connectivity and its inter-network connectivity with the right frontoparietal network. Therefore, our findings support the relevance of the analysis of spontaneous BOLD fluctuations (e.g., by iFC) for behavior (He, Snyder, Zempel et al., 2008; De Luca, Beckmann, De Stefano et al., 2006; Kelly, Uddin, Biswal et al., 2008; Raichle 2015).

8.1.2. Age-related differences in visual processing speed and intrinsic functional connectivity of the ventral attention/cingulo-opercular network

We analyzed visual processing speed and iFC within the ventral attention/cingulo-opercular network in a cross-sectional sample of healthy adults from the age of 20 to the late 70s. After peaking in the early 20s, visual processing speed starts to decrease (Espeseth, Vangkilde, Petersen et al., 2014; McAvinue, Habekost, Johnson et al., 2012). In line with this trajectory, in our sample, we also observed a linear reduction of visual processing speed. Moreover, some regions of the ventral attention/cingulo-opercular network also followed that linear pattern: anterior and middle cingulate cortex, middle frontal gyri, bilateral insula, and left cerebellum.

Cross-sectional studies (e.g., Betzel, Byrge, He et al., 2014; He, Qin, Liu et al., 2014; Meier, Desphande, Vergun et al., 2012; Onoda, Ishihara, and Yamaguchi 2012) have reported age-related decreases in iFC within the ventral attention/cingulo-opercular network. Decreases in functional connectivity within this network have also been noted during task performance (e.g., visuospatial working memory and attentional inhibition or conflict tasks) (Archer, Lee, Qiu et al., 2016). However, age-related decreases are not

exclusive of the ventral attention/cingulo-opercular network; the iFC within frontoparietal control, default mode, visual, and somatomotor networks has also been shown to decrease over the lifespan (e.g., Andrews-Hanna, Snyder, Vincent et al., 2007; Betzel et al., 2014). What our results add to the existing knowledge is the specificity of the association between the decreased iFC within the ventral attention/cingulo-opercular network and the age-related individual differences in visual processing speed.

Within the ventral attention/cingulo-opercular network, the iFC of the insula was significantly related to visual processing speed. This relationship was not explained by individual differences in gender, education, total brain volume, or insular gray matter. Previous studies have shown a significant correlation of left insular iFC with visuospatial intelligence in healthy elderly (Onoda et al., 2012), and global cognitive state in healthy elderly and patients with incipient Alzheimer's disease (He et al., 2014). Visual processing speed is frequently acknowledged as a fundamental aspect of cognition, including fluid intelligence, especially in the elderly (e.g., Deary, Johnson, and Starr 2010). Thus, our results suggest that visual processing speed is a cognitive mechanism that could explain the previous findings of insular iFC with general neuropsychological measures.

The ventral attention/cingulo-opercular network's regions feature interesting anatomical and morphological characteristics. First, the insula is concealed lobe of the brain inside the frontal, temporal, and parietal opercula (Figure 1). A series of short U-shaped white matter tracts connect the frontal operculum—i.e., inferior frontal gyrus pars opercularis, triangularis, and orbitalis—with the anterior insular cortex, and the sub-central gyrus (Brodmann area 43) with the posterior insular cortex (Catani, Dell'acqua, Vergani et al., 2012). In hominoid primates, the insula (as well as the anterior cingulate cortex) contains large spindle-shaped, bipolar neurons in layer 5, the "von Economo neurons" (Allman, Tetreault, Hakeem et al., 2010; Craig 2009). Functionally, a major role of the insula on the level of awareness of the subjects has been proposed (Craig 2009).
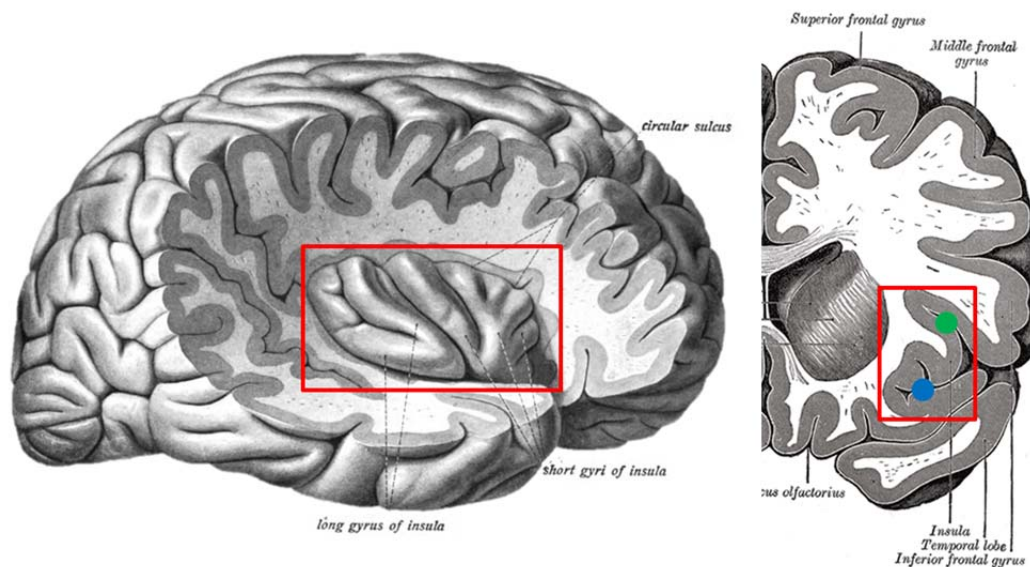
Figure 1. Anatomical localization of the insula in the human brain. (*Left*) The insula (inside red square) is a lobe hidden by the frontal, temporal, and parietal opercula. This is one reason for the name "cingulo-opercular" network—the first part of the name refers to the anterior *cingulate* cortex. (Right) Coronal section of the brain showing the insula between the frontal (green circle) and temporal (blue circle) opercula. Image on the left modified from Sobotta's Textbook and Atlas of Human Anatomy 1908, Public Domain, commons.wikimedia.org. Image on the right modified from Henry Gray (1918) Anatomy of the Human Body, Public Domain, via Wikimedia Commons.

