Functional networks in the aging brain – A view on task dependent regional changes and intrinsic functional connectivity

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Zusammenfassung

Die vorliegende Dissertation umfasst drei Studien, in denen mit funktioneller Magnetresonanztomographie altersbedingte Veränderungen funktioneller Netzwerke im menschlichen Gehirn untersucht werden. Während die erste Studie aufgabenabhängige regionale Hirnaktivität untersuchte, beruhten Studien 2 und 3 auf einem meta-analytischen Ansatz sowie der Untersuchung der aufgabenunabhängigen, d. h. intrinsischen, Aktivität des Gehirns.

Der Fokus der ersten beiden Studien liegt auf altersabhängigen Veränderungen der Aktivität von Hirnregionen, welche mit der Durchführung einer sensomotorischen Aufgabe als auch einer visuellen Aufmerksamkeitsaufgabe einhergeht. Dabei wurde eine altersbedingte Abnahme neuronaler Selektivität, d. h. eine zunehmende neuronale Dedifferenzierung besonders berücksichtigt. In Studie 1 führten 101 Probanden zwei unterschiedliche Aufgaben durch; eine sensomotorische- sowie eine visuelle Aufmerksamkeitsaufgabe. Es konnte eine Interaktion zwischen dem Alter und der mit der jeweiligen Aufgabe einhergehenden Hirnaktivität gezeigt werden. Genauer gesagt, ging eine regionale altersbedingte Abnahme neuronaler Aktivität in aufgabenbezogenen Hirnregionen mit einer erhöhten neuronalen Aktivität in anderen Hirnregionen einher. Diese zusätzliche Rekrutierung findet jedoch nicht nur innerhalb eines funktionellen Netzwerkes statt, sondern über verschiedene Netzwerke hinweg und spiegelt eine verringerte Differenzierung der zugrunde liegenden Netzwerke wider. Dieser Effekt betont die Relevanz, Veränderungen regionaler neuronaler Aktivierung über die Aktivierungsmuster verschiedener funktioneller Netzwerke hinweg zu untersuchen.

Die zugrunde liegenden interregionalen Mechanismen für diese altersabhängigen Veränderungen wurden in der zweiten Studie näher untersucht. Dort wurde die Kommunikation zwischen denjenigen Regionen aus Studie 1, die einer Dedifferenzierung über verschiedene Netzwerke hinweg unterlagen, untersucht. Dazu wurde die Korrelation

neuronaler Aktivitätsverläufe, d. h. die funktionelle Konnektivität (FC), dieser „netzwerkspezifischen“ Regionen im aufgabenunabhängigen Zustand des Gehirns betrachtet. Darüber hinaus wurde Regionen, die eine funktionelle Verbindung mit allen netzwerkspezifischen Regionen aufzeigten, ebenfalls in die FC-Analyse eingebunden. Diese „netzwerkübergreifenden“ Regionen wurden mit Hilfe eines meta-analytischen Ansatzes ermittelt. Mit den Ergebnissen aus Studie 1 übereinstimmend, zeigte Studie 2 eine verringerte Konnektivität für funktionelle Verbindungen zwischen den Netzwerken. Darüber hinaus spiegelt eine verringerte intrinsische Kopplung zwischen den netzwerkspezifischen und den netzwerkübergreifenden Hirnregionen eine altersbedingt veränderte „top-down“-Kontrolle wider, welche ebenfalls eine Dedifferenzierung der aufgabenspezifischen neuronalen Aktivität hervorrufen könnte. Dies deutet darauf hin, dass Veränderungen intrinsischer Verbindungen regionale Aktivitätsveränderungen reflektieren und somit einen Einfluss auf allgemeine altersbedingte Verhaltensmuster haben könnten.

Die dritte Studie unterstützt diese Annahme. Hier wurden altersbedingte FC-Veränderungen als mögliche neuronale Grundlage altersbedingter Verhaltensanpassungen in Aufgaben, welche eine kognitive Handlungskontrolle erfordern, untersucht. Im ersten Experiment dieser Studie wurde eine altersbedingte Verschlechterung der Reaktionszeiten in einer Reiz-Reaktions-Inkompatibilitätsaufgabe festgestellt. Im zweiten Experiment wurde eine altersbedingte Abnahme der intrinsischen Konnektivität innerhalb des Netzwerkes, das mit Reiz-Reaktions-Inkompatibilitätsaufgaben assoziiert ist, gezeigt. Diese intrinsischen Veränderungen werden als ein mögliches neuronales Substrat für die gezeigten altersbedingten Verhaltensdefizite diskutiert.

Zusammen zeigen die drei Studien, dass altersbedingte Veränderungen interregionaler Kommunikation zum einen aufgabenabhängige regionale Aktivierungs-veränderungen, zum anderen aber auch Verhaltensveränderungen widerspiegeln. Der intrinsische Zustand des

Gehirns ist damit ein wichtiger Untersuchungsgegenstand, um altersbedingte Veränderungen im menschlichen Gehirn besser verstehen zu können.

Abstract

Based on functional magnetic resonance imaging (fMRI) the present dissertation comprises three studies dealing with age-related changes within and between functional networks in the healthy human brain. Study 1 was based on regional task-dependent neural activity whereas studies 2 and 3 rest upon a meta-analytic approach and the analysis of the task-independent state of the brain.

The focus of the first two studies was on regional task-dependent and interregional task-independent changes between nodes of two different functional networks, the sensorimotor network and the visual attention network, thereby addressing an age-related reduction of neural selectivity, i.e., dedifferentiation. In study 1 an age-by-task interaction indicates that a reduction of functional specificity, i.e., dedifferentiation, in the aging brain may be counteracted by an increased recruitment of additional regions not only within, but also across functional networks. This finding emphasizes that comparing activation patterns across different functional networks is necessary to investigate age-related alterations of neural activation. Moreover, this effect prompts considerations on the nature of lifespan-dynamics of the human brain as it suggests that the mapping between regional processes and experimental tasks may undergo age-related changes.

On the basis of this task-dependent phenomenon, the second study investigates the network underpinnings of such age-related changes by analyzing the interregional integration of regions underlying a dedifferentiation across different functional systems (derived from study 1). In particular, the correlation of the task-independent neural activity-courses, i.e., resting-state functional connectivity (FC), of these regions was examined. Additionally, the FC analysis included regions that were functionally associated will all of the initial regions, i.e., „task general" regions. In line with regional activation changes reported in study 1, we found diminished anti-correlated FC for inter-system connections. Moreover, the observed

reduced intrinsic coupling between system-specific and task-general regions might reflect age-related deficits in top-down control possibly leading to dedifferentiation of task-specific brain activity. Hence, the results indicate that intrinsic FC changes concur with regional activity changes in the healthy aging brain, thus contributing to common age-related behavioral changes.

Study 3 hardens this assumption. In the first part of this study an age-related behavioral decline for conflict processing, induced by spatial stimulus-response incompatibility, was demonstrated. In the second experiment decreases in intrinsic functional connectivity between nodes of the network associated with incompatibility-induced response conflicts were unveiled. These age-related changes in interregional communication are suggested to be a neural substrate for the age-dependent performance decline in response conflict solution.

Together, these studies demonstrate that age-related intrinsic interregional communication changes are a potential neural substrate for both task-dependent changes in regional activation and behavioral in healthy older adults thereby amplifying the fundamental relevance of the intrinsic brain state for understanding the human aging brain.

General Introduction

Due to the constantly increasing global life expectancy, understanding the aging process will be one of the greatest challenges for future societies. As the number of individuals aged 70 and above is growing, it is of utmost socioeconomic importance to promote functional independence and quality of life in this group. Thus, a key element in dealing with the "graying of the world" must be to delineate mechanisms of the healthy human brain that counteract the general age-related structural and functional deterioration and contribute to maintaining effective information processing, which is essential for functional independence. Moreover, a better understanding of age-related alterations in the healthy human brain is an important prerequisite to understand the differences between changes caused by neurodegenerative disorders and those caused by "normal" physiological aging processes.

One fundamental principle of human brain functioning is the dynamic interplay and exchange of information between brain regions, i.e., functional integration (Friston, 2002). Consequently, the effective interaction of distinct brain regions is an elementary mechanism for an efficient functional integration. As the natural environment generally requests multisensory processing, such cooperation cannot be limited to regions with a similar function but rather comprises nodes of different functional brain systems (Ghazanfar and Schroeder, 2006). For instance, to successfully grasp an object, neural activation within brain regions related to the motor, the somatosensory, the visual, and the attention system is required (Nathan et al., 2012). Hence, interregional integration not only within but also across functional brain systems represents a neural substrate for effective information processing.

In the past decade, neuroimaging studies provided ample evidence for massive changes in brain structure and neural activity with age (Salthouse, 2011; Ferreira and Busatto, 2013). The

interregional integration across functional systems may be affected by such alterations as well.

Dedifferentiation across functional systems

Beside age-related region-specific changes in structure and function (for review see Raz et al., 2005; Dennis and Cabeza, 2008), aging has been associated with changes in the relative contribution of brain regions to task performance. Over ten years ago, Cabeza (2002) described a phenomenon that suggets less lateralized prefrontal actvitiy during task performance in older adults than in younger ones. Morevover, older adults seem to recruit additional frontal regions for tasks that are primarily dependent on posterior brain regions in young adults (Davis et al., 2008; Dennis and Cabeza, 2008). Park and colleagues (2004) demonstrated such reduction of neural selectivity within the ventral temporal cortex. In older adults face processing was found to be associated with reduced activity in task-related regions (e.g., the fusiform face area) and, simultaneously, with increased activity in regions not considered to be task-relevant (e.g., the parahippocampal place area). These effects (i.e., a more diffuse activation pattern and less selective activity in task-relevant regions) were demonstrated across a variety of tasks (Madden et al., 1999; Townsend et al., 2006; Grady et al. 1994). Moreover, there is evidence for such dedifferentiation *across* different tasks within a particular functional system (Dennis and Cabeza, 2011). For instance, the right-hemispheric frontal regions associated with spatial processing and spatial working memory in young adults were more strongly recruited for verbal working memory in older adults (Reuter-Lorenz et al., 2000). These results support the notion that brain aging is associated with a process of dedifferentiation. This process seems to span multiple tasks (i.e., processing demands within a particular functional system) and represents a viable explanation for some age-related differences in brain activity. However, while this process has been demonstrated to occur

across hemispheres, brain regions, and tasks within a particular functional system, little is known about age-related changes in neural selectivity *across* different functional systems.

Such dedifferentiation across functional systems may be part of the global changes in healthy aging like alterations of local processing or less efficient connectivity (Grady 2008), which entail changes in resource allocation and computational strategies.

These considerations motivated the first study of this dissertation. In Study 1, age-related changes in the regional selectivity of neural activation across two functional systems were examined. To this end, 102 healthy adults between 21 and 71 years were investigated in a cross-sectional functional magnetic resonance imaging (fMRI) study. We analyzed two functional systems: the visual attention system (Corbetta et al., 1991) and the motor system (Rizzolatti and Luppino, 2001). In detail, we tested for age-related changes in regional specificity across both functional systems in regions that were significantly associated either.

Such cross-domain effects would provide evidence for our hypothesis that an age-related loss of neural specificity is not limited to (within-system) stimulus-evoked effects (e.g. faces; see Goh et al. 2010) or to "dedifferentiation" within a particular functional system (e.g. visual domain; see Grady et al. 1994) but represents a more general phenomenon. Moreover, these effects prompt considerations on the nature of functional specialization, a concept, which fundamentally implies that a given mental function is localized in a particular cortical area (Eickhoff and Grefkes 2011).

Intrinsic functional connectivity between and within brain networks

As demonstrated in Study 1, an age-related loss of neural specificity is not constrained to a particular functional system but rather also evident between systems. It may hence be speculated that changes in functional network interactions (i.e., interregional integration) may underlie this effect. From a multitude of studies, there is converging evidence that functional

connectivity (FC) is modulated by age and that these changes affect behavior. In detail, disruptions of task-relevant connections were frequently reported resulting in less efficient task-performance (Daselaar et al., 2006; Madden et al., 2010; Clapp et al., 2011; Nagel et al., 2011). These studies underline the importance of FC between task-relevant brain regions and the influence of age on these connections, which in turn might affect behavior.

Analyzing task-dependent regional activation changes with age is one standard method to examine age-related changes in brain activity. For instance, phenomena like compensation and dedifferentiation (for review see Grady, 2012) were discovered due to the intense monitoring of age differences in local brain activity while participants were performing a certain task. Moreover, detecting the cross-domain effects in Study 1 must also be ascribed to the analysis of task-dependent brain activity. However, more recently, fMRI protocols have been developed to investigate brain activity while the subject is not engaged in any specific task (i.e., resting-state fMRI). This approach is based on spontaneous fluctuations of neural activity in the human brain even without any external input (Buckner et al., 2008). Thus, even when the participant is apparently at rest, the brain is not. By analyzing the correlations of these fluctuations between different regions, a measure of interregional functional connectivity obtained (i.e., resting-state functional connectivity, RS-FC).

Biswal et al. (1995) demonstrated in their pioneering resting-state investigation that functionally related brain areas show significant RSCF. Moreover, there is compelling evidence that coherent RS-FC is an important requirement for healthy brain functioning (Fox and Raichle, 2007; van den Heuvel et al., 2009), and even related to task performance in older adults (Andrews-Hanna et al., 2007; Persson et al., 2007; Park et al., 2010). However, little is known about the relation of intrinsic communication (FC) between task-relevant regions and cognitive performance with age. It is hence been of particular interest whether aberrant

intrinsic FC within or between brain networks constitutes a mechanism for deteriorated resource allocation, accounting for common difficulties in older adults' task performance.

Moreover, there is only little information on aberrations in neural networks, underlying a dedifferentiation across functional systems as suggested in Study 1. This raises the question as to what extent the interaction within and between functional systems (i.e., FC) becomes less differentiated as a consequence of healthy aging. Investigating such cross-domain FC may also provide additional insights into general physiological changes across multiple brain systems with healthy aging, which are not accessible by the analysis of local activity pattern changes. Additionally, improved knowledge of age-related changes in FC may also provide an important backdrop for the assessment of network pathology caused by neurodegenerative disorders. Recently, Lehmann et al. (2013) demonstrated that the clinico-anatomical heterogeneity in Alzheimer`s disease is driven by aberrant RS-FC of specific functional networks. Moreover, it is assumed that the cognitive deficits in Alzheimer`s disease may be attributed to a disruption of FC within and across functional brain networks (for review, see Delbeuck et al., 2003).

In Study 2, these issues were addressed by investigating age-related alterations of intrinsic FC between those regions of the visual-attention and sensorimotor systems that showed a loss of task-related activation specificity with age (derived from the Study 1). It is worth mentioning that functional connectivity is defined as the temporal correlation of neurophysiological activity of spatially remote brain areas (Friston et al., 1993). However, a correlation neither implies a causal relationship, nor does it reflect a direct connection between two brain regions. Rather, there is evidence that FC, in particular between different functional systems, may also be mediated by task-general regions interacting with regions from either system (Eickhoff and Grefkes, 2011). Consequently, almost any FC analysis would benefit from the inclusion of such multilaterally correlated brain regions, as it offers

additional information about the mechanisms underlying the change of network interactions. These considerations promoted the implementation of such task-general regions into the FC analysis of the second study. Consequently, we investigated changes in intrinsic FC in a large adult sample (n = 399) between brain regions that were associated with the visual-attention or the sensorimotor system and showed a change of functional specificity with aging as well as with task-general regions that are functionally related to all of these specific regions and might mediate connectivity between them. Moreover, the implementation of task-general regions permits a more global view on intrinsic changes between functional networks and their relation to cognitive performance.

In support of the putative relation between behavioral performance and RS-FC characteristics, the third study focused on analyzing intrinsic FC changes in a network associated with cognitive action control. In detail, our data suggests that healthy aging is accompanied with less efficient performance during a stimulus-response compatibility task, reflected by an increased reaction time and error rate in contrast to younger adults especially during the incompatibility condition. During that condition, a lateralized stimulus requires a contralateral response. However, the neural mechanisms behind such deteriorated top-down control of action in the elderly (for review see Craik and Salthouse, 2008) still needs to be elucidated. Analogous to the second study, age differences in the intrinsic FC pattern were analyzed in regions associated with responding under conditions of spatial incompatibility (Cieslik et al., 2010). To this, a two-experiment study was conducted. In the first experiment the behavioral consequences of an age-related decline for response conflict solution were examined whereas the second experiment investigates the intrinsic FC properties for conflict-related brain regions.

References

Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., Lustig, C., Head, D., Raichle, M.E., and Buckner, R.L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron* 56**,** 924-935.

Biswal, B., Yetkin, F.Z., Haughton, V.M., and Hyde, J.S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 34**,** 537-541.

Buckner, R.L., Andrews-Hanna, J.R., and Schacter, D.L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 1124**,** 1-38.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging* 17**,** 85-100.

Cieslik, E.C., Zilles, K., Kurth, F., and Eickhoff, S.B. (2010). Dissociating bottom-up and top-down processes in a manual stimulus-response compatibility task. *J Neurophysiol* 104**,** 1472-1483.

Clapp, W.C., Rubens, M.T., Sabharwal, J., and Gazzaley, A. (2011). Deficit in switching between functional brain networks underlies the impact of multitasking on working memory in older adults. *Proc Natl Acad Sci U S A* 108**,** 7212-7217.

Corbetta, M., Miezin, F.M., Dobmeyer, S., Shulman, G.L., and Petersen, S.E. (1991). Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. *J Neurosci* 11**,** 2383-2402.

Craik, F.I.M., and Salthouse, T.A. (2008). *The handbook of aging and cognition.* New York: Psychology Press.

Daselaar, S.M., Fleck, M.S., Dobbins, I.G., Madden, D.J., and Cabeza, R. (2006). Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study. *Cereb Cortex* 16**,** 1771-1782.

Davis, S.W., Dennis, N.A., Daselaar, S.M., Fleck, M.S., and Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cereb Cortex* 18**,** 1201-1209.

Delbeuck, X., Van Der Linden, M., and Collette, F. (2003). Alzheimer's disease as a disconnection syndrome? *Neuropsychol Rev* 13**,** 79-92.

Dennis, N.A., and Cabeza, R. (2008). "Neuroimaging of healthy cognitive aging," in *Handbook of aging and cognition,* eds. T.A. Salthouse & F.E.M. Craig. (New York: Psychological Publishing Group).

Dennis, N.A., and Cabeza, R. (2011). Age-related dedifferentiation of learning systems: an fMRI study of implicit and explicit learning. *Neurobiol Aging* 32**,** 2318 e2317-2330.

Eickhoff, S.B., and Grefkes, C. (2011). Approaches for the integrated analysis of structure, function and connectivity of the human brain. *Clin EEG Neurosci* 42**,** 107-121.

Ferreira, L.K., and Busatto, G.F. (2013). Resting-state functional connectivity in normal brain aging. *Neurosci Biobehav Rev* 37**,** 384-400.

Fox, M.D., and Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8**,** 700-711.

Friston, K. (2002). Beyond phrenology: what can neuroimaging tell us about distributed circuitry? *Annu Rev Neurosci* 25**,** 221-250.

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

Ghazanfar, A.A., and Schroeder, C.E. (2006). Is neocortex essentially multisensory? *Trends Cogn Sci* 10**,** 278-285.

Goh, J.O., Suzuki, A., and Park, D.C. (2010). Reduced neural selectivity increases fMRI adaptation with age during face discrimination. *Neuroimage* 51**,** 336-344.

Grady C.L. (2008) Cognitive neuroscience of aging. *Ann N Y Acad Sci* 1124, 127–144.

Grady, C. (2012). The cognitive neuroscience of ageing. *Nat Rev Neurosci* 13**,** 491-505.

Grady, C.L., Maisog, J.M., Horwitz, B., Ungerleider, L.G., Mentis, M.J., Salerno, J.A., Pietrini, P., Wagner, E., and Haxby, J.V. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. *J Neurosci* 14**,** 1450-

Lehmann, M., Madison, C.M., Ghosh, P.M., Seeley, W.W., Mormino, E., Greicius, M.D., Gorno-Tempini, M.L., Kramer, J.H., Miller, B.L., Jagust, W.J., and Rabinovici, G.D. (2013). Intrinsic connectivity networks in healthy subjects explain clinical variability in Alzheimer's disease. *Proc Natl Acad Sci U S A* 110**,** 11606-11611.

Madden, D.J., Costello, M.C., Dennis, N.A., Davis, S.W., Shepler, A.M., Spaniol, J., Bucur, B., and Cabeza, R. (2010). Adult age differences in functional connectivity during executive control. *Neuroimage* 52**,** 643-657.

Madden, D.J., Gottlob, L.R., Denny, L.L., Turkington, T.G., Provenzale, J.M., Hawk, T.C., and Coleman, R.E. (1999). Aging and recognition memory: changes in regional cerebral blood flow associated with components of reaction time distributions. *J Cogn Neurosci* 11**,** 511-520.

Nagel, I.E., Preuschhof, C., Li, S.C., Nyberg, L., Backman, L., Lindenberger, U., and Heekeren, H.R. (2011). Load modulation of BOLD response and connectivity predicts working memory performance in younger and older adults. *J Cogn Neurosci* 23**,** 2030-2045.

Nathan, D.E., Prost, R.W., Guastello, S.J., Jeutter, Dc, and Reynolds, N.C. (2012). Investigating the neural correlates of goal-oriented upper extremity movements. *NeuroRehabilitation* 31**,** 421-428.

Park, D.C., Polk, T.A., Hebrank, A.C., and Jenkins, L.J. (2010). Age differences in default mode activity on easy and difficult spatial judgment tasks. *Front Hum Neurosci* 3**,** 75.

Park, D.C., Polk, T.A., Park, R., Minear, M., Savage, A., and Smith, M.R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proc Natl Acad Sci U S A* 101**,** 13091-13095.

Persson, J., Lustig, C., Nelson, J.K., and Reuter-Lorenz, P.A. (2007). Age differences in deactivation: a link to cognitive control? *J Cogn Neurosci* 19**,** 1021-1032.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., and Acker, J.D. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex* 15**,** 1676-1689.

Reuter-Lorenz, P.A., Jonides, J., Smith, E.E., Hartley, A., Miller, A., Marshuetz, C., and Koeppe, R.A. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *J Cogn Neurosci* 12**,** 174-187.

Rizzolatti, G., and Luppino, G. (2001). The cortical motor system. *Neuron* 31**,** 889-901.

Salthouse, T.A. (2011). Neuroanatomical substrates of age-related cognitive decline. *Psychol Bull* 137**,** 753-784.

Townsend, J., Adamo, M., and Haist, F. (2006). Changing channels: an fMRI study of aging and cross-modal attention shifts. *Neuroimage* 31**,** 1682-1692.

Van Den Heuvel, M.P., Mandl, R.C., Kahn, R.S., and Hulshoff Pol, H.E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Hum Brain Mapp* 30**,** 3127-3141.

STUDY 1

Activation shift in elderly subjects across functional systems: an fMRI study

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	Writing and adapting the paradigm code
	Data acquisition
	Reviewing and adapting the analysis code
	Statistical analysis
	Interpretation of results
	Preparing figures
	Writing the paper
Total contribution:	80%

Abstract

The functional specificity of brain areas is diminished with age and accompanied by the recruitment of additional brain regions in healthy older adults. This process has repeatedly been demonstrated within distinct functional domains, in particular the visual system. However, it is yet unclear, whether this phenomenon in healthy aging, i.e., a reduced activation of task-associated areas and increased activation of additional regions, is also present across different functional systems. In the present functional imaging study, comprising 102 healthy subjects, we therefore assessed two distinct tasks engaging the sensory-motor system and the visual attention system, respectively. We found a significant interaction between age and task in the parietal operculum bilaterally. This area as part of the sensory-motor system showed an age-related decrease in its BOLD-response to the motor task and an age-related increase of neural activity in response to the visual attention task. The opposite response pattern, i.e., reduced visual attention activation and increased response to the motor task, was observed for regions associated to the visual task: the superior parietal area 7A and the dorsal pre-motor cortex. Importantly, task performance was not correlated with age in either task. This age-by-task interaction indicates that a reduction of functional specificity in the aging brain may be counteracted by the increased recruitment of additional regions not only within, but also across functional domains. Our results thus emphasize the need for comparisons across different functional domains to gain a better understanding of age-related effects on the specificity of functional systems.

1. Introduction

Physiological processes during healthy aging lead to widespread and apparently massive changes in brain structure and neural activity (for review see Goh 2011). Using functional magnetic resonance imaging, age-related changes in regional activation patterns have been consistently reported in a variety of functional domains including attention (Madden et al. 2002; Cabeza et al. 2004), visual perception (Grady et al. 1994; Levine et al. 2000; Iidaka et al. 2002) and working memory (Rypma and D'Esposito 2000; Grossman et al. 2002). Over the last years, several phenomenological and mechanistical accounts have been proposed for the description of these changes in functional activation (cf. Reuter-Lorenz and Park 2010), e.g., the ''posterior–anterior shift with aging'' and the ''hemispheric asymmetry reduction in older adults (HAROLD, Cabeza 2002). A prominent line of arguments supports the concept of de-differentiation (Grady et al. 1994; Park et al. 2004). This concept postulates that neural representations, which are well segregated in young adults, are considerably less selectively recruited in older subjects (Logan et al. 2002). That is, during a particular task (e.g., face processing) neural activity is reduced within regions associated with task performance in young adults (e.g., the fusiform face area) and simultaneously increased in regions that are not considered to be task-relevant (e.g., the parahippocampal place area). Reduction of regional selectivity with healthy aging has already been demonstrated within several functional systems (Grady et al. 1994; Townsend et al. 2006; Carp et al. 2011) and represents a plausible explanation for age-related differences in brain activity. Moreover, Dennis and Cabeza (2011) demonstrated evidence for de-differentiation across tasks within a particular functional domain (learning) by contrasting age-related effects in an implicit to those in an explicit memory task. De-differentiation within a particular functional system thus seems to span multiple tasks, i.e., processing demands. In contrast, very little is known about age-related changes in (regional) specificity across different functional systems. Such ''de-

differentiation'' across functional systems may be a part of the global changes in healthy aging like alterations of local processing or less efficient connectivity (Grady 2008), which entails changes in resource allocation and computational strategies. In the present study, we address this question by examining age-related changes in the regional specificity of neural activation across functional systems. Therefore, 102 healthy subjects between 21 and 71 years were investigated in a cross-sectional fMRI study. We analyzed two functional systems that show age-related within-domain changes in functional specificity; the visual attention system (Grady et al. 1994) and the motor system (Carp et al. 2011). In detail, we tested for age-related changes in regional specificity across both functional systems in those regions that were significantly associated with one of these. The specific purpose was to identify brain regions that show a decrease of neural activation with age for one task (e.g., visual attention) and an increase of activation in response to the other task (e.g., motor). Given reports of an age-related decline in visual attention (Kramer and Madden 2008) and motor performance (Kaasinen and Rinne 2002; Krampe 2002; Seidler et al. 2010), we deliberately employed tasks in which substantial changes in task performance with age were not expected, i.e., simple letter counting (visual attention) and finger tapping (motor). Also important to our endeavor, these tasks can be expected to feature a limited choice of alternative solution strategies as well as clearly distinguishable neuronal correlates. In particular, we expected to find specific brain areas for each task, in which one task evokes significantly higher activity than the other. Our main focus was then to assess age-related activation shifts across tasks (and hence functional systems) by testing for age-by-task interactions within these task-associated regions. Such cross-domain effects would provide evidence for our hypothesis that an age-related loss of neural specificity is not limited to stimulus-evoked effects (e.g., faces; see Goh et al. 2010) or to ''de-differentiation'' within a distinct functional system (e.g., visual domain; see Grady et al. 1994), but represents a more general phenomenon.

