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Neural correlates of age-related changes in cognitive action control

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"For neuroscientists the brain is the last biological frontier. It is seen as the repository of learning, thinking, deciding, acting, feeling angry, afraid, loving, remembering, forgetting, even consciousness itself."

(From: Can neuroscience change our minds – Hilary and Steve Rose 2016, p. 3)

Zusammenfassung

Der demographische Wandel bedingt ein zunehmendes Interesse am gesunden Altern des Gehirns. Entlang der Lebensspanne ist Letzteres mit Veränderungen kognitiver Performanz in verschiedenen Domänen verknüpft. Es wird u.a. eine altersassoziierte Abnahme kognitiver Handlungskontrolle in vielen Bereichen beobachtet. Bei der Analyse von Handlungskontrollprozessen werden *bottom-up* und *top-down* gerichtete Unterprozesse unterschieden. Bisherige Studien gesunden Alterns zeigten sowohl eine Abnahme als auch eine Zunahme der regionalen Hirnaktivität im höheren Alter. Dies führte zur Entwicklung einer Vielzahl von Theorien altersspezifischer neuronaler Veränderungen und bedingte eine zunehmend integrative Betrachtung dieser Veränderungen entlang der Lebensspanne, u.a. im Kontext dynamischer Prozesse von Neuroplastizität. Die neuronalen Korrelate der altersassoziierten Abnahme der Fähigkeit erfolgreich kognitive Handlungskontrolle auszuüben, sind zu einem großen Teil noch unklar. In unserer funktionellen Magnetresonanztomographie Studie einer populationsbasierten Stichprobe (n=266, 18-85 Jahre) untersuchten wir deshalb die altersbedingten Veränderungen der o.g. Unterprozesse kognitiver Handlungskontrolle mittels Verwendung des räumlichen Stimulus-Reaktions-Kompatibilitäts (SRK) Paradigmas. Dieses umfasst zwei Bedingungen: Unter der kompatiblen Bedingung ist eine ipsilaterale manuelle Reaktion auf den präsentierten Stimulus erforderlich, wohingegen die inkompatible Bedingung eine kontralaterale Reaktion erfordert und somit vor allem *top-down* gerichtete Prozesse kognitiver Handlungskontrolle bedingt. Aufgabenbezogene Performanz (Reaktionszeit und Fehlerrate) wurde ermittelt und in die Analyse der Bildgebungsdaten einbezogen. Alter wurde als Kovariate aufgenommen. Wir führten unsere Studie mit der zugrundeliegenden Hypothese durch, dass sich die altersassoziierte Veränderung der kognitiven Handlungskontrolle auf behavioraler und neuronaler Ebene abbilden lässt. Wir erwarteten, dass sie mit Performanz-bezogenen neuronalen Veränderungen in Verbindung steht und sich in neuronaler Hyperaktivierung äußert. Auf behavioraler Ebene konnten wir eine altersassoziierte Abnahme der kognitiven Handlungskontrolle bestätigen. Auf neuronaler Ebene replizierten wir das generelle mit dem SRK Paradigma assoziierte Netzwerk und identifizierten die neuronalen Korrelate der *bottom-up* und *top-down* gerichteten Prozesse. Innerhalb dieses Netzwerks fanden wir bei der Bearbeitung Inkompatibilitäts-basierter Reaktionskonflikte eine altersassoziierte Hyperaktivierung im bilateralen intraparietalen Sulcus (IPS), superioren parietalen Lappen, Kleinhirn, rechten inferioren frontalen Gyrus, dorsolateralen präfrontalen Cortex (DLPFC), midcingulären Cortex und in der linken anterioren Insel (aIns). Wir stellten heraus, dass schlechtere altersassoziierte Performanz sowohl mit *bottom-up* als auch mit *top-down* gerichteten Prozessen bei der Bearbeitung des SRK Paradigmas in Verbindung steht. Gemäß unserer Hypothesen und Ergebnisse wird die altersassoziierte Abnahme der kognitiven Handlungskontrolle v.a. durch regionale Hyper- und nicht Hypoaktivierung abgebildet. Wir identifizierten aIns, DLPFC und IPS als die entscheidenden neuronalen Korrelate. Die erhöhte Aktivierung der linken aIns spiegelt möglicherweise den altersassoziierten erhöhten Bedarf an Kontrolle und Aufrechterhaltung der Aufgabenanforderungen beim Vorliegen von Inkompatibilität wider. Hyperaktivierung des rechten DLPFC könnte ein Korrelat erfolgreicher Unterdrückung nicht gewünschter Reaktionen bei der Bearbeitung der Aufgabe sein. Die entscheidende Rolle des IPS wird durch eine Alters- und Performanz-assoziierte Hyperaktivität herausgestellt. Unsere Ergebnisse reflektieren somit möglicherweise Schwierigkeiten bei der Überwindung *bottom-up* gerichteter räumlicher Orientierungsprozesse und den Bedarf zusätzlicher kontrollierender Verarbeitungsschritte bei der Auseinandersetzung mit Inkompatibilität, welche mit höherem Alter wahrscheinlicher werden. Unsere Ergebnisse legen einen signifikanten Einfluss des Alters auf kognitive Handlungskontrolle nahe, welcher auf neuronaler Ebene geteilte Varianz mit Performanz-assoziierten Veränderungen aufweist. Die identifizierte regionale Hyperaktivierung ist möglicherweise kompensatorisch für komplementäre Netzwerkveränderungen (v.a. funktionelle Konnektivität). Unsere Ergebnisse unterstützen zudem die Theorie der Neuroplastizität. Außerdem konnten wir eine mögliche altersbedingte Verringerung in der Fähigkeit, semantisches Wissen in aktuelle Aufgabenanforderungen zu integrieren, identifizieren, welche zu der beobachteten altersassoziierten Verschlechterung der Performanz beitragen könnte.

Summary

Demographic change leads to an increasing interest in the healthy aging of the brain. The latter has been associated with changes in different domains of cognitive performance across the lifespan, including an age-related deterioration in various aspects of cognitive action control. Analyzing processes of cognitive action control, *bottom-up* and *top-down* subprocesses can be differentiated. In previous studies of healthy aging both decreases and increases in regional brain activity have been associated with the aging brain, leading to multiple theories on age-specific neural alterations and yielding a shift to a more integrative view on brain changes over the life span, among others in the context of dynamic processes of neuroplasticity. The neural correlates of an age-related decline in successfully exerting cognitive action control are to a large extent still elusive. We investigated age-related changes of the subprocesses of cognitive action control by employing the spatial *stimulus-response compatibility* (SRC) task in a functional magnetic resonance imaging (fMRI) study of a population-based sample (n=266, 18-85 years). The SRC task comprises two conditions: under the compatible condition an ipsilateral manual reaction to the presented stimulus is required, whereas the incompatible condition necessitates a contralateral reaction and thus especially triggers *top-down* directed subprocesses of cognitive action control. Task-related performance (reaction time and error rate) was analyzed on a behavioral level and included in the analysis of the imaging data. Age was included as a covariate. We hypothesized that the influence of age on cognitive action control could be shown on a behavioral and on a neural level and that it is at least partially shared with performance-related effects across the lifespan on the neural level, potentially reflected by neural hyperactivity. On a behavioral level, our findings corroborated an age-related decline in cognitive action control. On a neural level, we replicated the general SRC task network and delineated neural correlates of *bottom-up* and *top-down* processes. Within this network we found age-related hyperactivity in bilateral intraparietal sulcus (IPS), superior parietal lobule, cerebellum, right inferior frontal gyrus, dorsolateral prefrontal cortex (DLPFC), mid-cingulate cortex and left anterior Insula (aIns) when dealing with incompatibility-induced response conflicts. We suggest that worse age-related performance is associated with both *bottom-up* and *top-down* processes when dealing with the SRC task. Based on our data, as hypothesized, age-related decline in cognitive action control is reflected in regional hyperactivity, rather than hypoactivity. We identified aIns, DLPFC and IPS as key neural correlates. Increased activation of left aIns potentially reflects the higher age-related demand for control and task-set maintenance dealing with incompatibility. Hyperactivity in right DLPFC might be a correlate of successful inhibition processes when dealing with the task. The integrational role of the IPS is highlighted by its age- and performance-related hyperactivity. Our findings may reflect difficulties in overriding *bottom-up* driven spatial orientation and the requirement for additional controlled processing steps dealing with incompatibility, which become more likely with age. We suggest a significant influence of age on cognitive action control, which is on a neural level at least partially shared with performance-related effects across lifespan. Regional hyperactivity might be compensatory for complementary network changes (esp. functional connectivity). Our findings moreover support the idea of neuroplasticity. Additionally, we identified a putative age-related decline in the ability to integrate semantic knowledge with current task demands that might contribute to the observed age-related decline in performance.

List of abbreviations

AGE	age
AGEres	residual age
aIns	anterior insula
aMCC	anterior mid-cingulate cortex
BDI-II	Beck Depression Inventory-II
bil	bilateral
BOLD	blood oxygenation level dependent
CNA	cognitive neuroscience of aging
C	compatible condition
CL	compatible left
CR	compatible right
CRUNCH	Compensation-Related Utilization of Neural Circuits Hypothesis
Demtect	Mild Cognitive Impairment and Early Dementia Detection
DLPFC	dorsolateral prefrontal cortex
DMN	default mode network
DMPFC	dorsomedial prefrontal cortex
dPMC	dorsal premotor cortex
EF	executive functions
EPI	echo-planar imaging
ER	error rate
ERC	error rate under the compatible condition
ERIC	error rate under the incompatible condition
ERICE	incompatibility effect on error rate
ERL	error rate for the left response side
ERR	error rate for the right response side
FC	functional connectivity
FEF	frontal eye field
FG	fusiform gyrus
fMRI	functional magnetic resonance imaging
FWE	family wise error
GLM	general linear model
GOLDEN aging	Growing Of Life Differences Explains Normal aging
HAROLD	Hemispheric Asymmetry Reduction in OLDer adults
hIP	human intraparietal sulcus
IC	incompatible condition
ICE	incompatibility effect
ICL	incompatible left
ICR	incompatible right
IFC	inferior frontal cortex
IFG	inferior frontal gyrus
INM	Institute of Neuroscience and Medicine
IPL	inferior parietal lobule
IPS	intraparietal sulcus
ITG	inferior temporal gyrus
JRC	Jülich Research Center
L	left
MCC	mid-cingulate cortex
MFG	middle frontal gyrus
MNI	Montreal Neurological Institute
MOG	middle occipital gyrus
mm³	millimeter³
MRI	magnetic resonance imaging
ms	milliseconds
MTG	middle temporal gyrus
PASA	Posterior-Anterior Shift with Aging
PFC	prefrontal cortex
PMC	premotor cortex
pMCC	posterior mid-cingulate cortex
PPC	posterior parietal cortex
pre-SMA	presupplementary motor area
R	right
RO	rolandic operculum
RT	reaction time
RTC	median RT for correct responses for the compatible condition
RTIC	median RT for correct responses for the incompatible condition
RTICE	incompatibility effect on reaction time
RTICEres	residual RTICE
RTL	median RT for correct responses for the left response side
RTR	median RT for correct responses for the right response side
s	seconds
SD	standard deviation
SFG	superior frontal gyrus
SMA	supplementary motor area
SPL	superior parietal lobule
SPM	Statistical Parametric Mapping
SR	stimulus-response
SRC	stimulus-response compatibility
STAC	Scaffolding Theory of Aging and Cognition
STAC-r	revisited Scaffolding Theory of Aging and Cognition
STN	nucleus subthalamicus
SVC	small volume correction
TPJ	temporoparietal junction
TPN	task-positive network
WM	working memory
VLPFC	ventrolateral aspects of PFC

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1 Introduction in the cognitive neuroscience of aging

Rising life expectancy and inter-individual differences in age-related cognitive performance have increased research interest in the *healthy aging* of the brain. Age-related decrease of cognitive capacity and effectiveness raises questions concerning the underlying neural mechanisms. *Cognitive neuroscience of aging (CNA)* aims at investigating the assumed link between cerebral aging and age-related changes of cognition. Processes of cerebral aging, which are reflected in decreasing activity and connectivity of some brain areas, as well as in augmenting recruitment of other parts are in the focus of current research in the CNA. These varying correlates have led to different theories regarding age-specific neural alterations. The effects of aging on cognition are usually captured with neuropsychological tests assessing frontal functions and experimental paradigms (Cabeza and Dennis, 2012) as well as cognitive performance measures such as the accuracy and the speed of response when performing a task (Korsch et al., 2014; Spreng et al., 2010; Cabeza, 2004). Lately, the focus of research in CNA has shifted from behavioral studies of cognition to neuroimaging studies. In CNA, functional magnetic resonance imaging (fMRI) now is an established brain imaging technology, investigating the regional age-related changes in brain structure and function and their relation to cognition and behavior (see review of Rajah and D'Esposito, 2005).

Decline in cognitive performance has been associated with various cognitive domains (e.g., basic cognitive processes such as processing speed and higher-order cognitive functions such as episodic memory or cognitive control; Lockhart et al. 2014) and brain areas such as the (pre-) frontal cortex (PFC), the parietal lobule and the hippocampus (for reviews see: Reuter-Lorenz and Lustig, 2016; Cabeza and Dennis, 2012; Reuter-Lorenz and Park, 2010; Drag and Bieliauskas, 2010; Salthouse, 2010; Reuter-Lorenz and Cappell, 2008; Proctor et al., 2005; Hedden and Gabrieli, 2004). The aim of our study is to specifically investigate the neural correlates of age-related changes in the domain of cognitive action control.

1.1 Cognitive action control

In the following section we will give a short introduction to the concept of cognitive (action) control and the associated subprocesses, before introducing the task employed in our study and pointing out the relevance and suitability of this task to investigate cognitive control processes.

1.1.1 Dissociating top-down and bottom-up processes

Among the aforementioned cognitive domains showing age-related decline is the *top-down* control over action as a prerequisite to overcome automated response tendencies and therefore to successfully react to a stimulus that is considered as non-intuitive in the context of a specific task. In contrast to *bottom-up* information processing of sensory input via perceptual analysis and converting the information in motor output, top-down processing involves informational flow based on previous knowledge and other cognitive factors, that is from higher to lower centers (Corbetta et al., 2002). The PFC provides the

requested top-down modulation by enhancing processing of relevant and simultaneously suppressing irrelevant information (Drag and Bieliauskas, 2010). The set of associated effortful top-down mental processes, diverse in nature but sharing a common dependency on the heterogeneous PFC, is also referred to as *executive functions (EF)*, executive processing or executive control. EFs require concentration and attention and are essential for dynamic, adaptive behavior in the context of a fast-moving environment (Diamond, 2013). As cognitive processes they support strategic organization when dealing with goal-oriented tasks. They can be described as the ability to successfully control one's actions and adjust previously learned behavior to overarching internally represented and quickly changing goals that have to be tackled and achieved. These control mechanisms are a core component of self-regulation and therefore essential for the preservation of mental and physical health (e.g. Martins et al., 2015; Cieslik et al., 2015b; Diamond, 2013; Miyake and Friedman, 2012; Mischel et al., 2011; Chan et al., 2008; Burgess and Simons, 2005; Miller and Cohen, 2001). They are not considered a unitary construct but further dissociated into subprocesses, both behaviorally as well as neurally (Spreng et al., 2017; Turner and Spreng, 2012; Miyake and Friedman, 2012). Cognitive flexibility (i.e. shifting between mental tasks or sets), the updating and monitoring of working memory (WM), and inhibition of dominant responses (inhibitory and interference control) have for a long time been postulated as the three core EFs (Diamond, 2013; Miyake et al., 2000). Friedman and Miyake (2017; 2012) updated this classification of three types of EFs and now postulate the 'unity/diversity framework' comprising one element that is common for all EFs and two additional specific processes for updating of WM and task switching. The inhibition-specific component is included in the common factor and thus part of the aforementioned EFs. Literature agrees on the fact that all EFs comprise the inhibition of irrelevant information, the coordination of simultaneous action, the manipulation of information within WM and control of episodic memory operations. This is in accordance with the findings that EFs show overlapping but unique signatures on a neural level after being fractioned into different components (Cabeza and Dennis, 2012).

Although not completely interchangeable, the concept of *cognitive control* is closely associated with EFs, especially with inhibition. Cognitive control refers to superordinate functions and processes of adaptability of the cognitive system to specific tasks. When exerting cognitive control, appropriate adjustments in perceptual selection and successful suppression of irrelevant actions, e.g., facing unpredictably changing task demands or overcoming prepotent dominant response tendencies, are crucial. Neural correlates of cognitive control organize the task's subordinate functions (WM, attention, action selection and inhibition). In addition, a representation of the task is encoded and maintained so that thoughts and actions can be aligned with internal goals and behavior can be initiated, coordinated and constantly adjusted (Botvinick and Braver, 2015; Botvinick et al., 2001; Chambers et al., 2009; Derrfuss et al., 2005). Employing cognitive control leads to activation in the prefrontal and fronto-lateral cortex, especially the inferior frontal junction (IFJ), (e.g. Barrett, 2013; Corbetta et al., 2008; Derrfuss et al., 2005; Braver et al., 2002). This prefrontal network shows demand-dependent patterns of activation (Goghari and MacDonald, 2009). Hence, cognitive control is an adequate surrogate for processes of inhibition on a conceptual and neural basis.

In our study we investigate *cognitive control of motor behavior* via a manual task, requiring reaction in form of motor response. Hereafter we will hence refer to processes of *cognitive action control* when investigating the subprocesses of EFs for refining findings of neural age-related correlates of response selection and inhibition processes.

1.1.2 The stimulus-response compatibility task

The spatial *stimulus-response compatibility (SRC)* task is a well-established paradigm to study *cognitive action control*, especially the different components of interference control required during conflict processing. It assesses the aforementioned *bottom-up* and *top-down* processes in motor control and has been used previously for healthy subjects as well as for psychiatric patients (Cieslik et al., 2015b; Cieslik et al., 2010). The SRC task is based on the psychological phenomenon that responses are faster and more accurate when the spatial properties between the stimulus and response are congruent, i.e. spatially compatible (Eimer, 1995; Fitts and Seeger, 1953). This has frequently been shown using the antisaccade task introduced by Hallet in 1978 (e.g. Pierce and McDowell, 2016; Ettinger et al., 2008; Munoz and Everling, 2004) and manual response SRC tasks investigating *cognitive action control* (see Proctor and Reeve, 1990). The performance in the spatial SRC task seems to be driven by two response selection processes and depends on the degree of stimulus-response overlap (Kornblum et al., 1990). The *compatible* (ipsilateral) response to a stimulus is facilitated by a reflexive attention towards the side of the presented stimulus, which leads to a direct response selection (Rubichi et al., 1997; Sheliga et al., 1997). On the other hand, being requested to react to a lateralized stimulus in an *incompatible* fashion (with the contralateral hand) requires additional cognitive control processes that can conceptually be divided into two subprocesses: First, participants have to inhibit the automatically generated ipsilateral response tendency through top-down control as well as reorientate towards the contralateral side. Second, the required incompatible response has to be volitionally initiated (Reuter-Lorenz and Park, 2010; Nee et al., 2007; Munoz and Everling, 2004; Hommel, 1997). Due to the different conditions employed in the task we suggest the SRC task to reflect both, a task with low to medium demand (compatible condition) and with high demands (incompatible condition). This classification will be important for interpreting the results in the context of theories in CNA. The difference between reaction time during the incompatible compared to the compatible condition is defined as the so-called *stimulus-response (SR) - incompatibility costs*.

1.1.3 Studies on stimulus-response incompatibility

The differentiation of subprocesses of cognitive action control with correlates on a behavioral and on a neural level, respectively, has been well established in previous studies using the SRC task (Langner et al., 2015; Cieslik et al., 2010). On the *behavioral* level performance during the incompatible condition correlates with worse performance compared to the compatible one, i.e. with lower response speed and a lower accuracy reflecting the impact of SR-incompatibility on speeded response selection (e.g. Ambrosecchia et al., 2015; Langner et al., 2015; Korsch et al., 2014).

On the *neural* level, correlates involved in these *bottom-up* and *top-down* processes have been identified separately for each subprocess as well as in form of a *general task network*: the bilateral dorsal premotor cortex (dPMC), the medial supplementary motor area (SMA), the right temporoparietal junction (TPJ), the cerebellum and the right caudate nucleus are consistently activated throughout all conditions and might therefore be associated with the general cognitive demands of the SRC task (Cieslik et al., 2010). Solving spatial incompatibility-induced response conflicts leads to an activation of a fronto-parieto-insular network including bilateral anterior insula, intraparietal sulcus (IPS), dPMC, pre-supplementary motor area (pre-SMA), and adjacent mid-cingulate cortex (MCC), as well as right TPJ and right DLPFC (Cieslik et al., 2015b; 2010; Matsumoto et al., 2004; Schumacher et al., 2003; Sylvester et al., 2003).

Proceeding from these established networks, we integrated behavioral performance on the SRC task (*SR-incompatibility costs*) in an fMRI study on this task. FMRI offers a high spatial resolution of neural activity during the SRC task. It non-invasively and indirectly measures brain activity as a change of local blood oxygenation level dependent (BOLD) due to an increased blood flow in a certain brain area (Sala-Llonch et al., 2015; Raichle and Mintun, 2006; Jäncke, 2005). It is an established neuroimaging technique connecting structure and function and allowing individual within-subject as well as group-level between-subjects analysis of brain activity. To pursue our goal of the study, we could hence acquire data of age- and task-related brain activity by including a cross-generational sample.

1.2 Healthy aging

Healthy aging implies cognitive decline with increasing age, which cannot be attributed to pathological processes or clinical pictures (Lockhart et al., 2014). Just as age-related changes in cognition vary inter-individually, so do structural brain phenotypes (Dickie et al., 2013). Before pointing out the influence of healthy aging on the processes of cognitive action control, we shortly give an overview of neural substrates of structural changes in the aging brain.