The functional complexity of the insula manifests beyond task involvement—i.e., also during resting state. Differential iFC has been revealed for the dorsal (i.e., with the rostral dorsolateral prefrontal, dorsal anterior cingulate cortex, rostral inferior parietal, and dorsal striatal regions) and ventral (i.e., pregenual anterior cingulate and orbitofrontal cortices, ventral striatal regions, and amygdala) insula (Touroutoglou, Hollenbeck, Dickerson et al., 2012). A tripartite functional parcellation (i.e., anterior dorsal, anterior ventral, and posterior) has also been reported (Chang, Yarkoni, Khaw et al., 2013): the anterior dorsal insular cortex shows preferential connectivity with frontoparietal association cortex, the ventral anterior does with the limbic cortex, and the posterior insular with somatosensory cortex (Uddin 2015). Evidence from structural connectivity in humans also supports the existence of neural networks within the insula (e.g., Cloutman, Binney, Drakesmith et al., 2012). Concerning the rest of the brain, a role in switching between the central executive network and the default mode network has been shown for the insula (Sridharan, Levitin, and Menon 2008).

Previous reports have noted a general role for the ventral attention/cingulo-opercular network in anxiety (e.g., Seeley, Menon, Schatzberg et al., 2007). The anterior insula, one of the main regions of the ventral attention/cingulo-opercular network, is a

hub of the human brain (Power, Schlaggar, Lessov-Schlaggar et al., 2013). The multiplicity of functional systems within the anterior insula could explain why, in our study, controlling for anxiety did not affect the association between insular iFC and visual processing speed. Previous studies have shown that the iFC strength between the dorsal anterior insula and the dorsal anterior cingulate cortex explains more variance in speeded executive control performance (i.e., Trail Making Test B) than in arousal to negative pictures. In contrast, the iFC strength between the ventral insula and the pregenual anterior cingulate cortex shows the opposite pattern (Touroutoglou et al., 2012). Thus, in line with previous evidence, our control analyses support an independent role of the insular iFC in visual processing speed.

The iFC of the ventral attention/cingulo-opercular network did not mediate the association between age and performance in a conventional measure of processing speed (i.e., the Trail Making Test A, TMT-A). The lack of mediation was explained by that measure's high reliance on motor speed (i.e., the task requires drawing lines to connect circles). Visual processing speed estimates that are derived by TVA-based paradigms are not affected by age-related motor slowing, as they depend on the accuracy of the report instead of on reaction time (e.g., Habekost, Petersen, and Vangkilde 2014). Thus, our results are based on a relatively clean measure of visual processing speed.

A relevant question is whether changes in white matter underlie the decrease in iFC and, thereby, the visual processing speed reduction that occurs in normal aging. Previous studies have described a relevant role for white matter integrity in the relationship between age and visual processing speed. For example, a study on elderly adults in their early 70s showed that a general white-matter integrity factor (i.e., explaining a significant part of the variance in fractional anisotropy of several white-matter tracts) is associated with a general factor of visual processing speed (Penke, Munoz Maniega, Murray et al., 2010). However, given the narrow age range of the participants in that study, the effect of age could not be tested.

Another study in a group of men above 55 years old did find that the integrity of myelin of late-myelinating regions like the genu of the corpus callosum (in contrast to those myelinating earlier, like the splenium) significantly mediates visual processing speed performance (Lu, Lee, Tishler et al., 2013). Although those results suggest an interesting biological mechanism, they include both motor (i.e., they used the Trail Making Test) and cognitive (i.e., they used both parts of the TMT, with part B including an additional executive control factor) confounds. Moreover, they are based on a sample

of only men. Thus, it remains to be elucidated whether white matter integrity—generally in the brain or of particular tracts—mediates the relation between (a) age and visual processing speed, (b) age and iFC, or (c) iFC and visual processing speed.

In sum, this cross-sectional study in a relatively large sample of healthy adults allowed us to investigate the relationship between iFC and visual processing speed in aging. We found a mediator role for the ventral attention/cingulo-opercular network's iFC in the relationship between age and visual processing speed. The iFC of the anterior insula within this network showed a prominent role for visual processing speed that is in line with previously reported associations with more global cognitive functions. Thus, our analyses revealed that the decreased iFC within the ventral attention/cingulo-opercular network is relevant for the age-related differences in visual processing speed among healthy adults.

8.2. Correlates of visual processing speed in the human behavior: complex object perception

In the third study of this dissertation, we assessed patients with MCI who are known to experience memory deficits. Memory deficits are a typical characteristic of MCI patients who will later develop AD dementia (Albert, DeKosky, Dickson et al., 2011); hence known as amnestic MCI or aMCI (Petersen 2004; Albert et al., 2011). Additionally, attentional deficits—such as reductions in visual processing speed—are found with increasing AD pathological load (Bublak, Redel, Sorg et al., 2011). Therefore, we focused on aMCI to investigate whether the degree of reduction in visual processing speed relates to complex visual object perception deficits.

Previous reports on patients with stroke (e.g., Duncan, Bundesen, Olson et al., 2003), Huntington's disease (e.g., Finke, Schneider, Redel et al., 2007), and posterior cortical atrophy (e.g., Neitzel, Ortner, Haupt et al., 2016) have shown that visual processing speed reduction is significantly associated with simultaneous object perception deficits. Given the more or less severe reduction in visual processing speed that occurs in aMCI, similar perceptual deficits could be also observed in these patients. Finding this type of deficits in aMCI—a common, slowly progressing form of pathological aging—could offer a new possibility of measuring the progression of cognitive symptoms and,

ultimately, of predicting outcomes; hence investigating these deficits poses clinical relevance.