2. Materials and Methods

2.1 Participants.

102 subjects participated in the experiment. To provide a balanced age and gender distribution, recruitment was stratified into subgroups [20–30 years: 20 subjects (mean age 25.5 years, 9 females); 30–40 years: 18 subjects (mean age 32.8 years, 8 females); 40–50 years: 22 subjects (mean age 44.9 years, 11 females); 50–60 years: 22 subjects (mean age 55.3, 11 females) and 60–70 years: 20 subjects (mean age 63.9, 11 females)]. All participants had normal or corrected to normal vision and no history of neurological or psychiatric episodes. Participants gave written informed consent to this study, which was approved by the Ethical Committee of the University of Bonn.

2.2 Neuropsychological and behavioral testing

All volunteers underwent neuropsychological and behavioral testing. They were right-handed as assessed by the Edinburgh Handedness Inventory (median: 92, IQR: 28.9; Oldfield 1971). Each participant was tested on the Mini-Mental State Examination (MMSE, Folstein et al. 1975) to exclude potentially sub-clinical cognitive impairment. The Trail Making Test A and B (Reitan 1955), and the Digit Symbol Substitution Test (DSST) of the German Version of the Wechsler Adult Intelligence Scale-III (Wechsler 1997; Aster et al. 2006) were administered to assess processing speed and task switching. For assessing motor speed, motor control, and dexterity, the finger tapping test (FTT; Halstead 1947; Behrwind et al. 2011) and the pointing task (PT; similar to the CAPSIT Parkinson's disease test battery; Defer et al. 1999) were performed.

2.3 fMRI paradigm

As we were interested in age-related changes in regional activation patterns, differential performance across the assessed age-range may represent an important confound. Hence, the experimental paradigm consisted of two simple tasks for which age-related changes in performance were not expected a priori: a visual attention task (COUNT) and a motor task (TAP). The former (COUNT) consisted of a letter counting task in which a random series of the letters 'E' and 'F' were visually presented on a screen. The black colored letters appeared on a white background for 400 ms with an stimulus-onset-asynchrony (SOA) of 400 ms. Subjects were asked to identify the number of times they saw a target letter ('E') and report the number of target letters after each block. This verbal answer was recorded as a measure of successful task-completion, but for technical limitations initiation time to answer could not be recorded. Given the sustained nature of our task, this reaction time would not have been representative of task performance anyways.

The motor task consisted of a bimanual repetitive finger tapping task, requiring the subjects to press response-buttons alternatively with their left and right index finger, respectively. To minimize inter-individual performance differences, participants practiced this task prior to scanning, attempting to match a tapping speed frequency of 5 Hz. During training, subjects were given feedback if they were tapping too slow (\4.6 Hz) or too fast ([5.4 Hz) and were instructed to speed up or slow down, respectively. After maintaining the requested tapping frequency seven times in a row, tapping speed was considered stable and subjects were moved to the scanner. To match the visual input between both tasks, the letter 'X' was presented in the same manner as the letter-sequence in the COUNT task (stimulus duration 400 ms, SOA 400 ms). Subjects were instructed to look on the screen but to disregard the letter 'X'. As the finger tapping was no speeded reaction task but rather asked

the subjects to perform internally triggered movements (cf. Hoffstaedter et al. 2013), this task likewise yielded no response times that could be analyzed in a meaningful fashion. Performance indicator for this task was determined by the response variability, i.e., the variance for the inter-response interval (IRI, Apitz et al. 2010) between the finger movements (left/right), reflecting motor coordination.

The study itself was set up as a block-design with either the TAP or the COUNT task being presented in each individual block for 24 s. Blocks of either task were repeated five times in a randomized sequence with breaks of 8 s between blocks served as implicit resting baseline. The paradigm was presented via a mirror installed on the head-coil through which the subjects followed the presentation of the paradigm on a TFT screen behind the scanner. To minimize head movements every subject was stabilized with pads within the head-coil.

2.4 fMRI data acquisition and pre-processing

Images were acquired on a Siemens Tim-Trio 3T whole-body scanner (Erlangen, Germany), using blood oxygenation level dependent (BOLD) contrast (2D-echo-planarimaging (EPI) pulse sequence, repetition time(TR) = 2,200ms, echo time (TE) = 30ms, in-plane resolution = 3.1 9 3.1 mm, 36 axial slices, 3.1 mm thick-ness) covering the whole brain. Image acquisition was preceded by three dummy scans to allow for longitudinal equilibrium that were discarded prior to further processing with SPM8 (www.fil.ion.ucl.ac.uk/spm). In the preprocessing, the EPI images were first corrected for head movement by affine registration using a two-pass procedure, by which images were initially realigned to the first image and subsequently to the mean of the realigned images. After realignment, the mean EPI image for each subject was co-registered to the Montreal Neurological Institute (MNI) gray matter template. For normalization the mean EPI images were segmented into gray matter, white matter and cerebral spinal fluid using the ‘‘unified segmentation’’ approach (Ashburner and Friston

2005). The resulting parameters of a discrete cosine transform, which define the deformation field necessary to move subject data into MNI space, were then combined with the deformation field transforming between the latter and the MNI single subject template. The ensuing deformation was subsequently applied to the individual EPI volumes which thereby were transformed into the MNI single subject space and resampled at 1.5 mm isotropic voxel size. The normalized images were spatially smoothed using an 8-mmfull width at half maximum (FWHM) Gaussian kernel to meet the statistical requirements for statistical inference by Gaussian random field theory and to compensate for residual macro-anatomical variations across subjects.

2.5 fMRI image analysis

The imaging data were analyzed using a General Linear Model as implemented in SPM8. Each experimental condition (TAP, COUNT) was separately modeled as a block-vector input function using the stimulus onset and the time of the respective block. The verbal answer of the COUNT condition and the instruction preceding each task-block were modeled separately to reduce confounding variance within the implicit baseline (breaks between blocks). Each input function was convolved with a canonical hemodynamic response function and its first-order temporal derivative to yield the final regressors. To improve analysis specificity the movement parameters (x-translation, y translation, z-translation, pitch, roll, and yaw) as estimated during image realignment were also included as confound regressors of no interest. Low-frequency signal drifts were filtered using a cut-off period of 128 s. Parameter estimates were subsequently calculated for each voxel using weighted least squares to provide maximum likelihood estimators based on the temporal autocorrelation of the data (Kiebel et al. 2003). For each subject, simple main effects for each of the two experimental conditions were computed by applying appropriate baseline contrasts. These individual first-level

contrasts were then fed to a random-effects group-analysis using an ANOVA (condition factor: TAP or COUNT, blocking factor subject) with age x condition effects entered as a covariate. Thus, the variance explained by age is estimated for each factor separately. The statistical design allowed, therefore, testing the effects of condition (mean across all subjects) and the effects of age on each condition separately. In a subsequent analysis, we also assessed potential gender differences and in particular possible task 9 gender interactions (indicating different cognitive strategies or neuronal correlates thereof between males and females) again using an ANOVA design with the same general setup but modeling male and female subjects as separate groups. In the modeling of variance components, violations of sphericity were allowed by modeling non-independence across images from the same subject and allowing unequal variances between conditions and subjects using the standard implementation in SPM8.

2.6 Contrasts and thresholding

The main effect of each task (TAP, COUNT) was delineated by contrasting the correspondent task regressor with the implicit baseline. Regional preference for a particular task was investigated by contrasting the task of interest against the other (e.g., TAP > COUNT) in conjunction with the main effect of the relevant task (e.g., TAP > baseline). In this context, it should be noted that such preferential activation does not imply task-specificity in the strict sense as, thus, would require to show the absence of activation in the respective other task. Providing evidence for absent effects, however, is not feasible with classical statistics, as a non-significant test does not imply proof of the null-hypotheses (absence of evidence is not evidence of absence). Within the statistical framework of classical inference, significantly stronger activation by, e.g., TAP relative to COUNT, in combination with significant activation for TAP may thus be deemed the best possible evidence that the respective area is

preferentially recruited by (in this example) the motor as compared to the visual attention task.

Given the aim of this study as outlined in the introduction, our main focus rested on testing for an age-by-task interaction within regions significantly associated with the respective task. We were thus interested in COUNT-associated regions (significantly higher activated during COUNT than during TAP) where activation decreases with age during COUNT but increases with age during TAP. Key to the investigated interaction-effects is thus the reduction of activation for one task in combination with an increase of activation for the other, i.e., a reduction of the relative differences in BOLD-response that results from activity levels across the two tasks becoming more similar.

To delineate such effects indicating a change in regional specificity across functional systems, we employed global conjunctions across the contrast for task-associated regions (e.g., TAP > baseline and TAP > COUNT) in conjunction with the respective age regressors (in this example, negative weighting of the age regressor for the TAP condition and positive weighting of the age regressor for the COUNT condition). Finally, age-related correlations on neural activation for both experimental tasks were identified by contrasting the task main effect with the correspondent age regressor. This was done for both the positive and negative weighted age regressor. As the present study not focuses on these age-related effects, these results will be reported in the supplementary material.

All different effects and covariate-analyses were thresholded at $p < 0.05$ (family wise error (FWE)-corrected for multiple comparisons at the voxel cluster level; clusterforming threshold at voxel level: $p < 0.001$), while the obtained activations were anatomically localized using the cytoarchitectonic maps of the Juelich–Duesseldorf Cytoarchitectonic Atlas (Zilles and Amunts 2010) as implemented in version 1.8 of the SPM Anatomy toolbox (Eickhoff et al. 2005, 2006b, 2007; www.fz-juelich.de/inm/ inm-1/spm_anatomy_toolbox).

2.7 Test for changes of grey matter probability

The repeatedly demonstrated age-related change of gray matter volume in the human brain (Ge et al. 2002; Sowell et al. 2003; Walhovd et al. 2005; Lehmbeck et al. 2006; Giorgio et al. 2010) provokes the assumption that such structural alterations may confound age-related findings in terms of neural activity. We therefore tested the gray matter probability for each region showing an age-by-task interaction. To this, normalized and segmented T1 images were used in which for every brain voxel a specific probability value for each brain tissue class (gray matter, white matter, and cerebrospinal fluid) is denoted. By correlating the mean gray matter probability values of all voxels within a relevant brain region with age, changes of the gray matter distribution were estimated.

3. Results

3.1 Neuropsychological and behavioral results

Performance for the MMSE was within the clinically normal range (mean: 29.2 ± 1.0, minimum: 27), indicating that no subject suffered from cognitive impairment. Performance for the neuropsychological tests performed outside the scanner was significantly correlated with age in our group of 102 subjects. In particular, we found that performance correlated negatively with age in tests related to attention (TMT-A, TMT-B and DSST; cf. Table 1) and motor control (PT and FTT; cf. Table 1). These results thus confirm that our cohort showed the expected decline in processing-speed and executive functions with increasing healthy age.

Table 1 | Neuropsychological test scores correlated with age

Test	*ρ(rho)*	*p Value*
Trail-Making Test A (TMT-A)**	0.48	<0.001
Trail-Making Test B (TMT-B)**	0.55	<0.001
Digit Symbol Substitution Test (DSST)°	-0.47	<0.001
PT (right)**	0.23	0.022
PT (left)**	0.19	0.049
FTT (right)°	-0.45	<0.001
FTT (left)°	-0.31	0.002

**data failed test for normality (Spearman Rank Correlation)
° data passes test for normality (Pearson Product Moment Correlation)

Analysis of the motor task specific performance indicator yielded no significant correlation of the individual IRI-variance with age, demonstrating stable task performance with increasing age. The performance for the letter counting task was determined by correlating the error rate (deviation from correct number of target letters) with age. Again, no significant correlation with age was found, indicating likewise a comparable performance between younger and older adults. In summary, the significant age-correlations for the more challenging neuropsychological tests administered outside the scanner together with the absent age-effects for the experimental conditions indicates that our subjects indeed show the expected general decline in cognitive-motor functioning, but this did not impact their performance in the deliberately simple experimental tasks.

3.2 Imaging Results

First, the general activation pattern for each task is described, respectively. Afterward, task associated regions, i.e., regions showing significantly higher activation during one task compared to the other task are reported. Several task-associated regions showed an age-by-task interaction. These regions are specified finally.

The local maxima of all reported activations and their anatomic classifications are listed in detail in the supplementary tables S2–S4.

Activation pattern during the motor task (TAP)

During the finger tapping task, a characteristic motor network consisting of the primary motor cortex (area 4a, 4p; Geyer et al. 1996), the supplementary motor area (SMA), the somatosensory cortex (area 1;Geyer et al. 1999), the secondary somatosensory cortex (parietal operculum, OP1-4; Eickhoff et al. 2006a; Eickhoff et al. 2006c), the frontal operculum close to the Pars opercularis (area 44; Amunts et al. 1999), the middle frontal gyrus as well as the thalamus, the basal ganglia and the cerebellum showed significant activation. Moreover, in accordance with the concurrent presentation of continuous visual input (letter 'X') we also observed significant activation in extrastriate visual areas (area 18, hOC3v; Amunts et al. 2000; Rottschy et al. 2007) and the inferior temporal gyrus (ventral stream for visual processing).

Activation pattern during the visual attention task (COUNT)

The letter counting task evoked significant activation in the primary visual cortex (area 17; Amunts et al. 2000), the extrastriate visual cortex (area 18, 19, hOC3v, hOC4v; see Rottschy et al. 2007 for hOC4v), the fusiform gyrus (area FG2; Caspers et al. 2012), inferior and superior parietal cortex (area PFm, area hIP3, area 7A; Caspers et al. 2006, 2008; Scheperjans et al. 2008a, 2008b), premotor cortex, pre-SMA, anterior insular cortex, thalamus, basal ganglia and cerebellum (Table S1).

3.2.2 Task-associated regions

During TAP, higher activation compared to COUNT (and significant activation over baseline) was found bilaterally in supplementary motor area (SMA) and adjacent caudal dorsal pre-motor regions, the primary motor cortex (area 4a, 4p), somatosensory cortex (area 3b, 1, 2; Geyer et al. 1999; Grefkes et al. 2001), the frontal (area 44) and parietal operculum (area

OP1), the thalamus and the cerebellum. Right-lateralized effects were observed in the middle frontal gyrus and the pallidum (Fig. 1). The COUNT condition evoked significantly higher activity than TAP (and baseline) bilaterally in the extrastriate visual cortex (area hOC3v, hOC4v, hOC5; Malikovic et al. 2007; Rottschy et al. 2007) extending into the middle and superior temporal gyrus (occipito-temporal cortex, cf. Fig. 1), the precentral gyrus and posterior inferior frontal gyrus (pre-motor area 6 extending into area 44), pre-SMA, the intraparietal areas hIP3 and hIP2 (Choi et al. 2006; Scheperjans et al. 2008a; b), superior parietal area 7A, the middle occipital gyrus and the anterior insular (Fig. 1).

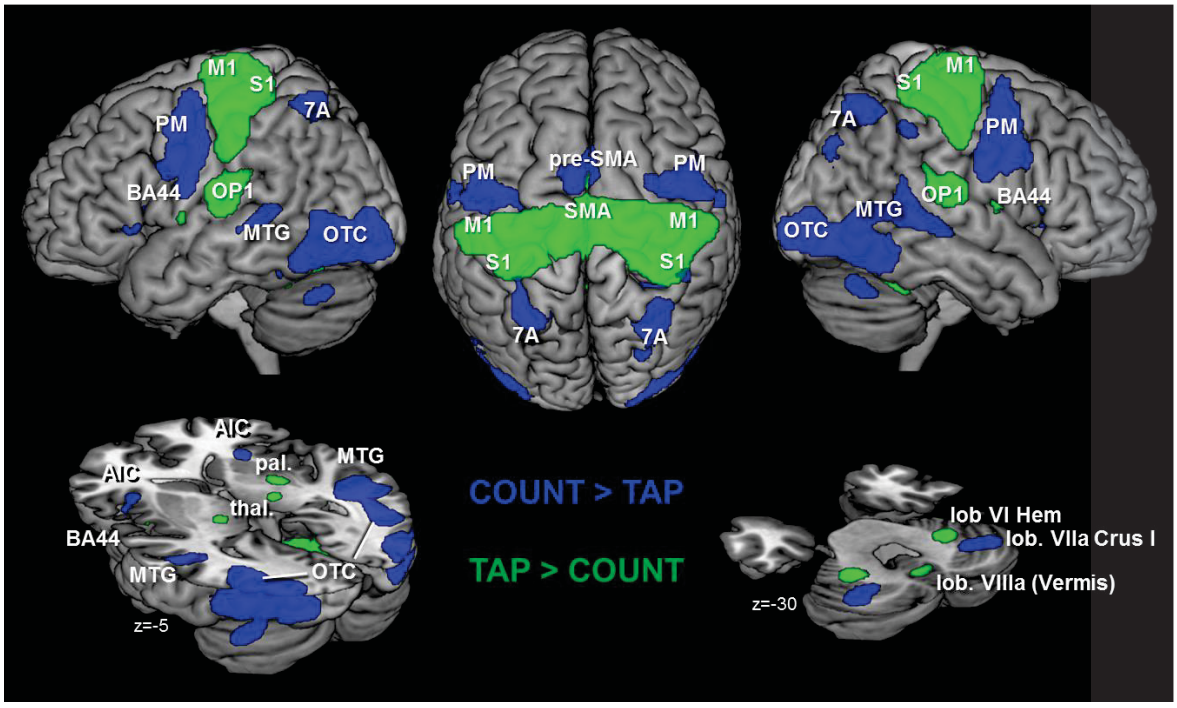


Figure 1 | Brain activation significantly stronger activated to either the visual attention task (blue cluster) or to the motor task (green cluster). M1: primary motor cortex; S1: primary somatosensory cortex; PM: pre-motor cortex; OP1: parietal opercular area 1, 7A: superior parietal area 7A; SMA: supplementary motor area; AIC: anterior insular cortex; put.: putamen; pal.: pallidum; thal.: thalamus; MTG: middle temporal gyrus; OTC: occipital cortex extending into temporal cortex; lob.: lobule (cerebellum); all results are FWE corrected on voxel level ($p<0.001$)

3.2.3 Age-related cross-domain effect (Age x Task interaction)

Subsequently, we tested for regions that were significantly associated with one of the two tasks, i.e., significant in the analyses presented in the last paragraph, and showed a significant age-by-task interaction. More precisely, we tested whether any of the TAP-associated regions (regions significantly more activated during TAP compared to COUNT or baseline) showed an age-related decrease of activation during TAP and an increase of activation during COUNT. Regions were only associated with TAP or COUNT, in the analysis above, if they showed a significant main effect of task, respectively.For the identification of COUNT-regions showing such an age-by-task interaction, we tested for COUNT-associated regions (significant main effects of COUNT > TAP and COUNT > baseline) in which activation decreased with age during COUNT, and increased with age during TAP. As depicted in Fig. 2, the superior parietal area 7A and rostral parts of the dorsal premotor cortex (DPMC) bilaterally showed this distinct activation pattern (Fig. 3). In contrast, for TAP-associated regions (defined by featuring significant main effects of TAP > COUNT and TAP > baseline), a pattern of decreased activation with age during TAP and simultaneously increased activation during COUNT would represent the respective age-by-task interaction indicating a shift of functional specificity. This kind of activation pattern was observed in the parietal operculum (parts of areas OP 1, OP 2, OP 3, and OP 4) bilaterally (Figs. 2, 3). In a subsequently conducted categorical analysis using a 2 9 2 factorial design [factor one: age (young/old) factor two: condition (count/tap)], these effects were confirmed, thereby strengthening our findings (cf. supplementary material).

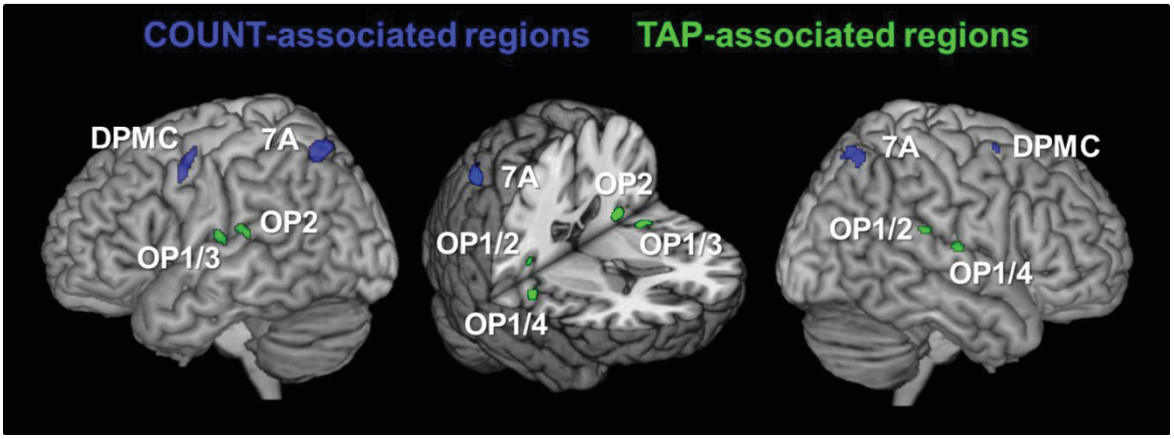
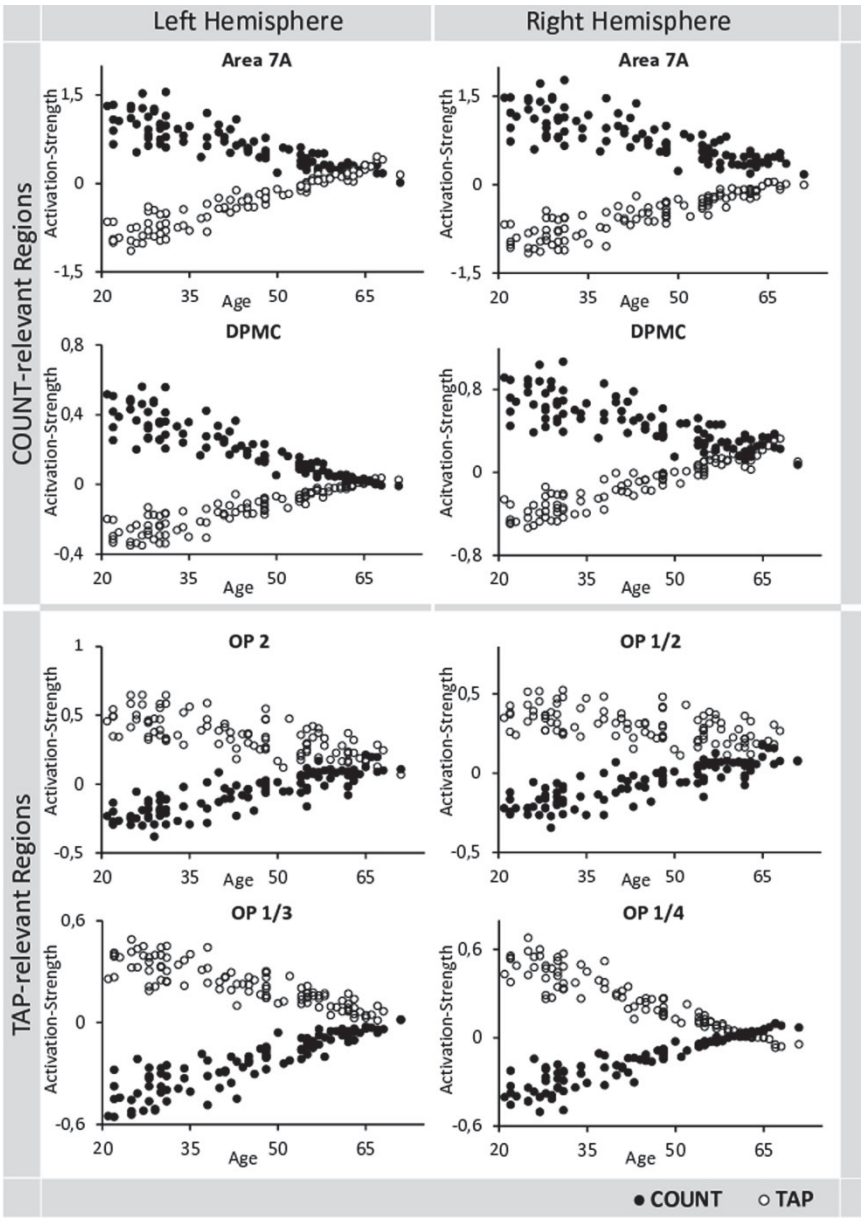


Figure 2 | Task associated regions showing an age-related increase of activation in response to their associated task and a decrease in response to the other task, i.e., an age-by-task interaction. Blue cluster: COUNT-associated regions showing a decrease of neural activation during COUNT and an increase during TAP; Green cluster: TAP-associated regions showing a decrease of neural activation during TAP and an increase during COUNT; DPMC: dorsal pre-motor cortex, OP(1-4): parietal opercular areas 1-4, 7A: superior parietal area 7A; FWE corrected on voxel level ($p<0.05$)

Figure 3 | Dependence of brain activation on age in task associated brain regions for both experimental conditions (TAP and COUNT). The activation strength reflects the beta-value of the voxel with the highest activation (maxima) in the respective cluster for each single subject. Each single dot therefore mirrors the change in BOLD signal by the respective condition in a single subject. COUNT-associated regions are represented by the four upper plots, whereas TAP-associated regions are represented by the four lower plots



3.3 Test for gender specific effects

The subsequently conducted gender-specific ANOVA yielded no significant interaction between task 9 gender or age 9 gender within any of the reported regions.

3.4 Test for changes of grey matter probability

The analysis of the gray matter probability for each region showing an age-by-task interaction revealed no significant correlations with age. Hence, confounding results related to structural changes in grey matter can be excluded for these regions.

4. Discussion

In this study, we investigated age-dependent changes in regional specificity of fMRI activity across two different functional systems: the motor system (task TAP), and the visual attention system (task COUNT). We first delineated brain regions significantly associated with either the motor or the visual attention task. A clearly differentiated activation pattern was observable for both tasks. Subsequently, we tested for age-by-task interactions within these regions. For the majority of regions within both task-associated networks no interaction was found. However, we identified specific sub-regions within both task-associated, i.e., differentiated, networks, showing such interaction by decreased activation during the associated task and increased activation during the other task, which resulted in reduced differences in evoked activation between both tasks. Such age-related changes of functional specificity were found in the superior parietal area 7A and the dorsal premotor cortex bilaterally within the COUNT-associated regions and the parietal opercular cortex (partly areas OP1, OP2, OP3, and OP4) within the TAP-relevant regions. Notably, the relative increase of activation in the task unrelated area may reflect a reduced de-activation, i.e., less inhibition of the BOLD-response relative to the implicit baseline. The lack of gender-specific differences for the regions showing this age-related interaction argues against potential

gender-specific mechanisms and toward a general phenomenon evident in both males and females.