1.2.1 Age-related changes in structural neuroimaging

The integrity of structure, function and functional connectivity (FC), of the glucose metabolism and of deposition of amyloid are the most prominent neuroimaging markers of age-related changes across the lifespan (Walhovd et al., 2014). Despite the absence of clinically significant impairments, healthy aging goes along with reduced cortical thickness and volume, white matter integrity and dopaminergic activity (Walhovd et al., 2014; Grady, 2008). Although aging shows high inter-individual variability and differences in vulnerability of decline of cognitive domains and the associated neural underpinnings, cross-sectional studies on age-related structural decline lead to replicable and consistent findings. Structural changes in grey and white matter can be found in form of global and regional atrophy (Sowell et al., 2003). Volumetric studies of grey matter point out that the steepest rate of decline can be found in the frontal lobes (esp. PFC), followed by parietal lobes. Temporal areas show less decline and occipital areas almost no loss of volume (Raz, 2004). Investigating white matter degradation delineates a pattern with pronounced anterior dysfunction. Both, declines in frontal grey and white matter show correlations with

decreases in cognitive functions. Significant correlation between deficits in EFs and an atrophic and dysfunctional PFC was confirmed by Gong et al. (2005). Structural changes in the *healthy aging* brain must hence be considered mediating variables contributing to age-related changes in cognitive control (Dennis and Cabeza, 2008; Raz et al., 2007; Cabeza, 2002; see Raz, 2004 for a detailed review).

The significant shrinkage of PFC and hippocampus as well as of the basal ganglia, especially the striatum, and the thalamus compared to other brain areas has to be kept in mind when interpreting our functional neuroimaging data across the lifespan. In combination with amyloid deposition, dopamine receptor depletion and other neurobiological deterioration these neural challenges determine adaptive processes of the brain. Combining structural and functional age-related findings often leads to paradoxical findings, highlighting the importance of the development of models in CNA integrating these multi-modal, often conflicting, results (Reuter-Lorenz and Park, 2010; Dennis and Cabeza, 2008; Cabeza, 2002). Before reviewing these studies, we will give an overview of behavioral and neural findings on *SR-incompatibility* in older age.

1.2.2 Age-related changes in cognitive action control

Previous studies have found an *age-related* increase in reaction time and error rate on a *behavioral* level after confrontation with incompatible top-down-controlled processes (Proctor et al., 2005). The increases in *spatial SR-incompatibility costs* were independent of global age-related slowing of cognitive processing speed and of other potential mediator variables (performance accuracy, motor speed, speeded visuomotor coordination and cognitive flexibility) (e.g. Langner et al., 2015; Grandjean and Collette, 2011; also see review of Proctor et al., 2005). These behavioral findings suggest a selective, age-related deficit in overcoming spatial *SR-incompatibility*, i.e. in cognitive action – particularly interference – control.

Martins et al. (2015) refer to the *reduced-inhibition hypothesis* by Hasher and Zacks (1988) emphasizing that older adults seem to be more distractible during tasks, which is interpreted as an age-related decline in the ability to inhibit irrelevant information due to WM overload. This hypothesis has been confirmed in various studies (for a recent review see Weeks and Hasher, 2014) and has been updated by including mediating factors (Reuter-Lorenz and Lustig, 2017). It has also been shown that the down-regulation and suppression of excessive, non-relevant activation as required by the SRC task is strongly altered with advancing age (Weeks and Hasher, 2014). Due to age-related deficits in modulation via prefrontal areas, neural noise can arise and cause less discriminant networks with older adults being prone to respond to similar, non-target stimuli (Drag and Bieliauskas, 2010). Interference control, i.e. the ability to differentiate between task-relevant and -irrelevant information, seems to be crucial when investigating age-specific alterations in cognitive performance, as impairment in this skill negatively interacts with further cognitive deficiencies such as WM (cf. Hasher and Zacks, 1988) that naturally emerge with advancing age (Korsch et al., 2014).

The aforementioned *top-down* and *bottom-up* subprocesses all show significant and distinctive neural age-related effects and appear to be implemented differently in the aging brain (Turner and Spreng, 2012; Cabeza and Dennis, 2012). Successful inhibitory control and its *neural* correlates have been studied extensively, especially for the group of younger adults (Buchsbaum et al., 2005), yielding findings in ventral and dorsal PFC with its subregions, pre-SMA, parietal areas, subthalamic nuclei (STN) and cerebellum (see reviews, e.g. Chikazoe, 2010; Chambers et al., 2009; Derrfuss et al., 2005). Testing for subcomponents of conflict processing such as action withholding, interference inhibition and action cancellation lead to both de- and increases in the *core inhibition network* (including the inferior frontal gyrus (IFG), right middle frontal gyrus (MFG), pre- SMA and basal ganglia cf. e.g. Jahfari et al., 2011; Swick et al., 2011; Sebastian et al., 2013a; Sebastian et al., 2013b). Incompatibility-related regional, especially frontal and parietal, *hyperactivity* in older compared to younger participants performing a task of response regulation other than the SRC task was reported by various imaging studies (e.g. Spreng et al., 2010; Zysset et al., 2007; Lee et al., 2006; Langenecker et al., 2004; Milham et al., 2002). These findings suggest that the identified age-related behavioral differences are also reflected on a neural level with hyper- or additional activity especially in prefrontal regions being a correlate of age-specific processing of response conflicts. Contrary, a *decrease* in (prefrontal) activity accounting for a decline in performance is also supported by previous findings in literature, potentially reflecting a reduced level of functioning (e.g. Martins et al., 2015; Spreng et al., 2010; Grady, 2008; reviews: Rajah and D'Esposito, 2005; Cabeza, 2002).

Based on *behavioral and neuroimaging* data, Korsch et al. (2014) postulated distinctive effects of aging on different conflict types (e.g., SRC vs. Stroop task), instead of a general age-dependent deterioration of interference control. They hypothesize differences in qualitative SRC processing between young and elderly subjects, with the latter using different strategies in dealing with interfering information. Lustig and Jantz (2015) also stress the task-dependence of age-related differences in interference and the relevance of these differences for the prevalence of behavioral relative to neural correlates of reduced cognitive control and increased inference as well as for the (compensatory) mechanisms employed. Hence, neural age-related effects and neurofunctional reorganization seem not only to differ between the EFs (e.g. Turner and Spreng, 2012), but also between nature and complexity of the task employed (Lustig and Jantz, 2015; Martins et al., 2015; Grady et al., 2006). This suggests an interference of ageing with subcomponents of conflict processing (such as action withholding, interference inhibition and action cancellation) rather than with conflict resolution in general, leading to a refinement of theories of cognitive aging (Sebastian et al., 2013a).

However, specification of neural correlates of the aforementioned subprocesses of response selection in *cognitive action control* in older age has not yet been accomplished to a differentiated and sufficient extent. In our study we thus use the spatial SRC task to identify the subprocesses specifically affected by healthy aging.

1.3 Review of models in cognitive neuroscience of aging

Sala-Llonch et al. (2015) point out the current shift in CNA from postulating and interpreting isolated findings of age-related changes in activity to a more integrative view on the changes in the healthy aging brain. This trend is captured by the description of the aging of the brain as a complex process of interrelated behavioral and neurobiological changes, continuously evolving over the life span (Gutchess, 2014). Having this in mind, the established classical theories and models of CNA will shortly be characterized before presenting and interpreting our results in the light of the state of research.

1.3.1 Age-related neural activity

Generally, based on functional neuroimaging studies, both decreases and increases in brain activity have been associated with the healthy aging brain, yielding a complex pattern of changes. The former are typically considered a correlate of general neural decline and are localized heterogeneously in the brain. Increases have largely been found in prefrontal areas, are linked to various theories and are in their respective context interpreted differently. Thus, the varying quality of activity as well as the interpretation of the various findings concerning neural correlates of general and task-specific aging and the incorporation of life-course influence and neuroimaging markers is the major challenge of CNA (Sala-Llonch et al., 2015; Rajah and D'Esposito, 2005; Cabeza, 2002).

Two opposing views dominate the field of CNA when interpreting the aforementioned complex patterns of age-related changes in neural activity and brain structure. The *compensatory approach* (Reuter-Lorenz and Cappell, 2008; Grady, 2008; Buckner, 2005; Cabeza, 2002) is a common interpretation of additional age-related activation – typically found in the PFC – and the basis of various theories in CNA. The contrary view is the concept of *dysfunctional dedifferentiation* (Goh, 2011; Cabeza, 2002; Park et al., 2001), according to which increased activation instead reflects deficits in transmission and processing leading to reduced functional specialization in the regions engaged in the task, a generalized – potentially compensatory – age-related spreading of activity and finally resulting in poorer performance. This reduced specificity of processes can also be reflected by decreases in activation (Lustig et al., 2007; Rajah and D'Esposito, 2005; Li et al., 2001). Perspectives of compensation as well as of dedifferentiation assume the existence of neural changes leading to deficient functions, with the compensatory approach being imprecise about the nature of those deficits. The dedifferentiation theory postulates deficits in dopaminergic neurotransmission as the basis of noisy internal cortical representations, hence preventing distinctive cortical representations and leading to deficits in functioning (Li et al., 2001). In the context of this theory, age-related increases of activity in PFC can be, but are not always, compensatory, as they may also cause unnecessary activity not beneficial for the task performance.

1.3.2 Cognitive models of compensation

Observed *compensation-related mechanisms* with typical patterns lead to the development of main cognitive

models. In general, they are all based on the observation of age-related hyperactivity in some brain areas to compensate for deficits in function in another brain region (Sala-Llonch et al., 2015).

Looking closer at the potentially compensatory increases in PFC, Cabeza (2002) established a bilateral pattern called the *Hemispheric Asymmetry Reduction in OLDer adults* (*HAROLD*) caused by decreased laterality effects in brain regions such as the PFC in older compared to younger adults. The latter usually show association of increased activity of the right PFC with inhibitory control. Compensating for reduced activity in this control region, older adults typically recruit additional brain regions such as the contralateral PFC (Garavan et al., 1999). This theory is well-established for prefrontal activity during WM tasks (Cabeza, 2002).

In the context of the HAROLD theory, Rajah and D'Esposito (2005) criticize the lack of differentiation of the effects of lateralization regarding the subregions of the PFC and of the potential underlying neural phenomena leading to the observed effects. Those again could be compensatory of nature, but also be based on dedifferentiation of function, primary deficits in function or a combination of all three. In order to account for the complexity of age-related neural changes, the authors performed a region-specific analysis of the subregions of the PFC. Based on this data they developed a model of aging, stating that neural degeneration in older age leads to dedifferentiation in the ventral PFC bilaterally and to deficits in function in the right dorsal and anterior PFC, with all these changes leading to functional compensation in left dorsal and anterior PFC (Rajah and D'Esposito, 2005). Simultaneously, findings in other studies comprise shared activity between young and old as a correlate of inhibitory control and greater and more bilateral age-related recruitment of ventro- and dorsolateral aspects of PFC (VLPFC and DLPFC) and parietal areas (Turner and Spreng, 2012; Mathis et al., 2009). The increase in activity with a rising conflict level of the tasks employed potentially reflects an age-related lack of cortical sensitivity and flexibility when facing higher demands (Prakash et al., 2009).

In addition to the HAROLD theory, the *Posterior-Anterior Shift with Aging (PASA)* (Grady et al., 1994) is another established and experimentally examined theory, as age-related PFC activity is consistently associated with a decrease of occipital activity across tasks. PASA is considered to be representative of functional compensation, as performance measures showed a positive correlation with the increase in frontal activity and a negative correlation with the occipital decrease in older age. Additionally, aging correlated with increased activation in parietal areas and led to reduced deactivations in the posterior midline cortex, but an increase of deactivation in the medial frontal cortex, making the PASA pattern generalizable (Davis et al., 2008).

As mentioned before, neuroimaging tasks of EFs typically show a strong bilateral pattern of activation in the (DL)PFC which is pronounced in older age (Turner and Spreng, 2012; Townsend et al., 2006; Raz et al., 2005). The increased activation in the task networks and the recruitment of those additional (e.g., prefrontal or contralateral) brain areas is a typical age-related finding that has historically been interpreted as compensatory for reduced age-related *FC* (see reviews, e.g. Park and Reuter-Lorenz, 2009; Dennis and

Cabeza, 2008; Cabeza, 2002). Investigating neural task networks, interregional *FC,* i.e. the correlation among the activity time course of regions involved in the task, reflects adaptive processes of communication between the nodes of the network. Both sufficient regional activation and inter-regional communication are pivotal for the functioning of the network (Jockwitz et al., 2017; Langner et al., 2015; Ferreira and Busatto, 2013). Langner et al. (2015) comment in their study of intrinsic interregional coupling on the potential bilateral interplay between changes in regional brain activation as mentioned before and the changes in FC investigated in their study. They postulate a multidimensional view concerning the relationship between brain and behavior in maintaining cognitive control, as changes in FC might be both, neural substrates constituting the necessity of *compensatory* increase in brain response (Turner and Spreng, 2012) and also *compensatory* themselves for brain areas of reduced or dedifferentiated function. The former aspect is supported by several resting-state studies suggesting age-related dedifferentiation in the form of overall increased inter-network connectivity in older compared to younger adults (Geerligs et al., 2015; Chan et al., 2014). Reduced FC in task networks such as the so-called task-negative default mode network (DMN, Schilbach et al., 2012; Buckner et al., 2008; Greicius et al., 2003) and the dorsal attention network (Corbetta et al., 2008), was reported consistently for older adults (e.g. Tomasi and Volkow, 2012; Damoiseaux et al., 2008; Andrews-Hanna et al., 2007), but could not be confirmed by (Jockwitz et al., 2017) in a recent study. The latter aspect of a potentially compensatory function of FC is challenged by heterogeneity in investigating age-related changes in FC in task-positive networks. Increases in FC in older age have been reported (Filippini et al., 2012) as well as decreases (Sala-Llonch et al., 2015; Geerligs et al., 2015). The study of Andrews-Hanna et al. (2007) specifically addresses the association of reduced FC and cognitive decline (EF and memory), correlating decreases in functional and structural connectivity. They assume a preferred disruption of higher-order systems (e.g., attention control) while preserving lower-order sensory systems across the lifespan leading to the observed diversity in age-related cognitive performance and findings in FC.

Cabeza and Dennis (2012) try to clarify the mostly vague and debatable term of compensation that is used to combine the paradoxical findings in CNA of significant decline in structure and function documented in the aging PFC and also confirmed age-related increase of FC in this area. Thus they developed an *age-related compensation model* and criteria defining 'attempted' as well as 'successful' compensation as a prerequisite for using this term. They found the HAROLD model to be linked to both, 'attempted' and 'successful' compensation. The former implies the recruitment of additional neural resources by older adults in order to compensate for mismatching resources in processing and demands of the task. When this leads to an effect in form of an improvement in cognitive performance, 'successful' compensation takes place. For the PASA hypothesis the findings indicated that the over recruitment of PFC was especially necessary for the older adults that showed the weakest occipital recruitment in order to sustain their performance. Including age-related changes of FC in their analysis, the authors could confirm both an posterior-anterior pattern consistent with the PASA model and a cross-hemispheric pattern in line with the HAROLD model. For all examined compensatory patterns (HAROLD, PASA and FC) the postulated definition criteria could be confirmed and supported.

1.3.3 Cognitive models of neuroplasticity

Over the lifespan cognitive performance first improves, than declines (Turner and Spreng, 2012). Longitudinal data of age-related changes in cognition show that after the age of 55 cognitive decline is evident across all domains, with processing speed decreasing even before the age of 55 (Salthouse, 2011; Schaie and Willis, 2010; Hedden and Gabrieli, 2004). Great variance in age-related changes on a cognitive and on a cerebral level has been pointed out frequently and partly been explained by processes of *neuroplasticity* leading to age-related step-wise functional reorganization of the brain (Goh and Park, 2009). Individual differences are included in novel models in the form of a so-called reserve or capacity (Lockhart et al., 2014). The functional model of inter-individual *cognitive reserve,* i.e. the ability to optimize or maximize neural performance by means of neural reserve or neural compensation, helps to explain task performance diverging from neural status (Stern, 2009).

The dynamic reorganizational processes of neuroplasticity seem not only to adjust across the lifespan but also to change in their activation patterns, depending in particular on the task demands (Sebastian et al., 2013a). The *Compensation-Related Utilization of Neural Circuits Hypothesis* (*CRUNCH)* (Reuter-Lorenz and Cappell, 2008) captures the observation that people – also in younger age – activate more cortical regions with increasing task load i.e. cognitive demand, until they have completely utilized their WM capacity. As the demand for inhibition exceeds the WM capacity, compensatory effects may arise due to a decline in the network, reflected by a reduced behavioral and neural performance (Sebastian et al., 2013a). Due to brain atrophy, older individuals might reach the limit of their neural resources at a lower level of demand, leading to plateauing brain activity or the aforementioned decrease in activity with increasing task difficulty. This theory is best established for prefrontal and parietal areas and when performing memory tasks. In his model of *Growing Of Life Differences Explains Normal aging (GOLDEN aging),* Fabiani (2012) postulates a shift of mental abilities across the lifespan, especially reflected by the aforementioned decrease in inhibitory functioning and thus of WM capacity of older adults (cf. reduced-inhibition hypothesis, Hasher and Zacks, 1988). As the scope of WM capacity varies inter-individually and over the lifespan, the additional recruitment of cognitive resources and thus increased brain activity is necessary in all situations where WM capacity is reached by high information load that needs to be processed in order to maintain the cognitive level (CRUNCH).

The idea of demand-dependent patterns of activation helps to integrate findings that on the first glance are counterintuitive, i.e. increases as well as decreases in the neural network of inhibition across the lifespan, especially in (right) prefrontal areas (Reuter-Lorenz and Lustig, 2017). If the requirements of a task are low to medium, the core and expanded inhibitory network would show hyperactivations, whereas high response complexity would go along with hypoactivations (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008). Still, there is a substantial number of older adults with a remarkable cognitive performance, who somehow manage to compensate for 'pathological' changes that are present in their cases as well as confirmed by their autopsies post mortem (Mitchell et al., 2002).

The *Scaffolding Theory of Aging and Cognition (STAC)* helps to integrate findings of substantial age-related neurobiological changes, such as decline in brain size and integrity of white matter, with widely preserved function and cognitive performance and even observed increased (prefrontal) activation. In this theory, the latter is seen as a continuous compensatory correlate – a process of scaffolding – of an adaptive brain, reacting to the aforementioned declines of activation and structure in various brain areas, strengthening their inefficient functioning. Scaffolding itself is a dynamic protective mechanism of neural plasticity, used to accomplish cognitive goals and facing cognitive challenges by developing alternative neural circuits across the lifespan and might even be strengthened by cognitive exercise. Due to its association with the cognitive tasks it is primarily related to the PFC (Reuter-Lorenz and Lustig, 2017; Park and Reuter-Lorenz, 2009).

The STAC model has been updated to account for longitudinal data. The *revisited STAC model (STAC-r)* is complemented by life-course factors that in combination with the life-span approach of the STAC theory refine the understanding of cognitive status and cognitive change over time. Those are factors of neural resource enrichment (enhancing and protective factors such as e.g., engagement in social and intellectual activities) and depletion (negative influences such as e.g., stress, depression or vascular disease), both supposed to influence the development of brain structure and function and thus of cognition across the lifespan (Reuter-Lorenz and Park, 2014). For the sake of completeness and due to its obvious parallels to STAC-r, concepts of *brain and cognitive reserve* should shortly be mentioned. Both forms could similarly to neural resource be influenced by the enriching and depleting factors included in the model. Due to this interplay, scaffolding could be considered a neural correlate of cognitive reserves, which are related to overall cognitive ability through its processes and strategies (Reuter-Lorenz and Park, 2014; Stern, 2012).

Distinguishing correlates of healthy aging from those of pathological changes is one of the challenges of CNA, but one which has been addressed more and more in the last years via including and integrating findings from neuroimaging and longitudinal studies (Hedden and Gabrieli, 2004). The latter led to a new hypothesis of 'brain maintenance' implying that the minimization of brain changes of any kind (chemical, structural and functional) best predicts the preservation of successful performance in older age. It was shown that people who lacked these changes showed little to no age-related cognitive decline (Nyberg et al., 2012). Nevertheless, cognitive losses, though showing high variability, are present in older age suggesting the existence of brain harming factors. Walhovd et al. (2014) conceive the age-associated cognitive decline as the result of a life-long multidimensional process. They propose that the accumulation of harming factors across the lifespan changes the brain in its structure and function with some regions (e.g., hippocampus) being especially vulnerable to these processes.

These dynamic theories, addressing effects of neuroplasticity and integrating neurobiological and behavioral findings, to date are the best approach in the attempt to define cognitive function in aging (Sala-Llonch et al., 2015; Reuter-Lorenz and Lustig, 2017). The diversity of established theories reflects the complexity of the underlying neural processes in CNA, the dynamic of research in this field due to a constantly increasing knowledge in neurobiology to be included in the analysis and the resulting

interpretative challenge. Finally, this integrative view opens up possibilities of intervening with processes of (healthy) aging and potentially influencing and training the aging brain.

1.4 Aim of our study

In line with the current state of research in CNA we assumed that the influence of age on cognitive action control is at least partially shared with performance-related effects across lifespan. We postulated that age-related influence on cognitive action control can be differentiated from other behavioral performance measures less dependent on cognitive action control. Hence, we included the behavioral incompatibility-costs as well as age as covariates in our analysis. Combining a behavioral and neural analysis the purpose of research was thus to identify and examine areas that change in their task-related activity with an increase in age and therefore can be specifically correlated with the observed age-dependent decline in cognitive action control. In line with previous findings in cognitive aging, we expected age-related effects specific to task and cognitive subcomponent during incompatibility-induced response conflicts. In order to extend and elaborate the current state of research in CNA, we pursued several *goals* in our study:

1) The first goal was to replicate and confirm previously shown increased *behavioral SR-incompatibility costs* including age-related changes of these costs in a substantially larger sample.

2) On a neural level we aimed at replicating the findings of a *general task (SRC)* and an *SR-incompatibility-related network* as described in previous literature and of *bottom-up* and *top-down subprocesses* employed during the SRC task.

3) After confirming *age-related* increases in spatial SR-incompatibility costs on a behavioral level and corroborating the aforementioned SRC network based on our data, we specifically investigated *neural correlates* of these age-related phenomena in the identified areas of the network. In order to delineate the different *subprocesses of cognitive action control* and their neural correlates in advanced age, we included the SRC paradigm in a behavioral and an fMRI analysis of a large population-based sample.

In summary, we aimed at examining the effect of healthy aging on overcoming incompatibility-induced response conflicts at a neural level. Based on current state of research in CNA and on SR-incompatibility we formulated and tested the following *hypotheses*:

1) *Age*-related influence on cognitive action control can be shown on a *behavioral* and on a *neural* level.
2) On a *neural* level, age-related differences are reflected in neural *hyper*- rather than *hypoactivity*.
3) By integrating and evaluating our findings in the context of established models of CNA, we can contribute to the *refinement* of a multidimensional view on the relationship of cognitive and cerebral aging.