Compared to healthy elderly participants, patients with aMCI showed, as a group, a reduction in visual processing speed. Patients with aMCI also showed signs of simultanagnosia—i.e., an inability to perceive multiple objects at a time. As expected, the degree of reduction in visual processing speed was associated with the level of simultaneous object perception deficits. On the one hand, this association was not explained by individual differences in the global cognitive state or verbal memory impairment, thus indicating the independence of the reduction in visual processing speed. On the other hand, simultaneous object perception deficits were not associated with the visual perceptual threshold or visual short-term memory capacity. The results of this study, thus, show a memory-independent deficit in aMCI in the simultaneous perception of objects and the impact of a reduction in visual processing speed that, arguably, could also be present in healthy aging (Ruiz-Rizzo, Bublak, Redel et al., 2017).

Simultaneous object perception was assessed with unlimited time using an experimental task at different complexity levels within (i.e., set size) and between (i.e., adjacent, embedded, and overlapping shapes) conditions. The use of this task is a notable strength of our study because the rate of visual *processing* was tackled, and not the speed of *responding* or visual *perception*, and visual processing speed has been classically linked more closely to decision accuracy than to decision time (Salthouse 2000). In sum, the association between performance in this time-unconstrained task and the visual processing speed estimates obtained from report accuracy in the whole report task indicates that the TVA-based visual processing speed parameter can validly predict deficits under unlimited viewing conditions (Ruiz-Rizzo et al., 2017).

The use of different conditions with increasing complexity allowed us to determine that simultaneous object perception deficits in patients with aMCI are not readily observed with simple 2-item tasks. Instead, those deficits emerge under the most complex conditions (i.e., more than three objects presented in an overlapping manner). Therefore, in our paper, we suggest that simultaneous object perception deficits could explain the particular sensitivity of complex visual memory tests in revealing memory deficits in aMCI patients (e.g., Kawas, Corrada, Brookmeyer et al., 2003) (Ruiz-Rizzo et al., 2017). Moreover, we propose that simultaneous object perception deficits could be the initial cognitive dementia symptoms (Ruiz-Rizzo et al., 2017), as indicated by the early

problems in spatial navigation (Laczo, Vlcek, Vyhnalek et al., 2009) or way-finding (Allison, Fagan, Morris et al., 2016)—which are more clearly seen in daily living.

In sum, in this case-control study, we showed simultaneous object perception deficits in a sample of patients diagnosed with amnestic mild cognitive impairment due to Alzheimer's disease. Revealing these deficits is not trivial and requires a somewhat more detailed assessment than the non-memory assessment typically done with screening measures. Moreover, we found that the degree of simultaneous object perception deficits significantly correlates with the corresponding degree of visual processing speed reduction. Based on these findings and those of previous studies, we suggest that the reduction of visual processing speed is a process that could underlie simultaneous object perception deficits. Finally, we propose that these deficits could signal a closer approaching to a more explicit AD dementia stage.

8.3. Limitations

The results presented in this Dissertation should be interpreted considering some limitations not outlined previously in each study. First, the first two studies are based on brain data obtained from fMRI. The BOLD signal measured with fMRI does not *directly* reflect neuronal activity (as explained in more detail in the **4. Introduction, 4.2. The resting human brain**). However, this issue has been discussed in the literature and, although not yet resolved, there is consistent evidence for the direct correlation between neural (and neuronal) activity and the BOLD signal response and fluctuations (e.g., Attwell and Iadecola 2002; Hall, Howarth, Kurth-Nelson et al., 2016; He et al., 2008; Logothetis, Pauls, Augath et al., 2001; Mantini, Perrucci, Del Gratta et al., 2007; Matsui, Murakami, and Ohki 2016; Lu, Zuo, Gu et al., 2007).

A second issue is the cross-sectional design of the second study. It has been proposed that longitudinal designs (i.e., the study of change in aging individuals) could allow obtaining "a purer measure of aging effects" in behavior (Sliwinski and Buschke 1999). Although this is true when trajectories are to be studied, longitudinal designs can result impractical (e.g., require a lifetime study) and be subject to selective attrition and training effects. Moreover, given that age cannot be manipulated experimentally, the effects of aging will always be based on correlations (Hedden and Gabrieli 2004).

Nonetheless, our results cannot be extrapolated to the aging process of an individual and could show, at least to some extent, cohort effects of our sample.

Finally, our third study lacks brain (imaging) data. In principle, the research question that motivated this study (i.e., determining the impact of visual processing speed on simultaneous object perception in aMCI) only required neuropsychological data. Moreover, the comprehensive neuropsychological and experimental testing demanded significant time and effort from patients. However, information on brain structure or function could have allowed us to examine whether the degree of simultaneous object perception deficits correlates with that of, e.g., gray matter atrophy or iFC of the ventral attention/cingulo-opercular network. Regardless, our findings invite to the further exploration of those possibilities, rather than being a limitation of them.

8.4. Future directions

The work presented in this Dissertation opens new questions for future research (see Box). For example, the ventral attention/cingulo-opercular network has a relatively high density of the nicotinic cholinergic receptor (Picard, Sadaghiani, Leroy et al., 2013). Recent evidence has shown an association of a lower density of this receptor (i.e., measured by receptor binding of a form of pyridine) in the medial thalamus with lower performance in the TMT-A in healthy elderly (Sultzer, Melrose, Riskin-Jones et al., 2017). Moreover, in mice, a muscarinic receptor antagonist has been shown to significantly reduce visual processing speed in a rodent version of the whole report paradigm (Fitzpatrick, Caballero-Puntiverio, Gether et al., 2017). Thus, future studies could examine the association between age-related differences in cholinergic depletion, iFC of the ventral attention/cingulo-opercular network, and visual processing speed.

Crucial for societal impact, coalescent lines of research should address how cognitive abilities can be maintained into old age to postpone or prevent pathologies leading to dementia (Lindenberger 2014; Hertzog, Kramer, Wilson et al., 2008). In this context, one pertinent question is whether the iFC within the ventral attention/cingulo-opercular network predicts gains from visual processing speed training in healthy elderly. Mechanisms of maintenance (i.e., preserved iFC similar to that of younger adults) or compensation (i.e., reorganization of iFC involving other networks) in the old brain (Lindenberger 2014) could anticipate the adequacy of such question.

Box. Pertinent questions for future research derived from the current work

Biological

Does a cholinergic depletion relate to the decreased iFC of the ventral attention/cingulo-opercular network in healthy aging?