4.1 Reduced specificity across functional domains

Activation in motor-associated regions increased during the visual attention task with age but decreases during the motor task, and vice versa, indicating a significant interaction between age and task (functional system). In particular, we found a reduced difference in TAP-COUNT evoked activation strength in elderly subjects within the parietal operculum bilaterally, which was partially attributed to lower activity of these regions during the TAP task (cf. Fig. 3). Moreover, these regions also showed a relative increase of activation below the implicit baseline (less inhibition) during COUNT with age. In analogy, we demonstrated the reverse pattern in two bilateral regions that were functionally associated with the COUNT task, namely area 7A within the superior parietal cortex and the rostral parts of the dorsal premotor cortex (DPMC). The reduced difference in activation strength may reflect reduced functional specificity and, in turn, increased integration between functional systems, which implicates ‘‘de-differentiation’’ across different functional systems. These shifts in functional response patterns may even represent a general pattern of age-related changes in brain activity. In this context, it is important to emphasize that we did not consider any effects within brain regions, which per se showed shared activation between both tasks. All regions reported above showed a clear preference for either the motor or the visual attention task as evident from the significant difference in the main effects. All identified regions actually featured deactivations in the ‘‘non-preferred’’ task in younger subjects (cf. Fig. 3). The obtained effects thus represent changes in recruitment of brain areas that are specifically associated with one of the tasks in younger subjects. To this end, it needs to be stressed that the observed effect do not reflect a ‘‘reversal of functional preference’’, i.e., there is no region

that is associated with TAP in younger and COUNT in older subjects. Rather, activation strength for both tasks (COUNT and TAP) tended to become more similar to each other and less different from the implicit baseline with increasing age for all regions. This pattern thus reflects a loss of neural specificity relative to the implicit resting baseline in one task and a relative de-activation in the other. In this context, it is worth-mentioning that the implicit baseline by no means represents an absolute zero reference without ongoing activity. It is well established that meaningful neural activity is also going on in the human brain during a ‘‘resting state’’ in which subjects are not focused on an external task (Raichle et al. 2001; Buckner et al. 2008; Schilbach et al. 2012). Independently of this relative reference to baseline, the revealed interaction effect may be interpreted as evidence for decreasing functional specificity of task-associated regions with age, in which neural activity becomes more similar to baseline for both tasks.

While the parietal operculum showed a significant preference for the TAP as opposed to the COUNT task and conversely area 7A and the dorsal premotor cortex showed a significantly stronger recruitment in the COUNT as opposed to the TAP task, it should be remembered that these regions are not exclusively recruited by finger tapping or visual attention tasks, respectively. Like any other region in the brain, these areas seem involved in many processes pertaining to motor execution, sensory processing or cognitive functions. The parietal operculum (OP1) as part of the secondary somatosensory cortex is involved in somatosensory integration (Eickhoff et al. 2010) and bimanual processing (Disbrow et al. 2001), but has also been implicated in tactile working memory, stimulus discrimination, and perceptual learning (Romo et al. 2002; Pleger et al. 2003; Burton et al. 2008). Likewise, area 7A is not only part of the dorsal visual stream and involved in visuospatial attention (Hahn et al. 2006; Kelley et al. 2008). It has also been associated with action observation (Buccino et al. 2001; Caspers et al. 2010), motor execution (grasping and sequential finger movements),

visuo-motor integration (Battaglia-Mayer and Caminiti 2002; Rizzolatti and Matelli 2003; Pellijeff et al. 2006) and mental simulation (Grezes and Decety 2001). The DPMC, finally, plays a role in several cognitive and motor related processes, e.g., conditional visuo-motor associations (Cieslik et al. 2012), response selection or motor imagery (Grafton et al. 1998; Naito et al. 1999; Toni et al. 1999). All three regions may thus be recruited by different functional systems depending on specific demands of the task at hand. It may hence be argued that these areas may implement processes rather than tasks (Eickhoff and Grefkes 2011), which then with age get differentially recruited to fulfill a given task.

The present data lead to the conclusion that the observed cross-domain effect reflects a functional plasticity throughout the human life-span leading to a less specific recruitment of neuronal processing. While each area maintains its process-specificity, the less specific recruitment of these processes manifests as a loss of specificity at the level of experimental tasks. In this context, a decrease of activation for one task may reflect reduced recruitment of this (in young subjects highly task-associated) process while conversely the same area, i.e., process, gets more recruited (less inhibited) in the context of another task. How the reduced activation of (in young subjects) task-associated regions and relative increase of activation in regions primarily associated with a different task in elderly are causally related, remains to be investigated. It was argued that insufficient activation of originally task-associated regions requires the recruitment of (auxiliary) processes or, conversely, that failure to inhibit competing processes leads to cross-talk and hence reduced task-associated activity (cf. discussion in Goh et al. 2010; Carp et al. 2011). However, the present data indicate that reduced task-specificity is present across functional systems rendering observations of age-related regional hypo- or hyperactivation condition on the actual task at hand.

4.2 The effect of decreased neural specificity across functional systems

Whether the observed less specific recruitment of neuronal processing is beneficial or detrimental for the respective behavioral performance cannot be answered from the current data as both tasks were kept deliberately simple to avoid confounding influences of task performance. Reduced neural specificity (at the level of regional activation in experimental tasks) has repeatedly been linked to age-related impairments of neural processing (Duverne et al. 2009) and performance declines (Li et al. 2001; Li and Sikstrom 2002). The present results deviate somewhat from this view as in spite of clear cross-domains effect resembling what has been termed ‘‘de-differentiation’’ within, e.g., the visual system; older subjects successfully performed both experimental tasks (COUNT and TAP). Given that this performance may be attributed to ceiling-effects in our simple tasks, we would not necessarily conclude a supportive effect of such shifts in recruitment. Nevertheless, we would propose that successful task performance at least argues against a clearly detrimental effect. In line with this view, Cabeza (2002) attributed compensatory effects to another aspect of less specific brain activation in elderly, namely bilateral activations in older adults during tasks that evoke unilateral activation in younger adults (HAROLD, cf. Reuter-Lorenz and Lustig 2005).

4.3 Summary

The present results demonstrate a significant age-by-task interaction across different functional domains, mirroring effects of ‘‘de-differentiation’’ previously demonstrated within distinct functional systems (Grady et al. 1994; Carp et al. 2011; Goh 2011). From the obtained behavioral data, we would argue that this less specific task-related recruitment of cortical areas should represent a non-detrimental process. On a more conceptual level, this age effect also prompts considerations on the nature of functional specialization as it suggests that the

mapping between regional processes and experimental tasks may undergo age-related changes. Our results thus emphasize that comparing activation patterns across different tasks (from different domains) is necessary to investigate age-related alterations of neural activation (cf. Grady 2012).

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References

Amunts K, Malikovic A, Mohlberg H, Schormann T, Zilles K (2000) Brodmann's areas 17 and 18 brought into stereotaxic space-where and how variable? Neuroimage 11:66-84

Amunts K, Schleicher A, Burgel U, Mohlberg H, Uylings HB, Zilles K (1999) Broca's region revisited: cytoarchitecture and intersubject variability. J Comp Neurol 412:319-341

Apitz C, Mackensen-Haen S, Girisch M, Kerst G, Wiegand G, Stuhrmann M, Niethammer K, Behrwind G, Hofbeck M (2010) Neonatal Marfan syndrome: unusually large deletion of exons 24-26 of FBN1 associated with poor prognosis. Klinische Padiatrie 222:261-263

Ashburner J, Friston KJ (2005) Unified segmentation. Neuroimage 26:839-851

Aster M, Neubauer A, Horn R (2006) Wechsler Intelligenztest für Erwachsene WIE. Deutschsprachige Bearbeitung und Adaptation des WAIS-III von David Wechsler (2.,korrigierte Auflage). Pearson Assessment, Frankfurt (Germany)

Battaglia-Mayer A, Caminiti R (2002) Optic ataxia as a result of the breakdown of the global tuning fields of parietal neurones. Brain 125:225-237

Behrwind SD, Dafotakis M, Halfter S, Hobusch K, Berthold-Losleben M, Cieslik EC, Eickhoff SB (2011) Executive control in chronic schizophrenia: A perspective from manual stimulus-response compatibility task performance. Behav Brain Res 223:24-29

Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, Seitz RJ, Zilles K, Rizzolatti G, Freund HJ (2001) Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. Eur J Neurosci 13:400-404

Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. Annals of the New York Academy of Sciences 1124:1-38

Burton H, Sinclair RJ, McLaren DG (2008) Cortical network for vibrotactile attention: a fMRI study. Hum Brain Mapp 29:207-221

Cabeza R (2002) Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging 17:85-100

Cabeza R, Anderson ND, Locantore JK, McIntosh AR (2002) Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage 17:1394-1402

Cabeza R, Daselaar SM, Dolcos F, Prince SE, Budde M, Nyberg L (2004) Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cereb Cortex 14:364-375

Carp J, Park J, Hebrank A, Park DC, Polk TA (2011) Age-related neural dedifferentiation in the motor system. PloS one 6:e29411

Caspers J, Zilles K, Eickhoff SB, Schleicher A, Mohlberg H, Amunts K (2012) Cytoarchitectonical analysis and probabilistic mapping of two extrastriate areas of the human posterior fusiform gyrus. Brain Struct Funct 212:481-495

Caspers S, Eickhoff SB, Geyer S, Scheperjans F, Mohlberg H, Zilles K, Amunts K (2008) The human inferior parietal lobule in stereotaxic space. Brain Struct Funct 212:481-495

Caspers S, Geyer S, Schleicher A, Mohlberg H, Amunts K, Zilles K (2006) The human inferior parietal cortex: cytoarchitectonic parcellation and interindividual variability. Neuroimage 33:430-448

Caspers S, Zilles K, Laird AR, Eickhoff SB (2010) ALE meta-analysis of action observation and imitation in the human brain. Neuroimage 50:1148-1167

Choi HJ, Zilles K, Mohlberg H, Schleicher A, Fink GR, Armstrong E, Amunts K (2006) Cytoarchitectonic identification and probabilistic mapping of two distinct areas within the anterior ventral bank of the human intraparietal sulcus. J Comp Neurol 495:53-69

Cieslik EC, Zilles K, Kurth F, Eickhoff SB (2010) Dissociating bottom-up and top-down processes in a manual stimulus-response compatibility task. J Neurophysiol 104:1472-1483

Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R (2008) Que PASA? The posterior-anterior shift in aging. Cereb Cortex 18:1201-1209

Defer GL, Widner H, Marie RM, Remy P, Levivier M (1999) Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov Disord 14:572-584

Dennis NA, Cabeza R (2011) Age-related dedifferentiation of learning systems: an fMRI study of implicit and explicit learning. Neurobiol Aging 32:2318 e2317-2330

Disbrow E, Roberts T, Poeppel D, Krubitzer L (2001) Evidence for interhemispheric processing of inputs from the hands in human S2 and PV. J Neurophysiol 85:2236-2244

Duverne S, Motamedinia S, Rugg MD (2009) The relationship between aging, performance, and the neural correlates of successful memory encoding. Cereb Cortex 19:733-744

Eickhoff SB, Amunts K, Mohlberg H, Zilles K (2006) The human parietal operculum. II. Stereotaxic maps and correlation with functional imaging results. Cereb Cortex 16:268-279

Eickhoff SB, Grefkes C (2011) Approaches for the integrated analysis of structure, function and connectivity of the human brain. Clin EEG Neurosci 42:107-121

Eickhoff SB, Heim S, Zilles K, Amunts K (2006) Testing anatomically specified hypotheses in functional imaging using cytoarchitectonic maps. Neuroimage 32:570-582

Eickhoff SB, Jbabdi S, Caspers S, Laird AR, Fox PT, Zilles K, Behrens TE (2010) Anatomical and functional connectivity of cytoarchitectonic areas within the human parietal operculum. J Neurosci 30:6409-6421

Eickhoff SB, Paus T, Caspers S, Grosbras MH, Evans AC, Zilles K, Amunts K (2007) Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. Neuroimage 36:511-521

Eickhoff SB, Schleicher A, Zilles K, Amunts K (2006) The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. Cereb Cortex 16:254-267

Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K (2005) A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25:1325-1335

Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189-198

Ge Y, Grossman RI, Babb JS, Rabin ML, Mannon LJ, Kolson DL (2002) Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. AJNR 23:1327-1333

Geyer S, Ledberg A, Schleicher A, Kinomura S, Schormann T, Burgel U, Klingberg T, Larsson J, Zilles K, Roland PE (1996) Two different areas within the primary motor cortex of man. Nature 382:805-807

Geyer S, Schleicher A, Zilles K (1999) Areas 3a, 3b, and 1 of human primary somatosensory cortex. Neuroimage 10:63-83

Giorgio A, Santelli L, Tomassini V, Bosnell R, Smith S, De Stefano N, Johansen-Berg H (2010) Age-related changes in grey and white matter structure throughout adulthood. Neuroimage 51:943-951.

Goh JO (2011) Functional Dedifferentiation and Altered Connectivity in Older Adults: Neural Accounts of Cognitive Aging. Aging Dis 2:30-48

Goh JO, Suzuki A, Park DC (2010) Reduced neural selectivity increases fMRI adaptation with age during face discrimination. Neuroimage 51:336-344

Grady CL (2008) Cognitive neuroscience of aging. Ann N Y Acad Sci 1124:127-144

Grady CL (2012) The cognitive neuroscience of ageing. Nat Ref Neurosci 13:491-505

Grady CL, Maisog JM, Horwitz B, Ungerleider LG, Mentis MJ, Salerno JA, Pietrini P, Wagner E, Haxby JV (1994) Age-related changes in cortical blood flow activation during visual processing of faces and location. J Neurosci 14:1450-1462

Grafton ST, Fagg AH, Arbib MA (1998) Dorsal premotor cortex and conditional movement selection: A PET functional mapping study. J Neurophysiol 79:1092-1097

Grefkes C, Geyer S, Schormann T, Roland P, Zilles K (2001) Human somatosensory area 2: observer-independent cytoarchitectonic mapping, interindividual variability, and population map. Neuroimage 14:617-631

Grezes J, Decety J (2001) Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. Hum Brain Mapp 12:1-19

Grossman M, Cooke A, DeVita C, Alsop D, Detre J, Chen W, Gee J (2002) Age-related changes in working memory during sentence comprehension: an fMRI study. Neuroimage 15:302-317

Hahn B, Ross TJ, Stein EA (2006) Neuroanatomical dissociation between bottom-up and top-down processes of visuospatial selective attention. Neuroimage 32:842-853

Halstead WC (1947) Brain and intelligence: A quantitative study of the frontal lobes. University of Chicago Press, Chicago (IL)

Iidaka T, Okada T, Murata T, Omori M, Kosaka H, Sadato N, Yonekura Y (2002) Age-related differences in the medial temporal lobe responses to emotional faces as revealed by fMRI. Hippocampus 12:352-362

Hoffstaedter F, Sarlon J, Grefkes C, Eickhoff SB. 2012. Internally vs. externally triggered movements in patients with major depression. Behavioural brain research. 228:125-132.

Kaasinen V, Rinne JO (2002) Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. Neurosci Biobehav Rev 26:785-793

Kelley TA, Serences JT, Giesbrecht B, Yantis S (2008) Cortical mechanisms for shifting and holding visuospatial attention. Cereb Cortex 18:114-125

Kiebel SJ, Glaser DE, Friston KJ (2003) A heuristic for the degrees of freedom of statistics based on multiple variance parameters. Neuroimage 20:591-600

Kramer AF, Madden DJ (2008) Attention. In: Craik FIM, Satlhouse TA (eds.) The handbook of aging and cognition 3rd edn. Psychology Press, New York: pp 189-249

Krampe RT (2002) Aging, expertise and fine motor movement. Neurosci Biobehav Rev 26:769-776

Lehmbeck JT, Brassen S, Weber-Fahr W, Braus DF (2006) Combining voxel-based morphometry and diffusion tensor imaging to detect age-related brain changes. Neuroreport 17:467-470.

Levine BK, Beason-Held LL, Purpura KP, Aronchick DM, Optican LM, Alexander GE, Horwitz B, Rapoport SI, Schapiro MB (2000) Age-related differences in visual perception: a PET study. Neurobiol Aging 21:577-584

Li SC, Lindenberger U, Sikstrom S (2001) Aging cognition: from neuromodulation to representation. Trends Cogn Sci 5:479-486

Li SC, Sikstrom S (2002) Integrative neurocomputational perspectives on cognitive aging, neuromodulation, and representation. Neurosci Biobehav Rev 26:795-808

Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL (2002) Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. Neuron 33:827-840

Madden DJ, Turkington TG, Provenzale JM, Denny LL, Langley LK, Hawk TC, Coleman RE (2002) Aging and attentional guidance during visual search: functional neuroanatomy by positron emission tomography. Psychol Aging 17:24-43

Malikovic A, Amunts K, Schleicher A, Mohlberg H, Eickhoff SB, Wilms M, Palomero-Gallagher N, Armstrong E, Zilles K (2007) Cytoarchitectonic analysis of the human extrastriate cortex in the region of V5/MT+: a probabilistic, stereotaxic map of area hOc5. Cereb Cortex 17:562-574

Nagel IE, Preuschhof C, Li SC, Nyberg L, Backman L, Lindenberger U, Heekeren HR (2009) Performance level modulates adult age differences in brain activation during spatial working

Nagel IE, Preuschhof C, Li SC, Nyberg L, Backman L, Lindenberger U, Heekeren HR (2011) Load modulation of BOLD response and connectivity predicts working memory performance in younger and older adults. J Cogn Neurosci 23:2030-2045

memory. Proc Natl Acad Sci U S A 106:22552-22557

Naito E, Ehrsson HH, Geyer S, Zilles K, Roland PE (1999) Illusory arm movements activate cortical motor areas: a positron emission tomography study. J Neurosci 19:6134-6144

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97-113

Park DC, Polk TA, Park R, Minear M, Savage A, Smith MR (2004) Aging reduces neural specialization in ventral visual cortex. Proc Natl Acad Sci U S A 101:13091-13095

Park DC, Reuter-Lorenz P (2009) The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol 60:173-196

Pellijeff A, Bonilha L, Morgan PS, McKenzie K, Jackson SR (2006) Parietal updating of limb posture: an event-related fMRI study. Neuropsychologia 44:2685-2690

Pleger B, Foerster AF, Ragert P, Dinse HR, Schwenkreis P, Malin JP, Nicolas V, Tegenthoff M (2003) Functional imaging of perceptual learning in human primary and secondary somatosensory cortex. Neuron 40:643-653

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. P Natl Acad Sci USA 98:676-682

Reitan RM (1955) The relation of the trail making test to organic brain damage. J Consult Psychol 19:393-394

Reuter-Lorenz PA, Lustig C (2005) Brain aging: reorganizing discoveries about the aging mind. Curr Opin Neurobiol 15:245-251

Reuter-Lorenz PA, Park DC (2010) Human neuroscience and the aging mind: a new look at old problems. J Gerontol B Psychol Sci Soc Sci 65:405-415

Rizzolatti G, Matelli M (2003) Two different streams form the dorsal visual system: anatomy and functions. Exp Brain Res 153:146-157

Romo R, Hernandez A, Zainos A, Lemus L, Brody CD (2002) Neuronal correlates of decision-making in secondary somatosensory cortex. Nat Neurosci 5:1217-1225

Rottschy C, Eickhoff SB, Schleicher A, Mohlberg H, Kujovic M, Zilles K, Amunts K (2007) Ventral visual cortex in humans: cytoarchitectonic mapping of two extrastriate areas. Hum Brain Mapp 28:1045-1059

Rypma B, D'Esposito M (2000) Isolating the neural mechanisms of age-related changes in human working memory. Nat Neurosci 3:509-515

Scheperjans F, Eickhoff SB, Homke L, Mohlberg H, Hermann K, Amunts K, Zilles K (2008) Probabilistic maps, morphometry, and variability of cytoarchitectonic areas in the human superior parietal cortex. Cereb Cortex 18:2141-2157

Scheperjans F, Hermann K, Eickhoff SB, Amunts K, Schleicher A, Zilles K (2008) Observer-independent cytoarchitectonic mapping of the human superior parietal cortex. Cereb Cortex 18:846-867

Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, Kwak Y, Lipps DB (2010) Motor control and aging: links to age-related brain structural, functional, and biochemical effects. Neurosci Biobehav Rev 34:721-733

Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW (2003) Mapping cortical change across the human life span. Nat Neurosci 6:309-315.

Toni I, Schluter ND, Josephs O, Friston K, Passingham RE (1999) Signal-, set- and movement-related activity in the human brain: an event-related fMRI study. Cereb Cortex 9:35-49

Townsend J, Adamo M, Haist F (2006) Changing channels: an fMRI study of aging and cross-modal attention shifts. Neuroimage 31:1682-1692

Walhovd KB, Fjell AM, Reinvang I, Lundervold A, Dale AM, Eilertsen DE, Quinn BT, Salat D, Makris N, Fischl B (2005) Effects of age on volumes of cortex, white matter and subcortical structures. Neurobiol Aging 26:1261-1270

Wechsler D (1997) Wechsler Adult Intelligence Scale - 3rd Edition (WAIS-3). Harcourt Assessment, San Antonio (TX)

Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC (1996) A unified statistical approach for determining significant signals in images of cerebral activation. Hum Brain Mapp 4:58-73

Zilles K, Amunts K (2010) Centenary of Brodmann's map--conception and fate. Nat Rev Neurosci 11:139-145

Supplementary Material

Condition specific age-related effects

Regions that show significant age related effects on activations are shown in Figure S1. No positive correlation with respect to the implicit baseline with age was observable in both tasks.

As illustrated by Figure S1, negative correlation with age during TAP was found bilaterally in the primary motor cortex, pre-motor cortex, SMA, rolandic operculum, visual area hOC3v and left parietal operculum (area OP1), as well as in the cerebellum, basal ganglia (putamen) and thalamus (Table S1).

Within the COUNT-network, negative correlation with age was found bilaterally in SMA, pre-motor cortex, right intraparietal sulcus (area hIP2) and in the right visual areas hOC3v, hOC4, hOC5 and 18 (Fig. S1, Table S1).

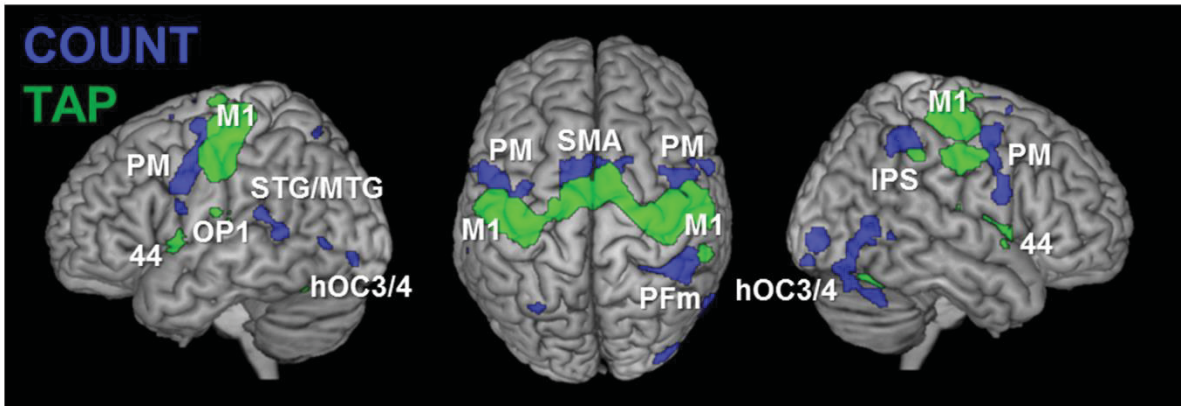

Figure S 1 | Regions showing a negative correlation with age. Green cluster: activation correlating negatively with age during TAP; Blue cluster: activation correlating negatively with age during COUNT; red cluster: conjunction of negatively correlated activation (TAP ∩ COUNT). OP: parietal operculum; 44: area 44; M1: primary motor cortex; PM: pre-motor cortex; SMA: supplementary motor area; PFm: inferior parietal area PFm; IPS: inferior parietal sulcus; hOC3/4v: extrastriate visual areas V3/V4.FWE corrected on voxel level ($p<0.05$).

Table S1-S4 | Macroanatomical and cytoarchitectonical classification of local maxima from reported activations. Coordinates related to MNI-space (x y z). Cytoarchitectonical classification by using the SPM Anatomy Toolbox V1.7 (Eickhoff SB et al. 2005; Eickhoff SB et al. 2006; Eickhoff SB et al. 2007). Cytoarchitectonic regions are assigned to local maxima at a probability of at least 40% within the maximum probability map. If two or more cytoarchitectonic areas show overlap in their probabilities for the respective local maxima (in sum at least 60%), the region with the highest probability was assigned to the maxima. All results are FWE-corrected on the voxel level.