2 Materials and Methods

2.1 Participants

Recruitment took place based on the pool of subjects of the neuroscientific population-based 1000BRAINS project. This project is conducted at the Institute of Neuroscience and Medicine (INM) at the Jülich Research Center (JRC), Germany (http://www.fz-juelich.de/inm/inm-1/DE/Forschung/1000_Gehirne_Studie/1000_Gehirne_Studie_node.html) and affiliated to the follow-up cohort of the longitudinal epidemiological Heinz Nixdorf Recall Study of risk factors for atherosclerosis, cardiovascular disease, cardiac infarction and death of the University Duisburg-Essen, Germany (Schmermund et al., 2002). Of our initial sample of 302 subjects, 291 were part of the 1000BRAINS study and 11 additional subjects were recruited via advertisement. Prior to inclusion all subjects gave informed written consent to the procedures and study protocol that had been approved by the health care ethics committee of the University Duisburg-Essen (reference number: 11-4678). The usage of the data of the 1000BRAINS project for our analysis of the brain function additionally was approved by the ethics committee of the University Düsseldorf (reference number: 5193).

From our initial sample complete fMRI datasets were available for n=297 subjects. Of these subjects, another 31 were excluded from the final analysis due to: (i) quality control and methodological problems during fMRI preprocessing, e.g., excessive head movements, anatomic conspicuities or failed normalization (n=12) or (ii) adjustment for behavioral performance, e.g., excessive ERs or RTs (n=19), resulting in a final sample of 266 subjects (see Table 1) with normal or corrected-to-normal vision (age range 18 to 85; mean age: 52.38 years ± 16.6; 120 females). Of our subjects 62 were left- and 204 right-handed as assessed by the Edinburgh Handedness Inventory with a cut-off of 70 (Oldfield, 1971). The subjects were drawn from a population-based sample, so that the presence of neurological or psychiatric diseases such as depression was not an exclusion criterion. As healthy aging in old subjects refers to the absence of neurodegenerative diseases, dementia was assessed and excluded via Mild Cognitive Impairment and Early Dementia Detection (Demtect) (Kalbe et al., 2004). A complete Demtect assessment was available for 252 subjects. In this test, all 252 subjects scored 9 points or more, so that dementia (defined by a test score of 0 - 8 points) according to the Demtect could be excluded. 219 of these 252 subjects scored 13 to 18 points corresponding with an appropriate cognitive power for their age. The remaining 33 subjects scored between 9 and 12 points and thus showed signs of a mild cognitive impairment. 3 of these subjects scored exactly 9 points, another 3 scored 10 points, 8 scored 11 points and the majority of 19 subjects scored exactly 12 points.

Self-assessment via Beck Depression Inventory-II (BDI I-II, Beck et al., 1996) was used to evaluate depression and was answered by 257 subjects. Of these, 241 subjects were not exhibiting relevant symptoms for depression as they scored less than 13 points in the BDI-II. Of the residual 16 subjects 12 scored between 14 and 19 points (corresponding with mild depressive symptoms), 2 between 20 and 28 (moderate symptoms) and 2 more than 29 points (severe depressive symptoms). The BDI-II score

showed a significant correlation with age of 0.063. This correlation is negligible as it is distinctly below the lower bound of a "small effect size" of r=0.1 (Cohen, 1992).

Table 1: Sample characteristics (n=266).

Age	Mean ± SD Median Range	52.38 years ± 16,6 56.00 years 18 – 85 years
Sex	Females Males	120 (45.1 %) 146 (54.9 %)
Handedness	Right-handed Left-handed	204 (76.7%) 62 (23.3%)
Demtect and BDI	Demtect: Mean ± SD BDI-II: Mean ± SD	15.42 ± 2.41 4.62 ± 5.36

Note: SD: standard deviation; %: percent; Demtect: Mild Cognitive Impairment and Early Dementia Detection; BDI-II: Beck Depression Inventory-II.

2.2 Experimental protocol

Our fMRI experiment was part of the study protocol of the 1000BRAINS project as described in the design paper of Caspers et al. (2014). The project was designed to investigate the variability of brain structure and function in the course of aging by taking into account various factors of influence. The study protocol thus comprised neuropsychological and motoric performance tests, as well as analysis of genetic data, laboratory parameters and multiple questionnaires before and after scanning. Recorded cranial magnetic resonance imaging (MRI) data included 3D-T1, 3D-T2, fluid attenuated inversion recovery, MR-Angiography, diffusion tensor imaging, Resting State MRI and the task-based fMRI session. All participants were placed comfortably in the scanner and equipped with a head coil with a mirror reflecting the screen behind the scanner which was displaying the SRC paradigm. Participants were instructed to respond as fast and correctly as possible to a briefly presented (200 milliseconds (ms)) lateralized stimulus (blue dot on a black ground) by button press. Presentation of stimuli consisted of two experimental conditions: the *compatible condition (C)* required a reaction to the occurrence of the lateralized stimulus with the matching, ipsilateral index finger, whereas the participants had to press with the contralateral index finger under the *incompatible condition (IC)*. This yielded four outcomes: Pressing with the left (L) index finger to a left-sided stimulus (*CL*, with *L and R referring to the respective stimulus side*) and the right *(CR)* index finger to a right-sided stimulus under the compatible condition and pressing with the right index finger to a left-sided stimulus *(ICL)* and the left index finger to a right-sided stimulus *(ICR)* for the incompatible condition (Fig. 1). To register the reaction to the stimuli both index fingers were positioned on MR-compatible response pads (LUMITouch Photon Control Inc.). The visual stimuli were

presented using the presentation software (version 18.1, https://neurobs.com/) on a computer with Microsoft Windows 7 Professional operating system (Intel® Core ™i7-2600). The experimental task was presented in 24 blocks, which were periodically alternated with rest periods ('baseline') of 15 to 19 seconds (s) (uniformly jittered). Each condition (C and IC) was thus presented in twelve individual blocks in the course of the whole experiment in a pseudo-randomized order and counterbalanced across all subjects. At the beginning of each task block an instruction was presented for 2 s stating which of the two experimental conditions (ipsi- or contralateral response) was required in the upcoming block. Each block included 13 to 16 randomized events (with 50% left-sided and 50% right-sided stimuli) allowing statistical separation of events entailing left- and right-sided stimuli and thus the analysis of side-specific neuronal responses in both experimental conditions (CL, CR, ICL, ICR) and ensuring that no anticipation effects (e.g. shorter RTs) could occur. Uniform jittering of the inter-stimulus interval determined intervals of 2 to 4.5 s within the block, triggering response readiness (Goghari and MacDonald, 2009). In sum, the fMRI experiment was conducted in a mixed design: task instructions (compatible and incompatible) were presented in blocks, image acquisition after stimulus presentation of left and right was event-related.

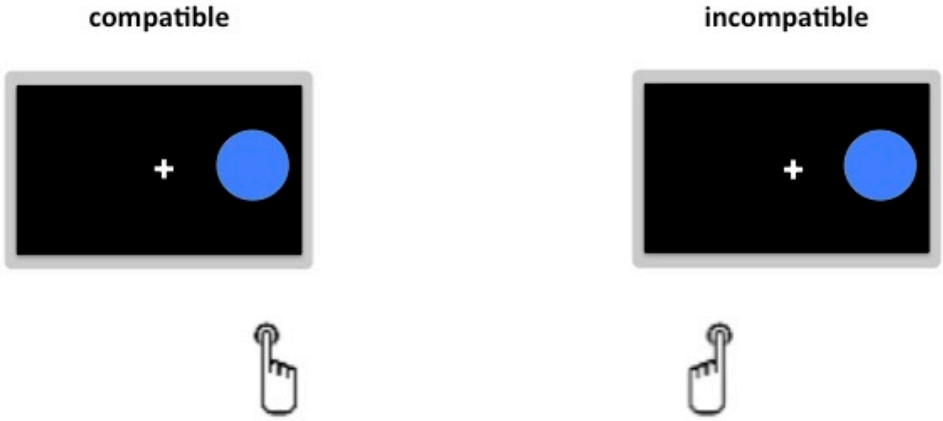

Fig. 1: Schematic illustration of the stimulus-response compatibility (SRC) paradigm. Performing the SRC task, participants were instructed to respond to a lateralized stimulus: the *compatible (C) condition* required a reaction to the lateralized stimulus with the matching, ipsilateral hand, whereas the participants had to press with the contralateral finger in order to fulfill the *incompatible (IC) condition*; own representation, based on the experiment of Fitts and Seeger (1953).

2.3 Functional magnetic resonance imaging

Image acquisition took place on a whole-body 3T Siemens Trio Tim MR scanner (Jülich, Germany) using gradient-echo echo-planar imaging (EPI) sequence to record BOLD contrast (33 axial slices, slice thickness 3.3 mm, distance factor 20%, bandwidth 2232 Hertz/Pixel, echo spacing 0.51 ms, repetition time 2,030 ms, echo time 30 ms, acquisition time 27:10, voxel resolution 3.1 x 3.1 x 3.3 millimeter^3 (mm^3), flip angle 80°, field of view read 200 mm) covering the whole brain. Four dummy images preceded the actual acquisition to allow for magnetic field saturation and were discarded before further processing (McRobbie et al., 2017). Analysis of the images was performed using Statistical Parametric Mapping (,) (Version 8, Wellcome Trust Center for Neuroimaging London, www.fil.ion.ucl.ac.uk/spm). Preprocessing

of the EPI images included head movement correction (translation and rotation) via realignment to the first image and subsequently to the mean of the realigned images, spatial normalization to the Montreal Neurological Institute (MNI) single-subject template by 'unified segmentation' (Ashburner and Friston, 2005), resampling at 2 x 2 x 2 mm^3 voxel size and smoothing of the normalized images using an 8 mm full width at half minimum Gaussian kernel, in order to accomplish the requirements of the general linear model (GLM) and to compromise residual anatomical variation (e.g. Windischberger et al., 2011; Kiebel et al., 2007; see Fig.2). The quality of these preprocessed images was individually and manually checked via SPM by two independent and experienced researchers.

2.4 Statistical analysis

2.4.1 Behavioral data

Subjects' behavioral performance, specifically reaction time (RT) and error rate (ER) during the fMRI experiments, was analyzed via MATLAB (The Math Works, Natick, MA) and IBM SPSS Statistics (version 23). RT was assessed by computing the intra-individual mean and median RT for correct responses for the compatible (C) and incompatible (IC) condition (RTC and RTIC) and the left and right response side (RTL and RTR) separately. ER, given as percentage of erroneous responses, was used as the measure of accuracy, also for each condition (ERC and ERIC) and side (ERL and ERR). The *incompatibility effect* (ICE) of RT, i.e. the incompatibility costs for each participant, was calculated as the difference between the median RT of the incompatible and compatible condition ($RTICE = RTIC - RTC$), the ICE of ER respectively ($ERICE = ERIC - ERC$). For further analysis we applied arcsine transformation to the ERs ($ER^{ARCSINE} = 2 * SIN^{-1} [\sqrt{(ER /100)}]$, see Cohen et al. 2003). The moving average over the whole sample was calculated for RTICE and RTC and compared to the respective z-statistic (transformation in the scale of the normal distribution; $z = (data_i - mean(data_i))/std(data_i)$) leading to the performance based exclusion of participants deviating more than three standard deviations from the respective average. Subjects with a mean ER or ERC over 30 % were also excluded. RTs under 150 ms or higher than 1,500 ms were classified as anticipation errors and missing response and discarded from the following analysis. Effects of incompatibility and age (covariates) on performance were then tested via ANCOVA in SPSS. For the subsequent fMRI analysis we considered the influence of the covariates RTICE and age (AGE) separately by excluding their shared variance. We thus generated two new variables by partialling out RTICE from AGE via linear regression yielding the residual AGE (variable AGEres) and vice versa, yielding the residual RTICE (variable RTICEres) after accounting for AGE. In sum, we included two separate sets of our covariates: AGE and RTICEres; RTICE and AGEres.

2.4.2 Imaging data

The fMRI data were analyzed using the GLM as implemented in SPM 8 (SPM, 2018c https://www.fil.ion.ucl.ac.uk/spm/software/spm8/, see Fig.2). Two different models, each including the whole sample of 266 subjects, were created comprising different aspects of the underlying hypothesis and will be characterized in the following section. The observed change in the BOLD signal was included as the dependent variable. In the first level analysis the experimental events of interest, i.e. individual trials separated per condition and per stimulus side were modeled using epochs of 200 ms from stimulus onset denoting the main and side specific task regressors (experimental trials: C, IC, CL, CR, ICL, ICR). The RT regressors were calculated as the intra-individual median RT per condition and side (RTC, RTIC, RTL, RTR) and also included in the design matrix. The regressor of the main ICE on RT was calculated by contrasting RTIC and RTC for each subject. All regressors were defined by delta functions convolved with a canonical hemodynamic response function and their first order temporal derivative. Trial-wise RTs were also incorporated as a parametric modulator into the four task regressors for excluding any variance that might be explained by RT between trials in each subject. A cut-off period of 128 s was used in order to filter low-frequency signal drifts. First-level single-subject parameter estimation was performed for computing simple main effects for each experimental condition per subject by applying appropriate baseline contrasts and no global scaling (cf. Fig. 2). Therefore parameter estimates were calculated for each voxel by means of weighted least squares in order to obtain maximum likelihood estimators (Kiebel et al., 2007). Error trials and six motion parameters containing movement parameters obtained during realignment were included as regressors of no interest in the design matrix.

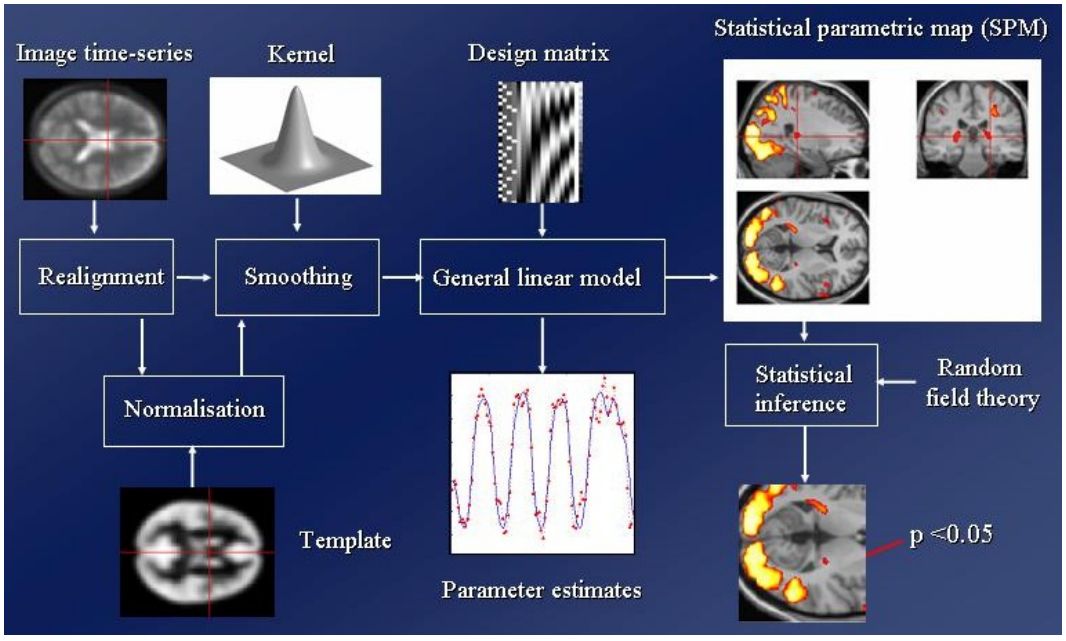

Fig. 2: **Graphical illustration and structure of the analysis of fMRI data: spatial preprocessing, modeling and statistical testing**, from: Friston, Karl (2011): Introduction to SPM Wellcome Trust Centre for Neuroimaging, University College London, http://www.scholarpedia.org/article/File:Analysis.jpg, Copyright © 1991, 1994-2017, The FIL Methods group.

The individual first-level contrasts were subsequently fed to a second-level group ANCOVA using a random-effects model to test the effects of incompatibility, age (AGE) and performance (i.e. RT incompatibility costs, RTICE) on brain activity. AGE and RTICE were therefore included as covariates. The resulting statistical parametric T-maps [SPM(T)] were then thresholded at $p < 0.05$ (cluster-level family wise error (FWE) - corrected with a cluster-forming threshold at voxel level of $p < 0.001$) and anatomically localized using version 23 of the SPM Anatomy toolbox (Eickhoff et al., 2013; Eickhoff et al., 2007; Eickhoff et al., 2005; http://www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html; see Fig. 2).

In the *first model category (model 1),* the main ICE i.e. the higher activation under the incompatible versus the compatible conditions over both sides (IC>C), as calculated via first level analysis, was included as main regressor (composite main effect) in the group level analysis with AGE and RTICE as covariates (CxAGE, ICxAGE, CxRTICE, ICxRTICE). Accounting for variance shared by these variables, model 1a included AGE and the residuum of RTICE (RTICEres) and model 1b RTICE and the residuum of AGE (AGEres) as covariates. For these models we applied small volume correction (SVC) by using the incompatibility main effect for our further analysis. We chose this specific main effect for our a priori SVC in order to analyze activity specifically in the predicted network of interest. For the SVC we, in line with the whole-brain analysis, also only report activations with $p <0.05$ (cluster-level FWE corrected).

In the *second model category (model 2),* we modeled regressors for the different task conditions (C and IC) separated by side respectively, yielding four task regressors (CL, CR, ICL, ICR). Each of these modeled task conditions was included separately as an individual regressor and in interaction with AGE and RTICE correspondingly, leading to 12 additional task regressors (CxAGE, CLxAGE, CRxAGE, ICxAGE, ICLxAGE, ICRxAGE, CxRTICE, CLxRTICE, CRxRTICE, ICxRTICE, ICLxRTICE, ICRxRTICE). Based on the four condition-specific regressors the main ICE was calculated analogously to model 1 ([ICR > CR] ∩ [ICL > CL]) and included in the design matrix. This calculation allowed for a sanity-check of the findings concerning the main ICE calculated via model 1 as ICR and ICL are part of the IC condition and CR and CL of the C condition. Model 2a included AGE and RTICEres and model 2b RTICE and AGEres as covariates. By application of appropriate linear contrast to the ANCOVA parameter estimates simple main effects of each condition (vs. the resting baseline), conjunctions and comparisons between experimental factors could be tested. To detect only task-positive effects when testing for comparisons between conditions we used the minimum conjunction analysis (Nichols et al., 2005) for each contrast. Voxels were therefore only declared active when passing the statistical threshold in each of the contrasts included in the tested conjunction. For instance, investigating left and right-sided compatible stimuli we masked the contrast with the respective simple main effect to ensure that only task-positive regions contributed to the analysis [(CL >CR) ∩ CL]. For our analysis and interpretations we again only considered clusters significant for which the activations exceeded a threshold of $p < 0.05$ (cluster-level FWE-corrected, cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 240$).

3 RESULTS

3.1 Behavioral Data

In the whole-sample mean RTC was 414.2 ms (standard deviation (SD) 68.5 ms) and RTIC 497.68 ms (SD 83.6 ms). Mean ERC was 2.15 % (SD 2.88 %), mean ERIC 4.74 % (SD 4.02 %) (Table 2). Correlation of advancing age with mean RT was significant for both RTC (0.263) and RTIC (0.396) as well as with ERC (0.191) an ERIC (0.203) (Table 2; Fig. 3a). Comparing the performance parameters separately per condition and in association with age yielded the following results: Response speed (mean RT) was higher and responses were more accurate (ER) for the compatible compared to the incompatible conditions as revealed by a paired one-sample t-test (RT: mean difference = -83.52, t = -37.53, $p < 0.001$; ER: mean difference = -2.59, t = -10.637, $p < 0.001$). Additionally, mean RT and ER were higher in advanced age (cut-off young (n=133) vs. old (n=133): median of 56.00 years; age as between factor in the ANOVA) under both conditions [RTC: $F(1, 264) = 11.17$, $p < .001$, $\eta_p^2 = 0.04$; RTIC: $F(1, 264) = 34.44$, $p < .001$, $\eta_p^2 = 0.12$; ERC: $F(1, 264) = 6.56$, $p < .05$, $\eta_p^2 = 0.02$; ERIC: $F(1, 264) = 14.65$, $p < .001$, $\eta_p^2 = 0.05$]. Fig. 3b illustrates the ICE on RT in the task as a function of age, which is strongly driven by the positive correlation of age and RTIC and not by an improvement of the RT under the compatible condition in advanced age (Table 2; Fig. 3a). Participants with higher RTICE showed a significantly positive correlation with RTC ($r= 0.198$; $p <0.01$), RTIC ($r = 0.596$; $p < 0.01$) and ERIC ($r = 0.192$; $p < 0.01$). The substantial correlation of RTC and ERC ($r=0.42$; $p = 0.5$) and the negative correlation of RTIC and ERIC ($r= -0.103$; $p=0.93$) were not significant.

Table 2: Descriptive statistics of reaction time (RT) and error rate (ER). Means, standard deviations (SD), minima and maxima in the compatible (C) and incompatible (IC) condition and their correlation with age, n=266.

	mean (SD)	**minimum; maximum**	**correlation r with age**
RTC (ms)	414.2 (68.5)	266.1; 627.6	0.263 ($p <0.01$)
RTIC (ms)	497.7 (83.6)	302.4; 716.8	0.396 ($p <0.01$)
RTICE (ms)	83.5 (36.3)	-0.9; 195.8	0.415 ($p <0.01$)
ERC (%)	2.2 (2.88)	0.0; 29.7	0.191 ($p <0.01$)
ERIC (%)	4.7 (4.02)	0.0; 29.8	0.203 ($p <0.01$)

Note: RTC: reaction time for compatible conditions; RTIC: reaction time for incompatible conditions; RTICE: incompatibility effect on reaction time; ERC: error rate for compatible conditions; ERIC: error rate for incompatible conditions; ms: milliseconds; %: percent.

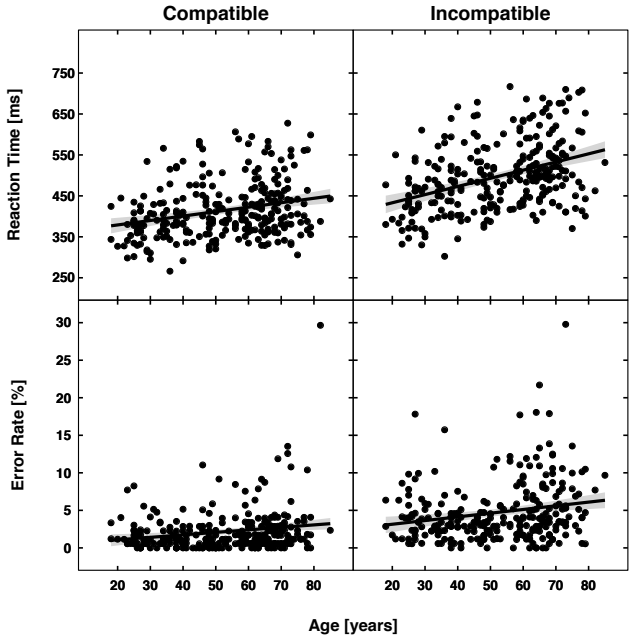

Fig. 3a: Correlation of age with performance: group-level mean reaction time (RT) and error rate (ER) in the spatial stimulus-response compatibility (SRC) task, separated for compatible (C) and incompatible (IC) conditions of the task and correlated with age (in years). *Note:* The grey area represents the 95%-confidence interval. ms: milliseconds; %: percent.