Cognitive

Do iFC age-differences within the ventral attention/cingulo-opercular network (or its connectivity with other networks) significantly predict the benefits of visual processing speed training in healthy aging?

Trajectory

Do iFC age-differences within the ventral attention/cingulo-opercular network occur before or simultaneously with visual processing speed reduction within the same person?

Clinical

Does decreased iFC within the ventral attention/cingulo-opercular network underlie the reduction in visual processing speed also in pathological aging (e.g., aMCI)?

Within a healthy group of older adults, there could be individuals who are already showing biomarker evidence of AD pathology. They would be at a 'preclinical stage' (Sperling, Aisen, Beckett et al., 2011). Thus, based on the findings presented here, future studies could investigate whether the iFC within the ventral attention/cingulo-opercular network differs between elderly subjects with a stronger suggestion of preclinical AD and those without it. Moreover, in line with this idea, whether a decreased iFC underlies the staged decline of visual processing speed also in pathological aging.

8.5. Conclusion

The critical insights obtained from the work presented in this Dissertation can be summarized in three points. First, in line with the most influential theories of visual attention, the results of the first study support a view of visual attention functions that capitalizes on its multiplicity also at the level of intrinsic connectivity networks. **Visual processing speed, in particular, can be 'mapped' onto the ventral attention/cingulo-opercular network**. The functional connectivity within this network and also with the right frontoparietal network can determine the level of visual processing speed.

The results of the second study indicate that **aging** (or the mere passing of time) in itself does not reduce visual processing speed. Instead, **the level of intrinsic functional connectivity of the insula with other medial frontal, cerebellar, and parietal regions of the ventral attention/cingulo-opercular network appear to contribute significantly**. Neurochemical changes in these areas could further underlie such contribution.

Finally, the results of the third study add to previous clinical evidence to suggest that a **reduction in visual processing speed underlies deficits in the simultaneous perception of objects in aMCI patients**. These often-overlooked deficits in patients whose clinically most obvious impairments in screening measures lie in memory speak for a possible marker of progression into dementia. The study of the intrinsic brain organization in these patients could help us understand the nature of these attention deficits.

In conclusion, this work allowed determining a **brain correlate** of visual processing speed in the intrinsic functional connectivity of the cingulo-opercular network, which is affected by normal aging. A **behavioral correlate** of visual processing speed was also determined in tasks that resemble daily visual scenes in patients at risk for Alzheimer's dementia. Future research should aim at establishing whether the neural correlate of visual processing speed found in healthy aging also holds for pathological aging (e.g., in patients at risk for Alzheimer's dementia).

8.6. References

Albert, M. S., S. T. DeKosky, D. Dickson, B. Dubois, H. H. Feldman, N. C. Fox, et al. 2011. "The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." *Alzheimers Dement* 7 (3):270-9. doi: 10.1016/j.jalz.2011.03.008.

Allison, S. L., A. M. Fagan, J. C. Morris, and D. Head. 2016. "Spatial Navigation in Preclinical Alzheimer's Disease." *J Alzheimers Dis* 52 (1):77-90. doi: 10.3233/JAD-150855.

Allman, J. M., N. A. Tetreault, A. Y. Hakeem, K. F. Manaye, K. Semendeferi, J. M. Erwin, et al. 2010. "The von Economo neurons in frontoinsular and anterior cingulate cortex in great apes and humans." *Brain Struct Funct* 214 (5-6):495-517. doi: 10.1007/s00429-010-0254-0.

Andrews-Hanna, J. R., A. Z. Snyder, J. L. Vincent, C. Lustig, D. Head, M. E. Raichle, et al. 2007. "Disruption of large-scale brain systems in advanced aging." *Neuron* 56 (5):924-35. doi: 10.1016/j.neuron.2007.10.038.

Archer, J. A., A. Lee, A. Qiu, and S. H. Chen. 2016. "A Comprehensive Analysis of Connectivity and Aging Over the Adult Life Span." *Brain Connect* 6 (2):169-85. doi: 10.1089/brain.2015.0345.

Attwell, D., and C. Iadecola. 2002. "The neural basis of functional brain imaging signals." *Trends Neurosci* 25 (12):621-5.

Betzel, R. F., L. Byrge, Y. He, J. Goni, X. N. Zuo, and O. Sporns. 2014. "Changes in structural and functional connectivity among resting-state networks across the human lifespan." *Neuroimage* 102 Pt 2:345-57. doi: 10.1016/j.neuroimage.2014.07.067.

Bublak, P., P. Redel, C. Sorg, A. Kurz, H. Forstl, H. J. Muller, et al. 2011. "Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease." *Neurobiol Aging* 32 (7):1219-30. doi: 10.1016/j.neurobiolaging.2009.07.012.

Bundesen, C., T. Habekost, and S. Kyllingsbaek. 2005. "A neural theory of visual attention: bridging cognition and neurophysiology." *Psychol Rev* 112 (2):291-328. doi: 10.1037/0033-295X.112.2.291.

Bundesen, C., S. Vangkilde, and A. Petersen. 2015. "Recent developments in a computational theory of visual attention (TVA)." *Vision Res* 116 (Pt B):210-8. doi: 10.1016/j.visres.2014.11.005.

Catani, M., F. Dell'acqua, F. Vergani, F. Malik, H. Hodge, P. Roy, et al. 2012. "Short frontal lobe connections of the human brain." *Cortex* 48 (2):273-91. doi: 10.1016/j.cortex.2011.12.001.

Chang, L. J., T. Yarkoni, M. W. Khaw, and A. G. Sanfey. 2013. "Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference." *Cereb Cortex* 23 (3):739-49. doi: 10.1093/cercor/bhs065.

Chechlacz, M., C. R. Gillebert, S. A. Vangkilde, A. Petersen, and G. W. Humphreys. 2015. "Structural Variability within Frontoparietal Networks and Individual Differences in Attentional Functions: An Approach Using the Theory of Visual Attention." *J Neurosci* 35 (30):10647-58. doi: 10.1523/JNEUROSCI.0210-15.2015.