Table S1 | Condition specific age-related effects

macro-anatomic classification	cytoarchitectonic classification	Lat	maxima (MNI)			T-Value
			X	Y	Z	
Age-related decrease of activation for the visual attention task						
medial superior frontal gyrus	6	L	-6	-2	68	6.61
intraparietal sulcus	hIP2	R	45	-36	41	6.03
		L	-41	-35	33	4.11
	hIP3	L	-41	-38	42	3.36
inferior parietal lobule	PFm	R	47	-45	51	4.32
precentral gyrus/ middle frontal gyrus	6	R	45	0	51	4.94
		L	-48	-8	47	5.13
middle temporal gyrus		L	-65	-47	8	4.18
superior temporal gyrus		L	-63	-39	15	3.89
lateral occipital sulcus	hOC5	R	53	-62	5	4.3
		L	-42	-66	3	3.86
inferior occipital gyrus	hOC3v	R	26	-90	-6	3.54
	hOC4	R	36	-90	-3	5.35
fusiform gyrus	GF2	R	42	-77	-20	4.19
cerebellum	Lobule VIIa	R	44	-62	-32	4.19
Age-related decrease of activation for the motor task						
precentral gyrus	6	R	33	-24	56	10.37
	4p	L	-36	-24	54	9.39
medial superior frontal gyrus	6	R	2	-8	56	5.04
		L	-2	-8	60	4.98
postcentral gyrus	2	R	26	-38	47	4.86
	3a	R	23	-35	48	3.87
	3b	R	51	-15	39	5.91
inferior frontal gyrus	44	R	50	6	3	4.41
		L	-50	2	6	3.9
parietal operculum	OP1	L	-48	-23	18	5.26
		R	41	-30	26	4.29
putamen		R	30	-2	-3	4.51
		L	-27	-12	12	3.83
thalamus		R	21	-15	8	4.26
		L	-18	-14	8	3.32

		R	21	-9	15	3.33
		L	-17	-11	0	3.83
inferior occipital gyrus	hOC3v	R	21	86	-5	4.42
cerebellum	Lobule V	R	8	-53	-6	3.9
		L	-17	-50	-24	5.31
	Lobule VI (Hem)	R	17	-51	-21	6.4
		L	-18	-51	-26	5.3

Table S2 | Task main effect

macro-anatomic classification	Cytoarchitectonic* classification	Lat	maxima (MNI)			T-Value
			X	Y	Z	
Activation pattern during the visual attention task						
inferior occipital gyrus	hOC4v	R	42	-83	-9	21.23
		L	-38	-86	-8	19.12
lateral occipital sulcus		R	47	-75	-8	21.46
		L	-45	-75	-6	22.75
	hOC5	R	48	-71	-2	21.40
superior occipital gyrus		R	27	-71	30	11.76
inferior temporal gyrus		R	45	-56	-17	16.05
intraparietal sulcus		R	27	-54	44	15.01
inferior parietal lobule	PFcm	L	-48	-36	20	13.66
	PF	R	-63	-38	12	11.24
intraparietal sulcus	hIP2	R	42	-42	41	10.79
		L	-42	-38	39	8.46
superior parietal lobule	7PC	L	-27	-54	50	12.03
middle frontal gyrus	6	R	51	2	47	21.66
		L	-51	8	50	24.56
postcentral gyrus	3b	R	60	0	20	10.23
middle occipital gyrus		L	-27	-69	30	9.95
medial superior frontal gyrus	6	L	-5	-3	65	20.55
inferior frontal gyrus	44	R	51	9	5	9.38
thalamus		R	14	-9	3	6.94
anterior insular lobe		R	32	21	8	11.63
		L	-35	20	6	8.97
putamen		R	21	3	8	7.20
		L	-23	5	2	10.03
cerebellum	lobule VIIa crus I	R	6	-77	-33	5.78
		L	-32	-63	-29	9.73
	lobule VI(Hem)	R	-11	-74	-21	8.07
		L	-9	-74	-23	9.67
Activation pattern during the motor task						

precentral gyrus	4p	R	35	-24	53	30.94
		L	-36	-26	53	27.90
	4a	L	-3	-24	53	16.09
medial superior frontal gyrus	6	L	-2	-11	59	20.14
middle temporal gyrus		R	50	-72	0	13.9
		L	-73	-71	5	9.42
inferior occipital gyrus		R	48	-80	-8	11.05
middle occipital gyrus	18	R	26	-99	6	10.29
		L	-24	-102	2	6.21
inferior occipital gyrus	hOC3v	L	-33	-96	5	7.52
inferior parietal lobule	PFcm	R	57	-33	14	10.40
		L	-50	-33	17	12.84
parietal operculum	OP1	R	59	-21	15	10,98
		L	-57	-17	15	12.66
middle frontal gyrus		R	44	42	2	6.15
thalamus		L	-15	-17	3	9.86
		R	15	-17	2	10.56
pallidum		R	26	-5	2	10.52
putamen		L	-27	2	0	11.12
cerebellum	lobule V	L	-3	-60	-15	18.2
	lobule VI(Hem)	R	15	-53	-18	14.35
		L	-17	-51	-21	17.63

Table S3 | Task-associated activation

macro-anatomic classification	cytoarchitectonic classification	Lat	maxima (MNI)			T-Value
			X	Y	Z	
Visual attention task associated regions						
inferior occipital gyrus	hOC3v	R	33	-92	-6	11.86
	hOC4v	L	-38	-86	-8	15.32
middle temporal gyrus		R	53	-42	6	9.24
		L	-53	-36	3	7.71
inferior temporal gyrus		R	45	-56	-15	13.53
superior temporal gyrus		R	51	-30	-2	8.02
fusiform gyrus	GF2	R	45	-62	-14	13.36
		L	-44	-66	-12	14.22
middle frontal gyrus		R	41	3	30	13.16
		L	-41	-6	41	16.58
superior frontal gyrus		R	45	2	50	9.93
		L	-50	5	51	13.8
superior occipital gyrus		R	27	-71	30	11.76
middle occipital gyrus		L	-27	-69	30	9.95
intraparietal sulcus	hIP3	R	42	-41	39	8.47
		L	-39	-38	39	6.38
superior parietal lobule	7PC	L	-27	-45	50	12.03

medial superior frontal gyrus	6	R	6	11	50	9.60
		L	-6	8	53	13.8
anterior insular lobe		R	32	21	9	8.11
		L	-38	17	6	6.33
cerebellum	lobule VIIa crus I	R	33	-62	-30	8.6
		L	-32	-62	-32	8.59
	lobule VI	L	-9	-74	-23	9.67
		R	11	-72	-23	7.78
Motor task associated regions						
postcentral gyrus	1	L	-53	-23	47	16.38
precentral gyrus	4a	L	0	-21	54	16.26
	4p	R	35	-24	51	30.94
		L	-36	-26	53	27.90
medial superior frontal gyrus	6	R	2	-11	56	19.17
		L	-2	-12	56	19.1
parietal operculum	OP1	R	59	-21	15	11.04
		L	-56	-17	15	12.45
frontal operculum		R	45	0	9	8.01
		L	-44	2	8	8.25
thalamus		L	-17	-18	3	8.86
		R	17	-18	3	9.46
pallidum		R	27	-8	0	7.52
cerebellum	lobule V	L	-3	-60	-15	18.20
	lobule VI(Hem)	R	15	-53	-18	14.32
		L	-17	-51	-21	17.59

Table S4 | Age-related cross domain effect

macro-anatomic classification	cytoarchitectonic classification	Lat	maxima (MNI)			T-Value
			X	Y	Z	
Visual attention task associated regions – cross domain effect						
superior parietal lobule	7A	R	36	-69	59	2.52
		L	-29	68	57	3.22
middle frontal gyrus	6	R	33	6	60	2.16
		L	-35	-2	54	2.51
Motor task associated regions – cross domain effect						
parietal operculum	OP1/4	R	50	-14	11	2.2
	OP1/3	L	-44	-15	14	2.48
	OP1/2	R	38	-33	20	2.28
	OP2	L	-36	-27	17	2.66

STUDY 2

Adult age-dependent differences in resting-state connectivity within and between visual-attention and sensorimotor networks

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Own contributions:	Conception and design of the study Data acquisition Reviewing and adapting the analysis code Statistical analysis Interpretation of results Preparing figures Writing the paper
Total contribution:	80%

Abstract

Healthy aging is accompanied by structural and functional changes in the brain, among which a loss of neural specificity (i.e., dedifferentiation) is one of the most consistent findings. Little is known, however, about changes in interregional integration underlying a dedifferentiation across different functional systems. In a large sample (n = 399) of healthy adults aged from 18 to 85 years, we analyzed age-dependent differences in resting-state (RS) (task-independent) functional connectivity (FC) of a set of brain regions derived from a previous fMRI study. In that study, these regions had shown an age-related loss of activation specificity in visual-attention (superior parietal area 7A and dorsal premotor cortex) or sensorimotor (area OP4 of the parietal operculum) tasks. In addition to these dedifferentiated regions, the FC analysis of the present study included "task-general" regions associated with both attention and sensorimotor systems (rostral supplementary motor area and bilateral anterior insula) as defined via meta-analytical co-activation mapping. Within this network, we observed both selective increases and decreases in RS-FC with age. In line with regional activation changes reported previously, we found diminished anti-correlated FC for inter-system connections (i.e., between sensorimotor-related and visual attention-related regions). Our analysis also revealed reduced FC between system-specific and task-general regions, which might reflect age-related deficits in top-down control possibly leading to dedifferentiation of task-specific brain activity. Together, our results underpin the notion that RS-FC changes concur with regional activity changes in the healthy aging brain, presumably contributing jointly to age-related behavioral changes.

1. Introduction

Effective information processing depends on the integrity of communication between the different nodes of functional brain systems. Through normal aging, substantial changes within and between brain networks occur (for review see Eyler et al., 2011; Grady, 2012). For example, it has been shown, that older adults exhibit lower connectivity within task-relevant networks and greater connectivity outside the task-relevant networks (Daselaar et al., 2006; Dennis et al., 2008; St Jacques et al., 2009). Moreover, changes of regional brain activity were repeatedly observed in older adults (cf. Eyler et al., 2011; Grady, 2012). These neural changes are in line with behavioral studies reporting increased associations between sensory, sensorimotor, and cognitive functions in elderly participants (Baltes and Lindenberger, 1997; Lindenberger and Baltes, 1994; Schaefer et al., 2006).

In a previous functional magnetic resonance imaging (fMRI) study, we investigated functional activation patterns in the sensorimotor and the visual attention systems in a large sample of healthy subjects between 20 and 70 years of age (Roski et al., 2013). When testing for age-related effects across both functional domains (visual attention and sensorimotor control), we found reduced activation in several task-relevant regions as well as increased activation in regions that are less activated in younger adults. This effect holds substantial similarity to the repeatedly observed age-related process of dedifferentiation, i.e., a loss of neural specificity within distinct functional systems (for review see Reuter-Lorenz and Park, 2010). Little is known, however, about the aberrations in neural networks, i.e., inter-regional integration, underlying a dedifferentiation across different functional systems as observed in that previous fMRI study. This raises the question to which extent the interaction within and between functional systems becomes less differentiated as a consequence of healthy aging. In this context it should be noted that age-related changes in the interplay between visual attention processes and the sensorimotor system might provide additional insights into the

physiological changes across multiple brain systems with healthy aging. In addition to providing a complementary, network-based perspective on age-related dedifferentiation across systems, improved knowledge of age-related changes in functional integration may also provide an important background for the assessment of network pathology caused by neurodegenerative disorders. For example, it is assumed that the cognitive deficits in Alzheimer`s disease may be attributed to the disease's severe effects on functional networks marked by a profound disruption of functional connectivity (FC) within and across brain networks (for review see Delbeuck et al., 2003). In this context, however, it remains an open question whether similar age-related FC changes in connectivity between/within the sensorimotor and visual-attention systems may also be found in healthy aging, as suggested by the previously observed, dedifferentiated, recruitment pattern.

These considerations promoted the current analysis of age-related changes in functional integration between regions of the visual-attention and sensorimotor systems that were previously shown to feature reduced functional specificity with increasing age. In other words, our aim was to address the changes in network interactions underlying the observed dedifferentiation across functional domains. This goal was pursued by investigating age-related alteration of task-independent, i.e., resting-state (RS), FC between regions (functional seeds) of the visual-attention or sensorimotor systems that show a dedifferentiated recruitment pattern with increasing age. In this context it should be noted that temporally correlated brain activity in spatially distinct regions (i.e., functional connectivity) may not only arise from direct interaction (Eickhoff and Grefkes, 2011). Rather, functional connectivity, in particular between different functional systems, may also be mediated by task-general regions interacting with regions from either system. The inclusion of these regions (in addition to the functionally defined seed regions) in the FC analysis should hence offer insights into the

mechanisms underlying the change of network interactions between the visual-attention and sensorimotor systems in the elderly.

In the present study, we investigated changes of RS-FC between functional seeds that showed an age-related dedifferentiated recruitment pattern as well as with task-general regions that are functionally related to all of these. The functional seeds were defined based on results from a previous fMRI study (Roski et al., 2013), whereas the task-general brain regions were identified via meta-analytic connectivity modeling (MACM; Eickhoff et al., 2010; Robinson et al., 2010). Once these task-general regions were defined, a two-step RS-FC network analysis was performed. In the first step, the task-independent connectivity pattern of all regions was analyzed in a large adult sample (n = 399). In the second step, age-related changes in task-independent FC for this set of seed regions were analyzed in the same sample. This approach of examining the RS-FC including task-general regions in a large sample of healthy subjects should provide insights into age-related changes in the functional coupling between brain regions involved in sensorimotor and visual attention processing.

2. Material and Methods

The initial seed regions for the current connectivity analysis were provided by regions that showed a less differentiated neural activity pattern across the sensorimotor and the visual attention systems with age, i.e., an age-by-task interaction (Roski et al., 2013). As mentioned above, additional task-general regions (i.e., regions that consistently interact with each of these seed regions) were defined using MACM. The ensuing set of brain regions (seed regions from the fMRI study and task-general regions from the MACM analysis) were analyzed in a two-step RS-FC network analysis to unveil (i) the task-independent inter-regional FC within the combined set of brain regions, and (ii) to analyze age-related changes of FC within this network. All specified analyses are described in detail in the following sections.

2.1 Definition of seed regions

2.1.1 *Seed regions based on fMRI*

Seed regions were derived from a previous fMRI study on age-related changes in neural correlates of sensorimotor and visual attention processing (Roski et al., 2013). For the present study, only regions that showed an age-by-task interaction were included (Fig. 1): bilateral area OP4 of the parietal operculum (Eickhoff et al., 2006a; Eickhoff et al., 2006b) showed a decrease in activation during a motor task (finger tapping) but an increase in activation during a visual attention task (target letter counting) in elderly participants. In contrast, bilateral superior parietal area 7A (Scheperjans et al., 2008a; Scheperjans et al., 2008b) and the rostral part of the dorsal premotor cortex (dPMC; cf. Amiez et al., 2006; Brown et al., 2004; Ford et al., 2005) showed the opposite pattern: an age-related decrease in activation during the visual attention task and an increase in activation during the motor task.

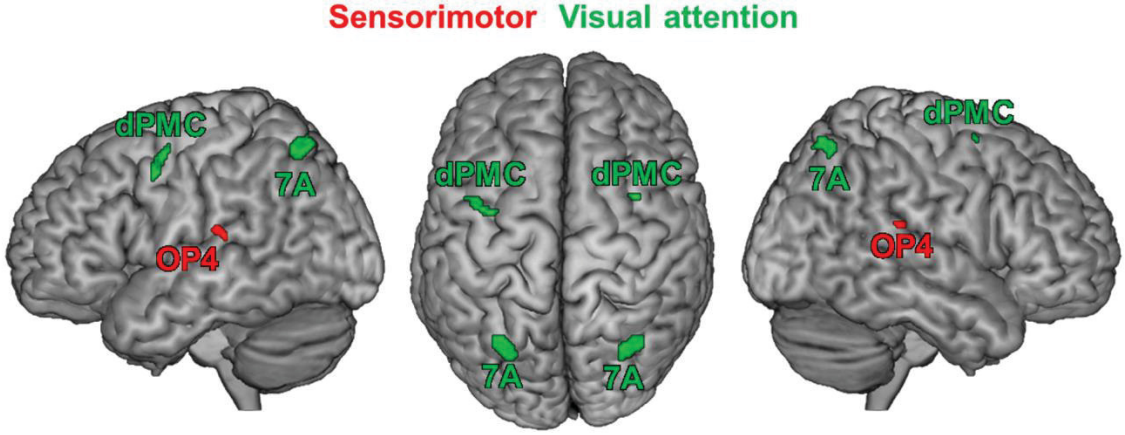


Figure 1 | Regions showing an age by task interaction as reported in a previous study (Roski et al., 2013). These regions represent the fMRI-based seed regions for the present study. Green color denotes regions associated with visual attention; red color denotes regions associated with sensorimotor processing. 7A, superior parietal lobule area 7A (cytoarchitectonically defined; Scheperjans et al., 2008a,b); dPMC, dorsal premotor cortex; OP4, area OP4 of the parietal operculum (cytoarchitectonically defined; Eickhoff et al., 2006a,b).

2.1.2 Task-general regions

Besides these functionally defined seeds, we also included task-general regions in the current analysis. We considered those regions to be task-general since, across tasks, they showed a consistent functional relation to each of the regions derived from the fMRI study. To identify these regions, we first mapped the task-dependent co-activation pattern for each of the above-mentioned seed regions using MACM. Subsequently, a conjunction analysis across the resulting co-activation maps using a minimum statistic approach revealed those regions that were functionally related to all fMRI-based seeds.

Here we used the BrainMap database (Laird et al., 2009, 2011; www . brainmap . org) to assess the co-activation pattern of each seed (Eickhoff et al., 2010), considering all experiments which reported stereotaxic coordinates from normal mapping studies (no interventions and no group comparisons) in healthy subjects using either fMRI or positron emission tomography (PET). These inclusion criteria yielded (at the time of analysis) ~ 7200 functional neuroimaging experiments. For each individual seed region (left/right OP4, 7A, DPMC) we proceeded as follows: first, we identified the 100 experiments in BrainMap that reported activation closest to it (see Table 1). Then we tested for convergence across (all) foci reported in these experiments using the revised version (Eickhoff et al., 2009) of the activation likelihood estimation (ALE) approach. Using random-effects inference, the ALE maps reflecting the convergence of co-activations with each seed region, were thresholded at $p < 0 . 05$ (cluster-level family wise error corrected; cluster-forming threshold: $p < 0 . 001$ at voxel level) and converted to Z-scores for visualization (see supplementary material Figure S1). As experiments were selected by activation close to the seed, highest convergence will be observed in the seed region (cf. Table 1). Significant convergence in other brain regions in turn indicates consistent co-activation over experiments and, hence, FC with the seed (Jakobs et al., 2012).

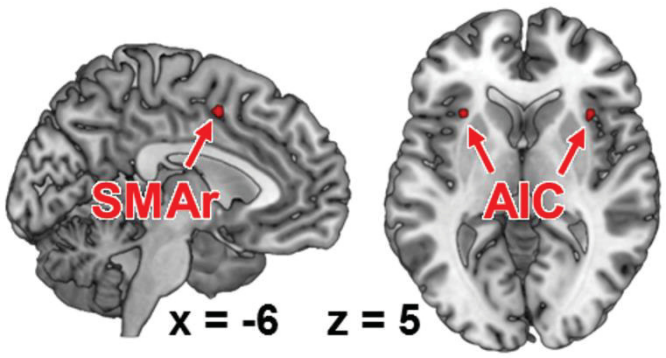
To identify task-general regions for the subsequent RS-FC analysis, i.e., regions that were significantly co-activated with all seeds, we performed a conjunction analysis across the respective MACM results using the conservative minimum statistic (Nichols et al., 2005). This approach showed that the bilateral anterior insular cortex (AIC; MNI: − 32, 20, 6; 36, 18, 4) was consistently co-activated with all seed regions (Figure 2). Also a region within the rostroventral supplementary motor cortex (SMAr; 2, 0, 56), rostrally bordering the pre-SMA and ventrally bordering the middle cingulate cortex (Palomero-Gallagher et al., 2008, 2009; Hoffstaedter et al., 2012), was consistently co-activated with each seed region. Both regions were hence defined to hold a task-general function across sensorimotor and visual attention processes.

Table 1 | Location of seed regions and maximum distance to relevant foci within BrainMap

Seed Region	Peak coordinate (MNI: x,y,z)	Maximum distance (mm)
7A left	-29, -66, 57	6.9
7A right	32, -66, 56	7.1
OP4 left	-44, -17, 12	7.3
OP4 right	50, -14, 11	7.4
dPMC left	-41, 2, 50	5.7
dPMC right	35, 6, 60	7.8

Note. dPMC - dorsal premotor cortex; OP4 – area OP4 of the parietal operculum; 7A - superior parietal lobule area 7A.

Figure 2 | Functional intersection of all co-activation maps of each fMRI-based seed region, as revealed by meta-analytic connectivity modeling. These regions represent those brain areas that were functionally connected to all of our seed regions (i.e., task-general regions). AIC, anterior insular cortex; SMAr, rostroventral supplementary motor area.



2.1.3 Combined set of seed regions – fMRI-based seed regions and task-general regions

The fMRI-based seed regions (visual attention and sensorimotor) and the MACM-derived task-general seed regions conjointly represented the combined set of our seed regions, comprising sensorimotor area OP4 and attention-related dPMC and area 7A, as fMRI-based seed regions, as well as SMAr and AIC as task-general regions (Fig. 3).

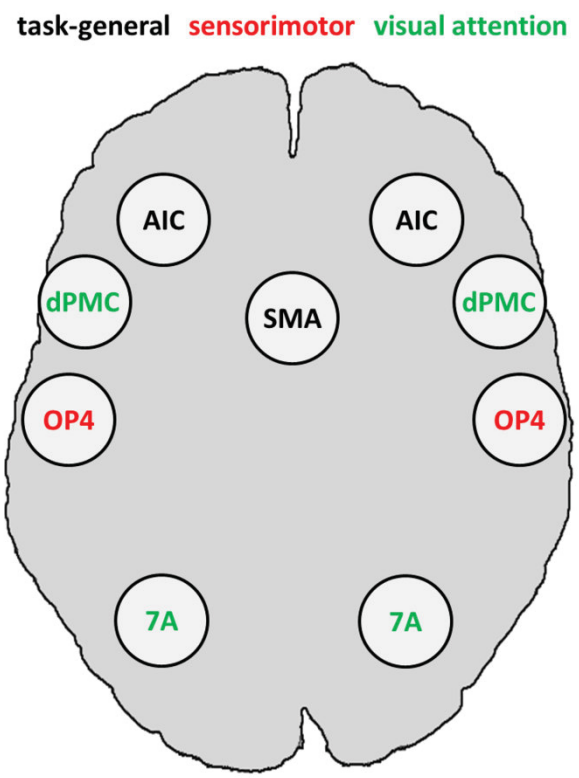


Figure 3 | Combined set of seed regions (schematic), comprising fMRI-based seed regions (visual attention and sensorimotor) derived from Roski et al. (2013) and task-general regions derived from meta-analytic connectivity modeling. 7A, superior parietal lobule area 7A; AIC, anterior insular cortex; dPMC, dorsal premotor cortex; OP4, area OP4 of the parietal operculum; SMAr, rostro-ventral supplementary motor area.

2.2 Resting-state analysis

A RS-FC network analysis was implemented to analyze the task-independent FC between these seed regions and its change with age for all possible connections between the combined set of seed regions (fMRI-based and task-general).

2.2.1 Sample

Inter-regional RS-FC for the combined set of seed regions was assessed by using resting state fMRI data from 399 healthy volunteers, aged 18 to 85 years (*Mean* = 41.8, *SD* = 16.8, *Median*

= 41, *IQR* = 29). All participants (46% female) were without any record of neurological or psychiatric disorders and gave their written informed consent to participate in the study. The data were contributed by four sites (see Table 1). Joint (re-)analysis of the data was approved by the local ethics committee of the Heinrich Heine University Düsseldorf.

Table 2 | Characteristics of the Sample

Source Site	n	Mean Age (Range)	Sex: Male (%)	Measurement Parameters[a]
RWTH University Hospital Aachen, Germany	47	36.5 (19-59)	46	3T / 250 / 2.2 / 30 / 80° / 3.1 × 3.1 × 3.1 mm³
	28	63.4 (55-72)	71	3T / 270 / 2.2 / 30 / 90° / 3.1 × 3.1 × 3.1 mm³
Research Centre Jülich, Germany	51	28.3 (18-59	57	3T / 250 / 2.2 / 30 / 90° / 3.1 × 3.1 × 3.1 mm³
	100	45.1 (21-71)	48	3T / 300 / 2.2 / 30 / 90° / 3.1 × 3.1 × 3.1 mm³
ICBM, Montreal, Canada[b]	41	40.6 (19-78)	42	1.5T / 256 / 2.0 / 50 / 90° / 4.0 × 4.0 × 5.5 mm³
NKI, Rockland, NY, USA[b]	132	42.3 (18-85)	59	3T / 260 / 2.5 / 30 / 80° / 3.0 × 3.0 × 3.0 mm³

Note. ICBM, International Consortium for Brain Mapping; NKI, Nathan S. Kline Institute.
[a] Measurement parameters: magnetic field strength of the scanner / number of acquired volumes / repetition time (in s) / echo time (in ms) / flip angle / voxel size.
[b] These data were selected from the datasets included in Biswal et al. (2010) and made publicly available via the 1000 Functional Connectomes Project (http://fcon_1000.projects.nitrc.org).

2.2.2 Imaging and pre-processing

During scanning participants were instructed to let their mind wander but not to fall asleep which was confirmed by post-scan debriefing. For each subject the RS EPI images were acquired using blood-oxygen-level-dependent (BOLD) contrast (cf. Table 1). Image acquisition was preceded by dummy images allowing for magnetic field saturation which were discharged prior to further processing using SPM8 (www.fil.ion.ucl.ac.uk/spm). The EPI

images were first corrected for head movement by affine registration using a two-pass procedure. For normalization the mean EPI images were segmented into grey matter, white matter and cerebrospinal fluid using the "unified segmentation" approach (Ashburner and Friston, 2005). The resulting parameters of a discrete cosine transform, which define the deformation field necessary to move subject data into MNI space, were then combined with the deformation field transforming between the latter and the MNI single-subject template. The ensuing deformation was subsequently applied to the individual EPI volumes which thereby were transformed into the MNI single-subject space and resampled at 1.5 mm isotropic voxel size. Finally, images were smoothed by a 5-mm FWHM Gaussian to meet requirements of the general linear model and compensate for residual anatomical variations.

2.2.3 Analysis

Functional connectivity analyses may be influenced by several confounds such as physiological processes, e.g., fluctuations related to cardiac and respiratory cycles and in particular motion-related effects (Bandettini and Bullmore, 2008; Fox et al., 2009). In order to reduce spurious correlations, variance that could be explained by the following nuisance variables was removed from the time series of each voxel's time series (Reetz et al., 2012; Satterthwaite et al., 2013; zu Eulenburg et al., 2012): i) the six motion parameters derived from the image realignment ii) the first derivatives of the six motion parameters iii) mean grey matter, white matter and cerebrospinal-fluid signal per time point as obtained by averaging across voxels attributed to the respective tissue class in the SPM8 segmentation. All nuisance variables entered the model as first and second order terms. Following confound removal data was band pass filtered preserving frequencies between 0.01 and 0.08 Hz (Biswal et al., 1995; Fox and Raichle, 2007; Greicius et al., 2003). The time course of each seed region was then extracted for each subject as the first eigenvariate of all grey-matter voxels located within 5

mm of the peak coordinate. For each subject the time-series data of all seed regions was then cross-correlated to quantify the degree of functional connectivity between the seed regions. The ensuing pair-wise correlation coefficients were subsequently transformed into Fisher's Z scores. Statistically significant connectivity was assessed via one-sample t-tests ($p<0.05$, corrected for multiple comparisons using the false discovery rate). Subsequently, the same Fisher-Z transformed correlation coefficients for each connection were rank-correlated with age to test for age-related changes in inter-regional coupling. The results of this correlation analysis were regarded significant if they passed a threshold of $p < .05$, corrected for multiple comparisons using the false discovery rate. Finally, we analyzed the connectivity in the 100 youngest and 100 oldest participants for all connections showing significant age-related changes, to corroborate the correlational findings. Moreover, this analysis permits a more detailed analysis of each age-related change of RS-FC to test, e.g., if an age-related FC increase represents a significant change from negative to positive FC or from negative to absent FC. The former pattern would imply an inversion of the RS communication (i.e., an increased functional interplay for relevant regions), while the latter would imply a loss of communication between brain regions.

3. Results

We found significant RS-FC for several connections within the combined set of seed regions. Significant positive coupling was found for: (i) SMAr with bilateral OP4 and bilateral AIC; (ii) left AIC with bilateral OP4; (iii) right AIC with bilateral OP4 and right area 7A; (iv) bilateral dPMC with ipsilateral area 7A; (v) right DPMC with left area 7A; (vi) interhemispheric connections between bilateral regions AIC, dPMC, OP4, and area 7A (see Fig. 4A). Noticeably, positive coupling was thus predominately found between regions with similar functional preferences (in the fMRI study), i.e., intra-domain connections (Fig 4A).

Significant negative coupling (i.e., anti-correlations) was found for the following connections: (i) SMAr with bilateral area 7A and right dPMC; (ii) bilateral OP4 to bilateral area 7A and dPMC; (iii) right AIC with bilateral dPMC and left AIC with left dPMC (see Fig. 4B). Negative RS coupling was thus predominantly observable for inter-domain connections (Fig. 4B), i.e., for regions with differing functional preferences in the original fMRI study.