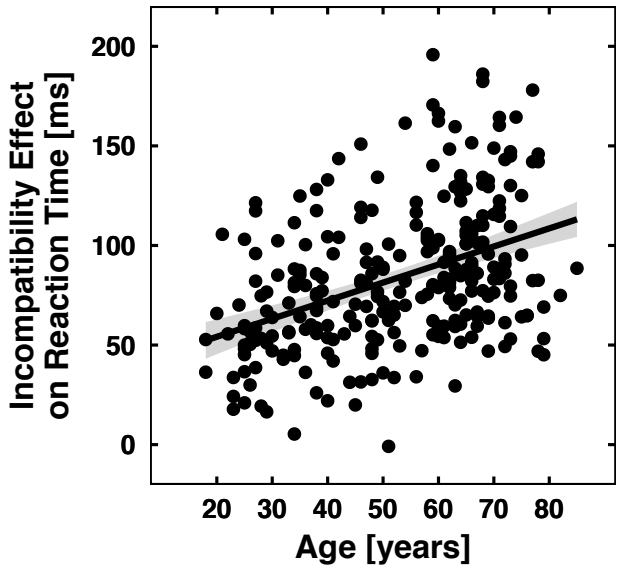

Fig. 3b: Incompatibility effect (ICE): i.e. difference between incompatible (IC) and compatible (C) conditions on reaction time (RT) in the spatial stimulus–response compatibility (SRC) task as a function of age (in years). *Note:* The grey area represents the 95%-confidence interval. ms: milliseconds.

3.2 Imaging data

3.2.1 First model category: incompatibility effect as main regressor

INCOMPATIBILITY MAIN EFFECT (model 1): The *first model category* presented on p. 18 contained regressors for the main ICE main and for both conditions (C and IC) as well as AGE and RTICE as covariates. Based on this model, we looked at the main ICE contrasting incompatible vs. compatible (IC > C) responses over both sides and not including side or stimulus-specific distinctions. We wanted to identify brains areas showing stronger activation during the incompatible compared to the compatible condition and thus illustrate and replicate the network associated with the *top-down control processes* of the

SRC task. In our population-based sample a bilateral network consisting of DLPFC, premotor cortex (PMC), IPS and adjacent superior parietal lobule (SPL), anterior insula (aIns), (pre-)SMA extending into MCC and cerebellum was associated with this effect. Additional activation was found in the left inferior parietal lobule (IPL) (see Fig. 4, Table 3). Contrasting compatible with incompatible responses did not yield any significant activation.

SHARED VARIANCE OF THE INCOMPATIBILITY MAIN EFFECT AND THE COVARIATES (model 1): Using model 1, we then separately tested the influence of higher age and higher RT ICE on the aforementioned incompatibility network. We used the models 1a and 1b to ensure that only the residuum of the respective second covariate was included in the analysis (RTICEres in model 1a and AGEres in model 1b) and applied SVC using the incompatibility main effect for the further analysis. An increase in age correlated with significant higher activation in bilateral IPL, MFG and cerebellum and in left IFG and SPL (Fig. 5 A; Table 4 A; model 1a; ICE ∩ AGE; k=154). Positively linked to higher RT ICE (RT incompatibility costs) on a behavioral level we found hyperactivity in left IPS (Fig. 5 B; Table 4 B; model 1b; ICE ∩ RTICE; k=154). Hyperactivity linked to both covariates (higher age and RT incompatibility costs; ICE ∩ AGE ∩ RTICE) was not found.

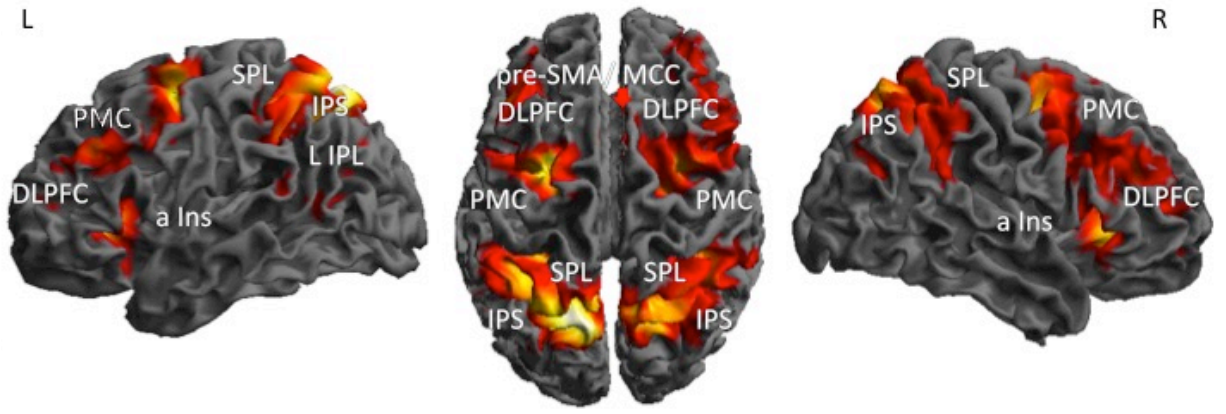

Fig. 4: Incompatibility main effect: Incompatible vs. compatible responses (IC > C). Brain areas showing stronger activation during the incompatible compared to the compatible conditions. Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 240$). *Note*: aIns: anterior Insula; DLPFC: dorsolateral prefrontal cortex; IPL: inferior parietal lobule; IPS: intraparietal sulcus; L: left; MCC: mid-cingulate cortex; PMC: premotor cortex; pre-SMA: presupplementary motor area; R: right; SPL: superior parietal lobule.

Table 3: Regions showing significant higher activation for incompatible vs. compatible conditions in the whole sample.

Macroanatomical structure	x	y	z	Histological Assignment	t-score
Cluster 1 (k=17506)					
L DLPFC	-24	-2	48	Area 6d3	12.96
R DLPFC	26	-2	48	Area 6d3	9.53
R insula lobe	30	24	0		9.46
L MCC	-6	12	46		8.89
L insula lobe	-28	22	2		8.67
R pre-SMA	30	-2	62	Area 6d3	7.48
Cluster 2 (k=12135)					
L SPL	-12	-68	52	Area 7a	13.56
L IPS	-32	-46	42	Area hIP1, hIP3	10.89
R SPL	18	-64	52	Area 7a	10.42
R IPS	36	-44	42	Area hIP3	8.79
L IPL	-30	-70	28	Area hIP5	6.68
Cluster 3 (k=2314)					
R cerebellum (crus 1)	32	-64	-28	lobule VIIa crusi (Hem), lobule VI (Hem)	7.38
L cerebellum (crus 1)	-32	-64	-28	lobule VIIa crusi (Hem), lobule VI (Hem), lobule V (Hem)	7.16
Cerebellar vermis	0	-62	-32	lobule IX (Verm), VIIIb (Verm), IV (Hem)	7.08
Cluster 4 (k=316)					
L MTG	-44	-60	8		4.43

Note: Coordinates *x*, *y*, *z* of the cluster's peak voxel refer to Montreal Neurological Institute (MNI) space; histological assignments indicate the major part(s) of each cluster. DLPFC: dorsolateral prefrontal cortex; IPL: inferior parietal lobule; IPS: intraparietal sulcus; L: left; MCC: midcingulate cortex; MTG: middle temporal gyrus; pre-SMA: presupplementary motor area; R: right; SPL: superior parietal lobule. *References for histological assignments*: Area 6: Geyer (2003); Area 7: Scheperjans et al. (2008); Area hIP1, hIP3: Choi et al. (2006); Area hIP5: Richter et al. (2018), Scheperjans et al. (2008); Lobule IV, V, VI, VII, IX: Diedrichsen et al. (2009). All activations exceed a threshold of $p < 0.05$ (cluster-level FWE-corrected, $k \geq 240$).

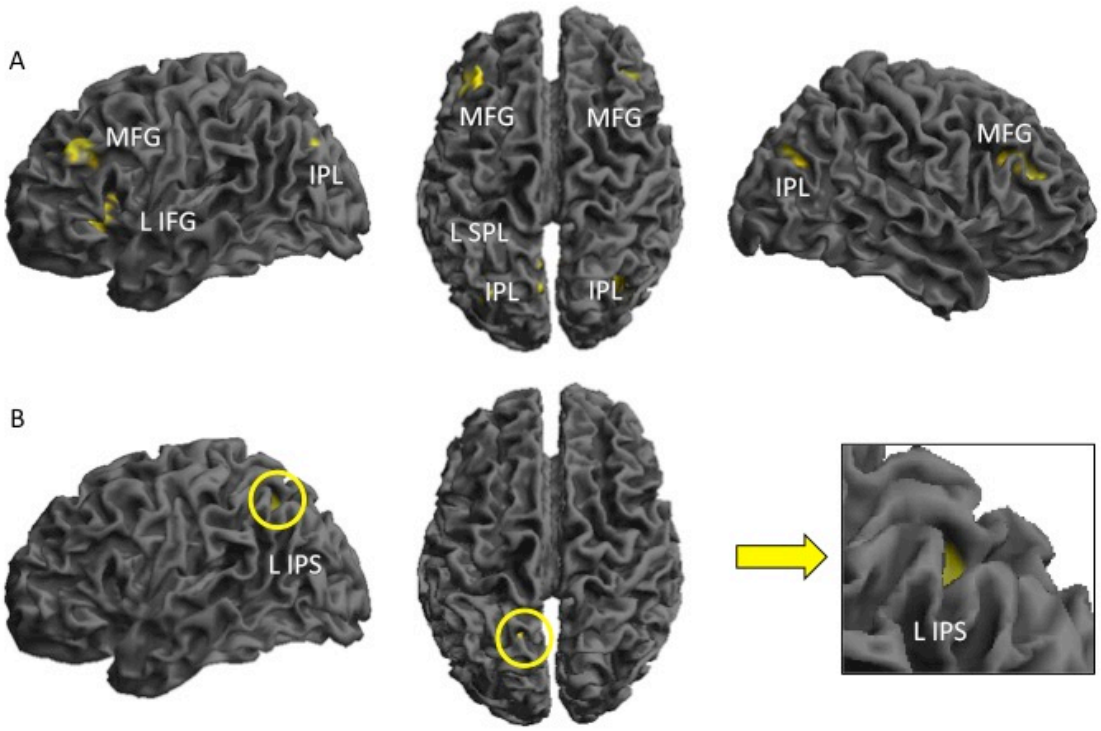

Fig. 5 A: Activity in bilateral IPL, MFG and cerebellum and left IFG and SPL positively linked to an increase in age (ICE ∩ AGE)**.** Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 240$). *Note:* ICE: incompatibility effect; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; MFG: middle frontal gyrus; SPL: superior parietal lobule.

Fig. 5 B: Activity positively linked to higher RT incompatibility costs in left IPS (ICE ∩ RTICE)**.** Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 240$). *Note*: IPS: inferior parietal sulcus; RT: reaction time; RTICE: incompatibility effect on reaction time.

Table 4: Regions showing significant increased activation for higher age (4 A) and higher RT incompatibility costs (4 B).

Macroanatomical structure	**x**	**y**	**z**	**Histological Assignment**	**t-score**
Table 4 A					
Cluster 1 (k=377)					
R cerebellum (crus 1)	16	-76	-26	lobule VIIa crusi, VI crusi (Hem)	4.46
Cluster 2 (k=284)					
L cerebellum (crus 1)	-32	-64	-28	lobule VIIa crusi, VI crusi, V (Hem)	4.26
Cluster 3 (k=206)					
R MFG	34	38	20	Area ifs 1	
Cluster 4 (k=238)					
L IFG (p. triangularis)	-42	30	28	Area 45	4.57
L MFG	-44	26	38		3.28

Cluster 5 (k=200)						
	R IPL	38	-72	30	Area hIP5, hIP8; Area PGp	4.12
Cluster 6 (k=168)						
	Cerebellar vermis	0	-60	-28	lobule IX, VIIIa and b (Verm), nucleus fastigii, interposed nucleus	4.86
Cluster 7 (k=166)						
	L SPL	-2	-66	58	Area 7a, 7p	4.06
Cluster 8 (k=164)						
	L IFG (p. orbitalis)	-26	22	-4	Area Fo3	3.97
Cluster 9 (k=157)						
	L IPL	-34	-74	28	Area hIP5	3.86
Table 4 B						
Cluster 1 (k=229)						
	L IPS	-22	-56	50	Area hIP1, hIP3	4.54

Note: Coordinates *x*, *y*, *z* of the cluster's peak voxel refer to Montreal Neurological Institute (MNI) space; histological assignments indicate the major part(s) of each cluster. R: right; L: left; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; IPS: intraparietal sulcus; MFG: middle frontal gyrus; RT: reaction time; SPL: superior parietal lobule. *References for histological assignments*: Lobule VI, VII: Diedrichsen et al. (2009); Area 45: Amunts et al. (1999); Area hIP1, hIP3, hIP5, hIP8: Choi et al. (2006), Scheperjans et al. (2008); Area 7a, 7p: Scheperjans et al. (2008); Area Fo3: Henssen et al. (2016). All activations exceed a threshold of $p < 0.05$ (cluster-level FWE-corrected, $k \geq 240$).

3.2.2 Second model category: side- and condition specific analysis of the task

SRC TASK EFFECT AND INCOMPATIBILTY MAIN EFFECT (model 2): For a replication of the established SRC task effect and consecutive analysis of side-related effects for both the compatible and the incompatible condition (C and IC), we used model 2 (see p. 18) that included the four task regressors (CL, CR, ICL, ICR).

The general SRC task effect, i.e. detection of, attention and orientation to the target stimuli, planning and executing of motor response, was calculated as a composite main effect of all four conditions (CL ∩ CR ∩ ICL ∩ ICR) and is illustrated by Fig. 6 A. Here we saw activation of the brain regions, which were consistently activated across all conditions of the task contrasted against baseline. Significant activation was found in clusters (see Table 5 A) comprising bilateral SPL, PMC and cerebellum. Moreover, the left IPS, aIns and anterior MCC (aMCC) showed significant activation.

In this extended model 2 we confirmed our aforementioned findings (IC > C, see Fig. 4) associated with the main ICE by contrasting the incompatible responses of both sides with the compatible ones ([ICR > CR] ∩ [ICL > CL]). The first component of this conjunction delineates the voxels, which are more

activated under the incompatible than under the compatible condition for right-sided stimuli. The latter component tests analogously for left-sided stimuli. We performed a conjunction analysis of this conjunction of differential contrasts between incompatible and compatible conditions with the composite main effect of the incompatible conditions (ICR ∩ ICL), in order to ensure that we included only those regions showing significant activation in the incompatible condition. This approach was also applied for further conjunctions. Increased executive control in the incompatible condition yielded activation in bilateral PMC, IPL, IPS, SPL, cerebellum, left insula and left IFG (see Fig. 6 B; Table 5 B). All activations exceeded a threshold of $p < 0.05$ (cluster-level FWE-corrected with a cluster-forming threshold at voxel level of $p < 0.001$, $k=194$).

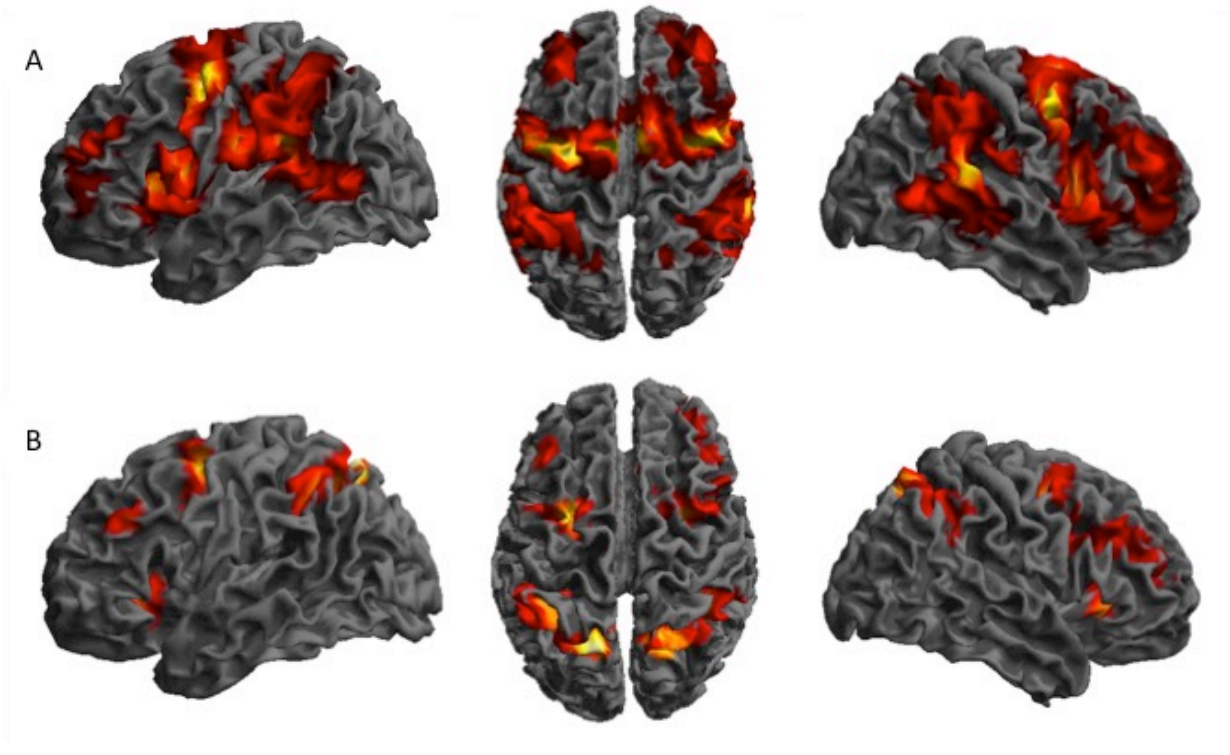

Fig. 6 A: General task effect: Regions consistently activated across all conditions (CL ∩ CR ∩ ICL ∩ ICR), contrasted against baseline. Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 240$). *Note*: CL: compatible left; CR: compatible right; ICL: incompatible left; ICR: incompatible right.

Fig. 6 B: Incompatibility main effect: Incompatible vs. compatible responses ([ICR > CR] ∩ [ICL > CL]) ∩ ICR ∩ ICL) Brain areas showing stronger activation during the incompatible compared to the compatible conditions. Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 240$). *Note*: CL: compatible left; CR: compatible right; ICL: incompatible left; ICR: incompatible right.

Table 5: General task effect (5 A). Brain regions consistently activated during all conditions contrasted against baseline (CL ∩ CR ∩ ICL ∩ ICR). **Incompatibility main effect: Incompatible vs. compatible responses (5 B).** Brain areas showing stronger activation during the incompatible compared to the compatible conditions ([ICR > CR] ∩ [ICL > CL]) ∩ ([ICR ∩ ICL]).

Macroanatomical structure	x	y	z	Histological Assignment	t-score
Table 5 A:					
Cluster 1 (k=60370)					
L aMCC	-6	4	48		33.6
L precentral gyrus	-34	-6	48		31.1
R posterior-medial frontal gyrus	8	2	60		29.25
R precentral gyrus	40	-2	46		27.14
R IPL	66	-36	18	Area PF, Area TE 3	24.64
Cluster 2 (k=4246)					
Cerebellar vermis	2	-66	-16	lobule VI (Verm), V (Hem)	20.69
R cerebellum (crus 1)	38	-54	-30	lobule VIIa crusi, VI (Hem)	19.11
L cerebellum (crus 1)	-34	-58	-30	lobule VIIa crusi, VI (Hem), IX, interposed nucleus, dentate nucleus	17.00
Table 5 B					
Cluster 1 (k=6996)					
L MFG	-26	-2	52	Area 6d3	10.67
R MFG	26	-2	48	Area 6d3	8.62
R IFG (p.orbitalis)	28	26	-6	Area Fo3	7.7
L MCC	-6	14	44		7.06
R insula lobe	38	24	2		6.19
Cluster 2 (k=2648)					
L SPL	-12	-68	52	Area 7a	12.42
L IPS	-32	-46	40	Area hIP1, hIP2	9.11
L IPL	-40	-46	44	Area hIP1, hIP2, hIP3, hIP6	8.28
Cluster 3 (k=2204)					
R SPL	20	-64	52	Area 7a	9.98
R IPS	40	-44	42	Area hIP1, hIP2, hIP3	7.74
R IPL	54	-42	32	Area PFcm, PF, PFm	4.43
Cluster 4 (k=570)					
L insula lobe	-28	22	-2	left Area Fo3	6.67
Cluster 5 (k=300)					
L IFG (p. triangularis)	-42	30	32		5.94
Cluster 6 (k=291)					
R cerebellum (crus 1)	32	-64	-30	lobule VIIa crusei, VI (Hem)	6.48
Cluster 7 (k=247)					
L cerebellum (crus 1)	-34	-64	-30	lobule VIIa crusei, VI (Hem)	5.89

Note: Coordinates *x*, *y*, *z* of the cluster's peak voxel refer to Montreal Neurological Institute (MNI) space; histological assignments indicate the major part(s) of each cluster. aMCC: anterior midcingulate cortex; CL: compatible left; CR: compatible right; ICL: incompatible left; ICR: incompatible right; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; IPS: intraparietal sulcus; L: left; MFG: middle frontal gyrus; R: right; SPL: superior parietal lobule. *References for histological assignments*: Area PF, PFcm, PFm: Caspers et al. (2008, 2006), Area TE3: Morosan et al. (2005); Lobule VI, VII, IX: Diedrichsen et al. (2009); Area 6d3: Geyer (2003); Area Fo3: Henssen et al. (2016); Area 7a: Scheperjans et al. (2008); Area 45: Amunts et al. (1999); hIP1, hIP2, hIP3: Choi et al. (2006), Scheperjans et al. (2008). All activations exceed a threshold of $p < 0.05$ (cluster-level FWE-corrected, $k \geq 194$).