Cloutman, L. L., R. J. Binney, M. Drakesmith, G. J. Parker, and M. A. Lambon Ralph. 2012. "The variation of function across the human insula mirrors its patterns of structural connectivity: evidence from in vivo probabilistic tractography." *Neuroimage* 59 (4):3514-21. doi: 10.1016/j.neuroimage.2011.11.016.

Coste, C. P., and A. Kleinschmidt. 2016. "Cingulo-opercular network activity maintains alertness." *Neuroimage* 128:264-72. doi: 10.1016/j.neuroimage.2016.01.026.

Craig, A. D. 2009. "How do you feel--now? The anterior insula and human awareness." *Nat Rev Neurosci* 10 (1):59-70. doi: 10.1038/nrn2555.

De Luca, M., C. F. Beckmann, N. De Stefano, P. M. Matthews, and S. M. Smith. 2006. "fMRI resting state networks define distinct modes of long-distance interactions in the human brain." *Neuroimage* 29 (4):1359-67. doi: 10.1016/j.neuroimage.2005.08.035.

Deary, I. J., W. Johnson, and J. M. Starr. 2010. "Are processing speed tasks biomarkers of cognitive aging?" *Psychol Aging* 25 (1):219-28. doi: 10.1037/a0017750.

Dosenbach, N. U., K. M. Visscher, E. D. Palmer, F. M. Miezin, K. K. Wenger, H. C. Kang, et al. 2006. "A core system for the implementation of task sets." *Neuron* 50 (5):799-812. doi: 10.1016/j.neuron.2006.04.031.

Duncan, J., C. Bundesen, A. Olson, G. Humphreys, R. Ward, S. Kyllingsbaek, et al. 2003. "Attentional functions in dorsal and ventral simultanagnosia." *Cogn Neuropsychol* 20 (8):675-701. doi: 10.1080/02643290342000041.

Espeseth, T., S. A. Vangkilde, A. Petersen, M. Dyrholm, and L. T. Westlye. 2014. "TVA-based assessment of attentional capacities-associations with age and indices of brain white matter microstructure." *Front Psychol* 5:1177. doi: 10.3389/fpsyg.2014.01177.

Finke, K., C. M. Dodds, P. Bublak, R. Regenthal, F. Baumann, T. Manly, et al. 2010. "Effects of modafinil and methylphenidate on visual attention capacity: a TVA-based study." *Psychopharmacology (Berl)* 210 (3):317-29. doi: 10.1007/s00213-010-1823-x.

Finke, K., W. X. Schneider, P. Redel, M. Dose, G. Kerkhoff, H. J. Muller, et al. 2007. "The capacity of attention and simultaneous perception of objects: a group study of Huntington's disease patients." *Neuropsychologia* 45 (14):3272-84. doi: 10.1016/j.neuropsychologia.2007.06.006.

Fitzpatrick, C. M., M. Caballero-Puntiverio, U. Gether, T. Habekost, C. Bundesen, S. Vangkilde, et al. 2017. "Theory of Visual Attention (TVA) applied to mice in the 5-choice serial reaction time task." *Psychopharmacology (Berl)* 234 (5):845-855. doi: 10.1007/s00213-016-4520-6.

Habekost, T., A. Petersen, and S. Vangkilde. 2014. "Testing attention: comparing the ANT with TVA-based assessment." *Behav Res Methods* 46 (1):81-94. doi: 10.3758/s13428-013-0341-2.

Hall, C. N., C. Howarth, Z. Kurth-Nelson, and A. Mishra. 2016. "Interpreting BOLD: towards a dialogue between cognitive and cellular neuroscience." *Philos Trans R Soc Lond B Biol Sci* 371 (1705). doi: 10.1098/rstb.2015.0348.

He, B. J., A. Z. Snyder, J. M. Zempel, M. D. Smyth, and M. E. Raichle. 2008. "Electrophysiological correlates of the brain's intrinsic large-scale functional architecture." *Proc Natl Acad Sci U S A* 105 (41):16039-44. doi: 10.1073/pnas.0807010105.

He, X., W. Qin, Y. Liu, X. Zhang, Y. Duan, J. Song, et al. 2014. "Abnormal salience network in normal aging and in amnestic mild cognitive impairment and Alzheimer's disease." *Hum Brain Mapp* 35 (7):3446-64. doi: 10.1002/hbm.22414.

Hedden, T., and J. D. Gabrieli. 2004. "Insights into the ageing mind: a view from cognitive neuroscience." *Nat Rev Neurosci* 5 (2):87-96. doi: 10.1038/nrn1323.

Hertzog, C., A. F. Kramer, R. S. Wilson, and U. Lindenberger. 2008. "Enrichment Effects on Adult Cognitive Development: Can the Functional Capacity of Older Adults Be Preserved and Enhanced?" *Psychol Sci Public Interest* 9 (1):1-65. doi: 10.1111/j.1539-6053.2009.01034.x.

Kawas, C. H., M. M. Corrada, R. Brookmeyer, A. Morrison, S. M. Resnick, A. B. Zonderman, et al. 2003. "Visual memory predicts Alzheimer's disease more than a decade before diagnosis." *Neurology* 60 (7):1089-93.

Kelly, A. M., L. Q. Uddin, B. B. Biswal, F. X. Castellanos, and M. P. Milham. 2008. "Competition between functional brain networks mediates behavioral variability." *Neuroimage* 39 (1):527-37. doi: 10.1016/j.neuroimage.2007.08.008.

Laczo, J., K. Vlcek, M. Vyhnalek, O. Vajnerova, M. Ort, I. Holmerova, et al. 2009. "Spatial navigation testing discriminates two types of amnestic mild cognitive impairment." *Behav Brain Res* 202 (2):252-9. doi: 10.1016/j.bbr.2009.03.041.

Lindenberger, U. 2014. "Human cognitive aging: corriger la fortune?" *Science* 346 (6209):572-8. doi: 10.1126/science.1254403.