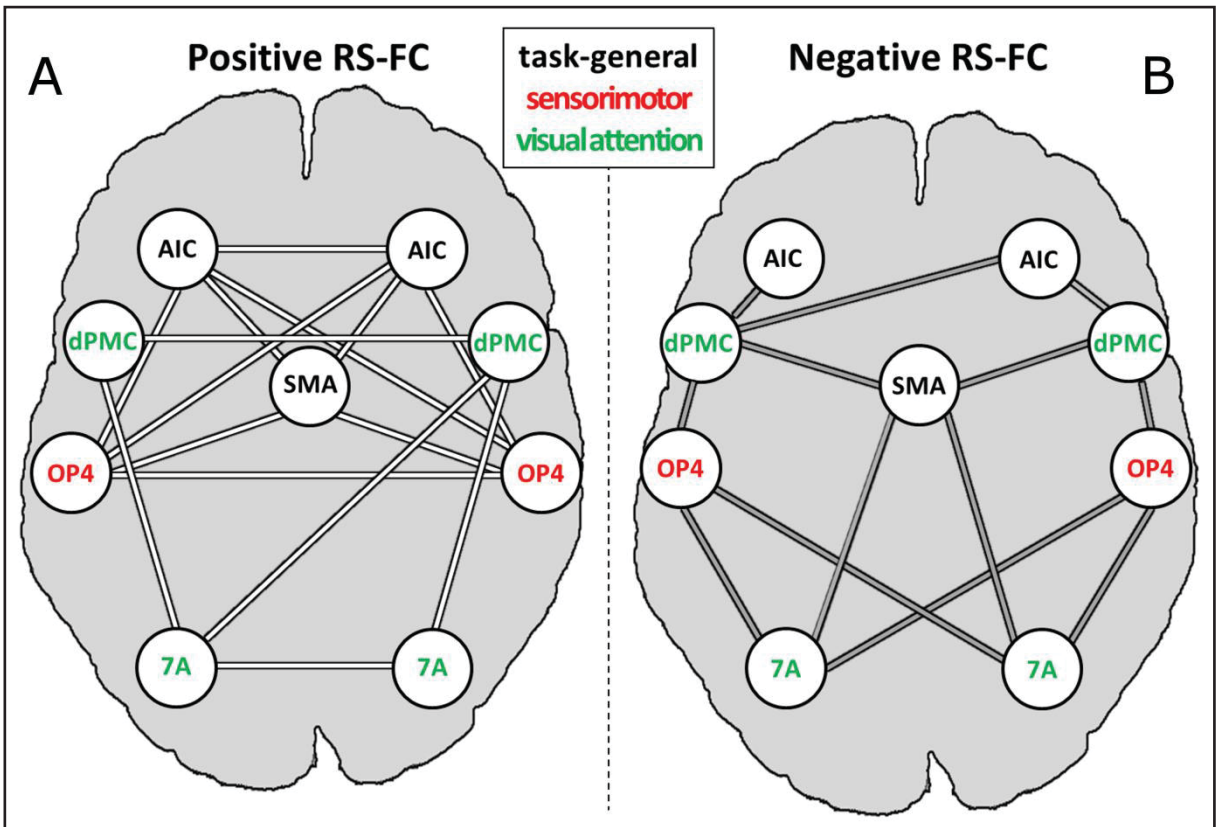


Figure 4 | General positive (A) and negative (B) inter-regional resting-state functional connectivity (RS-FC) for the combined set of seed regions. Regions labeled in green are associated with the visual attention system; regions labeled in red are associated with the sensorimotor system [as indicated by the previous fMRI study (OP4, dPMC, and 7A; Roski et al., 2013)]; regions labeled in gray have no functional preference (i.e., task-general regions). 7A, superior parietal lobule area 7A; AIC, anterior insular cortex; dPMC, dorsal premotor cortex; OP4, area OP4 of the parietal operculum; SMAr, rostroventral supplementary motor cortex.

For several connections, significant age effects on RS-FC were found (Fig. 5). Specifically, RS-FC between SMAr and bilateral AIC and OP4, respectively, decreased with age. Also, the interhemispheric connectivity between left and right area OP4 and left and right AIC decreased with age. In contrast, an age-related increase of RS-FC was found for the bilateral

connection of the DPMC and area 7A to the SMAr. Furthermore, area 7A bilaterally showed increased RS-FC to ipsilateral area OP4, whereas the right area 7A additionally showed an age-related increase of FC to the contralateral OP4. The supplementary extreme-group analysis in which we directly compared the 100 youngest and 100 oldest participants yielded significant differences for all connections that showed a significant association between RS-FC and age (see Table 3), corroborating the age-related correlational findings.

Table 3 | Age differences in intrinsic functional connectivity

Connection	Mean r_{young}	Mean r_{old}	Correlation with age (r_s)
L 7A – L OP4	-0.164***	-0.087***	0.15
L 7A - SMAr	-0.111***	-0.004	0.22
R 7A – L OP4	-0.175***	-0.093***	0.20
R 7A – R OP4	-0.151***	-0.071***	0.16
R 7A - SMAr	-0.077***	0.019	0.20
L AIC – R AIC	0.515***	0.445***	-0.18
L dPMC - SMAr	-0.022	0.067**	0.19
R dPMC - SMAr	-0.041	0.042	0.16
L OP4 – R OP4	0.472***	0.322***	-0.24
L OP4 - SMAr	0.107***	0.025	-0.16
R OP4 - SMAr	0.154***	0.078***	-0.17
SMAr – L AIC	0.289***	0.200***	-0.14
SMAr – R AIC	0.314***	0.212***	-0.16

Note. Mean r_{young} and mean $r_{elderly}$ denote group-averaged functional connectivity (FC) in the 100 youngest and 100 oldest participants, respectively. R, right; L, left; 7A – superior parietal area 7A; OP4 – area OP4 of the parietal operculum; SMAr – rostroventral supplementary motor area; AIC – anterior insular cortex; dPMC – dorsal premotor cortex.
**significant at $p < .001$, ***significant at $p < .0001$.

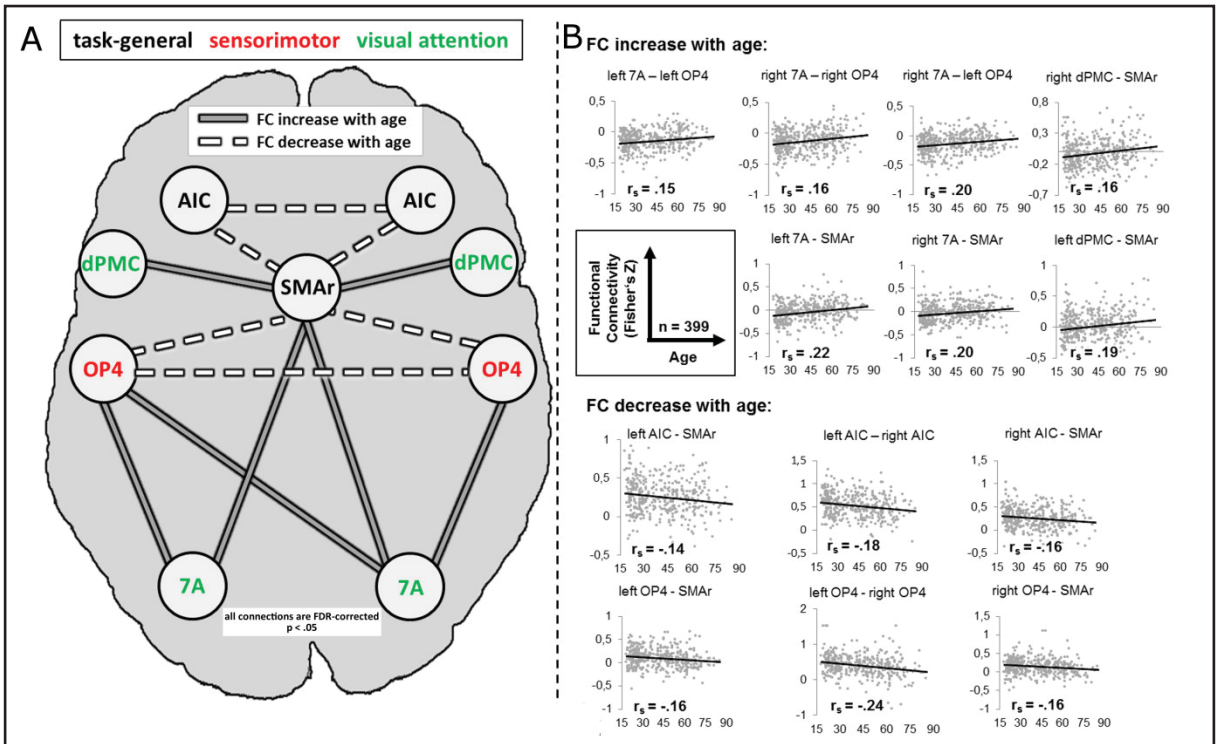


Figure 5 (A) | Alteration of resting-state functional connectivity (FC) with age (schematic). White lines reflect significant positive resting-state FC between regions (independent of age); gray lines reflect significant negative resting-state FC between regions (independent of age). Dotted lines reflect a significant decrease [p < 0 . 05, corrected for multiple comparisons using the false discovery rate (FDR)] of FC with age; solid lines reflect a significant increase (p < 0 . 05, FDR-corrected) of FC with age.
(B) Scatter plots for each age-affected interregional connection. Black line = linear regression line; rs = Spearman correlation coefficient: a negative value reflects a decrease of FC with age, whereas a positive value reflects an increase of FC with age. 7A, superior parietal lobule area 7A; AIC, anterior insular cortex; dPMC, dorsal premotor cortex; OP4, area OP4 of the parietal operculum; SMAr, rostroventral supplementary motor cortex.

4. Discussion

The present study investigated age-related differences in task-independent FC among a set of brain regions that was based on a previous fMRI study (Roski et al., 2013) to show a dedifferentiated recruitment pattern for visual-attention or sensorimotor demands (sensorimotor area OP4 and attention-related areas 7A and dPMC). This set was supplemented by task-general regions showing significant co-activation with all functional seeds across a broad range of tasks as identified by MACM analyses (SMAr and bilateral AIC). Together, these regions were used as seed regions for a network RS-FC analysis. This analysis demonstrated that regions belonging to the same functional domain show positive FC

with each other, whereas regions belonging to different functional domains are anti-correlated with each other. The analysis of age-related changes in the RS-FC within the network revealed selective alterations of inter-regional connections, highlighting potential neural correlates of common age-related behavioral changes.

4.1 Main effects of resting-state functional connectivity

The RS-FC analysis showed significant positive or negative correlations between RS activity of several seeds. When contrasting the RS-FC pattern with the task-dependent connectivity pattern (MACM), some connections showed corresponding FC, whereas other connections showed no FC congruency (for a detailed discussion see supplementary material). Positive RS-FC was predominantly observed between brain regions associated with similar functional systems (Figure 5A), whereas negatively correlated RS-FC was predominantly observed between regions belonging to different functional systems (see Figure 5B). In other words, RS activity in regions with similar functional characteristics appears to be positively correlated, whereas RS activity in regions with different functional properties is negatively correlated. In summary, the (original) functional distinction of the combined set of seed regions was well corroborated by its RS-FC pattern. Our results are thus in line with previous studies showing temporal correlations across functionally related areas, thereby forming RS networks that mirror task-related functional systems (De Luca et al., 2006; Smith et al., 2009; Biswal et al., 2010).

In turn, we found that negative FC was predominantly found between regions from different domains. These results underline an intrinsic, functionally driven organization of the human brain and are supported by studies showing that regions with apparently opposing functionality are negatively correlated in their RS-FC (Greicius et al., 2003; Roskies et al., 2013; Schlegel et al., 2013).

4.2 Age-dependent differences in RS-FC

First of all, it is noteworthy that not all connections showed age-related changes, arguing against a general and unspecific age-related decline in the task-independent functional coupling between brain regions. Instead, it appears that changes across the lifespan occur selectively. Connections that showed age-related changes, however, mostly featured reductions of functional correlations, as both positive and negative RS-FC moved closer to zero with age. In other words, the task-independent functional correlation (i.e., negative or positive RS-FC) within and between the present networks appears to be diminished in older adults (see Figure 5B) making the network structure less distinct. According to the "disconnection" hypothesis proposed by O'sullivan et al. (2001), such functional "disruptions" in a network are associated with deteriorated white matter integrity and poorer cognitive performance across several functional domains. In line with this, a decreased FC within a distinct network, i.e., the default-mode network (Andrews-Hanna et al., 2007; Tomasi and Volkow, 2012), which is relevant for internally directed mental states including remembering, planning, and related cognitive functions (Greicius et al., 2003; Fransson, 2005; Buckner and Carroll, 2007) was demonstrated with age. In contrast to this, our findings indicate less RS communication between different task-related networks (i.e., visual-attention and sensorimotor networks). Nevertheless, we also found a few connections showing an increase in FC. The healthy aging brain is thus not only subject to functional decline but rather responds selectively to presumable structural or biochemical neuronal changes in the elderly. Again, this finding is particularly important in that it underlines that connectivity is not reduced per se, which may potentially be deemed to reflect systematic confounds. Rather, we found decreased (closer to zero), increased, or unchanged connections in our large sample.

4.2.1 Age-dependent differences in RS-FC within the sensorimotor system

The present results showed an age-related reduction of the task-independent interhemispheric connection of the left and right area OP4. This region is assumed to play a role in sensorimotor integration processes, such as incorporating sensory feedback into motor actions (Rizzolatti and Wolpert, 2005; Halsband and Lange, 2006) and tactile object recognition and manipulation (Inoue et al., 2002; Wasaka et al., 2005). As a consequence of the decreased interhemispheric FC for this region, a diminished communication within this "sensorimotor feedback" system may develop in advanced age. A study on age-related behavioral slowing in sensorimotor tasks, suggesting a dysregulation of sensorimotor processing (Yordanova et al., 2004), corroborates this assumption. In line with this, increased age is associated with slower performance in speeded motor tasks (Salthouse, 2000). Finally, even in simple tasks (i.e., auditory and visual choice reactions), age-related changes within the sensorimotor system appear to affect performance (Yordanova et al., 2004). Although area OP4 represents only a single node within the sensorimotor system, the altered task-independent coupling for this regions may indicate a neural correlate of the above-mentioned behavioral difficulties observed in older adults.

4.2.2 Age-dependent differences in RS-FC between visual-attention and sensorimotor-related regions

Age-related increases in RS-FC were observed for inter-system connections, i.e., between sensorimotor-related and visual attention–related regions (OP4—7A; see Figure 5). Importantly, RS-FC showed an anti-correlated pattern between those regions in the young subsample (Figure 4B). Thus, in young adults, task-independent neural activity in OP4 is accompanied by deactivation of area 7A and vice versa. This anti-correlation appears to be diminished in older adults, as RS-FC increased with age, approaching zero (see Figure 5). In

other words, switching or mutual suppression (both of which would result in anti-correlation) between both sensorimotor and visual-attention network activity seems to be deteriorated in advanced age, potentially resulting in less distinct processing. This effect corroborates the fMRI study the functional seed regions were derived from (Roski et al., 2013). In that study we observed less differentiated task-dependent neural activity within areas 7A and OP4 in older adults, i.e., their activation patterns became less specific with age. Hence, the age-related changes of RS-FC observed here might reflect the previously demonstrated age-related alteration of a task-dependent activation pattern. Changes of intrinsic connectivity may hence be considered as a potential predictor for changes in task-dependent activation.

4.2.3 Age-dependent differences in RS-FC between task-specific regions and task-general seeds

Decreased RS-FC was observed between OP4 and the task-general SMAr, suggesting reduced communication between these regions with age. A similar effect was found for the attention-related area 7A. Here RS-FC was negative in the young subsample (see Table 3), the age-related FC increase (toward zero) reflects a loss of this anti-correlation, i.e., again a reduced communication. In other words, with age SMAr shows a less distinct connectivity with sensorimotor and visual attention related regions. In contrast, we found no significant age-related changes in RS-FC between the second task-general region (i.e., AIC in each hemisphere), and the task-specific regions.

The AIC is known to be a highly integrative region with relevance for the processing of somatosensory, cognitive and social-emotional information (Kurth et al., 2010). Likewise, the SMA is known to integrate neural information relevant for the internal generation of movements (Picard and Strick, 1996; Jenkins et al., 2000; Thickbroom et al., 2000; Crosson et al., 2001; Weeks et al., 2001; Cunnington et al., 2002). In line with this, we here identified the

task-general regions SMAr and AIC by significant task-based FC to all of the fMRI-based seeds. Hence, both regions seem to subserve higher-order cognitive processes interacting with both sensorimotor and visual attention specific regions. In their influential study, Dosenbach et al. (2006) proposed a "core system for the implementation of task sets." In that study, SMA and bilateral AIC were shown to be associated with the initiation and the maintenance of mental task sets. Notably, the present task-general regions closely correspond to this "core system" found by Dosenbach and colleagues. In another line of studies it was shown that regions in a very similar position as our task-general SMAr and AIC do not respond in a task-specific manner but rather to the degree of personal salience across tasks (e.g., Craig, 2002; Curtis and D'Esposito, 2003; Kerns et al., 2004). This "salience network" is thought to integrate highly processed sensory data with visceral, autonomic, and hedonic information (Damasio, 2000), so that the organism can decide what to do (or not to do) next. The reduced RS-FC with age between SMAr and the task-specific regions may hence imply difficulties for older adults to initiate, maintain, and switch activation in task-relevant functional systems. At the behavioral level, such difficulties were demonstrated for older adults during global task switching (Wasylyshyn et al., 2011) and dual-tasking (Verhaeghen et al., 2003; Just et al., 2008), that is, in situations where different mental task sets have to be constantly (re-)initiated or simultaneously maintained. The demonstrated age-related reduction in RS-FC between task-set control regions and task-specific regions (related to visual attention or sensorimotor processing) may reflect these difficulties at the neural level.

Moreover, our results also indicated a decreased functional coupling within the task-general network, i.e., between the SMAr, left and right AIC. As mentioned before, these regions represent basic nodes within a network assumed to be involved in task-switching and dual-tasking processes. The reduced intercommunication of these regions in older adults strengthens our above interpretation that intrinsic age-related changes possibly mediate task-

switching and dual-tasking difficulties in older adults. In line with this, increased task-switching costs were interpreted in terms of an age-related impairment in the ability to internally differentiate among task sets (Keith et al., 2004).

In summary, we found reduced task-independent communication within the task-general regions as well as between the task-general region SMAr and the functional seed regions. The reduced communication within the task-general regions may reflect difficulties for older adults during task-switching and dual-tasking. Moreover, the reduced communication to the functional seed regions (sensorimotor and visual attention) may indicate more task specific impairments for older adults. In line with this, the interaction of the visual-attention and sensorimotor systems seems to be deteriorated in older adults (Szturm et al., 2013), possibly provoked by a deteriorated communication with the task-set system (task-general regions).

At the neural level, these intrinsic changes of intercommunication within and between the task-set system and functional seed regions might also explain the reduced distinctiveness of task-independent brain activity in the two functional systems (sensorimotor and visual attention), as found in our former study (Roski et al., 2013). In particular, the interplay of both systems may be controlled less precisely, potentially resulting in less distinct regional activations of task-specific brain regions. Finally, an increased RS-FC with age was observed for the connection between the visual-attention-related dPMC and the task-general SMAr. In contrast to the decreased communication between the attention-related area 7A and task-general SMAr, this age-related increase reflects an enhancement of communication for this connection. In line with this, it was shown that older (vs. younger) adults often recruit more frontal regions to successfully perform a visual attention task (Ansado et al., 2012; Li et al., 2013). Our findings of decreased FC between 7A and SMAr and increased FC between dPMC and SMAr thus reflects that the communication between the more posterior area 7A and SMAr declines with age, whereas the communication between the more anterior dPMC and

SMAr is enhanced. This effect may reflect an intrinsic posterior-to-anterior shift in aging (PASA; cf. Davis et al., 2008) for cognitive control within the visual attention system and, moreover, demonstrates that the PASA-effect, previously reported for regional brain activity, may also extend to RS-FC.

4.3 Limitations and future directions

First, the current cross-sectional study offers the advantages of a large sample. However, some drawbacks have to be mentioned. Although a relation between age and changes in the interregional connection is clear, the causality between both is not positively determinable. In other words, there is no information on which variable caused the other. Moreover, we cannot completely exclude that additional variables, e.g., structural or neurochemical alterations, may influence the findings of the current study. In future research, the combination of structural MRI (e.g., diffusion tensor imaging), functional MRI, and neurochemical measurements, may extend the understanding of the causalities on FC changes in the aging brain. Second, since the analyzed functional networks reflect only parts of the visual-attention or sensorimotor system that showed an age-related loss of neural specificity, inferences from our results on age-related RS-FC changes between entire functional networks have to be regarded with caution. Nevertheless, our study indicates that healthy aging is associated with task-independent connectivity changes within and across task-specific brain network nodes. Furthermore, the current sample was derived by four different sites. Although all participants were screened for psychiatric and neurological disorders, the threshold for sub-clinical cognitive impairments may vary between them. Hence, the sample may contain some patients with sub-clinical symptoms. Finally, in the current sample we were unable to relate individual FC parameters to performance. Further studies should hence combine performance measurements with neuroimaging during task performance and task-free states in the same

participants. This would permit investigating more direct relations of different age-related neural changes, their interdependencies, and their association with performance (see, e.g., Andrews-Hanna et al., 2007; Madden et al., 2010; Schulte et al., 2011).

4.4 Conclusions

The present study corroborates the notion that RS activity reflects the functional organization of the human brain (De Luca et al., 2006; Biswal et al., 2010), as RS activity in regions with similar functional characteristics was positively correlated, whereas RS activity in regions with different functional properties was negatively correlated but also revealed anti-correlation between task-specific and (co-activated) task general regions. Second, age-related changes in network FC seem to be connection-specific, as not all RS connections were affected, and changes comprised both increases and decreases in RS-FC. Third, the majority of the observed age-related changes indicated a reduction of communication in the aging brain, as both correlations and anti-correlations were attenuated. Task-general regions, presumably relevant for the implementation and maintenance of task sets, showed reduced interregional RS-FC, in line with well-known difficulties of older adults in task-switching or dual-tasking. Furthermore, the communication between system-specific brain regions and the global task-set system seems to be intrinsically deteriorated, potentially leading to less differentiated regional brain activity during visual-attention and sensorimotor tasks, respectively (Roski et al., 2013). Finally, an age-related posterior-to-anterior shift was observed for the RS connectivity between areas of the visual attention system, in line with the PASA the-ory (Davis et al., 2008). In conclusion, our findings demonstrate that previously observed behavioral and functional brain activity changes concur with intrinsic FC changes in the healthy aging brain.

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References

Amiez, C., Kostopoulos, P., Champod, A.S., and Petrides, M. (2006). Local morphology predicts functional organization of the dorsal premotor region in the human brain. *J Neurosci* 26**,** 2724-2731.

Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., Lustig, C., Head, D., Raichle, M.E., and Buckner, R.L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron* 56**,** 924-935.

Ansado, J., Monchi, O., Ennabil, N., Faure, S., and Joanette, Y. (2012). Load-dependent posterior-anterior shift in aging in complex visual selective attention situations. *Brain Res* 1454**,** 14-22.

Ashburner, J., and Friston, K.J. (2005). Unified segmentation. *Neuroimage* 26**,** 839-851.

Baltes, P.B., and Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol Aging* 12**,** 12-21.

Bandettini, P.A., and Bullmore, E. (2008). Endogenous oscillations and networks in functional magnetic resonance imaging. *Hum Brain Mapp* 29**,** 737-739.

Biswal, B., Yetkin, F.Z., Haughton, V.M., and Hyde, J.S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 34**,** 537-541.

Biswal, B.B., Mennes, M., Zuo, X.N., Gohel, S., Kelly, C., Smith, S.M., Beckmann, C.F., Adelstein, J.S., Buckner, R.L., Colcombe, S., Dogonowski, A.M., Ernst, M., Fair, D., Hampson, M., Hoptman, M.J., Hyde, J.S., Kiviniemi, V.J., Kotter, R., Li, S.J., Lin, C.P., Lowe, M.J., Mackay, C., Madden, D.J., Madsen, K.H., Margulies, D.S., Mayberg, H.S., Mcmahon, K., Monk, C.S., Mostofsky, S.H., Nagel, B.J., Pekar, J.J., Peltier, S.J., Petersen, S.E., Riedl, V., Rombouts, S.A., Rypma, B., Schlaggar, B.L., Schmidt, S., Seidler, R.D., Siegle, G.J., Sorg, C., Teng, G.J., Veijola, J., Villringer, A., Walter, M., Wang, L., Weng, X.C., Whitfield-Gabrieli, S., Williamson, P., Windischberger, C., Zang, Y.F., Zhang, H.Y., Castellanos, F.X., and Milham, M.P. (2010). Toward discovery science of human brain function. *Proc Natl Acad Sci U S A* 107**,** 4734-4739.

Brown, M.R., Desouza, J.F., Goltz, H.C., Ford, K., Menon, R.S., Goodale, M.A., and Everling, S. (2004). Comparison of memory- and visually guided saccades using event-related fMRI. *J Neurophysiol* 91**,** 873-889.

Buckner, R.L., and Carroll, D.C. (2007). Self-projection and the brain. *Trends Cogn Sci* 11**,** 49-57.

Bzdok, D., Langner, R., Schilbach, L., Jakobs, O., Roski, C., Caspers, S., Laird, A.R., Fox, P.T., Zilles, K., and Eickhoff, S.B. (2013). Characterization of the temporo-parietal junction by combining data-driven parcellation, complementary connectivity analyses, and functional decoding. *Neuroimage* 81C**,** 381-392.

Craig, A.D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 3**,** 655-666.

Crosson, B., Sadek, J.R., Maron, L., Gokcay, D., Mohr, C.M., Auerbach, E.J., Freeman, A.J., Leonard, C.M., and Briggs, R.W. (2001). Relative shift in activity from medial to lateral frontal cortex during internally versus externally guided word generation. *J Cogn Neurosci* 13**,** 272-283.

Cunnington, R., Windischberger, C., Deecke, L., and Moser, E. (2002). The preparation and execution of self-initiated and externally-triggered movement: a study of event-related fMRI. *Neuroimage* 15**,** 373-385.

Curtis, C.E., and D'esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends Cogn Sci* 7**,** 415-423.

Damasio, A.R. (2000). *The feeling of what happens: body and emotion in the making of consciousness.* Orlando: Mariner Books.

Daselaar, S.M., Fleck, M.S., Dobbins, I.G., Madden, D.J., and Cabeza, R. (2006). Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study. *Cereb Cortex* 16**,** 1771-1782.

Davis, S.W., Dennis, N.A., Daselaar, S.M., Fleck, M.S., and Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cereb Cortex* 18**,** 1201-1209.

De Luca, M., Beckmann, C.F., De Stefano, N., Matthews, P.M., and Smith, S.M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage* 29**,** 1359-1367.

Delbeuck, X., Van Der Linden, M., and Collette, F. (2003). Alzheimer's disease as a disconnection syndrome? *Neuropsychol Rev* 13**,** 79-92.

Dennis, N.A., Hayes, S.M., Prince, S.E., Madden, D.J., Huettel, S.A., and Cabeza, R. (2008). Effects of aging on the neural correlates of successful item and source memory encoding. *J Exp Psychol Learn Mem Cogn* 34**,** 791-808.

Dosenbach, N.U.F., Visscher, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.S.C., Burgund, E.D., Grimes, A.L., Schlaggar, B.L., and Petersen, S.E. (2006). A core system for the implementation of task sets. *Neuron* 50**,** 799-812.

Eickhoff, S.B., Amunts, K., Mohlberg, H., and Zilles, K. (2006a). The human parietal operculum. II. Stereotaxic maps and correlation with functional imaging results. *Cereb Cortex* 16**,** 268-279.

Eickhoff, S.B., and Grefkes, C. (2011). Approaches for the integrated analysis of structure, function and connectivity of the human brain. *Clin EEG Neurosci* 42**,** 107-121.

Eickhoff, S.B., Jbabdi, S., Caspers, S., Laird, A.R., Fox, P.T., Zilles, K., and Behrens, T.E. (2010). Anatomical and functional connectivity of cytoarchitectonic areas within the human parietal operculum. *J Neurosci* 30**,** 6409-6421.

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., and Fox, P.T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp* 30**,** 2907-2926.

Eickhoff, S.B., Schleicher, A., Zilles, K., and Amunts, K. (2006b). The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. *Cereb Cortex* 16**,** 254-267.

Eyler, L.T., Sherzai, A., Kaup, A.R., and Jeste, D.V. (2011). A review of functional brain imaging correlates of successful cognitive aging. *Biol Psychiatry* 70**,** 115-122.

Ford, K.A., Goltz, H.C., Brown, M.R., and Everling, S. (2005). Neural processes associated with antisaccade task performance investigated with event-related FMRI. *J Neurophysiol* 94**,** 429-440.

Fox, M.D., and Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8**,** 700-711.