BOTTOM-UP PROCESSES – DETECTION OF AND ATTENTION TO THE STIMULI (model 2): Using model 2 we delineated brain areas, that are associated with stimulus-driven orienting to and bottom-up processing of the respective stimulus as shown by Cieslik et al. (2010). We performed a conjunction analysis over the areas showing activation for left-sided stimuli (CL ∩ ICL) and those showing higher activation for the left-sided stimuli in both conditions compared to the compatible right-sided condition ([CL > CR] ∩ [ICL > CR]). As reorientation from one stimulus-side to the opposite side requires top-down processes and would confound the investigation of bottom-up processes, we did not include the incongruent contralateral stimuli (ICR) in our conjunctions. The equivalent contrast for right-sided stimuli was calculated (CR ∩ ICR ∩ [CR>CL] ∩ [ICR>CL]). ICL was not included (cf. above). By means of the first conjunctions (CL ∩ IC respective CR ∩ ICR) we ensured to include only those voxels showing task-positive activation, i.e. higher activity responding to left-sided resp. right-sided stimuli relative to baseline. We tested for regions where both individual conditions (CL and ICL respective CR and ICR) evoked significant activation. Via the second component we tested if the delineated side-related task-positive effects were higher compared to the respective opposite stimuli side and thus could exclude activity related to the general task performance.

The pattern of activity for left- and right-sided stimulus-driven bottom-up effects was similar: Activation was found in IPS, SPL, pallidum, thalamus and inferior temporal gyrus (ITG) contralateral to the stimulus side as well as in the ipsilateral cerebellum (see Fig. 7 A and B; Table 6 A and B). Moreover, left-sided stimuli evoked additional activation in contralateral cerebellum, dPMC, MFG, IFG and bilateral caudate (Fig. 7 A, Table 6 A). All activations survived a threshold of $p < 0.05$ (cluster-level FWE-corrected with a cluster-forming threshold at voxel level of $p < 0.001$, $k=194$).

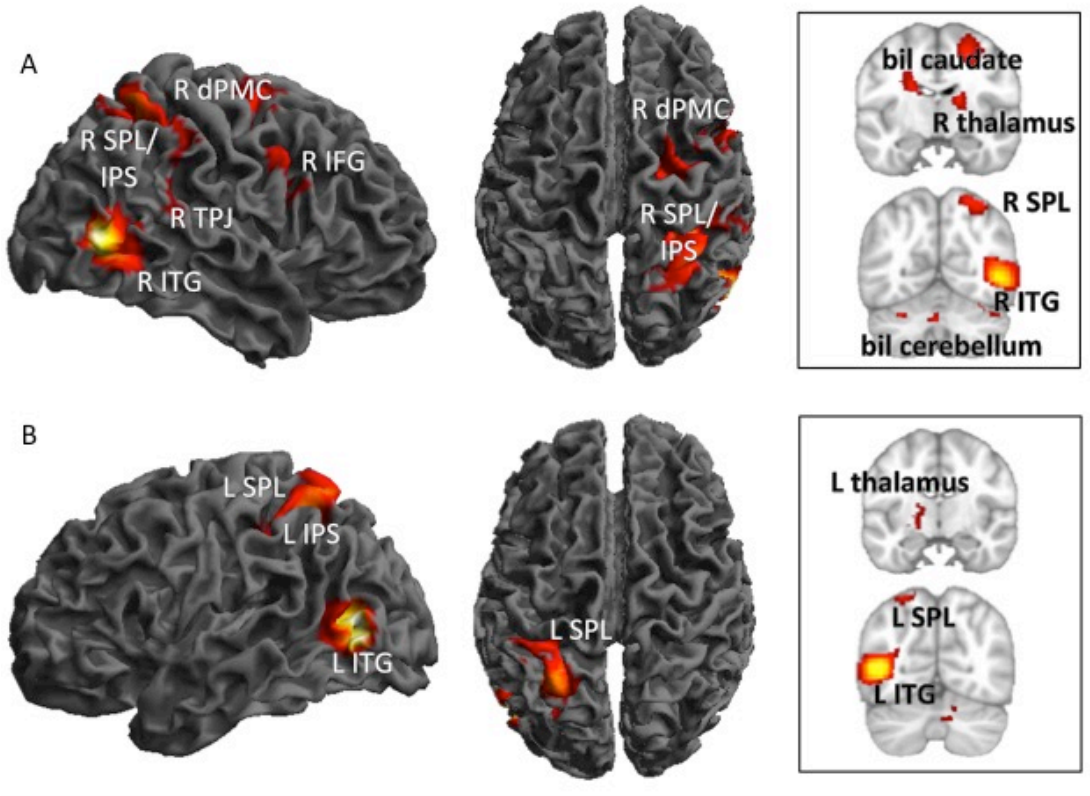

Fig. 7 A: Brain regions showing significantly stronger activation for stimulus-driven bottom-up effects for left-sided stimuli. Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 194$). *Notes:* Bil: bilateral; dPMC: dorsal premotor cortex; IFG: inferior frontal gyrus; IPS: intraparietal sulcus; ITG: inferior temporal gyrus; L: left; R: right; SPL: superior parietal lobule; TPJ: temporoparietal junction.

Fig 7 B: Brain regions showing significantly stronger activation for stimulus-driven bottom-up effects for right-sided stimuli. Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 194$). *Notes*: IPS: intraparietal sulcus; ITG: inferior temporal gyrus; L: left; R: right; SPL: superior parietal lobule.

Table 6: Brain regions showing significantly stronger activation for stimulus-driven bottom-up effects for left-sided stimuli (6 A). Brain regions showing significantly stronger activation for stimulus-driven bottom-up effects for right-sided stimuli (6 B).

Macroanatomical structure	x	y	z	Histological Assignment	t-score
Table 6 A					
Cluster 1 (k=2146)					
R TPJ, IPS, SPL	34	-56	58	Area hIP1, hIP2, hIP3, Area 7PC	8.71
Cluster 2 (k=1319)					
R MTG	50	-68	2	Area hOc5 (V5/MT), h0c4la	14.52
Cluster 3 (k= 741)					
R precentral gyrus (dPMC)	26	-10	52	Area 6d3, 6d1	6.78
R MFG	36	-2	58	Area 6d3	6.61

Cluster 4 (k=722)						
	L caudate	-22	-8	26	Caudate bridges, medial	5.47
	L thalamus	-20	-20	22	Thalamus (premotor, parietal, visual)	5.07
Cluster 5 (k=644)						
	R IFG (p.opercularis)	54	10	32	Area 44, 45	5.87
	R precentral gyrus	52	6	36	Area 44, Area ifj2	5.64
	R MFG	36	14	26		3.93
Cluster 6 (k=277)						
	R thalamus	18	-8	14	Thalamus (prefrontal, premotor, motor, somatosensory)	5.98
	R pallidum	18	0	10	Putamen (bridges, medial), Globus Pallidus (ext.lamina, subcapsular)	4.27
Cluster 7 (k=277)						
	L cerebellum (crus 1)	-10	-72	-32	lobule V, VI (Hem), VIIa (Crusi), VIIIa (Hem)	5.53
	Cerebellar vermis	0	-64	-32	lobule VIIIa (Hem), VIIIb (Verm), IX (Verm)	5.13
Cluster 8 (k=24)						
	R cerebellum (crus 1)	12	-76	-16	lobule VI (Hem) , VIIa crusi (Hem)	7.46

Table 6 B

Cluster 1 (k=1427)						
	L IPS, SPL	-30	-54	56	Area hIP3, Area 7PC	8.93
Cluster 2 (k=1226)						
	L MTG	-46	-74	4	Area h0c4la, h0c5	
Cluster 3 (k=337)						
	L pallidum	-26	-16	-2	Globus Pallidus (extern, int. and ext. lamina)	6.67
	L thalamus	-18	-22	12	Thalamus (premotor, motor, prefrontal, parietal, visual, somatosensory)	4.34
Cluster 4 (k=324)						
	Cerebellar vermis (3)	4	-52	-16	Nucleus fastigii, lobule IX (Verm), VIIIb (Verm), IV	6.48
	R cerebellum	4	-60	-22	Nucleus fastigii, lobule V (Hem), interposed nucleus	5.35

Note: Coordinates *x*, *y*, *z* of the cluster's peak voxel refer to Montreal Neurological Institute (MNI) space; histological assignments indicate the major part(s) of each cluster. IFG: inferior frontal gyrus; IPL: inferior parietal lobule; IPS: intraparietal sulcus; L: Left; MFG: middle frontal gyrus; MTG: middle temporal gyrus; R: Right, SPL: superior parietal lobule. *References for histological assignments:* Area hIP1, hIP2, hIP3: Scheperjans et al. (2008); Choi et al. (2006), Area 7PC: Scheperjans et al. (2008), Area h0c5 (V5/MT): Malikovic et al. (2007), Area h0c4la: Malikovic et al. (2016); Area 6d1, d3: Geyer (2003), Area Fo3: Henssen et al. (2016), Caudate/Thalamus/Globus Pallidus/Putamen: Behrens et al. (2003), Area 44,45: (Amunts et al., 1999), Area 3a: Geyer et al. (2000, 1999), Area 2: Grefkes et al. (2001), Area PFt: Caspers et al. (2008, 2006), Area TE3: Morosan et al. (2005), Lobule IV, V, VIII, IX: Diedrichsen et al. (2009). All activations exceed a threshold of $p < 0.05$ (cluster-level FWE-corrected, $k \geq 194$).

AGE AS A COVARIATE (model 2a): To specifically examine effects of aging on the aforementioned incompatibility network based on model 2, we added subject age as a covariate for each task regressor (CxAGE, CLxAGE, CRxAGE, ICxAGE, ICLxAGE, ICRxAGE) in model 2a (AGE and RTICEres as covariates). To investigate the influence on the compatible and incompatible condition separately, we first performed a conjunction analysis of the compatible vs. the incompatible conditions with the areas associated with compatible conditions and age only ([C > IC] ∩ CxAGE). The first component of this conjunction delineates the voxels, which are more activated under the compatible than under the incompatible condition. The latter component then tests which of those voxels show stronger activation in association with higher age. We found activation in bilateral visual and auditory cortex, aIns, MCC and left cerebellum and right fusiform gyrus (FG; see Fig. 8 A and Table 7 A).

Analogously, we contrasted incompatible vs. compatible conditions and tested for spatial overlap effects with the voxels activated in association with higher age under the incompatible condition only ([IC > C] ∩ ICxAGE). Activation was found in bilateral IPS and SPL, cerebellum, right IFG, DLPFC, MCC and left aIns (see Fig. 8 B and Table 7 B). In a next step we used the same contrast (IC vs. C conditions) as the first component of a conjunction and added those areas, that showed stronger activation under incompatible than under compatible conditions in association with higher age only, thus applying a more strict approach in order to identify age-related differences in neural activity for this task ([IC > C] ∩ [IC x AGE > C x AGE]). This conjunction yielded activation of bilateral middle frontal and orbital gyrus, IFG, cerebellum, left temporal pole and right pallidum, thalamus and caudate (see Fig. 8 C and Table 7 C). Applying this strict approach to delineate voxels showing stronger activation under compatible compared to incompatible conditions in association with higher age only ([C > IC] ∩ [C x AGE > IC x AGE]) did not yield any significant results.

Finally, we aimed to identify areas that showed higher activation under compatible compared to incompatible conditions but were also less activated with higher age ([C > IC] ∩ [-C x AGE]). Those areas might be associated with the DMN, a network that typically shows deactivations during sensorimotor tasks such as the spatial SRC task applied in our experiment. The areas showing a negative correlation with age for the compatible condition were bilateral precuneus and middle orbital gyrus as well as left IPL, superior FTG and middle temporal gyrus (MTG; see Fig. 8 D and Table 7 D). We did not find areas showing a negative correlation of age and the incompatible condition by including only those areas showing higher activation under incompatible compared to compatible conditions ([IC > C] ∩ [-IC x AGE]).

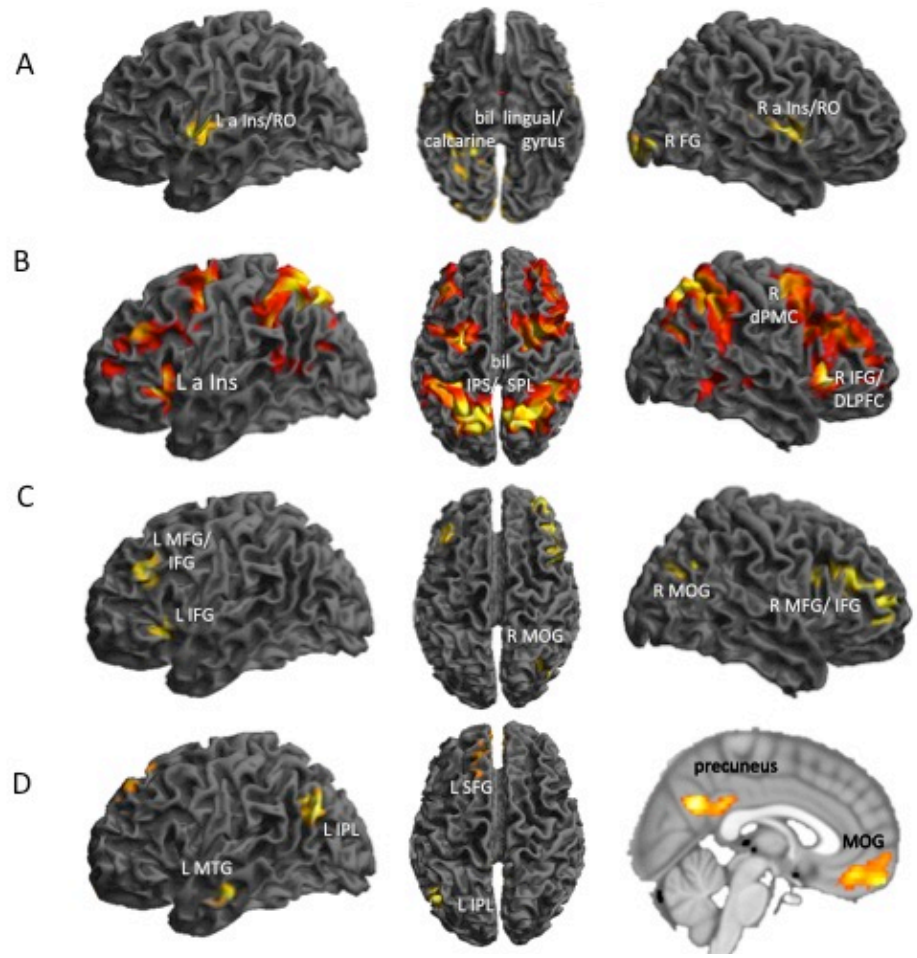

Fig. 8 A: Brain areas showing stronger activation for compatible (C) vs. incompatible (IC) conditions and a positive correlation with age for compatible conditions ([C > IC] ∩ CxAGE). Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 194$). *Notes:* aIns: anterior Insula; bil: bilateral; FG: fusiform gyrus; L: left; R: right; RO: rolandic operculum.

Fig 8 B: Brain areas showing stronger activation for incompatible (IC) vs. compatible (C) conditions and a positive correlation with age under incompatible conditions ([IC > C] ∩ ICxAGE). Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 194$). *Notes:* aIns: anterior Insula; bil: bilateral; DLPFC: dorsolateral prefrontal cortex; dPMC: dorsal premotor cortex; IFG: inferior frontal gyrus; IPS: intraparietal sulcus; L: left; R: right; SPL: superior parietal lobule.

Fig 8 C: Brain areas positively correlated with higher age during incompatible (IC) compared to compatible (C) conditions ([IC > C] ∩ [IC x AGE > C x AGE]). Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 194$). *Note:* IFG: inferior frontal gyrus; L: left; MFG: middle frontal gyrus; MOG: middle occipital gyrus; R: right.

Fig 8 D: Default mode network (DMN) with pronounced midline structures associated with age-related deactivations under compatible (C) conditions in areas showing stronger activation for compatible vs. incompatible conditions ([C > IC] ∩ [-C x AGE]). Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 194$). *Note:* IPL: intraparietal lobe; L: left; MOG: middle occipital gyrus; MTG: middle temporal gyrus; SFG: superior frontal gyrus.

Table 7: Brain areas showing stronger activation for compatible (C) vs. incompatible (IC) conditions and a positive correlation with age for compatible conditions (7 A). Brain areas showing stronger activation for incompatible (IC) vs. compatible (C) conditions and a positive correlation with age under incompatible conditions (7 B). Brain areas positively correlated with higher age during incompatible (IC) compared to compatible (C) conditions (7 C). Brain areas showing stronger activation for compatible vs. incompatible conditions and a negative correlation with age for compatible conditions (7 D).

Macroanatomical structure	x	y	z	Histological Assignment	t-score
Table 7 A					
Cluster 1 (k=1876)					
L cerebellum (IV-V)	-8	-60	2	lobule V (Hem), VI (Hem)	4.92
R FG	32	-42	-10	Area FG3	4.79
L lingual gyrus	-12	-62	8	Area h0c1 (V1), h0c2 (V2)	4.63
R calcarine gyrus	22	-56	12	Area h0c2 (V2)	4.57
Cluster 2 (k=998)					
L RO	-50	-8	14	Area OP3 (VS), OP4 (PV)	4.84
L insula lobe	-36	-4	14		4.35
L superior temporal lobe	-54	-4	6	Area TE 1,2,3, Area 44	4.31
Cluster 3 (k=878)					
R insula lobe	38	-4	12	Area OP3 (VS), lateral putamen	5.04
R temporal pole	58	0	4	Area TE 1.2, TE 3, OP4 (PV)	4.47
Cluster 4 (k=217)					
L MCC, SPL	-6	-32	42	Area 4A, Area 5M	4.49
R MCC	12	-38	38		4.07
Cluster 5 (k=196)					
R lingual gyrus	18	-102	-4	Area h0c1 (V1), h0c2 (V2), h0c3 (V3), h0c4 (V4)	4.55
R inferior occipital gryus	32	-94	-8	Area h0c3 (V3), h0c4 (V4)	4.19
Table 7 B					
Cluster 1 (k=19585)					
R DLPFC	-24	-4	42		10.32
R IFG	32	24	0	Area 6d3	10.20
L insula lobe	-28	22	0		8.97
R MCC	8	16	44		8.08
Cluster 2 (k=13876)					
L IPS	-24	-62	52	Area hIP3	10.4
R SPL	12	-66	52	Area 7A	10.12
R IPS	38	-46	42	Area hIP1, hIP2	9.95
L SPL	-6	-56	-54	Area 5M, 7A, 7P	9.34
Cluster 3 (k=2443)					
L cerebellum (crus 1)	-32	-64	-28	Lobule VI (Hem), VIIa crusi (Hem)	7.46

Cerebellar vermis	0	-62	-32	Lobule IX (Verm), VIIIb (Verm)	7.10
R cerebellum (crus 1)	30	-64	-26	Lobule VI (Hem), VIIa crusi (Hem)	6.61
Table 7 C					
Cluster 1 (k=1314)					
R MFG	38	32	26		4.99
R IFG (p. triangularis)	44	16	28		4.66
R middle orbital gyrus	34	52	4	Area Fp1	4.64
Cluster 2 (k=747)					
L cerebellum (crus 1)	-34	-62	-30	Lobule VI (Hem), VIIa crusi (Hem)	4.76
Cerebellar vermis	0	-60	-28	Lobule IX (Verm), VIIa and b (Verm)	4.74
Cluster 3 (k=368)					
R cerebellum (crus 1)	16	-76	-26	Lobule VI (Hem), VIIa crusi (Hem)	4.70
Cluster 4 (k=299)					
L IFG (p. triangularis)	-42	28	28		4.88
L MFG	-38	38	32		3.68
Cluster 5 (k=256)					
R MOG	38	-70	30	Area hIP5	4.84
Cluster 6 (k=251)					
L IFG (p.orbitalis)	-26	22	-4	Area Fo4, Fo5	4.37
L middle orbital gyrus	-22	24	-10	Area Fo3	4.11
L temporal pole	-48	18	-6	Area Fo5	3.35
Cluster 7 (k=201)					
R pallidum	14	0	4	Globus pallidus (extern), Putamen (medial, bridges)	4.23
R thalamus	22	-16	20	Thalamus (premotor, prefrontal)	3.88
R caudate	20	-10	22	Caudate (bridges)	3.68
Table 7 D					
Cluster 1 (k=1056)					
L precuneus	-6	-54	18		5.26
R precuneus	8	-48	22		5.21
Cluster 2 (k=1064)					
L rectal gyrus	-6	44	-14	Area Fp1, Fp2	5.43
L middle orbital gryus	-4	62	-4	Area Fp1, Fp2	4.27
R middle orbital gyrus	6	62	-6	Area Fp1, Fp2	3.95
Cluster 3 (k=485)					
L IPL	-54	-70	30	Area PGp, PGa, PFm	4.99
Cluster 4 (k= 248)					
L MTG	-60	-10	-18		5.14
Cluster 5 (k= 194)					
L SFG	-14	44	46		4.17

Note: Coordinates *x*, *y*, *z* of the cluster's peak voxel refer to Montreal Neurological Institute (MNI) space; histological assignments indicate the major part(s) of each cluster. IFG: inferior frontal gyrus; IPS: intraparietal sulcus; FG: fusiform gyrus; L: left; MFG: middle frontal gyrus; MOG: middle occipital gyrus; MTG: middle temporal gyrus, R: right; RO: rolandic operculum; SFG: superior frontal gyrus; SPL: superior parietal lobule. *References for histological assignments*: Cerebellum (VI, VII a and b, IX;): Diedrichsen et al. (2009); Area FG 3: Caspers et al. (2013); Area h0c1, h0c2: Amunts et al. (2000); Area h0c3, h0c4: Rottschy et al. (2007), Kujovic et al. (2013); Area OP3, OP 4: Eickhoff et al. (2006); Area TE 1, 2, 3: Morosan et al. (2005, 2001), Area 44: Amunts et al. (1999); Area 5M, 7A, 7P: Scheperjans et al. (2008); Area 4a: Geyer et al. (1996); Area hIP1, hIP2, hIP3: Choi et al. (2006); Area hIP5: Richter et al. (2018), Scheperjans et al. (2008); Area Fp1, 2: Bludau et al. (2014); Area Fo3,4,5, Globus pallidus, putamen, thalamus, caudate: Behrens et al. (2003); Area PGp, PGa, PFm: Caspers et al. (2008, 2006). All activations exceed a threshold of $p < 0.05$ (cluster-level FWE-corrected, $k \geq 194$).