Logothetis, N. K., J. Pauls, M. Augath, T. Trinath, and A. Oeltermann. 2001. "Neurophysiological investigation of the basis of the fMRI signal." *Nature* 412 (6843):150-7. doi: 10.1038/35084005.

Lu, H., Y. Zuo, H. Gu, J. A. Waltz, W. Zhan, C. A. Scholl, et al. 2007. "Synchronized delta oscillations correlate with the resting-state functional MRI signal." *Proc Natl Acad Sci U S A* 104 (46):18265-9. doi: 10.1073/pnas.0705791104.

Lu, P. H., G. J. Lee, T. A. Tishler, M. Meghpara, P. M. Thompson, and G. Bartzokis. 2013. "Myelin breakdown mediates age-related slowing in cognitive processing speed in healthy elderly men." *Brain Cogn* 81 (1):131-8. doi: 10.1016/j.bandc.2012.09.006.

Mantini, D., M. G. Perrucci, C. Del Gratta, G. L. Romani, and M. Corbetta. 2007. "Electrophysiological signatures of resting state networks in the human brain." *Proc Natl Acad Sci U S A* 104 (32):13170-5. doi: 10.1073/pnas.0700668104.

Matsui, T., T. Murakami, and K. Ohki. 2016. "Transient neuronal coactivations embedded in globally propagating waves underlie resting-state functional connectivity." *Proc Natl Acad Sci U S A* 113 (23):6556-61. doi: 10.1073/pnas.1521299113.

Matthias, E., R. Schandry, S. Duschek, and O. Pollatos. 2009. "On the relationship between interoceptive awareness and the attentional processing of visual stimuli." *Int J Psychophysiol* 72 (2):154-9. doi: 10.1016/j.ijpsycho.2008.12.001.

McAvinue, L. P., T. Habekost, K. A. Johnson, S. Kyllingsbaek, S. Vangkilde, C. Bundesen, et al. 2012. "Sustained attention, attentional selectivity, and attentional capacity across the lifespan." *Atten Percept Psychophys* 74 (8):1570-82. doi: 10.3758/s13414-012-0352-6.

Meier, T. B., A. S. Desphande, S. Vergun, V. A. Nair, J. Song, B. B. Biswal, et al. 2012. "Support vector machine classification and characterization of age-related reorganization of functional brain networks." *Neuroimage* 60 (1):601-13. doi: 10.1016/j.neuroimage.2011.12.052.

Neitzel, J., M. Ortner, M. Haupt, P. Redel, T. Grimmer, I. Yakushev, et al. 2016. "Neuro-cognitive mechanisms of simultanagnosia in patients with posterior cortical atrophy." *Brain*. doi: 10.1093/brain/aww235.

Onoda, K., M. Ishihara, and S. Yamaguchi. 2012. "Decreased functional connectivity by aging is associated with cognitive decline." *J Cogn Neurosci* 24 (11):2186-98. doi: 10.1162/jocn_a_00269.

Penke, L., S. Munoz Maniega, C. Murray, A. J. Gow, M. C. Hernandez, J. D. Clayden, et al. 2010. "A general factor of brain white matter integrity predicts information processing speed in healthy older people." *J Neurosci* 30 (22):7569-74. doi: 10.1523/JNEUROSCI.1553-10.2010.

Petersen, R. C. 2004. "Mild cognitive impairment as a diagnostic entity." *J Intern Med* 256 (3):183-94. doi: 10.1111/j.1365-2796.2004.01388.x.

Picard, F., S. Sadaghiani, C. Leroy, D. S. Courvoisier, R. Maroy, and M. Bottlaender. 2013. "High density of nicotinic receptors in the cingulo-insular network." *Neuroimage* 79:42-51. doi: 10.1016/j.neuroimage.2013.04.074.

Power, J. D., B. L. Schlaggar, C. N. Lessov-Schlaggar, and S. E. Petersen. 2013. "Evidence for hubs in human functional brain networks." *Neuron* 79 (4):798-813. doi: 10.1016/j.neuron.2013.07.035.

Raichle, M. E. 2015. "The restless brain: how intrinsic activity organizes brain function." *Philos Trans R Soc Lond B Biol Sci* 370 (1668). doi: 10.1098/rstb.2014.0172.

Ruiz-Rizzo, A. L., P. Bublak, P. Redel, T. Grimmer, H. J. Muller, C. Sorg, et al. 2017. "Simultaneous object perception deficits are related to reduced visual processing speed in amnestic mild cognitive impairment." *Neurobiol Aging* 55:132-142. doi: 10.1016/j.neurobiolaging.2017.03.029.

Sadaghiani, S., R. Scheeringa, K. Lehongre, B. Morillon, A. L. Giraud, and A. Kleinschmidt. 2010. "Intrinsic connectivity networks, alpha oscillations, and tonic alertness: a simultaneous electroencephalography/functional magnetic resonance imaging study." *J Neurosci* 30 (30):10243-50. doi: 10.1523/JNEUROSCI.1004-10.2010.

Salthouse, T. A. 2000. "Aging and measures of processing speed." *Biol Psychol* 54 (1-3):35-54.

Schneider, M., P. Hathway, L. Leuchs, P. G. Samann, M. Czisch, and V. I. Spoormaker. 2016. "Spontaneous pupil dilations during the resting state are associated with activation of the salience network." *Neuroimage* 139:189-201. doi: 10.1016/j.neuroimage.2016.06.011.

Seeley, W. W., V. Menon, A. F. Schatzberg, J. Keller, G. H. Glover, H. Kenna, et al. 2007. "Dissociable intrinsic connectivity networks for salience processing and executive control." *J Neurosci* 27 (9):2349-56. doi: 10.1523/JNEUROSCI.5587-06.2007.

Sestieri, C., M. Corbetta, S. Spadone, G. L. Romani, and G. L. Shulman. 2014. "Domain-general signals in the cingulo-opercular network for visuospatial attention and episodic memory." *J Cogn Neurosci* 26 (3):551-68. doi: 10.1162/jocn_a_00504.