Fox, M.D., Zhang, D., Snyder, A.Z., and Raichle, M.E. (2009). The global signal and observed anticorrelated resting state brain networks. *J Neurophysiol* 101**,** 3270-3283.

Fransson, P. (2005). Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. *Hum Brain Mapp* 26**,** 15-29.

Grady, C. (2012). The cognitive neuroscience of ageing. *Nat Rev Neurosci* 13**,** 491-505.

Greicius, M.D., Krasnow, B., Reiss, A.L., and Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A* 100**,** 253-258.

Halsband, U., and Lange, R.K. (2006). Motor learning in man: a review of functional and clinical studies. *J Physiol Paris* 99**,** 414-424.

Hoffstaedter, F., Sarlon, J., Grefkes, C., and Eickhoff, S.B. (2012). Internally vs. externally triggered movements in patients with major depression. *Behav Brain Res* 228**,** 125-132.

Inoue, K., Yamashita, T., Harada, T., and Nakamura, S. (2002). Role of human SII cortices in sensorimotor integration. *Clin Neurophysiol* 113**,** 1573-1578.

Jakobs, O., Langner, R., Caspers, S., Roski, C., Cieslik, E.C., Zilles, K., Laird, A.R., Fox, P.T., and Eickhoff, S.B. (2012). Across-study and within-subject functional connectivity of a right temporo-parietal junction subregion involved in stimulus-context integration. *Neuroimage* 60**,** 2389-2398.

Jenkins, I.H., Jahanshahi, M., Jueptner, M., Passingham, R.E., and Brooks, D.J. (2000). Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow. *Brain* 123 (Pt 6)**,** 1216-1228.

Just, M.A., Keller, T.A., and Cynkar, J. (2008). A decrease in brain activation associated with driving when listening to someone speak. *Brain Res* 1205**,** 70-80.

Keith, C., Reddy, R.A., Hahn, H., Lang, H., and Tschierske, C. (2004). The carbosilane unit as a stable building block for liquid crystal design: a new class of ferroelectric switching banana-shaped mesogens. *Chem Commun (Camb)***,** 1898-1899.

Kerns, J.G., Cohen, J.D., Macdonald, A.W., 3rd, Cho, R.Y., Stenger, V.A., and Carter, C.S. (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science* 303**,** 1023-1026.

Kurth, F., Zilles, K., Fox, P.T., Laird, A.R., and Eickhoff, S.B. (2010). A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct Funct* 214**,** 519-534.

Laird, A.R., Eickhoff, S.B., Fox, P.M., Uecker, A.M., Ray, K.L., Saenz, J.J., Jr., Mckay, D.R., Bzdok, D., Laird, R.W., Robinson, J.L., Turner, J.A., Turkeltaub, P.E., Lancaster, J.L., and Fox, P.T. (2011a). The BrainMap strategy for standardization, sharing, and meta-analysis of neuroimaging data. *BMC Res Notes* 4**,** 349.

Laird, A.R., Eickhoff, S.B., Kurth, F., Fox, P.M., Uecker, A.M., Turner, J.A., Robinson, J.L., Lancaster, J.L., and Fox, P.T. (2009). ALE Meta-Analysis Workflows Via the Brainmap Database: Progress Towards A Probabilistic Functional Brain Atlas. *Front Neuroinform* 3**,** 23.

Laird, A.R., Fox, P.M., Eickhoff, S.B., Turner, J.A., Ray, K.L., Mckay, D.R., Glahn, D.C., Beckmann, C.F., Smith, S.M., and Fox, P.T. (2011b). Behavioral interpretations of intrinsic connectivity networks. *J Cogn Neurosci* 23**,** 4022-4037.

Li, L., Gratton, C., Fabiani, M., and Knight, R.T. (2013). Age-related frontoparietal changes during the control of bottom-up and top-down attention: an ERP study. *Neurobiol Aging* 34**,** 477-488.

Lindenberger, U., and Baltes, P.B. (1994). Sensory functioning and intelligence in old age: a strong connection. *Psychol Aging* 9**,** 339-355.

Madden, D.J., Costello, M.C., Dennis, N.A., Davis, S.W., Shepler, A.M., Spaniol, J., Bucur, B., and Cabeza, R. (2010). Adult age differences in functional connectivity during executive control. *Neuroimage* 52**,** 643-657.

Nichols, T., Brett, M., Andersson, J., Wager, T., and Poline, J.B. (2005). Valid conjunction inference with the minimum statistic. *Neuroimage* 25**,** 653-660.

O'sullivan, M., Jones, D.K., Summers, P.E., Morris, R.G., Williams, S.C., and Markus, H.S. (2001). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology* 57**,** 632-638.

Palomero-Gallagher, N., Mohlberg, H., Zilles, K., and Vogt, B. (2008). Cytology and receptor architecture of human anterior cingulate cortex. *J Comp Neurol* 508**,** 906-926.

Palomero-Gallagher, N., Vogt, B.A., Schleicher, A., Mayberg, H.S., and Zilles, K. (2009). Receptor architecture of human cingulate cortex: evaluation of the four-region neurobiological model. *Hum Brain Mapp* 30**,** 2336-2355.

Picard, N., and Strick, P.L. (1996). Motor areas of the medial wall: A review of their location and functional activation. *Cerebral Cortex* 6**,** 342-353.

Reetz, K., Dogan, I., Rolfs, A., Binkofski, F., Schulz, J.B., Laird, A.R., Fox, P.T., and Eickhoff, S.B. (2012). Investigating function and connectivity of morphometric findings--exemplified on cerebellar atrophy in spinocerebellar ataxia 17 (SCA17). *Neuroimage* 62**,** 1354-1366.

Reuter-Lorenz, P.A., and Park, D.C. (2010). Human neuroscience and the aging mind: a new look at old problems. *J Gerontol B Psychol Sci Soc Sci* 65**,** 405-415.

Rizzolatti, G., and Wolpert, D.M. (2005). Motor systems. *Curr Opin Neurobiol* 15**,** 623-625.

Robinson, J.L., Laird, A.R., Glahn, D.C., Lovallo, W.R., and Fox, P.T. (2010). Metaanalytic connectivity modeling: delineating the functional connectivity of the human amygdala. *Hum Brain Mapp* 31**,** 173-184.

Roski, C., Caspers, S., Lux, S., Hoffstaedter, F., Bergs, R., Amunts, K., and Eickhoff, S.B. (2013). Activation shift in elderly subjects across functional systems: an fMRI study. *Brain Struct Funct*.

Roskies, A.L., Schweitzer, N.J., and Saks, M.J. (2013). Neuroimages in court: less biasing than feared. *Trends Cogn Sci* 17**,** 99-101.

Rottschy, C., Kleiman, A., Dogan, I., Langner, R., Mirzazade, S., Kronenbuerger, M., Werner, C., Shah, N.J., Schulz, J.B., Eickhoff, S.B., and Reetz, K. (2013). Diminished activation of motor working-memory networks in Parkinson's disease. *PLoS One* 8**,** e61786.

Salthouse, T.A. (2000). Aging and measures of processing speed. *Biol Psychol* 54**,** 35-54.

Satterthwaite, T.D., Elliott, M.A., Gerraty, R.T., Ruparel, K., Loughead, J., Calkins, M.E., Eickhoff, S.B., Hakonarson, H., Gur, R.C., Gur, R.E., and Wolf, D.H. (2013). An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *Neuroimage* 64**,** 240-256.

Schaefer, S., Huxhold, O., and Lindenberger, U. (2006). Healthy mind in healthy body? A review of sensorimotor - cognitive interdependencies in old age. *Eur Rev Aging Phys Act* 3**,** 45-54.

Scheperjans, F., Eickhoff, S.B., Homke, L., Mohlberg, H., Hermann, K., Amunts, K., and Zilles, K. (2008a). Probabilistic maps, morphometry, and variability of cytoarchitectonic areas in the human superior parietal cortex. *Cereb Cortex* 18**,** 2141-2157.

Scheperjans, F., Hermann, K., Eickhoff, S.B., Amunts, K., Schleicher, A., and Zilles, K. (2008b). Observer-independent cytoarchitectonic mapping of the human superior parietal cortex. *Cereb Cortex* 18**,** 846-867.

Schlegel, A., Alexander, P., Sinnott-Armstrong, W., Roskies, A., Tse, P.U., and Wheatley, T. (2013). Barking up the wrong free: readiness potentials reflect processes independent of conscious will. *Exp Brain Res*.

Schulte, T., Muller-Oehring, E.M., Chanraud, S., Rosenbloom, M.J., Pfefferbaum, A., and Sullivan, E.V. (2011). Age-related reorganization of functional networks for successful conflict resolution: a combined functional and structural MRI study. *Neurobiol Aging* 32**,** 2075-2090.

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., and Beckmann, C.F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A* 106**,** 13040-13045.

St Jacques, P.L., Dolcos, F., and Cabeza, R. (2009). Effects of aging on functional connectivity of the amygdala for subsequent memory of negative pictures: a network analysis of functional magnetic resonance imaging data. *Psychol Sci* 20**,** 74-84.

Szturm, T., Maharjan, P., Marotta, J.J., Shay, B., Shrestha, S., and Sakhalkar, V. (2013). The interacting effect of cognitive and motor task demands on performance of gait, balance and cognition in young adults. *Gait Posture*.

Thickbroom, G.W., Byrnes, M.L., Sacco, P., Ghosh, S., Morris, I.T., and Mastaglia, F.L. (2000). The role of the supplementary motor area in externally timed movement: the influence of predictability of movement timing. *Brain Res* 874**,** 233-241.

Tomasi, D., and Volkow, N.D. (2012). Aging and functional brain networks. *Mol Psychiatry* 17**,** 471, 549-458.

Verhaeghen, P., Steitz, D.W., Sliwinski, M.J., and Cerella, J. (2003). Aging and dual-task performance: a meta-analysis. *Psychol Aging* 18**,** 443-460.

Wasaka, T., Nakata, H., Akatsuka, K., Kida, T., Inui, K., and Kakigi, R. (2005). Differential modulation in human primary and secondary somatosensory cortices during the preparatory period of self-initiated finger movement. *Eur J Neurosci* 22**,** 1239-1247.

Wasylyshyn, C., Verhaeghen, P., and Sliwinski, M.J. (2011). Aging and task switching: a meta-analysis. *Psychol Aging* 26**,** 15-20.

Weeks, R.A., Honda, M., Catalan, M.J., and Hallett, M. (2001). Comparison of auditory, somatosensory, and visually instructed and internally generated finger movements: a PET study. *Neuroimage* 14**,** 219-230.

Weimann, J.M., and Marder, E. (1991). *Neurobiology of Motor Program Selection: New Approaches to Mechanisms of Behavioral Choice* Manchester, UK: Manchester University Press.

Yordanova, J., Kolev, V., Hohnsbein, J., and Falkenstein, M. (2004). Sensorimotor slowing with ageing is mediated by a functional dysregulation of motor-generation processes: evidence from high-resolution event-related potentials. *Brain* 127**,** 351-362.

Zu Eulenburg, P., Caspers, S., Roski, C., and Eickhoff, S.B. (2012). Meta-analytical definition and functional connectivity of the human vestibular cortex. *Neuroimage* 60**,** 162-169.

Supplementary Material

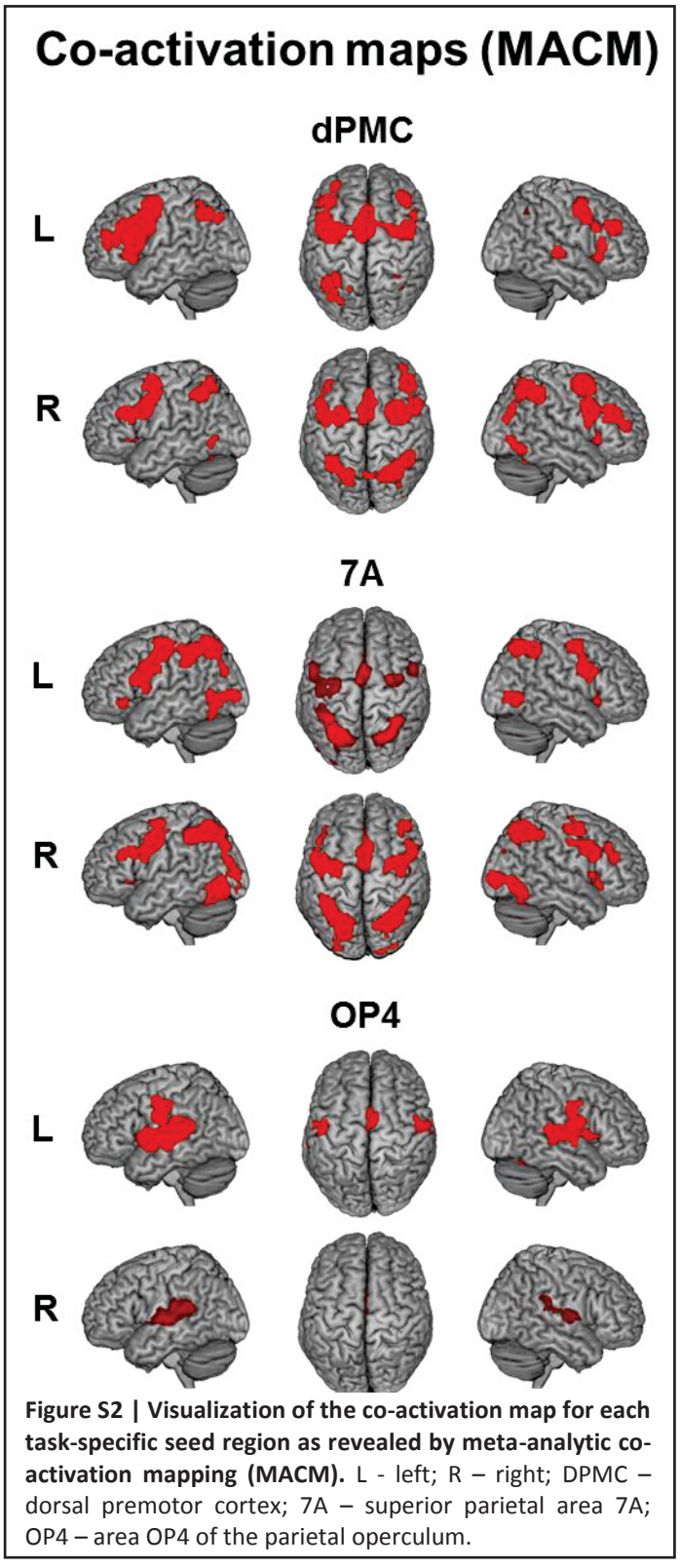

Figure S2 | Visualization of the co-activation map for each task-specific seed region as revealed by meta-analytic co-activation mapping (MACM). L - left; R – right; DPMC – dorsal premotor cortex; 7A – superior parietal area 7A; OP4 – area OP4 of the parietal operculum.

Task-dependent FC (MACM) vs. RS-FC

The task-general regions, AIC and SMAr, were defined by significant task-dependent FC to all other seed region. In contrast to this, the RS-FC pattern revealed a different and more diverse connectivity pattern between these task-general regions and the original seeds. For the connections between the sensorimotor related seed regions and the task general seed regions, RS-FC shows a congruent connectivity pattern compared to task-dependent FC (MACM). This is in line with a number of studies showing that neural activity during task performance has a similar neuro-anatomical distribution at rest, a phenomenon that is assumed to derive from continuing intrinsic neural activity during task performance (Tsodyks et al., 1999;Fox et al., 2006;Fransson, 2006). Moreover, this finding underlines the assumption that task-dependent neural properties represent an approximately linear superimposition of task-evoked neural activity and ongoing RS activity (Arieli et al., 1996;Tsodyks et al., 1999). In contrast to this coherent FC pattern between task dependent and task-independent RS-FC, SMAr showed positive RS-FC with sensorimotor region OP4 bilaterally, whereas negative RS-FC was found with the attention-related regions 7A and dPMC bilaterally (see Fig. 5A/B). In other words, although SMAr was defined by significant co-activation with bilateral 7A and dPMC, it was actually anti-correlated with these regions in the RS-FC analysis. A similar pattern was found for AIC with the exception that no significant FC was observed between AIC and 7A. Hence, the intrinsic communication pattern between this set of brain regions obviously differs from that found in task-dependent state. This observation is in line with several studies that compared neural activity patterns during rest with those obtained during task performance (see, e.g., Hampson et al., 2002;Jiang et al., 2004;Nir et al., 2006). Potentially, reorganization may be in charge, involving facilitation and depression of synapses (Weimann and Marder, 1991), leading to changes in the intrinsic correlation structure (Fox and Raichle, 2007). As a second possibility, again a superimposition of RS activity and task-dependent activity is

assumed (Fox et al., 2006). In contrast to the aforementioned superimposition, now the correlation structure of intrinsic activity remains constant between task and rest leading to changes in regional correlations observed during task performance (Fox et al., 2006). In summary, for some connections, interregional task-dependent FC corresponds with RS-FC, whereas other connections showed no FC congruency. However, the mechanisms underlying spontaneous neural activity are not fully understood, and the degree to which the correlation structure of intrinsic activity changes under task conditions remains an unanswered question. Nevertheless, our findings indicate that the correlation of interregional FC between spontaneous activity and task-dependent activity depends on the individual connection under study. Future research focusing on this issue may provide more comprehensive insights into intrinsic brain activity and its relation to and overlap with task-evoked activity.

Supplementary references

Arieli, A., Sterkin, A., Grinvald, A., Aertsen, A., 1996. Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. Science 273, 1868-1871.

Fox, M.D., Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8, 700-711.

Fox, M.D., Snyder, A.Z., Zacks, J.M., Raichle, M.E., 2006. Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. Nat Neurosci 9, 23-25.

Fransson, P., 2006. How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. Neuropsychologia 44, 2836-2845.

Hampson, M., Peterson, B.S., Skudlarski, P., Gatenby, J.C., Gore, J.C., 2002. Detection of functional connectivity using temporal correlations in MR images. Hum Brain Mapp 15, 247-262.

Jiang, T., He, Y., Zang, Y., Weng, X., 2004. Modulation of functional connectivity during the resting state and the motor task. Hum Brain Mapp 22, 63-71.

Nir, Y., Hasson, U., Levy, I., Yeshurun, Y., Malach, R., 2006. Widespread functional connectivity and fMRI fluctuations in human visual cortex in the absence of visual stimulation. Neuroimage 30, 1313-1324.

Tsodyks, M., Kenet, T., Grinvald, A., Arieli, A., 1999. Linking spontaneous activity of single cortical neurons and the underlying functional architecture. Science 286, 1943-1946.

Weimann, J.M., Marder, E., 1991. Neurobiology of Motor Program Selection: New Approaches to Mechanisms of Behavioral Choice Manchester University Press, Manchester, UK.

STUDY 3

Aging and response conflict solution: Behavioural and functional connectivity changes

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Own contributions:	Data acquisition (parts of the resting state data) Preparing parts of the figures Writing parts of the method section (resting state) Correcting the whole manuscript
Total contribution:	20%

Abstract

Healthy aging has been found associated with less efficient response conflict solution, but the cognitive and neural mechanisms remain elusive. In a two-experiment study, we first examined the behavioural consequences of this putative age-related decline for conflicts induced by spatial stimulus–response incompatibility. We then used resting-state functional magnetic resonance imaging data from a large, independent sample of adults (n = 399; 18–85 years) to investigate age differences in functional connectivity between the nodes of a network previously found associated with incompatibility-induced response conflicts in the very same paradigm. As expected, overcoming interference from conflicting response tendencies took longer in older adults, even after accounting for potential mediator variables (general response speed and accuracy, motor speed, visuomotor coordination ability, and cognitive flexibility). Experiment 2 subsequently revealed selective age-related decreases in functional connectivity between bilateral anterior insula, pre-supplementary motor area, and right dorsolateral prefrontal cortex. Meta-analytic functional profiling using the BrainMap database then showed these age-sensitive nodes to be more strongly linked to highly abstract cognition, as compared with the remaining network nodes, which in turn were more strongly linked to more concrete action-related processing. These findings indicate changes in interregional coupling with age among task-relevant network nodes that are not specifically associated with conflict resolution per se. Rather, our behavioural and neural data jointly suggest that healthy aging is associated with difficulties in properly activating non-dominant but relevant task schemata necessary to exert efficient cognitive control over action.

1. Introduction

Healthy aging is associated with performance deterioration in several cognitive domains, among them the top-down control of action (for reviews, see Craik and Salthouse, 2008; Park and Schwarz, 2000; Proctor et al., 2005; Salthouse, 1991; but see Verhaeghen, 2011). Such cognitive control over action is required when automatic response tendencies need to be overcome. A well-established paradigm to study cognitive action control is the spatial stimulus–response compatibility (SRC) task, in which the stimuli and the speeded responses they call for either match or mismatch spatially (Fitts and Deininger, 1954). In this task, a matching (i.e. spatially compatible) stimulus–response (S-R) mapping is given if the occurrence of a lateralized stimulus requires an ipsilateral response, while a mismatching (i.e. spatially incompatible) S-R mapping is given if a lateralized stimulus requires a contralateral response. Successful performance in incompatible conditions necessitates overcoming the automatically activated ipsilateral response tendency through top-down control according to the current task set (i.e., "Respond contralaterally!"). Conceptually, this intentional "overcoming of automatic response tendencies" in SRC tasks consists of two processes: inhibiting the prepotent compatible response and initiating the nondominant incompatible one (cf. Hommel and Prinz, 1997).

In terms of performance, these top-down-controlled processes are reflected by an increase in reaction time (RT) and error rate, relative to compatible trials. This effect, in turn, was found to further increase with age (see Proctor et al., 2005, for a review). Previous studies, however, are sparse and often did not consider potential confounds. The age-related RT slowing on incompatible trials might thus not (only) be related to a selective impairment in exerting cognitive control but might rather be due to a general slowing of information processing or motor execution with age (Salthouse, 1996). Our first experiment, therefore, aimed to reproduce the increase in S-R incompatibility costs with age and, if found, examine

whether the age-related increase is independent of age differences in potential confounds such as speed in compatible response selection, motor speed, speeded visuomotor coordination, and cognitive flexibility.

As for the neural underpinnings, overcoming spatial S-R incompatibility was found to activate a fronto-parieto-insular network comprising bilateral anterior insula, intraparietal sulcus (IPS), dorsal premotor cortex (dPMC), pre-supplementary motor area (pre-SMA) and adjacent midcingulate cortex, as well as right temporoparietal junction (TPJ) and right dorsolateral prefrontal cortex (DLPFC) (Cieslik et al., 2010; Matsumoto et al., 2004; Schumacher et al., 2003; Sylvester et al., 2003). With respect to age, Lee et al. (2006) reported increased incompatibility-related activity in older (vs. younger) adults in right DLPFC, anterior cingulate cortex, and left inferior parietal cortex. This age-related regional hyperactivity might have reflected compensatory processing during the solution of response conflicts in advanced age.

Besides regional activation, however, efficient communication between the nodes of the involved network is pivotal. At the neural level, this communication should be reflected by interregional functional connectivity (FC), that is, correlations among the activity time courses of task-relevant regions. Several age-related differences in FC have previously been observed (for reviews, see Ferreira and Busatto, 2013; Goh, 2011), even in the absence of changes in regional activation strength (Grady, 2005; Madden et al., 2010). As a consequence, performance differences with age might also arise from changes in FC among relevant brain regions (Chen et al., 2009; Stevens, 2009).

Two studies reported age-dependent decreases in FC within the networks involved in motor control and task switching, respectively (Madden et al., 2010; Wu et al., 2007), but to our knowledge, potential FC changes with age between brain regions related to solving response conflicts have not been examined yet. Therefore, using a large adult sample with a

wide age range, our second experiment tested age-related differences in intrinsic FC between brain regions associated with responding under conditions of spatial S-R incompatibility. These regions were derived from a previous functional magnetic resonance imaging (fMRI) study that used exactly the same paradigm to uncover incompatibility-related regional brain activity (Cieslik et al., 2010). Our second experiment was thus performed in an independent sample for which no SRC-related performance measures were available. Nevertheless, basing our FC analysis on an a priori defined brain network specifically associated with the cognitive process of interest provided a strong functional-neuroanatomical link between behavioural and connectivity changes with age, as investigated in Experiments 1 and 2, respectively.

To summarize, the goals of our investigation were two-fold: (1) We aimed to examine the effect of age on overcoming incompatibility-induced response conflicts at the behavioural level, including the analysis of potential mediator variables. (2) After corroborating an age-related increase of the behavioural SRC effect in Experiment 1, we sought to investigate age effects on the intrinsic functional coupling between those brain regions that are specifically activated by such incompatibility-induced response conflicts. Juxtaposing these two complementary methodological approaches, we aimed to obtain converging evidence for the mechanisms underlying age-related differences in solving spatial incompatibility-induced response conflicts.

2. Experiment 1

Experiment 1 examined whether aging is related to difficulties in solving response conflicts induced by spatial S-R incompatibility, even when potential mediator variables (see below) are taken into account. Although previous findings are not completely consistent (Bonin-Guillaume et al., 2000; Grandjean and Collette, 2011; Lee et al., 2006; Proctor et al., 2005; Simon and Wolf, 1963; Smulders et al., 1999), we predicted that the slowing of responses

under conditions of spatial S-R incompatibility would be stronger in older participants. We further expected that this effect persisted after partialling out variance explained by general response speed, response accuracy, motor speed, speeded visuomotor coordination, and cognitive flexibility.

2.1. Method

2.1.1. Sample

The sample comprised 26 young (M = 24.9, SD = 2.8, range = 20–29 years; 9 female) and 27 older (M = 59.4, SD = 6.8, range = 50–73 years; 9 female) paid volunteers, which all had normal or corrected-to-normal vision and no history of psychiatric or neurologic disorders. In order to exclude participants with dementia or clinically relevant cognitive impairments, we administered a multiple-choice vocabulary test (MWT-B; Lehrl, 2005) that assesses crystallized verbal intelligence. The test score, ranging from 0 to 37, was previously shown to decrease with increasing dementia severity (Kessler et al., 1995). All our participants fell into the normal range, with the older subsample even achieving significantly higher test scores [M = 30.8; range = 23–35) than the younger subsample (M = 25.9; range = 19–32; two-sample t-test of the subsample difference: $t(51) = -4.89$, $p < .001$]. Participants gave written informed consent to the study, which had been approved by the local ethics committee of the RWTH Aachen University Hospital.

2.1.2. Task and procedure

Participants performed a manual SRC task (Behrwind et al., 2011; Cieslik et al., 2010) requiring speeded button-press responses with the left- or right-hand index finger to lateralized visual stimuli (red dots). In trials with compatible S-R mapping, participants were to respond as fast and correctly as possible with their ipsilateral hand (e.g. with their left hand to a left-sided stimulus), while in trials with incompatible S-R mapping, participants were to

respond with their contralateral hand (e.g. with their right hand to a left-sided stimulus). Stimuli were presented for 200 ms each and separated by an interstimulus interval of 1300–1700 ms (uniformly jittered).

The compatibility of the spatial S-R mapping was varied between blocks and indicated at each block's beginning by a brief verbal instruction shown for 500 ms at the centre of the screen. Fifteen blocks of either condition were presented in pseudorandom order, separated by uniformly jittered intervals of 4.1–4.5 s, with each block containing 21–24 trials (left/right stimuli presented in random order, equally distributed across blocks).

The experiment was run in a dimly lit room using a standard PC and the software Presentation 11.3 (www.neurobs.com). Reaction time (RT) and accuracy were recorded. To make the testing more comfortable and prevent decreasing attention due to fatigue, the 30 task blocks were split into five sessions (containing 3 compatible and 3 incompatible blocks each), which were separated by resting breaks of up to 5 min. Before the experiment, participants performed a range of neuropsychological tests (see below).