THE BEHAVIORAL INCOMPATIBILITY EFFECT AS A COVARIATE (model 2b): Analogously to the analysis of subject age we included the behavioral RT ICE as a covariate in our analysis based on model 2b (covariates: RTICE and AGEres; CxRTICE, ICxRTICE, CLxRTICE, CRxRTICE, ICLxRTICE, ICRxRTICE). As we were specifically interested in performance-related changes in neural task-evoked activity, we applied the strict approach presented above (see 6c). We identified the areas showing increased activation under the incompatible compared to the compatible conditions and then performed a conjunction with those voxels showing activation for this contrast only in association with a higher behavioral RT ICE ([IC > C] ∩ [IC x RTICE > C x RTICE]). This conjunction yielded activation of bilateral cluster of IPS and IPL, extending into SPL on the left side, and of the cerebellar vermis (see Fig. 9 and Table 8).

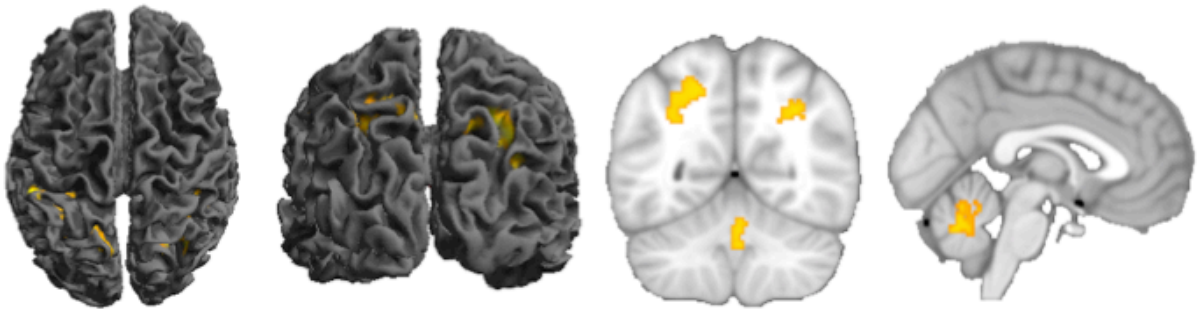

Fig. 9: Brain areas positively correlated with higher behavioral incompatibility costs (RT ICE) during incompatible (IC) compared to compatible (C) conditions. ([IC > C] ∩ [IC x RTICE > C x RTICE]). Significant at $p < 0.05$ (cluster-level FWE-corrected: cluster-forming threshold at voxel level of $p < 0.001$, $k \geq 194$). *Note*: RT: reaction time; RT ICE: incompatibility effect on reaction time.

Table 8: Brain areas positively correlated with higher behavioral RT ICE during incompatible (IC) compared to compatible (C) conditions.

Macroanatomical structure	x	y	z	Histological Assignment	t-score
Table 8					
Cluster 1 (k=707)					
L IPS	-32	-44	38	Area hIP1, hIP2, hIP3	4.10
L IPL	-50	-40	42	Area PFt	4.06
L SPL	-12	-70	50	Area hIP8, 7A	3.80
Cluster 2 (k=690)					
R IPS	30	-62	40	Area hIP5, hIP6	5.07
R IPL	46	-42	32	Area PFcm	4.39
Cluster 3 (k=199)					
Cerebellar vermis (9)	4	-60	-30	lobule IX (vermis),VIIa and b (verm), interposed nucleus, nucleus fastigii	4.35

Note: Coordinates *x*, *y*, *z* of the cluster's peak voxel refer to Montreal Neurological Institute (MNI) space; histological assignments indicate the major part(s) of each cluster. IPL: inferior parietal lobule; IPS: intraparietal sulcus; L: left; R right; SPL: superior parietal lobule. *References for histological assignments:* Area hIP1, hIP2, hIP3: Choi et al. (2006); Area hIP5, hIP6, hIP8: (Richter et al., 2018), Scheperjans et al. (2008); Area PFt, PFcm: Caspers et al. (2008, 2006); Area 7A: Scheperjans et al. (2008); Lobule VII, IX, nuclei: Diedrichsen et al. (2009). All activations exceed a threshold of $p < 0.05$ (cluster-level FWE-corrected, $k \geq 194$).

4 DISCUSSION

The major behavioral findings of our study are the confirmation of the behavioral *SR-incompatibility costs* and an age-related increase of these costs in our sample. On the neural level, we were able to replicate the *general task (SRC) network* and the *incompatibility-related network* with the *top-down* and *bottom-up processes* involved. Additionally, we were able to delineate brain areas showing *age-related hyperactivity* during our SRC task. More precisely, we could identify neural correlates of *subprocesses of cognitive action control*. These age-related increases in activation partially overlapped with activation related to higher behavioral *SR-incompatibility costs*. Thus, our data corroborate a significant influence of age on cognitive action control, which seems at least partially shared with performance-related effects across the lifespan. In addition, we found task-specific age-related alterations in the DMN, potentially contributing to recent hypotheses on the functional role of the DMN and its involvement in high-order learning, adaptation and optimization processes that might be pronounced in early adulthood.

In the following sections we discuss our findings in the context of the theories of CNA. We analyze the effect of healthy aging on overcoming incompatibility-induced response conflicts both on a behavioral and on a neural level. Lastly, we will point out limitations of the study and future directions for research in CNA and conclude with the main implications of our SRC study.

4. 1 Behavioral data

Our behavioral results corroborate previous findings of a difference in RT and ER between compatible and incompatible responses in manual SRC tasks. These *SR-incompatibility costs* in RT have consensually been interpreted as correlates of the additional 'computational load' that is required when reacting to the presentation of incompatible stimuli (Cieslik et al., 2015b; Cieslik et al., 2010; Matsumoto et al., 2004). In line with previous work (Langner et al., 2015; Grandjean and Collette, 2011; Proctor et al., 2005) our findings go beyond this mere replication of incompatibility costs in a substantially larger sample.

Our results furthermore provide evidence of worse *age-related* performance responding to both spatially compatible and incompatible stimuli, which is reflected in a significant increase of behavioral *SR-incompatibility costs* with age. This age-specific ICE on RT is strongly driven by the positive correlation of age and RTIC and not by an improvement of the RT under the compatible condition in advanced age. Worse performance in older subjects is reflected by both slower response speed and lower accuracy in response to the stimuli. Higher age-related RTs do not account for more accurate responses during the task. We thus cannot confirm a speed-accuracy trade-off shift towards higher accuracy leading to the higher RT in older age as postulated in earlier studies (e.g. Cieslik et al., 2010; Smith and Brewer, 1995; Rabbitt, 1979). Previous data suggests that age-related decline in performance goes beyond a general cognitive slowing and might be a selective age-related deficit in cognitive action control (Langner et al., 2015; Gazzaley et al., 2005).

Both on a behavioral and on a neural level, EFs have been shown to split into different subcomponents (Turner and Spreng, 2012). Reacting to an incompatible stimulus, cognitive control processes are required that can conceptually be divided into subprocesses (see introduction, Reuter-Lorenz and Park, 2010; Nee et al., 2007; Munoz and Everling, 2004; Hommel, 1997) with respective behavioral and neural correlates (Langner et al., 2015; Cieslik et al., 2010). These additional *top-down control* processes (i.e. higher computational load, see above) can lead to our higher RTs, but usually cannot account for higher ERs which au contraire would rather be caused by dysfunctional control mechanisms and thus can only partly explain our findings. This suggests the presence of different age-related changes leading to deficits in cognitive performance. Tam et al. (2015) specifically investigated the age-related effects on the neural correlates and mechanisms underlying intra-individual RT variability, corroborating age-related changes in these mechanisms and supporting the concept of functional plasticity as a mechanism to maintain cognitive control on a high level over the lifespan.

We included the behavioral incompatibility costs as a covariate in the subsequent analysis of the imaging data, linking our data on behavioral and neural correlates of subprocesses of cognitive action control.

4.2 Imaging data

4.2.1 Replication of task networks

Before investigating age- and performance- related effects we performed a 'sanity check' of our data making sure we could replicate findings concerning the *general task (SRC) effect* and the *SR-incompatibility effect* with the *bottom-up* and *top-down processes* involved (Cieslik et al., 2010) in our sample. Testing for all conditions against baseline, we confirmed the involvement of brain areas of the *general SRC task effect*, reflected in an activation of bilateral PMC, SPL extending into left IPS, cerebellum and left aIns. The brain regions showing activation during the SRC task are known to be associated with the *two response selection processes* in visuospatial tasks of reflexive *attention* towards visual stimuli with consecutive direct *automatic response activation* of motor responses for compatible stimuli and additional cognitive control processes involving subprocesses of *inhibition, reorientation and volitional initiation of motor sets* for the incompatible stimuli (Cieslik et al., 2015b; Cieslik et al., 2010). Our (ventral) fronto-parieto-insular *SR-incompatibility-related task network* (consisting of bilateral DLPFC, PMC, SPL, IPS, cerebellum, aIns, (pre-) SMA, MCC, as well as left IPL in model 1 and bilateral PMC, IPL, SPL, IPS and cerebellum, as well as left aIns and IFG in model 2), reflecting modulating *top-down* effects independent of direction, was in line with previously identified brain networks involved in solving spatial SR-incompatibility. Cieslik et al. (2010) also found activation in a fronto-parieto-insular network including bilateral dPMC, IPS, aIns, pre-SMA, MCC, right TPJ and right DLPFC. The putative *task-positive network (TPN)* which is involved in a variety of attention-demanding externally-driven cognitive tasks and that consists of DLPFC, IPL, IPS, orbital gyrus, frontal eye field (FEF), inferior precentral sulcus, SMA, pre-SMA, MTG, insula and frontal operculum

(Fox et al., 2005) also resonates with our findings. The general elements of the spatial cognitive model as postulated by Barrett (2013) are well reflected by our *incompatibility-related task network*. They involve first of all perceptual-attentional components, requiring awareness of the stimulus and leading to sensation and then to representational and motor-intentional operations of aiming. Literature on *inhibitory theory* agrees on the fact that *attention regulation* is crucial to all cognitive functions, especially to WM (Lustig et al., 2007; Hasher et al., 1999). Successful down-regulation, i.e. inhibition, of excessive activation and non-relevant stimuli is the decisive step in the inhibition process and shows extensive inter-individual and age-related differences (Lustig et al., 2007). When trying to understand which of these processes are specifically associated with aging, the involved task-related areas have to be understood in their function and functional connectivity and therefore will be analyzed in the context of established theories and networks of CNA in the following sections. Corbetta et al. (2008) extensively reviewed the two interacting, but partially segregated, i.e. the dorsal and ventral, fronto-parietal networks involved in attention processes. Both show activation associated with (unexpected) target detection and reorientation to stimuli, which is also intuitively reflected in our incompatibility and age- related findings. The *dorsal fronto-parietal network* is supposed to be responsible for goal-directed *top-down* control mechanisms and includes dorsal parietal areas such as IPS and SPL and dorsal frontal areas along the precentral sulcus extending into the FEF. The right hemisphere dominant *ventral fronto-parietal network* consists of the TPJ, the ventral supramarginal gyrus and ventral frontal cortex, especially MFG and IFG, frontal operculum and aIns. In the context of these two networks the ventral network is considered a 'circuit breaker' of the dorsal system, responsible for interrupting and resetting ongoing activity by detection of reorientation to relevant stimuli or distractors and thus is suppressed when attention is focused (Corbetta et al., 2008; Corbetta and Shulman, 2002). The reflection of these networks representing subprocesses of cognitive action control in our task network again underlines the applicability of the SRC task investigating neural correlates of these control processes.

Brain areas associated with stimulus-driven orienting to and *bottom-up processing* of the respective stimulus in our sample lead to a similar pattern of activity for left- and right-sided stimuli with a strong *lateralization* effect, except for the ipsilateral cerebellum, *contralateral* to the stimulus side. We found activation in contralateral IPS, SPL, pallidum, thalamus and ITG for right- and left-sided stimuli. The latter lead to a more extended network of distributed neural activity increases additionally recruiting contralateral cerebellum, dPMC, MFG, IFG and bilateral caudate (Fig. 7 A and B; Table 6 A and B). This *unilateral* pattern of frontal activity and activity of *right dPMC* dealing with left-sided stimuli, i.e. pressing with the left hand (Fig. 7 A) was not contingent on differences in thresholding or in the frequency of stimulus presentation that was equally balanced for both sides. A recent study on inter-hemispheric connection during grasping tasks supports evidence for lateralized patterns of dPMC dominance by pointing out that the right dPMC is responsible for planning and execution of action and also for recruiting the left dPMC that has to successfully perform this action. Begliomini et al. (2015) describe the connection between left and right dPMC as a 'bridge' between the hemispheres, with the respective hemisphere involved in the task demands always additionally recruiting the contralateral resources of the dPMC. These findings still

do not account for the observed side-specific dominance of right dPMC in our study. Langner et al. (2012) identified right PMC as a part of a supramodal network responsible for intrinsic alertness facing tasks of different modalities. They provide evidence for right-hemispheric dominance in sustaining response readiness dealing with auditory, tactile and visual stimuli. DPMC seems to be involved in both, non-motor attentional processes, especially facilitating cue detection, and processes of motor control (Kelley et al., 2008; Kansaku et al., 2004; Graziano et al., 2002). Hlustik et al. (2002) report a functional lateralization of the dPMC during sequential movement tasks. In right-handed participants, the left dPMC is involved when performing hand movements on both sides. Thus we would expect an activation of left-sided dPMC dealing with both right- and left-sided stimuli, as a correlate of automatic response activation during the spatial SRC task. After applying our contrast to delineate side-specific activation for the right side, i.e. subtracting neural activity of right-sided stimuli independent of motor response from compatible responses for left-sided stimuli, we might have eliminated simultaneous side-selective activations in dPMC on the left side, leading to the observed lack of increase in activity in left dPMC. In the aforementioned study of grasping actions, the monitoring role of dPMC is particularly evident when the less-skilled left hand is utilized, which potentially needs more control to successfully complete the task (Begliomini et al., 2015). These additional control processes might also account for increased unilateral involvement of MFG and IFG (cf. above). As our sample consisted of 62 left- and 204 right-handed participants (cf. above), our finding of a unilateral dominance of right dPMC in combination with increased right-sided frontal activity when reacting with the left, non-dominant hand is well in line with these results. Including handedness as a covariate in our analysis would be an important next step to refine and confirm this unilateral activation pattern.

Looking specifically at the functional differentiation of the IPS that was also involved in *bottom-up processes*, we also found hemispheric differences. For left-sided stimuli right IPS (human intraparietal sulcus (hIP) 3) was activated, whereas right-sided stimuli lead to activation of left IPS (hIP1, hIP2 and hIP3) as also found in our general task effect (see table 5B and 6A, p. 26 and 28). This hints at a functional and anatomical dissociation of the IPS as well as at side-specific differences as stated by Neyens et al. (2017) who replicated activity patterns of semantic similarity represented by left middle IPS (hIP1, hIP2, hIP3) across different experiments. The anterior parts of the IPS (hIP2, Choi et al., 2006) are specifically associated with reorientation of motor attention dependent of the task (Cieslik et al., 2010). All three areas typically are activated in tasks requiring spatially selective attention when competing distracters of the cue are present which potentially enter the WM, leading to stronger activation compared to situations without distracters (Neyens et al., 2017). Activation in *area hIP3 of contralateral IPS* is*,* as already found by Cieslik et al. (2010), in line with its function in coding stimulus-driven visuospatial bottom-up input from the visual cortex (especially extrastriate visual areas such as V5, see table 6A, p. 28) contralateral to the stimulus side. After reorienting towards the cue, the information is forwarded by the IPS to the closely associated *PMC,* by which it can be used to compute the respective movement and which thus links sensory information and motor responses. In combination with the IPS, neural activity increase of the PMC when dealing with compatible stimuli might facilitate the initiation of the required motor response and hence lead to the

behavioral advantage in form of a shorter RT (Cieslik et al., 2010). We can corroborate and emphasize lateralization effects in stimulus-driven bottom-up processes as reviewed by Silver and Kastner (2009) and confirmed by Cieslik et al. (2010) for both, left- and right-sided stimuli and the functional role of IPS and PMC in a significantly bigger sample.

4.2.2 Top-down processes and their neural correlates

Compared to bottom-up responses discussed above, dealing with *incompatible* stimuli leads to the involvement of further areas (see the *SR-incompatibility-related task network* after contrasting incompatible vs. compatible responses; section 3.2.1, Fig. 4 and Fig. 6 B, pp. 21 and 25). Due to associated *top-down processes,* higher computational load is necessary, as the primed response needs to be inhibited before a contralateral motor response can be executed. Two meta-analyses of Eickhoff et al. (2012; 2009) examined networks showing activation during inhibitory control. Those consisted of aIns, IFC, DLPFC, dorsomedial PFC (DMPFC), ACC, posterior parietal cortex (PPC) and basal ganglia, with the right aIns showing the most significant peak. Zanto and Rissman (2015) review neuroimaging studies on top-down suppression and confirm a consistent fronto-parietal network involved in modulating these processes, independent of the task features that have to be suppressed (e.g., spatial locations or internal representations). Neural correlates of top-down processes in the spatial SRC task are aIns and IPS/TPJ, involved in maintenance and integration of task-sets, and right DLPFC and pre-SMA, playing a crucial role in the processes of inhibition and volitional movement initiation (Cieslik et al., 2010). The aforementioned regions are well reflected in our task network consisting of bilateral DLPFC, PMC, SPL, IPS, cerebellum, aIns, (pre-) SMA, MCC, as well as left IPL in model 1 and bilateral PMC, IPL, SPL, IPS and cerebellum, as well as left aIns and IFG in model 2. In the next sections we comment on the identified, incompatibility-related areas in the light of current literature before including age-related effects in our discussion.

Investigating the neural basis of inhibition, the literature agrees that the *PFC* with its distinct cytoarchitectonic areas and functional axes (for a review see Fuster, 2015) is a core element of inhibition processes and especially in young adults associated with inhibitory control (Garavan et al., 1999). Within the PFC, inhibition has been associated with different regions, varying between DLPFC, inferior frontal cortex (IFC) or orbitofrontal cortex, with especially literature in neuroimaging postulating the existence of diverse foci in PFC. From these areas, inhibition is effected on subcortical and posterior-cortical regions to successfully implement executive control (Aron et al., 2014). Both, DLPFC and IFC have shown high spatial variability across studies (Cieslik et al., 2016). The crucial role of *IFC* in processes of cognitive interference requiring inhibitory control was stressed and confirmed by a right hemisphere dominance of this area in recent studies of human lesion (Aron et al., 2014; Jonides et al., 2000). As the adjacent right aIns mostly coactivates with the right IFC when executing inhibitory control during various tasks, Cai et al. (2014) specifically analyzed these two subregions of the right fronto-opercular cortex in order to identify neurobiologically and functionally dissociable elements of inhibitory control. The right IFC is involved particularly in early stages of the inhibitory control processes by initiating a stop and control process

whereas the right aIns is characterized by stimulus characteristics and accuracy and thus determining the outcome. Being closely connected to motor frontal lobe areas, the right *DLPFC* is not only responsible for monitoring motor behavior and inhibiting activity in posterior associative and in sensory cortices (Cieslik et al., 2013; Bates and Goldman-Rakic, 1993), but it also plays an encompassing modulating role in cognitive control processes (Badre and D'Esposito, 2009). In studies using SRC-related tasks, the DLPFC has constantly been referred to, especially when generating antisaccades, i.e. incompatible reactions (Ettinger et al., 2008; Ettinger et al., 2005; Ford et al., 2005; DeSouza et al., 2003; McDowell et al., 2002). It, when activated individually, correlates with a superior task performance (Zheng et al., 2008; Snitz et al., 2005; MacDonald, 2000). This superordinate, top-down-directed role of the DLPFC is reflected by connectivity not only to the frontal, but also to the parietal lobe and the PMC (Cieslik et al., 2013; Lu et al., 1994; Andersen et al., 1990), which enables the DLPFC to effectively execute its frequently reported top-down modulations (especially suppressions) of other areas in stimulus-driven action inhibition (cf. above). Within the DLPFC multiple networks and functional connectivity to different areas have been reported, proving the existence of differentiable correlates of cognitive action control with especially the anterior network being involved in processes of attention and action inhibition (for a detailed review see Cieslik et al., 2013). In line with these findings we suggest that incompatibility-related activation of DLPFC in our data is a correlate of successful inhibition of the prepotent ipsilateral reaction in favor of the desired incompatible reaction.

From our SR-incompatibility-related network, areas also showing connectivity to motor frontal lobe areas such as the DLPFC are *SMA* and *pre-SMA*. The latter is part of the dorsomedial frontal cortex and connected with the basalganglia (striatum and STN) and with the rostral IFC (Aron et al., 2014; 2011). In its structural and functional connectivity with the latter, the anterior SMA has been classified as a 'negative motor area' as manual movements and speech arrest when the area is stimulated (Filevich et al., 2012). Findings concerning the potential functions of the pre-SMA lead to the hypotheses of the pre-SMA generating a control signal, which leads to implementation of inhibitory control via rostral IFC (Aron, 2011; Fried et al., 1991). Furthermore, Cieslik et al. (2011) in an SRC-related experiment found out, that pre-SMA is responsible for inhibition of automatic response tendencies in incompatible trials. Pre-SMA shows close connections to aIns and MCC, altogether being involved in task-set implementation (Langner et al., 2015; Kurth et al., 2010; Dosenbach et al., 2007) and the aMCC/pre-SMA especially having a mediating role in activating the task set (Cieslik et al., 2015a). In their meta-analysis Cieslik et al. (2015a) postulate that core regions involved in processes of inhibition (right aIns and right TPJ) are not, as often argued, generally controlled via inhibition through the PFC. AIns and TPJ act rather indirectly, monitoring the relevant task sets and implementing inhibitory control by activating those areas relevant for processing in cases of discrepancies between the goals and the predominant task sets. In another meta-analysis investigating studies using antisaccade tasks to study cognitive action control, the association of aMCC to various aspects of eye movement control was confirmed. Medial FEF and aMCC were especially involved with increased control demands in antisaccades compared to prosaccades and were part of a dorsal, fronto-parietal network suggesting the relevance of these areas when responding to visual and especially

incompatible stimuli during various cognitive control processes (Cieslik et al., 2016). With the increased incompatibility-related activity of MCC and pre-SMA in our data we support their mediating roles, especially in task-set implementation, control processes and inhibition, when dealing with the SRC task.