Sliwinski, M., and H. Buschke. 1999. "Cross-sectional and longitudinal relationships among age, cognition, and processing speed." *Psychol Aging* 14 (1):18-33.

Sperling, R. A., P. S. Aisen, L. A. Beckett, D. A. Bennett, S. Craft, A. M. Fagan, et al. 2011. "Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." *Alzheimers Dement* 7 (3):280-92. doi: 10.1016/j.jalz.2011.03.003.

Sridharan, D., D. J. Levitin, and V. Menon. 2008. "A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks." *Proc Natl Acad Sci U S A* 105 (34):12569-74. doi: 10.1073/pnas.0800005105.

Sturm, W., A. de Simone, B. J. Krause, K. Specht, V. Hesselmann, I. Radermacher, et al. 1999. "Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere." *Neuropsychologia* 37 (7):797-805.

Sturm, W., and K. Willmes. 2001. "On the functional neuroanatomy of intrinsic and phasic alertness." *Neuroimage* 14 (1 Pt 2):S76-84. doi: 10.1006/nimg.2001.0839.

Sultzer, D. L., R. J. Melrose, H. Riskin-Jones, T. A. Narvaez, J. Veliz, T. K. Ando, et al. 2017. "Cholinergic Receptor Binding in Alzheimer Disease and Healthy Aging: Assessment In Vivo with Positron Emission Tomography Imaging." *Am J Geriatr Psychiatry* 25 (4):342-353. doi: 10.1016/j.jagp.2016.11.011.

Touroutoglou, A., M. Hollenbeck, B. C. Dickerson, and L. Feldman Barrett. 2012. "Dissociable large-scale networks anchored in the right anterior insula subserve affective experience and attention." *Neuroimage* 60 (4):1947-58. doi: 10.1016/j.neuroimage.2012.02.012.

Uddin, L. Q. 2015. "Salience processing and insular cortical function and dysfunction." *Nat Rev Neurosci* 16 (1):55-61. doi: 10.1038/nrn3857.

Vangkilde, S., J. T. Coull, and C. Bundesen. 2012. "Great expectations: temporal expectation modulates perceptual processing speed." *J Exp Psychol Hum Percept Perform* 38 (5):1183-91. doi: 10.1037/a0026343.

Vangkilde, S., A. Petersen, and C. Bundesen. 2013. "Temporal expectancy in the context of a theory of visual attention." *Philos Trans R Soc Lond B Biol Sci* 368 (1628):20130054. doi: 10.1098/rstb.2013.0054.

Wiegand, I., A. Petersen, K. Finke, C. Bundesen, J. Lansner, and T. Habekost. 2017. "Behavioral and Brain Measures of Phasic Alerting Effects on Visual Attention." *Front Hum Neurosci* 11:176. doi: 10.3389/fnhum.2017.00176.

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10. CV

Adriana Lucía RUIZ RIZZO

April 15th 1986

Sincelejo (Colombia)

Education

2014.04 – 2017.11	**Ph.D. candidate in Systemic Neurosciences** Graduate School of Systemic Neurosciences, GSN LMU Munich. Marie Curie initial training network (EU 7th Framework)
2011.09 – 2013.09	**M.Sc. in Cognitive and Clinical Neuroscience** Maastricht University. Maastricht, Netherlands Enlazamundos and Colfuturo Scholarships Thesis: Neurocognitive Processes Associated with Peer Preference in Preschool Children
2003.07 – 2008.05	**B.A. in Psychology** Universidad de Antioquia. Medellín, Colombia 2nd place among 37 graduates. GPA: 4.49/5.0 Thesis: Description of the Neuropsychological Features of Explicit Memory in Adults with History of Major Depression from Adolescence

Publications

1. **Ruiz-Rizzo AL**, Bublak P, Redel P, Grimmer T, Müller HJ, Sorg C, Finke K. Simultaneous object perception deficits are related to reduced visual processing speed in amnestic mild cognitive impairment. **Neurobiol of Aging**. 2017 Jul; 55: 132-142

2. Londono AC, Castellanos FX, Arbelaez A, **Ruiz A**, Aguirre-Acevedo DC, Richardson AM, Easteal S, Lidbury BA, Arcos-Burgos M, Lopera F. An ^{1}H-MRS framework predicts the onset of Alzheimer's disease symptoms in PSEN1 mutation carriers. **Alzheimer's & Dementia**. 2014; 10(5): 552-61

3. Quiroz YT, Stern CE, Reiman EM, Brickhouse M, **Ruiz A**, Sperling RA, Lopera F, Dickerson BC. Cortical atrophy in presymptomatic Alzheimer's disease presenilin 1 mutation carriers. **J Neurol Neurosurg Psychiatry**. 2013; 84(5): 556-61

4. Quiroz YT, Ally BA, Celone K, McKeever J, **Ruiz-Rizzo AL**, Lopera F, Stern CE, Budson AE. Event related potential markers of brain changes in preclinical familial Alzheimer disease. **Neurol**. 2011 2; 77(5): 469-75

5. Quiroz YT, Budson AE, Celone K, **Ruiz A**, Newmark R, Castrillón G, Lopera F, Stern CE. Hippocampal Hyperactivation in Presymptomatic Familial Alzheimer's Disease. **Annals of Neurol**. 2010; 68(6): 865-75

6. **Ruiz-Rizzo AL**, Tirado V, Moreno C, Aguirre-Acevedo DC, Murillo O, Lopera F. [Comparison of neuropsychological performance according to the age of onset in subjects with Parkinson's disease and Parkinsonism] **Rev Neurol**. 2009; 49(3): 123-30

7. **Ruiz AL**. [Neuropsychological Alterations in patients with Major Depression]. **Acta Neurológica Colombiana**. 2009; 25(2): 75-83

8. **Ruiz-Rizzo AL**, Lopera F. [Explicit memory and major depression] **Iatreia**. 2008; 21(2): 177-85

Professional Experience

Research

2012.11 – 2013.08	Intern, Baby-BRAIN Group. Donders Institute. Radboud Universiteit Nijmegen (Nijmegen, Netherlands)
2008.04 – 2011.08	Assistant, Grupo de Neurociencias de Antioquia, Universidad de Antioquia (Medellín, Colombia)
2007.05 – 2007.11	Intern, Laboratory of Neurosciences, Universidad El Zulia, Alfa Program Studentship from the European Commission (Maracaibo, Venezuela)

Clinical

2009.01 – 2011.08	Neuropsychologist, Grupo de Neurociencias de Antioquia

Teaching

2015.05 – 2016.05	Tutor, Department of Psychology, LMU Munich.
2010.09 – 2011.08	Lecturer, Department of Psychology, Universidad de Antioquia.
2008.01 – 2011.06	Tutor, Faculty of Medicine, Universidad de Antioquia.