2.1.3. Neuropsychological tests

2.1.3.1. Finger Tapping

To assess finger motor speed, participants tapped as rapidly as possible for 10 s using their right and left index finger, respectively. The median number of taps from 3 trials per hand (separated by short breaks to prevent muscular fatigue) was used as the test score (cf. Dafotakis et al., 2008).

2.1.3.2. Pointing Task

To assess repetitive visuomotor coordination, participants performed series of rapid horizontal pointing movements alternating between two points 30 cm apart using their right and left

index finger, respectively (Defer et al., 1999). Median time needed for 10 touches per point from 3 series per hand was used as the test score.

2.1.3.3. Trail-Making Test (TMT)

Nonrepetitive visuomotor coordination ability was assessed using the TMT-A, which is a paper-and-pencil test requiring participants to connect spatially scattered numbers in ascending order by drawing lines as fast as possible (Reitan, 1955). Total execution time was used as the test score. The TMT-B additionally contains letters and requires participants to connect both item types alternatingly in ascending (numerical and alphabetical) order. Thus, the TMT-B necessitates continuous attentional switching between both item categories (numbers and letters) and poses moderate demands on working memory for maintaining the last item of one category in mind while searching for and connecting the item of the other category. The difference in time needed to complete versions B and A, respectively, is considered to reflect those aspects of cognitive flexibility (i.e. attentional switching and mnemonic updating) most validly (Sánchez-Cubillo et al., 2009) and was used as the test score (TMT-Diff).

2.1.4. Data analysis

Response speed was assessed via calculating intraindividual median RT for correct responses per condition; accuracy was assessed via calculating the intraindividual percentage of erroneous responses (error rate) per condition. Statistical group-level analysis was performed using SPSS 15.0. Initially, performance data were subjected to 2 × 2 analyses of variance (ANOVAs) with Age (young vs. old) as between-subject factor and SRC (compatible vs. incompatible) as within-subject factor. Subsequently, RT and error rate on S-R-compatible trials, finger tapping and pointing task scores, as well as TMT-A and TMT-Diff scores were

entered as predictors into a linear regression analysis with the SRC effect on RT as dependent variable. For each participant, this SRC effect (ΔRT%) was calculated as difference between median RT on incompatible and compatible trials, expressed as percent RT change on compatible trials: $\Delta RT\% = (RT_{incompatible} - RT_{compatible}) / RT_{compatible} \times 100$. If the multiple regression analysis revealed that the SRC effect on RT (i.e., ΔRT%) was significantly predicted by the variables entered, we would include these variables as covariates into a between-group analysis of covariance (ANCOVA) of ΔRT% to examine whether the group differences in the SRC effect persisted when accounting for other relevant sources of variance.

2.2. Results and discussion

2.2.1. ANOVAs

Results are shown in Fig. 1. Mean RT was significantly longer in older (vs. younger) participants [$F(1, 51) = 41.1$, $p < .001$, $\eta_p^2 = 0.45$] as well as under incompatible (vs. compatible) conditions [$F(1, 51) = 584.7$, $p < .001$, $\eta_p^2 = 0.92$]. Critically, the Age × SRC interaction effect was also significant [$F(1, 51) = 34.6$, $p < .001$, $\eta_p^2 = 0.40$], that is, the incompatibility-related RT slowing was stronger with age. This interaction was also reflected in significantly larger ΔRT% values in the older participants (mean ΔRT% = 15.5), relative to the younger ones (mean ΔRT% = 11.2), as revealed by a supplementary two-sample *t*-test [t(51) = −4.6, $p < .001$].

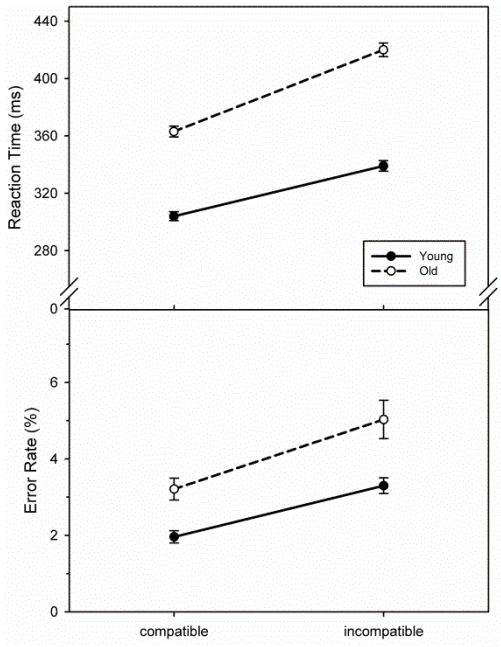

Figure 1 | Performance (group-level mean reaction time and error rate) in the spatial stimulus–response (S-R) compatibility task as a function of S-R mapping and age. Error bars represent the standard error of the mean. Connecting lines were added for illustrative purposes only.

Error rate was also significantly higher in older (vs. younger) participants [$F(1, 51) = 88.4$, $p < .001$, $\eta_p^2 = 0.63$] as well as under incompatible (vs. compatible) conditions [$F(1, 51) = 8.4$, $p = .006$, $\eta_p^2 = 0.14$]. There was, however, no significant Age × SRC interaction effect on error rate [$F(1, 51) = 0.2$], that is, the incompatibility-related accuracy decline was not stronger with age.

These results agree with previous reports (cf. Proctor et al., 2005) in showing that the impact of S-R incompatibility on speeded response selection increases with age. In their review, Proctor et al. mentioned that aging sometimes was also found to specifically affect error rate in incompatible conditions. As we did not find such an interaction, further studies are needed to assess whether an incompatibility-related accuracy decline with age is a reliable effect at all and, if so, on which specific, as-yet unknown methodological factors its presence and size depend. Given that in research on SRC effects, response speed is the dominant dependent measure, the main reason for the volatility of the age × compatibility interaction effect on accuracy might be the limited sensitivity of accuracy measures to the difficulty difference between compatible and incompatible conditions. In any case, as response speed during incompatible trials was apparently not traded off against increased accuracy in our task, the observed age × compatibility interaction effect on RT suggests that aging leads to deterioration in the efficiency of intentionally overcoming an automatically activated (dominant) response tendency in favour of another (non-dominant) response alternative. This conclusion, however, must be preliminary as long as the relevance of other variables that might account for this seemingly age-related difference has not been examined.

2.2.2. Linear regression analysis

Across the entire sample, multiple regression analysis revealed a significant linear relation ($R = .41$, $p = .017$) between the predictors entered (i.e., compatible-trial RT and error rate as well as finger tapping, pointing task, TMT-A, and TMT-Diff scores; cf. Table 1) and the relative impact of S-R incompatibility on RT (i.e., ΔRT%). This result demonstrates that a substantial part of variance (17%) in the impact of S-R incompatibility on RT is explained by these variables. Given this relationship, we included these predictors as covariates in an ANCOVA to test whether the difference in the relative impact of incompatibility between age groups persisted.

Table 1 | Means (Standard Deviations) and Difference Statistics of the Neuropsychological Test Scores in the Young and Old Subsamples of Experiment 1

Test Score	Young	Old	*t*-value	*p*-value
Tap	53.8 (6.6)	49.7 (6.4)	2.3	.027
Pointing	7.0 (1.4)	8.1 (2.4)	−2.0	.056
TMT-A	20.0 (4.5)	27.9 (10.0)	−3.8	.001
TMT-B	35.6 (10.3)	53.7 (24.6)	−3.5	.001
TMT-Diff	15.6 (8.7)	25.8 (22.1)	−2.2	.033

Note. Tap, Finger Tapping Task; Pointing, Pointing Task; TMT-A/-B, Trail Making Test version A/B; TMT-Diff, Difference between TMT-B and TMT-A scores.

2.2.3. ANCOVA

After partialling out variance explained by the predictors included in the above regression analysis, the between-group ANCOVA still yielded a significant main effect of age on ΔRT% [$F(1, 45) = 7.5$, $p = .009$, $\eta_p^2 = 0.14$]. Thus, compared with the above ANOVA and *t*-test results, the Age × SRC interaction effect on RT was somewhat reduced but not "explained away" by variability in response speed and accuracy on compatible trials as well as measures of motor speed, visuomotor coordination, and cognitive flexibility. Therefore, the age-related decline in the ability to overcome prepotent response tendencies appears to be specific and not

mediated by factors reflected in the measures used as covariates, corroborating our preliminary conclusion.

Extending previous research (Grandjean and Collette, 2011; Proctor et al., 2005), our analysis accounted for variance in variables that partly predicted the age-specific increase of the SRC effect. Importantly, this did not remove the influence of age on dealing with spatial S-R incompatibility. Our findings thus contradict the assumption that the age-related response slowing under conditions of S-R incompatibility is simply the result of a global slowing in processing speed (cf. Bonin-Guillaume et al., 2000). Furthermore, they indicate that the observed decline in cognitive action control with age is neither mediated by a shift of the speed–accuracy trade-off towards higher accuracy, nor by differences in motor speed, visuomotor coordination abilities, or cognitive flexibility. In sum, our behavioural data suggest that aging leads to a specific deficit in exerting cognitive control over automatically activated but irrelevant action tendencies. Potential mechanisms will be considered in the General Discussion in light of the results of Experiment 2.

3. Experiment 2

In Experiment 2, we examined age-related differences in intrinsic FC (i.e., FC at "rest") between brain regions involved in solving response conflicts that arise from S-R incompatibility. Intrinsic FC is increased between functionally and anatomically related brain regions (Fox et al., 2006; Fox and Raichle, 2007; Smith et al., 2009) and was found to predict both intraindividual trial-to-trial performance variability (Fox et al., 2007) and interindividual differences in neurological and psychiatric disease severity (see Zhang and Raichle, 2010, for a review). Thus, finding age-related variation in interregional FC strength would suggest adult age differences in neural coupling and, in turn, communication and interaction between brain regions. As we restricted our main analysis to regions specifically associated with responding

under conditions of S-R incompatibility, age-related reductions in the coupling between these regions could inform us about possible and plausible neural mechanisms behind the behavioural effects observed in Experiment 1.

3.1. Method

3.1.1. Definition of incompatibility-related seed regions

The regions of interest ("seeds") for the present investigation had previously been identified by fMRI in a normal adult sample (n = 24; mean age = 29 yrs.; age range = 20–59 yrs.) using the very same SRC task in the scanner that was used in Experiment 1 (Cieslik et al., 2010). More specifically, the SRC-related network examined in Experiment 2 resulted from contrasting brain activity during S-R-incompatible trials with that during S-R-compatible trials, in conjunction with the two main effects (vs. resting baseline) of incompatible trials with left- and right-handed responses, respectively. This network comprised bilateral IPS (hIP3; Scheperjans et al., 2008), anterior insula, dPMC (area 6; Geyer, 2004), pre-SMA and adjacent midcingulate cortex, as well as right TPJ (area PFm; Caspers et al., 2006) and DLPFC (see Fig. 2).

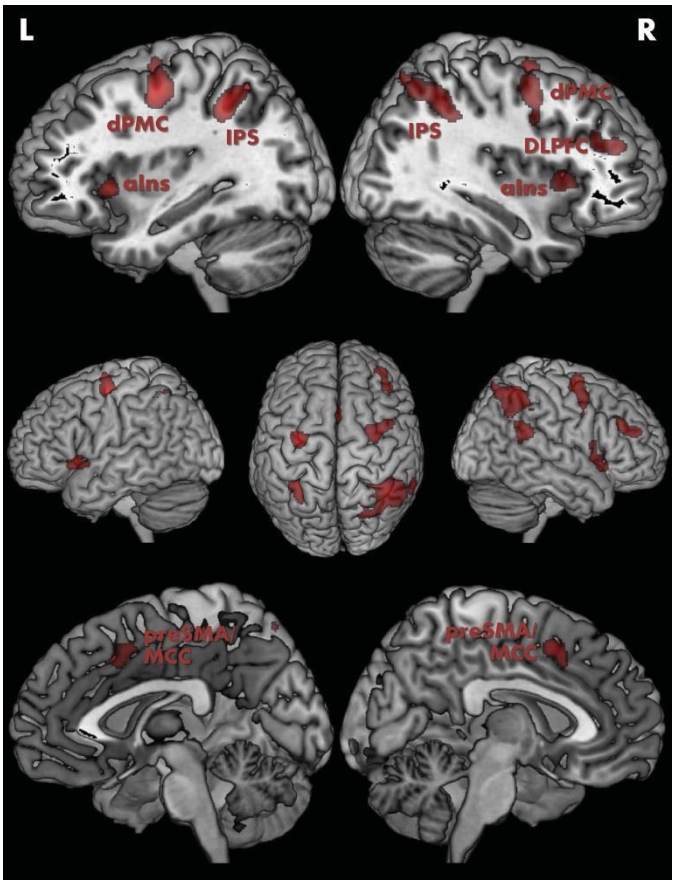

Figure 2 | Seed regions associated with solving spatial stimulus–response incompatibility as derived from Cieslik et al. (2010) for the network-based analysis of resting-state functional connectivity in Experiment 2. Abbreviations: L, left; R, right; aIns, anterior insula; DLPFC, dorsolateral prefrontal cortex; dPMC, dorsal premotor cortex; IPS, intraparietal sulcus; MCC, midcingulate cortex; preSMA, pre-supplementary motor area.

3.1.2. Sample

The analysis included resting-state fMRI data from 399 adults ranging from 18 to 85 (M = 41.8, SD = 16.8, Md = 41, IQR = 29) years of age. All participants (46% female) were without any record of neurological or psychiatric disorders and gave their written informed consent to the study. The data were contributed by four sites (see Table 2). Joint (re-)analysis of the data was approved by the local ethics committee of the Heinrich Heine University Düsseldorf.

Table 2 | Characteristics of the Sample in Experiment 2

Contribution Site	n	Mean Age (Range)	Sex: Male (%)	Measurement Parameters[a]
RWTH University Hospital Aachen, Germany	47	36.5 (19-59)	46	3 T / 250 / 2.2 / 30 / 80° / 3.1 × 3.1 × 3.1 mm³
	28	63.4 (55-72)	71	3 T / 270 / 2.2 / 30 / 90° / 3.1 × 3.1 × 3.1 mm³
Research Centre Jülich, Germany	51	28.3 (18-59)	57	3 T / 250 / 2.2 / 30 / 90° / 3.1 × 3.1 × 3.1 mm³
	100	45.1 (21-71)	48	3 T / 300 / 2.2 / 30 / 90° / 3.1 × 3.1 × 3.1 mm³
ICBM, Montreal, Canada[b]	41	40.6 (19-78)	42	1.5 T / 256 / 2.0 / 50 / 90° / 4.0 × 4.0 × 4.0 mm³
NKI/Rockland, Orangeburg, NY, USA[b,c]	132	42.3 (18-85)	59	3 T / 260 / 2.5 / 30 / 80° / 3.0 × 3.0 × 3.0 mm³

Note. ICBM, International Consortium for Brain Mapping; NKI, Nathan S. Kline Institute.

[a] Measurement parameters: magnetic field strength of the scanner / number of acquired volumes / repetition time (in s) / echo time (in ms) / flip angle / voxel size.

[b] These data were selected from the datasets included in Biswal et al. (2010) and made publicly available via the 1000 Functional Connectomes Project (http://fcon_1000.projects.nitrc.org).

[c] All but the participants of the NKI/Rockland sample were instructed to keep their eyes closed during the measurement.

3.1.3. Data acquisition and preprocessing

Gradient-echo echo-planar imaging (EPI) was used to record blood oxygen level–dependent (BOLD) activity in transversal slices covering the entire cerebrum (for detailed measurement parameters of the different samples, please see Table 2). Participants lay supine in the scanner and were instructed to let their mind wander without falling asleep. All data were jointly preprocessed and analysed using SPM8 (www.fil.ion.ucl.ac.uk/spm). Four dummy scans, which preceded image acquisition to allow for magnetic field saturation, were discarded prior to further analysis. Images were first corrected for head movement by affine registration using a two-pass procedure by which images were initially realigned to the first image and subsequently to the mean of the realigned images. Each participant's mean image was then spatially normalized to the Montreal Neurological Institute (MNI) single-subject template brain using the "unified segmentation" approach (Ashburner and Friston, 2005), and the ensuing deformation was applied to the individual EPI volumes. Hereby, volumes were resampled at 1.5 × 1.5 × 1.5 × mm³ voxel size. Images were then smoothed by a 5-mm full-width at half-maximum Gaussian kernel to meet the requirements of the general linear model and compensate for residual anatomical variation.

3.1.4. Data analysis

FC measures can be influenced by several confounds such as head movements and physiological processes (e.g., fluctuations due to cardiac and respiratory cycles; cf. Fox et al., 2009; Weissenbacher et al., 2009). In order to reduce spurious correlations, variance explained by the following nuisance variables was removed from each voxel's BOLD signal time series (Cieslik et al., 2013b; Jakobs et al., 2012; Satterthwaite et al., 2013): (i) the six motion parameters derived from the image realignment; (ii) the first derivatives of the six motion parameters, (iii) mean gray-matter, white-matter, and cerebrospinal-fluid signal intensity per time point as obtained by averaging across voxels attributed to the respective

tissue class in the SPM8 segmentation. All nuisance variables entered the regression model as first- and second-order terms, resulting in a total of 30 nuisance regressors. After confound removal, data were band-pass filtered preserving frequencies between 0.01 and 0.08 Hz, as meaningful resting-state correlations will predominantly be found in these frequencies given that the BOLD response acts as a low-pass filter (Biswal et al., 1995; Fox and Raichle, 2007; Greicius et al., 2003).

The time course of each seed region's BOLD signal was then extracted for each participant as the first eigenvariate of activity in all gray-matter voxels located within the respective cluster (cf. Cieslik et al., 2013b; Jakobs et al., 2012). For each participant, the time-series data of each seed region were correlated with each other, and the resulting Pearson correlation coefficients were transformed into Fisher's *Z* scores. The subsequent analysis of age-related changes in these interregional correlations (i.e., intrinsic FC values) was restricted to pairs of regions showing not only statistically significant (as assessed via one-sample *t*-tests) but *substantial* interconnectivity in the 100 youngest and/or 100 oldest participants. Specifically, since in rather large samples even relatively small correlations can be statistically significant, we restricted the study of age effects to those connections that showed intrinsic FC values of at least medium effect size (i.e., $r \geq .24$, corresponding to Cohen's $d \geq 0.5$) in the young and/or old subgroup. For these connections, age-related changes in interregional coupling were examined by rank-correlating participants' Fisher-*Z*-transformed FC values with age across the whole sample, with the influence of sex and data contribution site partialled out beforehand. The results of these Spearman correlation analyses were regarded significant if they passed a threshold of $p < .05$. As this study was of an exploratory nature, we report *p*-values uncorrected for multiple testing but mark those connections whose age-related change was large enough to survive Bonferroni correction. In addition to the correlational analyses, we performed an extreme-group comparison between the 25%

youngest (18–26 yrs., n = 102) and 25% oldest (55–85 yrs., n = 108) participants using multivariate analysis of variance (MANOVA) as implemented in SPSS 15.0.

3.1.5. Quantitative functional profiling

In order to quantitatively assess the functional significance of seed regions with either age-sensitive or age-insensitive FC, we analysed the correspondence of respective network nodes (or sub-networks) with descriptors for cognitive processes as provided by the BrainMap database (www.brainmap.org; Laird et al., 2009). Along with result coordinates from thousands of neuroimaging studies, this database contains meta-data that describe the "behavioural domain" of each experimental contrast included according to a pre-specified taxonomy (Fox et al., 2005). The main categories of this taxonomy of behavioural domains include cognition, action, perception, emotion and interoception, along with their respective subcategories (for a complete list, see www.brainmap.org/scribe). By filtering this database for experiments featuring activation within a particular region and performing statistical analysis on the descriptors of the selected experiments, functional roles of individual areas may then be characterized in an unbiased manner.

We analysed the behavioural domain meta-data of BrainMap experiments associated with assessed network nodes by way of forward and reverse inference (Bzdok et al., 2013b; Cieslik et al., 2013a; Clos et al., 2013; Eickhoff et al., 2011a; Rottschy et al., 2013). For forward inference, we used binomial tests [$p < .05$, corrected for multiple comparisons by thresholding the false-discovery rate (FDR)] to identify behavioural domains for which the probability of activation in the respective seed region(s) was significantly above chance. That is, we tested whether the probability of finding activation in voxels of interest given a particular behavioural domain [P(Activation | Domain)] was higher than the baseline probability of finding activation in those voxels across the entire database [P(Activation)]. Reverse inference identified the most likely behavioural domains given activation in voxels of

interest. This likelihood [P(Domain | Activation)] was derived from P(Activation | Domain), P(Domain) and P(Activation) using Bayes' rule. Significance was assessed by means of chi-square tests ($p < .05$, FDR-corrected for multiple comparisons).

To examine the specificity of the functional profiles of seed regions with age-sensitive vs. age-insensitive connections, we performed contrast analyses, which were restricted to those experiments in BrainMap that activated either set of seeds. The results of these quantitative comparisons were thresholded at $p < .05$ (FDR-corrected for multiple comparisons). For differential forward inference, we compared the activation probabilities between the two seeds given a particular behavioural domain; for differential reverse inference, we compared the probabilities of a particular behavioural domain being present given activation in one or the other seed (Bzdok et al., 2013b; Cieslik et al., 2013; Clos et al., 2013; Eickhoff et al., 2011a; Rottschy et al., 2013).

3.2. Results and discussion

3.2.1. Basic FC

Substantial positive resting-state FC (i.e., $r \geq .24$) was found for 19 connections (edges) between network nodes (see Table 3 and Fig. 3): (i) pre-SMA with bilateral anterior insula, bilateral dPMC, right DLPFC, and left IPS, respectively; (ii) right DLPFC with bilateral anterior insula, right dPMC, right IPS, and right TPJ, respectively; (iii) right anterior insula with right TPJ; (iv) right dPMC with bilateral IPS; (v) left dPMC with left IPS; and (vi) the interhemispheric connections between the bilateral clusters in anterior insula, dPMC, and IPS, respectively. Substantial negative FC values (i.e., $r \leq -.24$) were neither found in the young nor the old subgroup.

Table 3 | Adult Age Differences in Intrinsic Functional Connectivity Among Brain Regions Involved in Solving Response Conflicts

Pair of Regions	Mean r_{young}	Mean $r_{elderly}$	*Δr F*-score	Correlation with Age (r_s)
R DLPFC – L aIns	**.37**	**.21**	**23.39*****	***–.25***
R DLPFC – R aIns	**.50**	**.35**	**13.27*****	**–.23**
R DLPFC – pre-SMA/MCC	.36	.32	0.90	–.04
R DLPFC – R dPMC	.33	.32	0.04	.00
R DLPFC – R IPS	.45	.45	0.02	.01
R DLPFC – R TPJ	.27	.29	0.61	.00
L aIns – R aIns	**.71**	**.59**	**28.56*****	***–.30***
L aIns – pre-SMA/MCC	**.49**	**.28**	**44.56*****	***–.36***
R aIns – pre-SMA/MCC	**.55**	**.30**	**52.84*****	***–.39***
R aIns – R dPMC	**.28**	**.13**	**15.36*****	**–.24**
R aIns – R TPJ	.33	.29	0.58	–.12
pre-SMA/MCC – L dPMC	.26	.27	0.003	.00
pre-SMA/MCC – R dPMC	.35	.33	0.54	–.06
pre-SMA/MCC – L IPS	**.16**	**.24**	**6.90****	**.14**
pre-SMA/MCC – R IPS[a]	**.12**	**.23**	**12.57*****	**.18**
L dPMC – R dPMC	.51	.52	0.12	.02
L dPMC – L IPS	.41	.43	0.13	.05
R dPMC – L IPS	.37	.39	0.64	.05
R dPMC – R IPS	.36	.41	1.61	.08
L IPS – R IPS	.45	.44	0.08	.00

Note. Mean r_{young} and mean $r_{elderly}$ denote group-averaged functional connectivity (FC) in the 100 youngest and 100 oldest participants, respectively; *Δr F*-score denotes the *F*-statistic (df = 1, 206) for the comparison of the two FC-values between both subgroups. Pairs of regions showing a significant correlation (Spearman) between their mutual FC and age are set in bold; connections whose age-related FC change survived Bonferroni correction are additionally set in italics.

R, right; L, left; DLPFC, dorsolateral prefrontal cortex; aIns, anterior insula; pre-SMA, pre-supplementary motor area; MCC, midcingulate cortex; dPMC, dorsal premotor cortex; IPS, intraparietal sulcus; TPJ, temporoparietal junction.

[a] The intrinsic FC between this pair of regions just missed the threshold for medium effect size ($r \geq .24$).

** significant at $p < .01$; *** significant at $p < .001$.

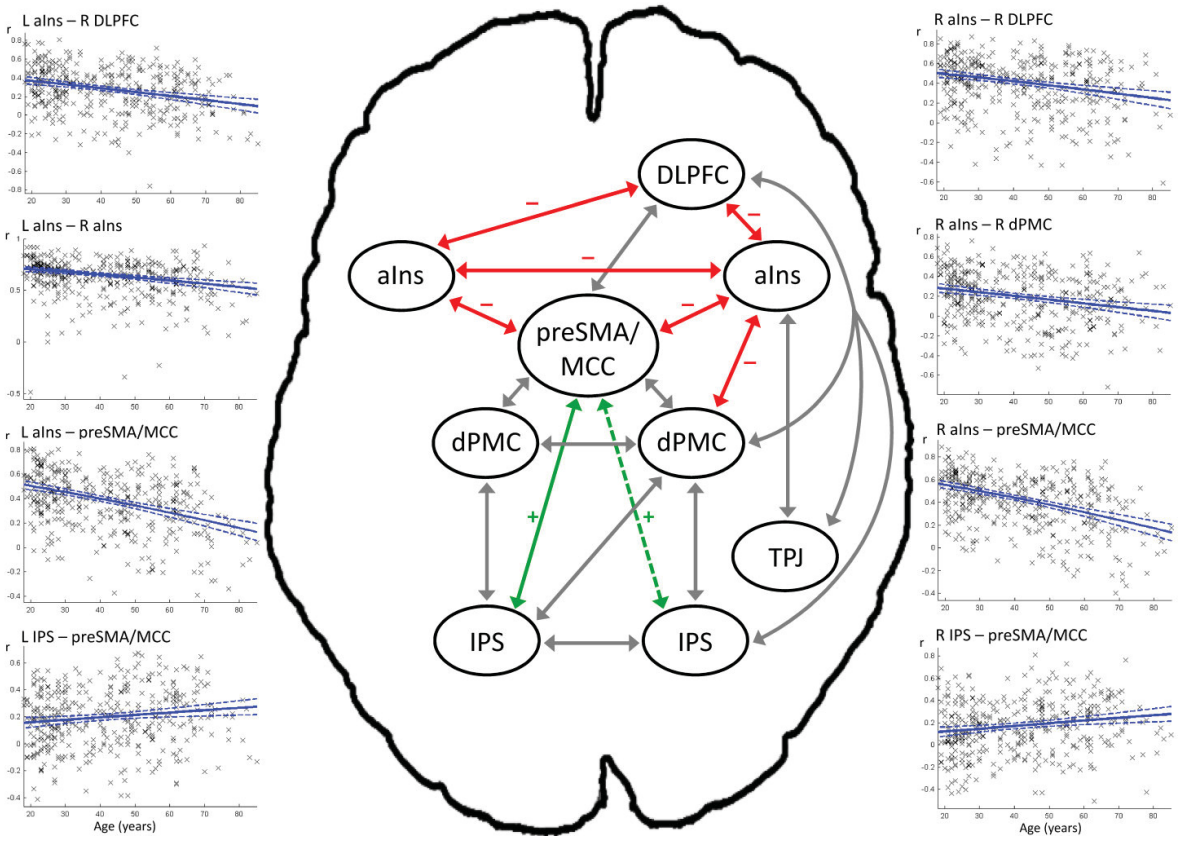

Figure 3 | Regions of the network derived from Cieslik et al. (2010) that showed substantial (i.e. of at least medium effect size) positive functional connectivity (FC) at rest in the 100 youngest and/or oldest participants are connected with solid lines (broken lines indicate significant FC just below the effect-size cutoff). Positive correlations between FC strength and age are marked green, negative correlations are marked red; absence of significant correlation with age is denoted in gray. Insets show scatter plots with linear regression lines for connections with significant correlations between FC strength and age. Abbreviations: TPJ, temporoparietal junction; see Fig. 2 for remaining abbreviations.