We found increased activation in *aIns* for the general task effect and SR-incompatibility-related in both our models. The multifunctional aIns region is generally associated with various processes (cognition, perception, socio-emotion) and involved in the integration of interactions with associated brain regions and the selection and maintenance of task-sets. In a recent meta-analysis (Langner et al., 2018) bilateral aIns was identified as a core neural correlate of processes of self-regulation when executing both cognitive control of emotion and of action. Especially left aIns is as a core region related to processes of the WM and thus crucial to successful execution of cognitive processes, whereas aIns in the right hemisphere is pivotal for monitoring and implementing task-sets (Cieslik et al., 2015a; Clos et al., 2014; Rottschy et al., 2013; Kurth et al., 2010; Dosenbach et al., 2007). In their meta-analysis on cognitive action control Cieslik et al. (2015a) stress the crucial role of right aIns and right IFJ for attentional processes, as those areas were involved in all tasks included in their analysis. Another meta-analysis shows that the IFJ is closely involved in processes of cognitive control, especially for updating task representations (Derrfuss et al., 2005). Trautwein et al. (2016) analyzed the established *model of human attention* postulating the involvement of two different functions: stimulus-driven reorientation and executive control of attention. These functions are supposed to overlap in areas such as left aIns, which share the underlying neural mechanisms and are characterized by a reverse activation pattern in the anterior TPJ, showing activation during stimulus-driven reorienting and deactivation when performing executive control. Corbetta et al. (2008) see the aIns as the source of the *top-down* signals necessary to modulate and limit activation of associated areas such as TPJ or DLPFC in reaction to specific task-relevant stimuli. The TPJ itself has also an integrational role dealing with task-sets and sensory input (Bzdok et al., 2013). Anterior TPJ furthermore shows connectivity with aIns facing situations that require executive control of attention (Trautwein et al., 2016; Bzdok et al., 2013). These findings concerning the involvement of *aIns in inhibition processes* are in line with the results of Cai et al. (2014) and lead to our interpretation of task-related insular activation. In our task the aIns potentially reflects the subprocesses necessary when dealing with the more complex incompatible condition by modulating associated areas in order to maintain the task-set. This view is supported by age-related increase of incompatibility-related activation in left aIns in our data, potentially reflecting the higher demand for control via aIns under the complex condition that is required with increasing age.

Involvement of *IPL and TPJ* when dealing with the demands of the SRC task was shown in the earlier study of Cieslik et al. (2010) and confirmed by our findings. The TPJ is the posterior portion of the superiortemporal sulcus and gyrus and is in structure and function closely connected to the IPL. There are neuroanatomical as well as functional and cytoarchitectonical definitions of these areas, leading to a variety in the nomenclature and areas assigned (Zhang and Li, 2014; Bzdok et al., 2013; Corbetta et al., 2008). The function of the IPL/TPJ area is especially characterized by its involvement in higher-order functions and in processes of bottom-up perception, response inhibition, memory retrieval, language processing and

(social) cognition. This variety of associated behaviors and conditions leading to an activation of IPL/TPJ led to a great heterogeneity in the range of naming these brain regions (Igelstrom and Graziano, 2017). As bottom-up attention is crucial for the SRC task employed in our study, we want to elaborate especially on the role of IPL/TPJ in stimulus-driven reorientation of attention. The activation of IPL/TPJ in these areas is especially found in situations of unexpected stimuli and those relevant for current behavior (Seghier, 2013; Corbetta et al., 2008; Corbetta et al., 2000). Furthermore, there are side-specific differences in IPL/TPJ and its connectivity with especially the right side showing crucial involvement in spatial attention detecting targets in unattended locations (Corbetta et al., 2002; 2000). Bzdok et al. (2013) confirmed differential functional modules in right TPJ and supplementary a rostro-caudal increase in cognitive complexity for left IPL (Bzdok et al., 2016). The latter finding might complement earlier data of a rostral to caudal shift in complexity from higher motor functions to spatial attention in right IPL (Caspers et al., 2011). Via fMRI Zhang and Li (2014) identified seven clusters of the IPL - the anterior, middle and posterior subregions. These regions show connectivity to somatomotor areas, to frontal gyri and to regions of the DMN (Schilbach et al., 2012; Buckner et al., 2008; Greicius et al., 2003) with hemispheric asymmetries of the connection patterns (Caspers et al., 2011). The aforementioned side-specific differences are only partly in line with our results, as we found activation in left (in our model 1, p. 18) and bilateral (in our model 2, p. 18) IPL in our SR-incompatibility-related, but not in our general task network. This focus on the SR-incompatibility network stresses the relevance of inferior parietal areas for processes of spatial shifting (Schrooten et al., 2017; Gillebert et al., 2013; Corbetta et al., 2000; review: Vandenberghe et al., 2012). Our results corroborate involvement of IPL/TPJ as a key region in the reorientation network when dealing with a spatial task.

Besides an activation of aIns we found activation of *PMC, IPS and SPL* testing for the general task and for the incompatibility main effect (both representing generalized top-down effects) as well as when specifically investigating stimulus-driven bottom-up processes. This substantial overlap within the *dorsal fronto-parietal attention network* (cf. above) suggests that both processes are reflected by the same neural correlates within PMC and IPS/SPL. These correlates seem to be core areas when dealing with SRC tasks, processing spatial features of both, stimuli and responses (Cieslik et al., 2010; Schumacher et al., 2007; 2003; Beurze et al., 2007). The action-related *PMC* is typically involved in processes of movement *selection*, especially in its central subregion and in combination with the parietal cortex areas, which are responsible for motor attention and processing of movement intentions (Genon et al., 2017; Grefkes and Fink, 2005; Rushworth et al., 2003). Within the dorsal fronto-parietal attention networks (Corbetta et al., 2008), *IPS* and *adjacent SPL* are the crucial areas of the PPC, with the IPS being involved in visuomotor and attentional processes, directing *spatial attention*. As mentioned above, IPS and PMC are modulated by e.g., TPJ and DLPFC and, depending on their input, map visual stimuli with the required – incompatible or compatible – motor response (Corbetta et al., 2008). Schrooten et al. (2017) confirm a robust and consistent activation of SPL during spatial shifts independent of its direction, whereas IPS seems at least in nonhuman studies to be sensitive to the side to which attention is directed and shows a functional differentiation of its cytoarchitectonic subregions and sides (Neyens et al., 2017). The left inferior parietal

cortex shows an association to motor intention, i.e. motor reaction to a stimulus (Rushworth et al., 2001; Davranche et al., 2011) whereas the right side is particularly related to visuospatial reorientation of attention and overriding bottom-up driven spatial orientation by coding visuospatial information (Grefkes and Fink, 2005; Rushworth et al., 2003; Nobre, 2001). In contrast, Davranche et al. (2011) hypothesize that the left IPS is the substrate for temporal orientation and more lateral inferior parietal regions on the left side correlate with motor aspects of reorienting attention. The latter regions have been associated with the selection and preparation of hand movements on both sides (Hesse et al., 2006). Increased activity of IPS was not only present in our SR-incompatibility-related task network. Participants with larger incompatibility costs showed a stronger recruitment of left IPS (in our model 1) and in bilateral IPS extending into left SPL (in our model 2), corroborating the idea of *difficulties in overriding processes of bottom-up spatial orientation reflected by IPS*. On a functional and a histological level we could only partly confirm the findings of Cieslik et al. (2011) of differences in the IPS between top-down processes (evoking activation in hIP1, hIP2 and hIP3) and bottom-up activation being focused on contralateral hIP3, i.e. the middle part of the IPS, which is responsible for stimulus-driven orientation. As bottom-up processes dealing with right-sided stimuli additionally lead to findings similar to the top-down correlates we cannot clearly assign posterior or anterior parts and their respective functions of IPS to these subprocesses. Having the aforementioned functions of IPS in mind, occupation with additional processing steps responsible for controlling the dominant reaction might lead to the observed worse performance during incompatible conditions. We come back to these implications in more detail, when we review our age-and performance related findings of the task network in the following sections.

Concluding this chapter, we briefly comment on the *cerebellum* that is bilaterally involved in both, bottom-up and top-down processes. During the SR-incompatibility-related task we found higher activity in bilateral lobule VIIa (cruisei) in both our models and in model 1 additionally in vermis (Diedrichsen et al., 2009). In light of our task and the cognitive control processes involved, our results perfectly undermine the findings of Buckner et al. (2011) who in their FC study on the organization of the human cerebellum delineated lobules VII as areas showing activation during cognitive tasks on e.g., WM or EFs, potentially contributing to processes of higher-level cognition. In their study on prefrontal-projecting cerebellar lobules Balsters et al. (2010) suggest a parallel between the development of cognition related cerebellar areas (Crus I, Lobules VI and VII) and the interconnected PFC, going beyond a mere somato-motor focused view of the cerebellum. On a more general level, the cerebellum modifies and enhances performance on tasks that require a timed response to a stimulus, potentially by improving motor planning or coordinating movement timing (Seidler et al., 2002; Horwitz et al., 2000; Ivry and Keele, 1989). Contributing to regulation of posture and locomotion, the cerebellar vermis is controlled via descending projections from cerebral motor areas (Coffman et al., 2011). These cerebellar functions fit well with the involvement of bilateral cerebellum in our task. Higher cerebellar activity is bilaterally correlated with higher age in both our models, suggesting that the initiation and performance-related enhancement of a context-dependent motor response might be stronger, i.e. more effortful in older age. This first suggestion of age-related effects on our SRC task networks leads to the next section of neural correlates of age-

related changes and their potential function.

4.2.3. Age-related differences in task-related brain activity

We included *age* as a covariate in our first model category (model 1, including the main ICE as main regressor) and in the second model category (model 2, including the four task regressors CL, CR, ICL, ICR) to specifically examine effects of aging on the aforementioned incompatibility network. Our results were partly overlapping between the two models as well as with the incompatibility network when investigated independently of age and with the neural correlates of increased RT incompatibility costs. We point out the most striking age-related findings in the following section.

Whereas the right IPL was not activated during the general incompatibility effect, we found bilateral age-related activity in model 1 (Fig. 5 A; Table 4 A), suggesting that the *left IPL*, an area particularly involved in spatial shifting (Corbetta et al., 2000), might be stronger and the *right IPL* additionally recruited by older adults dealing with the SRC task. The alignment of our results with previous findings in literature is exacerbated by the heterogeneity in the use of the term 'inhibition' and the vast number of tasks employed when testing for EFs and cognitive control. As Turner and Spreng (2012) confirmed in their meta-analysis, the age-related changes observed during processes requiring EFs are task-related and depend on the specific control process necessary for the respective task. Thus, our age-related activation of left IPL in the SRC task is only to a limited extend comparable with their findings in WM tasks of age-related increased activity in left IPL together with bilateral DLPFC and SMA. In their study, inhibitory control tasks showed age-related activity in right IFG and pre-SMA well confirmed by our findings of the age-related incompatibility effect in model 2 (bilateral IPS/SPL, cerebellum, left aIns and right IFG, DLPFC and MCC). For right aIns and frontal operculum, Turner and Spreng (2012) found involvement with inhibition for both younger and older adults. The age-related increase in *left aIns* of the incompatibility network (model 2) and its interpretation in the context of increased control mechanisms facing the incompatible condition have been commented on above. The lateralized activation of left aIns seems to be age-related, potentially reflecting the increased demand of stimulus-driven reorienting and executive control attention, i.e. functions which are supposed to overlap in left aIns (cf. above Trautwein et al., 2016). Increased bilateral age-related activity in lateral PFC is a finding shared by all EF tasks, especially in WM tasks (e.g. Townsend et al., 2006; Jonides et al., 2000) and also reflected in our task network. In the next paragraphs we will discuss our age-related findings in the context of the models of CNA introduced above.

HAROLD model: We found an incompatibility- and age-related activation of the *right DLPFC* when isolating areas showing activation under incompatible compared to compatible conditions (see Fig. 8 B and Table 7 B; model 2; pp. 31-33), which was not persistent after applying the more strict approach of only including age-related activation stronger under incompatible than compatible conditions (see Fig. 8 C and Table 7 C; model 2; pp. 31 and 33). This variability in the activation of right DLPFC suggests an

interpretation in the context of a (decreased) laterality effect in older adults in the sense of the HAROLD theory introduced above (Cabeza, 2002) as well as a task condition-dependent interpretation as referred to in CRUNCH theory (Park and Reuter-Lorenz, 2009). According to the former theory, older subjects tend to activate additional areas contralateral to the sites typically activated in younger age, classically leading to a bilateral pattern of activation in the PFC. The fact that we cannot confirm such a pattern of bilaterality might be based on the observation that the activity in PFC in older age is often asymmetric in strength per se and differently affected by ageing. The age-related recruitment of right PFC, more precisely of DLPFC as corroborated by our findings, might hence serve as a compensatory attempt to counterbalance reduced contralateral activity in this modulating control region in older age (Cabeza, 2002; Rypma et al., 2001). Our study thus not only supports the HAROLD theory and proves its generalizability on the SRC task, but also refines it by identifying the dorsolateral aspects of PFC as the areas being particularly involved in age-related processes of change. Additionally, the bilateral age-related activity in IPL (cf. above) might also illustrate and support the HAROLD theory of decreased laterality in older age.

Functional connectivity: Based on their WM tasks, Rypma et al. (2001) also postulate that aging affects dorsal regions of PFC and relate them to executive components of WM. Our results are well in line with the aforementioned relevance of DLPFC for processes of cognitive action control as addressed by the SRC task (Cieslik et al., 2013). The hyperactivity in DLPFC in our study was accompanied by activity in the MCC with its posterior parts (pMCC), amongst other areas, involved in movement direction and with its anterior aspects (aMCC) related to reward behavior and decision-making (Vogt, 2016). Interestingly, in the context of the SRC task, the areas involved in age-related FC change or decrease are right DLPFC, bilateral aIns, pre-SMA and aMCC. Observed age-related decline in the coupling of aIns and pre-SMA might cause deficits in task-set implementation and efficient inhibition via pre-SMA and lead to the worse age- and incompatibility related performance as well as to compensatory hyperactivity in these areas (Langner et al., 2015). In our data we indeed found age- and compatibility-related activation in bilateral aIns and aMCC, but only in left aIns and right MCC when contrasting for age-related correlations with the incompatible condition for which we suspected activation in aIns and pre-SMA to be crucial. Due to its age-related decrease in FC with left and right aIns, the age-correlated hyperactivity in right DLPFC might, in addition to the consistency with the HAROLD theory, as well be a complementary mechanism for reduced FC with age (Langner et al., 2015). The integration of structural and functional studies lead to new possibilities when interpreted in the context of the established models (Sala-Llonch et al., 2015), once again stressing the interdisciplinary context of CNA and the difficulties interpreting standalone models. Thus, Maillet and Rajah (2013) postulate that the commonly reported age-related atrophy of frontal grey matter triggers activity increases in the PFC. The extent of compensatory function of this hyperactivation again depends on integrity of more distal structures, especially in the medial temporal lobe, which correlate with PFC activity. This example reflects the increasing difficulty in uniting findings from the growing numbers of structural and functional studies in neuroimaging. With our findings we support the idea of (lateralized) regional age-related hyperactivity as being compensatory for decreased FC with other task-related areas.

CRUNCH model: In line with the CRUNCH hypothesis our findings are marked by a characteristic prefrontal change in activation dependent on the condition of the task. We found bilateral increase in activity in DLPFC for the general incompatibility effect independent of age, right-sided relatively increased neural recruitment in DLPFC interpreted in the sense of the HAROLD hypothesis when including age as a covariate and a lack of activation including age under the more strict approach, contrasting incompatible with compatible conditions and thus only including the condition with high demand. These varying activations across tasks might reflect the limited capacity in older age to activate task-relevant brain areas as related to in CRUNCH theory. Neurobiological changes in the aging brain potentially facilitate an overload in WM capacity in comparison to young subjects (Reuter-Lorenz and Cappell, 2008). Having this concept of dynamic compensation in mind, the pattern can be transferred to other task- and age- related brain areas. In situations with minimum to moderate degree of difficulty (compatible condition), an activation of necessary brain areas can be provided bilaterally (e.g., aIns, aMCC see Fig. 8 A and Table 7 A; pp. 31-32), whereas – with increasing difficulty (incompatible condition) a decrease in this broad activation leads to only side-specific activations (left aIns, right MCC, see Fig. 8 B and Table 7 B; pp. 31-32) which completely vanish under a more strict approach (Fig. 8 C and Table 7 C; pp. 31 and 33). This switch from demand-dependent hyper- to hypoactivity is implied in CRUNCH theory for prefrontal areas and is conceptually corroborated by our findings in different areas. The results of Sebastian et al. (2013a) additionally support the hypothesis of a CRUNCH-like prefrontal pattern as a possible explanation of age-related prefrontal increases in other than WM tasks, showing good performance and higher activation at tasks with low demands and deficits in both performance and activity with increasing task demands (Reuter-Lorenz and Lustig, 2017).

YOUNG PLUS pattern: Of the cortical subregions showing increased activation with higher age and incompatibility, right IFG, MFG, aIns and IPL are consistent with the *fronto-parietal neural core inhibition* network postulated by Sebastian et al. (2013b). These regions differ in their extent of activation during tasks of response inhibition. In *right MFG* dorsal and ventral attention networks overlap. Within the ventral attention network each node is involved in different aspects of bottom-up attention with the right MFG being involved in attention reorientation. It thus can be considered the transitional point between top-down and bottom-up control of attention (Japee et al., 2015; Corbetta et al., 2008). Age-related hyperactivity in this area might hence reflect the necessity of older adults to additionally recruit this gateway when dealing with the SRC task. Investigating inhibitory control regions, supported by our findings, inhibition was associated with hyperactivity in right IFG, IFJ and left medial superior frontal gyrus (SFG) in older compared to younger adults (Goldberg, 2017) and interpreted as the *young plus pattern* as these areas are commonly used by younger and over-recruited in older adults (Simmonds et al., 2008). This pattern of overall hyperactivation (Turner and Spreng, 2012) has to be distinguished from the *expanded inhibition deficit theory* (Dennis and Cabeza, 2008), characterized by *hypoactivtion* in the core inhibition network and parallel *hyperactivation* in an expanded network. The latter theory is based on a distinction between inhibitory control regions (exerting the inhibition) and inhibited regions (those affected by inhibition). The theory implies that older adults show a phenomenon of disinhibition (greater

activity) in the regions that should be inhibited, but a weaker activity in the control regions. When trying to compensate for their deficits of activating the latter, an increase in the alternative, e.g., contralateral, control regions would be expected. These hypotheses are supported by findings of neuroimaging studies with older adults showing less activity in the control regions (e.g. left IFC, a core inhibitory region in young adults; Jonides et al., 2000) and more in areas that are supposed to be inhibited. Jonides et al. (2000) additionally found an age-related decrease in left VLPFC during an inhibition task, suggesting that the area usually responsible for inhibitory control of the WM, loses its ability to efficiently inhibit interfering effects. Cabeza et al. (1997) found increased *insular* activity during a task correlating with worse performance interpreting it as a neural correlate of inhibition in older adults. In a selective attention task older adults managed to up-regulate activity required for the task, but not to down-regulate irrelevant activity (Gazzaley et al., 2005). Similar to the argumentation of Sebastian et al. (2013a) concerning the Simon task employed in their analysis, IFG and MFG are not involved in our general task and the SRC network, rather supporting the idea of the expanded compensatory inhibition network instead of a *young plus* pattern.

The goal of recent analyses as well as of this study is to resolve contradictions in existing literature by analyzing subprocesses of cognitive action control, EFs and especially inhibition separately, extending the number of meta-analyses in the past years (e.g. Sebastian et al., 2013a; Turner and Spreng, 2012; Swick et al., 2011; Nee et al., 2007) and refining theories of age-related changes. Sebastian et al. (2013a) point out that, across the tasks included in their analysis, they could not find a coherent de- or increase in the investigated inhibition network across tasks and that their results are not consistent with neither of the aforementioned theories, stressing the importance of targeted *task- and subcomponent specific* studies. After their quantitative meta-analysis on age-related process-specific EF changes, Turner and Spreng (2012) came to a similar conclusion, pointing out that the typical age-related brain pattern is strongly related to the specific process of EF being addressed. The individual EFs all have overlapping but unique neural correlates. This interdependence of age-related effects on inhibitory and attentional control and WM is also addressed by a recent revision of Reuter-Lorenz and Lustig (2017). They evaluate the results of the meta-analysis of Turner and Spreng (2012) and the consecutive meta-analysis of Sebastian et al. (2013a) as mainly consistent with the CRUNCH hypothesis, a dynamic model of cognitive aging. With our findings we are inclined to support this model and transfer the idea on various brain areas.

4.2.4. Performance-related differences in task-evoked brain activity across the lifespan

As mentioned in the introduction, to solve and refine the contradictory interpretations of compensatory mechanisms, the terms of 'attempted' and 'successful' compensation were amended to the HAROLD model. In order to examine whether recruitment of additional resources in older age also leads to changes in performance, we included behavioral incompatibility costs in our analysis. Independent of direction we investigated top-down modulated processes of reorientation of attention dealing with incompatible stimuli

and their correlation with *higher RT incompatibility costs*. These performance-related changes in neural activity in model 1 (activation of left IPS) were not shared by age-related changes, but in model 2, where the higher RT incompatibility costs reflected by activation in bilateral IPS, IPL and vermis and left SPL partly overlapped with the age-related incompatibility effect. Activation of *bilateral IPS* was present with both, higher age and lower levels of functioning, potentially reflecting the fact that difficulties in overriding the bottom-up driven spatial orientation requires further control mechanisms and processing steps which become more likely with age. In its negative correlation with performance in both models, activation in IPS might reflect lower flexibility or stronger dominance of the ipsilateral bottom-up processes, both yielding slower responses under the compatible condition. In the sense of the extended HAROLD model, age-related increases in IPS could be considered 'attempted' but not 'successful' compensation as they correlate with higher incompatibility costs. As the IPS is the only area sharing performance- and age-related activation in our task, we suggest that, in respect to the SRC task and in the context of the CRUNCH hypothesis, the subprocesses reflected by this area (i.e. visuospatial attention) are the crucial elements of cognitive action control correlating with worse, age-related performance. After having recruited IPS under the incompatible i.e. more difficult condition, older adults seem to exceed their capacity in processing and perform worse. This finding is supported by the overlapping activation of area hIP3 of the left IPS for both, the age- and the performance-correlated incompatibility effect. The posterior IPS (hIP3) is responsible for stimulus-driven orienting of visuospatial attention (Cieslik et al., 2010), a process crucial for successfully performing on the task. Its activation stresses the association of this processing step with worse age-related performance. On the right side the pattern was more heterogeneous, as activation was evoked in hIP1, hIP2 and hIP3 of IPS in correlation with age, but in hIP5 when including performance.