Main Awards and Grants

2016	FENS-IBRO/PERC travel grant to attend the FENS Forum 2016 in Copenhagen
2013	Alejandro Ángel Escobar Award in Biological Sciences and Physics for Research of Genetic Alzheimer's Due to E280A Mutation in the presenilin-1 (PS1) Gene in Families of Antioquia: An opportunity to develop preventive therapies
2008	Outstanding Undergraduate Researcher Award. Mayoralty of Medellin
2008	Talent Young Woman on Science and Technology award. Mayoralty of Medellin
2007	Grant for bachelor's research project from the Committee for the Development of Research, University of Antioquia

11. List of publications and manuscripts

1. Ruiz-Rizzo AL, Bublak P, Redel P, Grimmer T, Müller HJ, Sorg C, Finke K. Simultaneous object perception deficits are related to reduced visual processing speed in amnestic mild cognitive impairment. <u>Neurobiology of Aging.</u> 2017 Jul; 55: 132-142

2. Londono AC, Castellanos FX, Arbelaez A, **Ruiz A**, Aguirre-Acevedo DC, Richardson AM, Easteal S, Lidbury BA, Arcos-Burgos M, Lopera F. An 1H-MRS framework predicts the onset of Alzheimer's disease symptoms in PSEN1 mutation carriers. <u>Alzheimer's & Dementia</u>. 2014; 10(5): 552-61

3. Quiroz YT, Stern CE, Reiman EM, Brickhouse M, **Ruiz A**, Sperling RA, Lopera F, Dickerson BC. Cortical atrophy in presymptomatic Alzheimer's disease presenilin 1 mutation carriers. <u>Journal of Neurology, Neurosurgery, and Psychiatry</u>. 2013; 84(5): 556-61

4. Quiroz YT, Ally BA, Celone K, McKeever J, **Ruiz-Rizzo AL**, Lopera F, Stern CE, Budson AE. Event related potential markers of brain changes in preclinical familial Alzheimer disease. <u>Neurology</u>. 2011 2; 77(5): 469-75

5. Quiroz YT, Budson AE, Celone K, **Ruiz A**, Newmark R, Castrillón G, Lopera F, Stern CE. Hippocampal Hyperactivation in Presymptomatic Familial Alzheimer's Disease. <u>Annals of Neurology</u>. 2010; 68(6): 865-75

6. Ruiz-Rizzo AL, Tirado V, Moreno C, Aguirre-Acevedo DC, Murillo O, Lopera F. [Comparison of neuropsychological performance according to the age of onset in subjects with Parkinson's disease and Parkinsonism] <u>Revista de Neurología</u>. 2009; 49(3): 123-30

7. Ruiz AL. [Neuropsychological Alterations in patients with Major Depression]. <u>Acta Neurológica Colombiana</u>. 2009; 25(2): 75-83

8. Ruiz-Rizzo AL, Lopera F. [Explicit memory and major depression] <u>Iatreia</u>. 2008; 21(2): 177-85

9. Ruiz-Rizzo AL, Neitzel J, Müller HJ, Sorg C, Finke K. Distinctive correspondence between separable visual attention functions and intrinsic brain networks. <u>Submitted to Frontiers in Human Neuroscience.</u>

10. Ruiz-Rizzo AL, Sorg C, Müller HJ, Vangkilde S, Finke K. Decreased cingulo-opercular network functional connectivity mediates the impact of aging on visual processing speed. <u>Submitted to NeuroImage.</u>

12. Affidavit / Statutory declaration and statement

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation **Visual Processing Speed in the Aging Brain** selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation **Visual Processing Speed in the Aging Brain** is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, den 27. November 2017   **Adriana Lucía Ruiz Rizzo**

Munich, November 27, 2017   Unterschrift / Signature

13. Declaration of author contributions

Authors Study 1: *Adriana L. Ruiz-Rizzo, Julia Neitzel, Hermann J. Müller, Christian Sorg, Kathrin Finke*

The author of this dissertation is the first author of this manuscript. **A.L.R.R.**, K.F., and C.S. designed the study. J.N. acquired the data. **A.L.R.R.** analyzed the imaging data and drafted the manuscript, the revised manuscript, and the response to reviewers. **A.L.R.R.**, K.F., C.S., H.J.M., and J.N. wrote and revised critically the manuscript before submission as well as the response to reviewers and the revised version of the manuscript.

Authors Study 2: *Adriana L. Ruiz-Rizzo, Hermann J. Müller, Signe Vangkilde, Christian Sorg, Kathrin Finke*

The author of this dissertation is the first author of this manuscript. **A.L.R.R.**, K.F., and C.S. designed the study. **A.L.R.R.** acquired and analyzed the data, and drafted the manuscript. **A.L.R.R.**, K.F., C.S., H.J.M., and S.V. wrote and critically revised the manuscript before submission.

Authors Study 3: *Adriana L. Ruiz-Rizzo, Peter Bublak, Petra Redel, Timo Grimmer, Hermann J. Müller, Christian Sorg, Kathrin Finke*

The author of this dissertation is the first author of this paper. K.F. and P.B. designed the study. P.R. and T.G. recruited the patients and healthy controls and further assessed them. **A.L.R.R.** analyzed the data and drafted the manuscript. **A.L.R.R.**, K.F., P.B., C.S., H.J.M., P.R., and T.G. wrote and critically revised the manuscript before submission.