After this anatomical and functional dissociation of the involved areas, especially the *IPS*, we suggest that *worse age-related performance* is associated with both, *bottom-up* and *top-down* processes. Potentially, older adults have to be more engaged in attentional bottom-up processes when dealing with the task, and, in the sense of the CRUNCH theory and due to structural decline exhaust their cognitive capacities earlier compared to younger subjects by accomplishing additional control mechanisms. This is especially reflected by compensatory activation of bilateral IPS (esp. left hIP3). When older adults in addition have to perform top-down control, the capacity is exceeded and the compensation cannot be obtained, and hence they perform worse. These findings support the view that despite the range of potential compensational mechanisms, there is no possibility of unlimited over-compensation in older age. There might be an inter-individually differentiable maximum capacity of cognitive control processes – a different cognitive reserve (cf. Stern, 2012; Stern, 2009) – correlating with both increases in age and in task demands.

4.2.5 The default-mode-network and aging

On the behavioral level, we found worse performance for old relative to young subjects for both the compatible and the incompatible, conditions (cf. above, p. 19). Already when dealing with the *compatible*

condition and when trying to preserve a high cognitive performance during the task, older adults seem to be constrained in their compensatory capacity. On a neural level, we identified incompatibility- and age-related patterns of activity that could be characterized as dysfunctional compared to the younger subjects and in respect to the task demands. We did not find any significantly increased activation when *contrasting compatible with incompatible* condition, but when investigating *age-related* changes of this contrast (see Fig. 8 D and Table 8 D; pp. 31 and 33). We found relatively *increased neural recruitment of the DMN* (cf. above) with pronounced midline structures (bilateral posterior cingulate cortex (PCC)/precuneus, middle occipital gyrus (MOG), left IPL, superior FTG and MTG; for detailed reviews of the regions of the DMN see Dohmatob et al., 2017; Raichle, 2010; Buckner, 2005; Shulman et al., 1997) *negatively correlating with age* i.e. showing less activation with increased age. For incompatible compared to compatible conditions we could not identify any area showing deactivation with increased age. We will comment on the potential interplay of the DMN and age-related changes in cognitive control processes in the following sections.

In our study the *baseline* (rest period) was periodically alternated with all task blocks, i.e. both conditions. On a task-demand level, neural activation during the compatible condition with only bottom-up processes involved can be considered an approximation to *baseline* activity compared to the incompatible condition and the associated top-down mechanisms. The *DMN* refers to brain areas showing activation at the baseline in off-task periods when the subjects are resting in the scanner, facing only internal cognitive processes. The DMN is typically suppressed and deactivated when shifting to tasks that require cognitive and sensorimotor processing of external stimuli like the SRC task (cf. Langner et al., 2015; Bzdok et al., 2013; Fox et al., 2005; Gusnard et al., 2001). Literature on the DMN agrees that during 'easier' tasks more brain resources are unused, leading to task-independent processes of mind wandering that are based on memories, autobiographical details and semantic notions. These underlying processes lead to the finding of a relatively increased DMN activity during 'easier' compared to 'harder' tasks (Vatansever et al., 2015; Seli et al., 2016; Dohmatob et al., 2017). With increasing task difficulty younger adults typically show greater deactivation of the DMN and better performance (Fox et al., 2005), whereas suppression of the task-irrelevant DMN is less successful or even fails in older age, leading to lower performances in various tasks (Damoiseaux et al., 2008; Persson et al., 2007; Grady et al., 2006). In respect to our task conditions one could expect a relatively high activity of the DMN facing low cognitive demands, i.e. the compatible condition, and lower activity or suppression of the DMN dealing with the high demands of the incompatible condition. We found indeed higher activity of the DMN during the compatible ('easy' condition) compared to the incompatible ('hard' condition), but also an age-related dynamic that on a first glance is counter-intuitive to the aforementioned insufficient age-related suppression of the DMN. We intuitively would have expected a positive correlation of age and the DMN, especially during incompatibility. The negative correlation with age found during compatible conditions in our study necessitates a more differentiated view on the age-related changes in the DMN. We did not test specifically for task- and age-related changes in the DMN in our sample, but expect the functional role of the DMN to be crucial for interpreting our findings in respect to age-related cognitive control processes.

The DMN typically and intuitively anti-correlates with the TPN mentioned above (Spreng, 2012) with the degree of the anti-correlation being correlated with cognitive performance (Kelly et al., 2008). The balance of the TPN and DMN seems to be crucial for successfully processing cognitive demands and also depends on effectively recruiting the TPN (Spreng, 2012; Grady et al., 2006; Lustig et al., 2003). Goulden et al. (2014) point out that the salience network (Menon, 2015) links the DMN and networks of attentional tasks by helping to switch between task-unrelated and task-related activity. A failure in regulation of DMN activity via the salience network leads to deficits in processes of cognitive control (Bonnelle et al., 2012). Keeping in mind the functional role of the DMN, the observed *deactivation* of the DMN with advancing age (cf. above) could have different reasons: *First*, the age-related deactivation in our sample could be a correlate of age-related deficits or changes in the salience network (cf. above), responsible for switching between DMNs and TPNs, influencing both, cognitive performance and activation in the DMN. The aIns has a crucial role in the functioning of the salience network. The age-related changes in aIns were commented on above. Examining age-related changes in the salience network would be an important next step for conclusively interpreting our results. *Second*, one could assume that higher age leads to a generally *reduced baseline* activity that in a dysfunctional manner implies convergence of task and baseline activity, i.e. between the incompatible and compatible condition and hence potentially contributes to the age-related cognitive decline. This idea might also account for the lack of activation contrasting the compatible with the incompatible condition across the whole sample. *Third*, coming back to the idea of the CRUNCH, our finding might reflect the fact that during the compatible condition older adults succeed in suppressing the task-irrelevant DMN. While dealing with the 'easier' task demands they might be processing bottom-up processes with sufficient WM capacity, which might allow them to perform better than during the more demanding incompatible condition. During the latter they are involved with additional processing steps, trying to recruit the TPN. Age-related increase of activity in prefrontal and parietal regions as supported by our findings can be aligned with an over-recruitment of the TPN in older compared to young adults. The observed and aforementioned increased age-related frontal activity interpreted in the context of HAROLD and CRUNCH theory might, as argued by some authors, reflect an unsuccessful shift out of the DMN into an active TPN in older age (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008). Even if we cannot clearly identify the DMN as being associated with the worse incompatibility-related performance, the suppression of the DMN, i.e. task-irrelevant areas, could still be insufficient and be reflected in localized hyperactivities, overlaid by compensatory processes. In their fMRI study on RT variability in cognitive tasks across the lifespan, Tam et al. (2015) employed a Stroop task and found differences in the neural correlates between young and old subjects, associated with longer RTs. Older subjects showed increased activity in fronto-parietal attentional areas, whereas young subjects showed greater activity in the DMN in association with longer RTs, hinting at a potential functional involvement of the DMN in higher-order cognitive processes of control. Similar to the findings described before, insufficient suppression of the DMN leads to worse behavioral performance in both young and old subjects. It would be important to separately look at the good and bad performers within the 'young' group to rule out that the insufficient suppression of the DMN by the latter is the driving force in the negative age-related correlation of the DMN.

The *fourth* perspective that has to be included when interpreting our finding is the analysis of *FC within the DMN*. Park and Friston (2013) propose the essential idea that single brain structures support various functions and are involved in networks that again have characteristics dependent on context and time. In former studies investigating FC, an age-related decline of FC in the DMN was observed, but preserved in the TPN (Grady et al., 2006). Age-related changes in DMN connectivity correlate with cognitive abilities (Mevel et al., 2013). Andrews-Hanna et al. (2007) confirmed a disruption of the DMN with age and its association with cognitive decline across a range of domains, especially EFs and general slowing. Higher-order systems that support processes of cognition seem to be preferentially affected compared to lower-order systems that are only minimally affected by disruptions in FC. Investigating age- and task-load related effects on FC in the DMN, Sambataro et al. (2010) found decreased FC in the DMN in older adults who additionally had problems in efficiently suppressing the DMN. The observed age-related decline in the ability to modulate activity in relation to the task load was interpreted as a correlate of age-related deficits in cognitive control in the form of a deficient allocation of resources dealing with the WM task. In another study, regions of the DMN showed age-related reductions in their anti-correlation with task-networks, reflecting a reduced de-coupling of task-irrelevant regions, potentially interfering with task-relevant processes and leading to intrusions and worse task-related performance (Langner et al., 2015) and fitting well with an idea of dysfunctional dedifferentiation. Thus, age-related deactivations in the DMN as identified in our study could also reflect changes in FC within the DMN and account for worse age-related performance. Jockwitz et al. (2017) based their RS analysis on a sample also drawn from the 1000BRAINS study, allowing for a high level of comparability with our results. In their study, they could not find age-related changes in FC in the DMN, but age-related increases in FC in the executive fronto-parietal networks bilaterally. As the left network was associated with lower performance on a WM task, they interpreted the FC increases in older age as potentially compensatory, but with limited capacity.

Finally, we comment on a functional hypothesis and interpretation of the DMN as being responsible for higher-order control of human behavior on the top of a system of hierarchical brain systems (Dohmatob et al., 2017). According to the *semantic hypothesis* cognitive processes during passive states, as they are reflected by the DMN, are to a large part constituted by semantic processing (Binder et al., 1999). The latter comprises the ability to rapidly form logical, abstract associations and analogies between explicit conceptual knowledge as well as representations in memory ('semantics') and input of new stimuli. Via retrieval of stored semantics context- or task relevant associations are activated, allowing for purposeful predictions and thus facilitating perceptional and cognitive processes (Binder et al., 2009). The amount of required analogies depends on the complexity of the situation. Different from the connotation of the word 'passive', the human brain continuously generates predictions of the future, performs high-level computational 'off-line' processes and thus ensures successful adaptation to new states. This uniquely human ability is seen as the prerequisite not only of complex social interaction, but also of cultural creation, technological invention and optimization of behavior by recombination of semantics (Dohmatob et al., 2017; Binder et al., 2009; Bar, 2007; Binder et al., 1999). Tasks requiring episodic memory seem to

particularly depend on the integration of semantics. The memory is supposed to make information available that can be used to simulate future events (Schacter et al., 2007). In our study, the DMN might thus help to detect logical association between environmental information in form of the stimuli of the SRC task and internal models of the world, including past experiences and knowledge. Based on our findings, these internally directed processes seem to play an important role in the group of younger adults, potentially hinting at successful learning algorithms to adapt to the constantly changing environment in the course of adulthood. Our results suggest that these high-level computational learning processes change along the life cycle and may be boosted until a certain age. An age-related decline in the learning processes is in line with the findings that older adults generate fewer internal, episodic details but more external ones than younger adults when remembering past events or imagining future events (Addis et al., 2008). There seem to be clear age-related differences in the extent, direction and level of detail of memory and in the ability to integrate different information (Spreng and Levine, 2006). Deactivation of the DMN occurs, when the confronted stimulus requires (almost) no semantic processing (Binder et al., 2009). The observed negative correlation of age and the DMN, i.e. a deactivation of the DMN, would thus imply that older adults did not deploy semantics when dealing with the compatible condition. They are potentially less dependent on semantic knowledge during the 'easier' task, or – in the context of their worse performance – less successful in exploiting the high-level computational processes and integrating external stimuli with their internal models. Literature agrees on the challenge of defining a computational model of these internal processes – "it will probably require a form of regulation by which perception of the current world is suppressed while simulations of possible alternatives are constructed, followed by a return to perception of the present." (Buckner and Carroll, 2007). As pointed out by these authors, shifting perspective from the present environment to other past or future perspectives is a challenging process for the brain. At the same time it is crucial for the development and the preservation of the meta concept of the self (Povinelli, 2001). Our findings support the functional role of the DMN in high-order learning, control and adaptation processes across the lifespan. They could support the aforementioned idea that these learning processes change along the life cycle and may be boosted only until a certain point in adulthood. In the light of the semantic hypothesis, we could identify a potential age-related decline and dysfunction in 'off-line' capacity reflected by the DMN and in the ability to integrate information from various perspectives. These age-related changes might contribute to age-related decrease in cognitive performance. The causes and implications of these changes are – as pointed out in the course of the preceding discussion – in the context of our study only speculative in nature and require further investigations.

4.3 Methodological limitations

As stressed above, our task fMRI study focused on functional correlates of age-related performance and thus only on one aspect in the vast field of theories of aging. We did not include neurogenetical (see Reinvang et al., 2010 for a review) or neurochemical findings (e.g. theory of dopamingergic decline, Braver and Barch, 2002), intra-individual influences by the circadian arousal rhythm (Anderson et al., 2014), age effects on the cerebrovascular system affecting the neurovascular coupling (Rajah and D'Esposito, 2005)

or morphological changes going beyond structural abnormalities and pathologies excluded during quality control (e.g., decline in grey matter volume). Testing the correlation of structural brain volume and EFs in five different tasks, Elderkin-Thompson et al. (2008) identified prefrontal integrity as mediating variability in some EFs better than chronological age suggesting that brain morphology, esp. grey matter volume, should be included in a further analysis. See also Lu and Liu (2017) for an extensive review of methodological issues of the MRI studies of the aging brain. It is important to point out that the aforementioned different concepts and focuses of research are not mutually exclusive, but address different levels of cognitive decline (Drag and Bieliauskas, 2010) and would ideally be integrated in an interdependent model to account for inter- and intra-individual differences in behavioral and neural performance (Reuter-Lorenz and Lustig, 2017).

The problem of reduced comparability of different studies investigating 'inhibition' due to the inconsistency in defining and using this term and its related constructs was alluded to before (Reuter-Lorenz and Lustig, 2017). We tried to address this problem by introducing a working definition of EF and cognitive action control as tested in our SRC task and pointing out differences to other paradigms. Another important challenge in the context of an observable increasing lifespan is to define an appropriate cut-off between being 'young' and 'old'. There is no general definition of these terms as they are strongly determined by the population they are related to. In neuroscience some studies use 60 years as cut-off (e.g. Park and Festini, 2016; Reuter-Lorenz and Park, 2010) whereas we, in line with data on age-related cognitive decline (Salthouse, 2011; Schaie and Willis, 2010; Hedden and Gabrieli, 2004), defined the age of 55 as the bottom line for being considered 'old' in our sample. As the global healthy life expectancy constantly rose in the last years and in developed countries reaches up to approximately 75.2 years for females and 72 years for males (Hay, 2017), these cut-offs should be reconsidered in future studies. In a next step it would be interesting to divide our sample in smaller age groups to delineate 'good' vs. 'bad' performing old and young subjects respectively. These inter-individual differences per age group were neglected in our approach when including age as a covariate. As we studied a big population-based sample with continuous age distribution our data has sufficient power for this consecutive sub-analysis. Another limitation of our experiment is the cross-sectional design that could imply a cohort effect in addition to an age effect. It can be solved by a longitudinal, cross-generational design as already provided by the ongoing 1000BRAINS project. Due to the recruitment in only one German region, a transferability of our findings to other cultures cannot be ensured. The screening of our participants via BDI and DEMTECT (see p. 14) to exclude psychiatric and neurological disorders was performed at JRC under standardized conditions providing best possible comparability. We still want to allude to the limited sensitivity in completely excluding sub-clinical impairments as already suggested by the mild cognitive impairment prevalent in 33 of our participants. Investigating them separately would be also of interest in respect to potential correlates of neurocognitive disorders. Another potential bias that should not go unmentioned is the impairment of EFs by stress, sadness, loneliness or being physically unwell, factors which most likely show age-related differences in its manifestations. The PFC and EFs suffer disproportionately from these stressors that hardly can be excluded in an a experimental setting lasting only one day (Diamond, 2013).

4.4 Future directions

This work on neural correlates of healthy aging is amply motivated by global demographic trends. The proportion of elderly adults, especially in highly developed nations, substantially increases -"2050, there will be many more older adults in wealthy, developed countries (26%) than children under 15 (about 16% of total population)"(Cohen, 2003). As these older adults hold precious human capital and experience, it is in general interest of the society as well as important for the individuals themselves dealing with their daily routines, to stay healthy not just physically but also mentally. By now, the prevalence of dementia, especially of Alzheimer's disease, as the number one age-related neurocognitive disease of almost 40% in the population aged 80 years or more substantially threatens a society that aspires to age successfully and in a healthy manner (data from the United States without consideration of regional differences, Hebert et al., 2013). The associated costs, both financial and in form of the incredible mental and physical efforts for those affected as well as their families and caregivers involved, constitute the importance of interest in the preservation of a healthy aging brain. Research on resilience factors has been established in the last few years, making the idea of cognitive reserve as a protective factor and coping mechanism more and more prominent (Rentz et al., 2017; Stern, 2012; Stern, 2009; Drag and Bieliauskas, 2010). As discussed above, *neuroplasticity*, i.e. scaffolding, over the lifespan serves as the potential neural correlate of cognitive reserve ensuring a compensatory response to the cognitive decline until the capacity for plasticity and reorganization is exceeded. This capacity is limited by age-related neurobiological decline and strongly altered by pathological correlates of demential processes in the brain (Park and Reuter-Lorenz, 2009; Burke and Barnes, 2006). Still, to counteract these processes, in the context of this idea of neural scaffolding and having the STAC-r model, cognitive reserve as well as the trainability of EFs in mind, interventional programs have been created and evaluated, including lifestyle activities and trainings that are supposed to support age-related neuroplasticity. The effect of cognitive training seems to be durable over time, yet not transferable between cognitive domains or even between different tasks within one domain (Diamond, 2013; Park and Bischof, 2013; Goh and Park, 2009). Although not uncontroversial, high level of education has been related to lower cognitive decline across the lifespan and is hence seen as an indicator of cognitive reserve. So have intelligence and sensory abilities, altogether accounting for the increase in inter-individual variability with age (Drag and Bieliauskas, 2010). The aforementioned variables should be included in further analysis of age-related cognitive control. Developing and evaluating cognitive trainings with broad transfer effects in order to counteract cognitive decline and boost neuroplasticity should be an important future element pursuing the goal of a healthy aging population.

For a consecutive study it would be desirable to include FC data from our sample and thus to integrate different MRI modalities. This would allow for a more comprehensive view on age-related neural changes by directly testing and interpreting the performance-related and potentially compensatory alterations (cf. Andrews-Hanna et al., 2007) and prevent one-dimensional interpretations of relationships between brain and behavior. Investigating the FC within the DMN in our sample would be an important next step integrating findings of functional reorganization, structural and functional results across the lifespan and

considering their potential interdependence when interpreting age-related changes and variability in cognitive performance and their neural correlates.

4.5 Conclusions

We investigated age-related changes of subprocesses of cognitive action control by employing the SRC paradigm in an fMRI study of a large population-based sample. We observed that on a *behavioral* level, older adults performed worse under both the incompatible and the compatible condition, corroborating the assumed age-related decline in cognitive action control and a significant increase of behavioral *SR-incompatibility costs* with age. To investigate the associated *neural* correlates of healthy aging on overcoming incompatibility-induced response conflicts, we identified areas that change in their task-related activity with an increase in age. Before including age as a covariate, we replicated findings concerning the *general SRC task effect* and delineated neural correlates of *the bottom-up and top-down* processes involved in dealing with the SRC task in a significantly bigger sample compared to previous studies. We could corroborate lateralization effects in stimulus-driven bottom-up processes with the contralateral IPS and PMC being key neural substrates of these processes, responsible for integration of spatial information and an adequate motor response (Cieslik et al., 2010). Reflecting modulating *top-down* effects, we, in line with previous findings, confirmed a fronto-parieto-insular *SR-incompatibility-related task network*. Within the IPS, also being part of this network, top-down directed processes (hIP1, hIP2, hIP3), could be anatomically dissociated from the aforementioned bottom-up processes, mainly reflected by activation of hIP3, suggesting functional differences within neural substrates of the subprocesses underlying the SRC task.

The *age-related* increase of incompatibility-related activation (bilateral IPS, SPL, cerebellum, right IFG, DLPFC, MCC and left aIns) in this task network is in line with a hypothesized *hyperactivity* when dealing with incompatibility-induced response conflicts. We propose that lateralized activation of *left aIns* should represent a key neural correlate of age-related changes in cognitive action control, potentially reflecting the higher demand for control and *task-set maintenance* (Cieslik et al., 2015b) via aIns under the more complex condition that is required with increasing age. We suggest that the age-related increase of incompatibility-related activation in the right *DLPFC* is a correlate of successful *inhibition* (Cieslik et al., 2015b) of the prepotent ipsilateral reaction in favor of the desired incompatible reaction. As these prefrontal activation changes do not overlap with lower levels of functioning, the age effect can be specifically attributed to activity changes in DLPFC corroborating findings of higher prefrontal activity in older age reflecting reorganization in the sense of *dynamic compensatory processes* across the lifespan (cf. established theories of CNA as described above) during response conflicts. This finding provides an important extension of reports of reduced age-related FC for the DLPFC, indicating complementary mechanisms of age-related network changes (Langner et al., 2015).

Hyperactivity in IPS, which can be linked to both, *age and impaired cognitive control* (*higher behavioral incompatibility costs*), might be compensatory for morphological changes and/or changes in functional connectivity with prefrontal clusters. The overlap of increased activation in IPS for higher age and lower

levels of functioning highlights the role of this integrational region as a core neural correlate of age-related changes in cognitive action control. Our findings may hence reflect difficulties overriding bottom-up driven spatial orientation and the requirement for additional controlled processing steps, which become more likely with age. Based on our SR-incompatibility-related findings, we suggest that *worse age-related performance* is associated with both *bottom-up* and *top-down* processes when dealing with the SRC task, with aIns, DLPFC and IPS being key neural substrates. Thus, our data corroborate a significant influence of age on cognitive action control, which seems at least partially shared with performance-related effects across lifespan. Based on our data, age-related decline in cognitive action control is reflected in regional *hyperactivity*, rather than hypoactivity.

Based on the discussed putative compensatory processes reflected by the regional changes in activity, we strongly support the idea of *neuroplasticity* across the lifespan, accounting for variance in age-related performance and successful compensatory processes in higher age despite structural changes. Additionally, we agree with the *functional role of the DMN* in high-order learning processes that seem to change in the course of adulthood. We identified a putative age-related decline in the ability to integrate semantic knowledge with current task demands that might contribute to the observed age-related decline in performance. With our study we focused on healthy aging and its neural correlates which we see as one piece of the interdependent fields of CNA and the growing knowledge about the aging mind that altogether try to understand the very "last biological frontier" (Rose and Rose, 2016).

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