3.2.2. Age effects on FC

For several of the substantial connections, resting-state FC was found to decrease significantly with age (r_s range: −.23 to −.39; see Table 3 and Fig. 3). In particular, significant age effects were found for the connections between pre-SMA and right anterior insula as well as pre-SMA and left anterior insula, which both showed the largest FC decline with age. Age-related decreases in FC were furthermore found between right DLPFC and right anterior insula, right DLPFC and left anterior insula, right anterior insula and right dPMC, as well as between right and left anterior insulae. The connectivity between pre-SMA and left IPS was the only one that increased with age (r_s = .14). However, a similarly small but significant age-related

increase in FC at rest (r_s = .18) was found for pre-SMA and right IPS, whose intrinsic inter-connectivity in the older subgroup had just missed our effect-size criterion ($FC_{elderly}$ = .231).

The extreme-group MANOVA yielded a significant multivariate age effect [Pillai's trace: 0.34, $F(20, 187) = 4.76$, $p < .001$] as well as significant univariate differences for exactly the same connections that showed a significant association between intrinsic FC and age (see Table 3), fully corroborating the correlational findings. As supplementary analysis, an equivalent MANOVA was performed on the FC data before partialling out sex effects, yielding neither a main effect of sex (Pillai's trace: 0.10, p = .42), nor an interaction of sex with age (Pillai's trace: 0.08, p = .70).

3.2.3. Quantitative functional profiling of regions with vs. without age-related FC decline

For decoding the functional significance of network nodes with mainly age-sensitive vs. age-insensitive FC in an objective and quantitative way, we determined these nodes' significant associations with behavioural domains (and differences thereof) as provided by the BrainMap database. To recap, we conducted both forward and reverse inference analyses, with the former assessing the probability of activation in the respective region of interest given a particular behavioural domain and the latter assessing the probability of a behavioural domain given activation in a particular region of interest. Two sets of regions of interest were defined according to the results of the FC-by-age correlation analysis: The "age-sensitive set" comprised seed regions whose FC with several other seeds decreased with age (i.e., bilateral anterior insula, pre-SMA and right DLPFC), while the "age-insensitive set" comprised the remaining five seed regions (i.e., bilateral dPMC and IPS as well as right TPJ). The subsequent functional characterizations were based on all normal mapping experiments in healthy participants contained in BrainMap that reported at least one activation in each of the constituent regions of either set, with the following relaxation regarding pairs of bilateral homotopic seeds (i.e. anterior insula, dPMC, and IPS): to be included, it was sufficient for

experiments to report activation only in left or right anterior insula or left or right dPMC and IPS, respectively.

Forward and reverse inference alike indicated that both the age-sensitive and the age-insensitive sets were significantly associated with attention, while the age-insensitive set was additionally associated with visual motion perception (see Fig. S1 in Online Resource 1). The subsequent contrast analysis revealed that the age-sensitive set was more strongly associated with general cognitive processes according to forward inference, while the reverse inference analysis did not yield any significant difference (see Fig. 4). In contrast, the age-insensitive set was more strongly associated with action execution and visual motion perception, according to both forward and reverse inference (see Fig. 4).

Figure 4 | Differential associations of the age-sensitive (red) vs. age-insensitive (green) set of seed regions with behavioural domains of the BrainMap database. BrainMap meta-data were used to perform functional forward (left panel) and reverse (right panel) inference. Forward inference determines above-chance differences in activating either set of seeds given a particular behavioural domain, while reverse inference determines above-chance differences in domain presence given activation of either set of seeds. The baserate denotes the general probability of BrainMap activation of the given seeds.

3.2.4. Supplementary analyses

3.2.4.1. Age effects on FC in a control network

In order to collect additional evidence for the specificity of the age-related FC differences observed, we performed the very same analysis within a set of regions that were previously found to be collectively involved in the cross-modal processing of audiovisual emotional stimuli (Müller et al., 2012; see also Müller et al., 2011). This network comprised eight regions

of interest: bilateral fusiform gyrus, auditory cortex, amygdala, and the posterior aspect of superior temporal sulcus (for details, see Table S1 in Online Resource 1). Between these clusters, we found three connections of substantial size (i.e., FC ≥ .24) that showed significant (albeit only uncorrected) age-related FC differences: between both fusiform gyri (r_s = –.19), between both auditory cortices (r_s = –.24), and between both amygdalae (r_s = –.15).

3.2.4.2. Age effects on outside-network FC

A set of further analyses explored whether our seed regions showed age-related changes in FC with brain regions other than those constituting our a priori defined network. The rationale behind these exploratory whole-brain analyses was to falsify the hypothesis that age-dependent *inter*-network, rather than *intra*-network, changes in FC might drive the behavioural age effects observed in Experiment 1. To this end, we performed a set of seed-based analyses that tested for significant correlations of age with positive or negative resting-state FC between each of our nine seeds and any other voxel in the brain (for details, see Supplementary Methods in Online Resource 2). In brief, these analyses comprised tests for decreases in positive FC with age, indicating age-dependent reductions in neural coupling, and tests for increases in negative FC with age, indicating diminished neural anti-correlations in advanced age. For either case, the statistical maps obtained from each of the nine seed-based analyses were merged to identify regions that consistently showed significant age modulations of their FC with several seed regions.

With respect to declines in positive FC with age, these analyses revealed no additional regions (i.e., no regions outside the a priori task network) with significantly age-sensitive connections to more than half of the seed regions. In fact, only a few additional regions were observed with age-sensitive connections to just three or four seeds (see Fig. 5A). Importantly, these additional regions were mostly adjacent to, and partially overlapping with, one of the seeds (right DLPFC, right dPMC, right TPJ, pre-SMA). The only regions clearly outside the a

priori network showing at least some consistency in age-related coupling changes were found in left supramarginal gyrus, dorsal posterior cingulate cortex, and cerebellum (Fig. 5A).

Further, our exploratory whole-brain analysis revealed four clusters outside the target network (posterior cingulate cortex, anterior cuneus, left and right angular gyrus; see Fig. 5B) whose negative FC with six seed regions was inversely correlated with age. Beside these regions, there were several other clusters with age-sensitive anti-correlated connections to only a few seeds, in particular the dorsal and ventral medial prefrontal cortex, precuneus, medial occipital areas (V1, V2, V3), as well as left middle frontal and middle temporal gyri (Fig. 5B). Apart from the "early" visual areas in occipital cortex, all these clusters observed here were previously found to be part of the so-called "default-mode network" (Buckner et al., 2008; Greicius et al., 2003; Schilbach et al., 2012), which is typically deactivated during tasks that require sensorimotor processing such as our SRC task (Bzdok et al., 2013a, 2013b; Shulman et al., 1997; Toro et al., 2008).

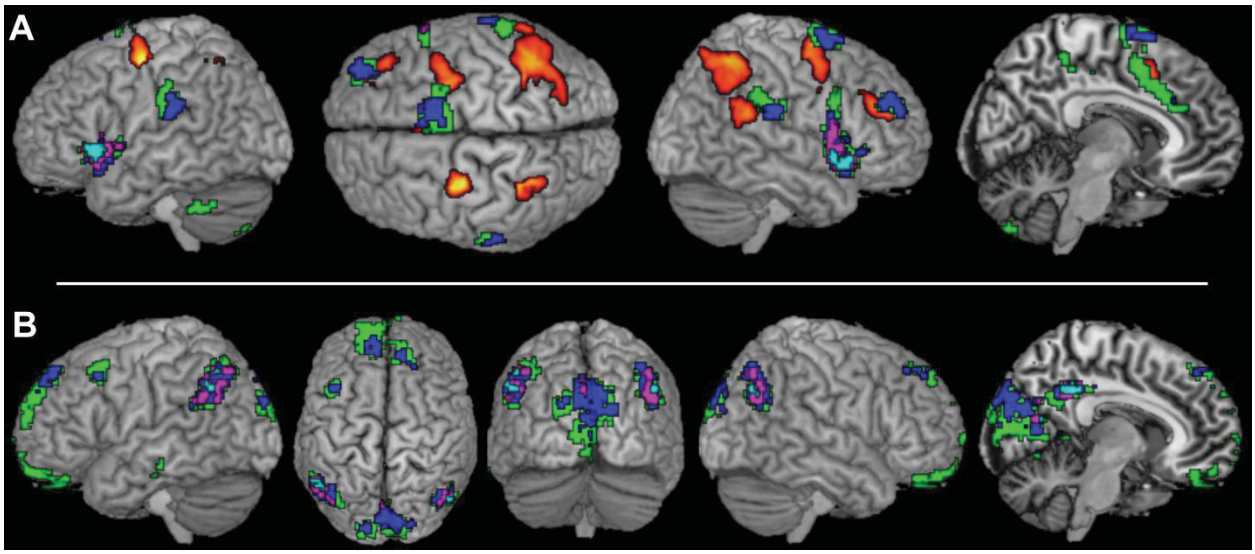

Figure 5 | Results of whole-brain seed-based analyses of functional connectivity (FC) rendered on a standard brain. Panel A depicts the a priori defined incompatibility-related network (red-to-yellow colour scale) together with overlays of regions with age-related decreases in positive FC with 3 (green), 4 (blue), 5 (violet), or 6 (cyan) nodes of the a priori defined network. Panel B depicts overlays of regions with age-related increases in negative FC (i.e., diminished anti-correlation) with 3 (green), 4 (blue), 5 (violet), or 6 (cyan) nodes of the a priori defined incompatibility-related network.

3.2.5. Discussion

Experiment 2 showed, first of all, substantial intrinsic FC between many regions associated with responding under conditions of spatial S-R incompatibility. Thus, the functionally defined, SRC task–related brain network is, to a large extent, functionally interconnected at rest as well. These findings attest to the "network status" of this set of brain regions (i.e., their intercommunication and interaction), in line with a recent study on the task-related effective connectivity among these regions (Cieslik et al., 2011). Importantly, we observed age-related decreases in intrinsic FC between several nodes of this network, with a predilection for reduced interconnectivity of the prefrontal and insular clusters. That is, FC between pre-SMA, anterior insula, and right DLPFC was particularly sensitive to age. These changes are in line with recent findings by Onoda et al. (2013), who reported similarly selective age effects on intrinsic FC within and between several resting-state networks defined via independent component analysis (i.e., significant age-related FC reductions between bilateral anterior insula and midcingulate cortex, but no FC changes within a bilateral fronto-parietal network or across both networks). Another earlier study reported decreased task-based FC with age among a set of brain regions associated with the cue-induced preparation for task switches (Madden et al., 2010). However, although several regions of this network overlapped with ours (among them right DLPFC, right TPJ, left IPS), a detailed comparison with our results is impossible, since the authors did not report FC measures for single pairs of regions but only an average score across several connections.

Notably, the majority of interregional connections (12 out of 19) that showed intrinsic FC of at least medium effect size was unaffected by age, or, in one case, even increased its strength with age. This provides evidence against the notion of a general age-related decline in the functional coupling between distant brain regions. Rather, our findings argue for selective changes in the efficiency of interregional communication and interaction across the

lifespan, suggesting age-related deterioration in some cognitive subprocesses but not in others. This reasoning is further supported by the results of our control analysis in a network associated with cross-modal emotional processing (Müller et al., 2012). In this network, we only found the interhemispheric connections between three pairs of homotopic seeds to be sensitive to age (Zuo et al., 2010). In Müller et al.'s analysis of task-related effective connectivity within this network, the authors observed that it was exactly these interhemispheric connections that were least important for selecting the best model. Together, this suggests that the few significant age-related changes in FC observed in our control analysis did not occur between nodes that subserve greatly different processing sub-functions. In contrast, we did find such age-dependent internodal (but no general interhemispheric) FC differences in our incompatibility-related target network, further underscoring the specificity of the changes observed therein.

The quantitative functional profiling revealed an association with attentional processing/control for both the age-sensitive and the age-insensitive parts of the task network, which is little surprising. The contrast analysis showed a stronger association of the age-sensitive sub-network with cognitive processing in general. Of note, BrainMap experiments are labelled as related to "general cognition" mostly if they do not fit into any of the more specific "cognition" subcategories, such as memory, attention, language, reasoning, social cognition, or cognition related to space or time. This argues for an association of this sub-network as a whole with some rather abstract, high-level cognitive process(es), possibly related to task-set control and implementation (cf. Dosenbach et al., 2006; Langner & Eickhoff, 2013). In contrast, the age-insensitive sub-network showed a stronger association with visual motion perception and action execution, which, together with its association with attention, points to its role in some intermediate-level, more concrete and action-oriented processing. That is, the communication between regions involved in abstract, high-level

cognitive processes deteriorates in advanced age, while it remains intact (or even increases) between regions involved in more concrete sensorimotor cognition. These differential profile patterns suggest that aging affects SRC task performance via impairing high-level control processes rather than conflict resolution per se, possibly mediated – at least in part – through an age-related decline in the neural coupling between brain regions implementing task sets.

Our supplementary analysis of whole-brain positive FC of each node of the incompatibility-related network did not reveal any outside-network regions whose connections to the target network were *consistently* (i.e., across more than four nodes) modulated by age. We, therefore, argue that the few age-sensitive connections between target- and outside-network regions that we did observe are too inconsistent to be a major driving force behind the age-related behavioural deficits in cognitive action control observed in Experiment 1. Of note, the only two clusters with age-sensitive connections to six task-network seeds were located in left and right anterior insula (i.e., in parts of the task network), corroborating our previous network-based findings. That is, the exploratory whole-brain analysis actually provided additional evidence that the key connectivity changes are located within rather than outside the network. Conversely, the analysis of whole-brain *negative* FC of each task-network node yielded a set of consistently age-sensitive connections to regions of the default-mode network, associated with internally oriented cognition (e.g., mnemonic, imaginary, introspective, or social-cognitive processes; cf. Binder et al., 1999; Bzdok et al., 2012; Buckner et al., 2008; Schilbach et al., 2012). The observed age-dependent reductions in anti-correlation between these regions and several of our task-related network nodes might thus reflect difficulties in recruiting task-relevant regions *selectively* in advanced age, leading to “intrusions” or interference from task-irrelevant cognition (cf. Mason et al., 2007; Roski et al., 2013a; Weissman et al., 2006). Such potentially dysfunctional age-related changes in FC between functionally distinct brain networks (i.e., neural de-differentiation) have been

recently reported for visual-attention and sensorimotor networks (Roski et al., 2013b) and might contribute to the behavioural deficits observed in Experiment 1 by undermining proper task-set implementation in the elderly.

In conclusion, Experiment 2 revealed selective age-related decreases in intrinsic FC predominantly among prefrontal and insular parts of a network that was previously found to be associated with solving incompatibility-induced response conflicts (cf. Cieslik et al., 2010). This result is in agreement with other reports about selective, rather than generalized, adult age differences in FC between distributed brain regions (cf. Ferreira and Busatto, 2013; Goh, 2011). Our findings in the task-related network were supplemented by the results of exploratory whole-brain FC analyses, which revealed no outside-network regions with consistent age-related reductions in their positive FC with nodes of the task network. These whole-brain analyses, however, detected some regions known to be part of the default-mode network that showed consistent age-related reductions in their functional anti-correlation (i.e., less negative FC) with several task-network nodes. Taken together, these exploratory findings corroborate our above conclusion and extend it by suggesting that the age-related behavioural deficits in speeded response conflict solution observed in Experiment 1 might partially result from a diminished de-coupling of regions subserving task-irrelevant cognition (cf. Weissman et al., 2006).

4. General discussion

In line with previous work (Grandjean and Collette, 2011; Proctor et al., 2005), we observed increased age-related costs of spatial S-R incompatibility. These costs were evident in the age-specific slowing of responses to spatially incompatible stimuli, while performance accuracy under conditions of incompatibility was not specifically reduced in advanced age. This suggests that elderly participants, although generally making more errors, manage spatial

S-R incompatibility the same way young adults do but, apparently, at the expense of speed. Importantly, this age-specific slowing of overcoming incompatibility was independent of response selection speed on compatible trials, which reflects automatic ("bottom-up") response activation and may be considered a marker of general information processing speed. The increase in age-related incompatibility costs remained also present after accounting for performance accuracy, motor speed, speeded visuomotor coordination, and cognitive flexibility. Together, these findings indicate that managing spatial S-R incompatibility is compromised in higher age, beyond a global slowing of cognitive processing and independently of potential mediator variables. Thus, extending earlier research, our results provide evidence for a selective deficit in cognitive action control in older age. The behavioural data alone, however, do not indicate which subprocesses during response conflict solution might be specifically affected by age. Next, therefore, the FC data will be discussed and examined for further clues to answer this question.

Several parts of the brain network involved in solving S-R incompatibility (Cieslik et al., 2010) showed a decrease in intrinsic FC strength with age. Besides changes in regional activity (cf. Lee et al., 2006), this intrinsic connectivity decline might contribute to the age-related drop in efficiency in response conflict resolution as observed in Experiment 1. Although our experiments do not provide direct evidence for this assumption (see section 4.1 for further discussion), it receives indirect support from the cognitive functions associated with the areas showing age-related connectivity changes: The age-related FC decrease was mainly confined to right DLPFC, bilateral anterior insula, and pre-SMA (including adjacent midcingulate cortex). In line with our functional profiling results, these heteromodal regions are involved in high-level, integrative aspects of the intentional control of attention and action (Cole and Schneider, 2007; Corbetta and Shulman, 2002; Langner et al., 2011; Posner and Petersen, 1990). More specifically, right DLPFC has been repeatedly associated with top-

down (i.e. rule-based and goal-oriented) response selection according to stimulus location (Cieslik et al., 2013b; Cisek, 2006; Eickhoff et al., 2011b; Langner et al., 2013; Schumacher et al., 2003). In a recent meta-analysis (Langner and Eickhoff, 2013), the same region was also found to be consistently related to sustaining attention to simple (non-spatial) tasks over time, in line with notions of its involvement in task-set monitoring (Shallice et al., 2008) and set-contingent biasing of sensorimotor processing (Corbetta et al., 2008). However, the coupling between right DLPFC and dPMC or pre-SMA/midcingulate cortex, respectively, was unaffected by age, suggesting that the modulatory influence of DLPFC on spatial S-R mapping and motor preparation, as presumably subserved by premotor regions (cf. Cieslik et al., 2011), is not directly altered in advanced age. Rather, the coupling decreased between DLPFC and bilateral anterior insula, which in turn demonstrated a substantial reduction in FC strength with pre-SMA. Thus, age-related changes in the impact of DLPFC signalling on premotor processing appear to be more indirect, presumably mediated via anterior insula–pre-SMA circuits.

Anterior insula and pre-SMA/midcinglulate cortex are anatomically and functionally tightly connected (Augustine, 1996; Taylor et al., 2009) and appear to be jointly involved in implementing (i.e. activating and maintaining) task sets (Dosenbach et al., 2007; Dosenbach et al., 2006; Kurth et al., 2010). Task-set maintenance may include the repeated reactivation of task rules, triggered, for instance, by the occurrence of an external imperative stimulus or internal signals from performance monitoring systems (see also Langner and Eickhoff, 2013; Sridharan et al., 2008). This view accords with the functions of “energizing” (i.e. activating) task schemata and monitoring their activation level, which were ascribed to dorsomedial prefrontal cortex and inferior lateral frontal cortex/anterior insula, respectively, based on human lesion studies (Shallice et al., 2008; Stuss et al., 1995). As pre-SMA was previously found to effectively modulate primary motor cortex activity on S-R-incompatible trials,

presumably via inhibiting the automatic activation of the ipsilateral response (Cieslik et al., 2011), the observed age-related decline in pre-SMA–insula coupling might lead to inefficiency in translating the instructed task set into appropriate top-down inhibitory signals and, thus, produce the specific RT slowing on incompatible trials in older age. This inefficiency might be aggravated by the additional FC decline between right anterior insula and right dPMC, which is involved in the cue-related preparation of speeded movements (Hoshi and Tanji, 2006; Langner et al., 2012; Weinrich and Wise, 1982). Finally, the reduced intrinsic coupling between anterior insula and right DLPFC with age may reflect diminished efficiency in transmitting reactive control signals from anterior insula to DLPFC. Such signalling, which may lead to adjustments of input expectations and associated biasing signals in DLPFC, has been suggested as a means by which the task-set maintenance system may counteract performance decline and (re)engage the mind in task-relevant processing with appropriate intensity (Langner and Eickhoff, 2013). In summary, the selective prefrontal and insular reductions in intrinsic FC strength with age could reflect increasingly dysfunctional levels of interaction between several task-relevant brain regions. These changes, in turn, might lead to reduced efficiency in using this network when task sets need to be implemented against prepotent response tendencies.

Taken together with the results of Experiment 1, our findings argue against an explanation purely based on a domain-general decline in cognitive efficiency with age, as suggested by the processing-speed theory of cognitive aging (Salthouse, 1996). Rather, it appears that aging might selectively affect some higher-level cognitive functions involved in task-schema activation and monitoring. The nature of these mental faculties may, in turn, contribute to the pervasiveness of age-related performance deficits across tasks that require maintaining and managing multiple task sets (e.g., dual-tasking or task switching; cf. Verhaeghen et al., 2003; Wasylyshyn et al., 2011). It might also explain the absence of

consistent aging effects in tasks that "only" require attentionally selecting among different stimuli or stimulus dimensions (e.g., flanker or Stroop tasks), rather than requiring the selection of responses depending on the current (but alternating) task set (see Verhaeghen, 2011, for a review).

Since SRC tasks require the block-wise alternating implementation of two opposing task sets (i.e., responding ipsi- vs. contralaterally), they should pose greater demands on task-set maintenance and monitoring, as compared to tasks that do not involve several task sets (cf. Logan, 2007; see also Los, 1996). In the context of task-switching, such set-level mixing costs are typically referred to as *global switch costs* (see Kiesel et al., 2010, for a review). A recent meta-analysis demonstrated that it is those global task-switching costs that are selectively increased in advanced age, while "local" (i.e. trial-level) switch costs largely remain unaffected by age (Wasylyshyn et al., 2011). The authors concluded that "…having to maintain two task sets does involve a[n age-related] deficit over and beyond the effects of general slowing" (p. 19). This agrees well with our above interpretation and converges with our neural findings (i.e., most severe FC decreases with age between regions associated with task-set implementation and maintenance).

The predominance of task-set maintenance over switching deficits in our interpretation of age differences in overcoming automatic response tendencies is further supported by our finding that the incompatibility × age interaction effect on RT was not abolished by taking cognitive flexibility into account. Cognitive flexibility, as assessed via the TMT-B–TMT-A difference, reflects the ability to rapidly switch between two different task sets (i.e., search for numbers vs. letters; cf. Sánchez-Cubillo et al., 2009). In contrast, the block-wise performance averaging in SRC tasks rather emphasizes the ability to retrieve and maintain an instructed task set in the face of competition from a second task set regularly used within the same task. Accordingly, our findings agree well with previous suggestions that keeping competing task

sets apart and suppressing the currently irrelevant one might constitute a core problem in advanced age (cf. Mayr and Liebscher, 2001; Vu and Proctor, 2008). As spatially compatible responses are highly overlearned, the S-R-compatible task set should produce substantial competition, thus making the opposing (incompatible) task set even more difficult to maintain. Coping with this biased competition might become harder with advancing age and form one of the mechanisms that contribute to the age-specific decline in managing S-R incompatibility.

Finally, although we did not investigate task-induced brain activity in the present study, we would like to comment briefly on the potential interplay between age-related changes in regional brain activation as observed previously and intrinsic interregional coupling as observed here. In fact, it has been repeatedly shown across a range of cognitive tasks that higher age is associated with the recruitment of additional (e.g. contralateral and/or prefrontal) brain regions (for reviews, see Cabeza, 2002; Dennis and Cabeza, 2008; Park and Reuter-Lorenz, 2009). Such age-related regional hyperactivity has often been interpreted as compensatory (cf. Grady, 2008; Reuter-Lorenz and Cappell, 2008). We suggest that reduced interregional coupling may be one of the neural changes with age that need to be compensated. Thus, as argued above, the observed FC changes could constitute the neural substrate of an age-related decline in the efficiency of modulatory control signalling, leading to greater functional brain responses to maintain similar levels of cognitive control (cf. Andrews-Hanna et al., 2007; Turner and Spreng, 2012). In other words, age-related reductions in FC might drive the additional recruitment of brain regions in higher age. Moreover, this interaction effect may well work both ways: age-related increases in FC, as observed here for pre-SMA–IPS connections, might also form a compensatory brain response to reduced or dedifferentiated functional brain activity. At any rate, acknowledging the possibility of compensatory changes across multiple dimensions of brain functioning should more generally

serve as a caveat against a potentially premature interpretation of unidimensional brain–behaviour relationships as either compensatory or dysfunctional.

4.1. Limitations and future directions

In Experiment 1, we relied on comparisons between two age categories (i.e., younger and older adults), which maximizes the sensitivity for age effects but, without intermediate age values, precludes investigating the trajectory of age-related changes. This drawback, however, does not apply to Experiment 2, where a large sample with a continuous age distribution was studied. Furthermore, both experiments share the limitations of a cross-sectional approach, which necessarily conflates age and cohort effects. Future studies using longitudinal designs should try to overcome these limitations.

A specific limitation to Experiment 2 is the hypothesis-driven selection of regions of interest based on a previous fMRI study (Cieslik et al., 2010). This preselection might have resulted in including clusters that reflect idiosyncrasies of Cieslik et al.'s study, but, importantly, it was based on the same task as used in Experiment 1. Also, supplementary seed-based whole-brain FC analyses indicated that we most likely did not miss any consistent age-related FC changes occurring outside the a priori defined task-relevant network, such as FC changes between regions that might only become relevant for successful SRC task performance in advanced age (cf. Cabeza, 2002). Furthermore, although all participants were screened for psychiatric and neurological disorders, the sensitivity of the screenings used at the four sites could be different. Therefore, it cannot be completely excluded that some participants with sub-clinical cognitive impairments were included.

Finally, behavioural and FC changes with age were examined in two separate experiments using data from independent, non-overlapping samples. This precluded us from directly relating individual FC parameters to performance measures. However, by

investigating FC in exactly the network that is associated with incompatibility-related processing in the paradigm of Experiment 1, we may still provide complementary evidence linked by functional neuroanatomy. In future research it would be desirable to combine performance and fMRI measurements in the same participants and to use several imaging modalities (e.g., task-related and resting-state fMRI) in order to arrive at a more comprehensive picture of neural changes with age, enabling direct tests of these changes' (potentially compensatory) interdependencies and associations with performance (cf. Andrews-Hanna et al., 2007; Madden et al., 2010; Schulte et al., 2011). Optimally, such studies would also consider morphological parameters. This would allow for investigating the question as to what degree age-related changes in behaviour, regional brain activity, and interregional FC are rooted in structural changes, for instance due to "silent" strokes, which could occur more frequently in frontal cortex.

4.2. Conclusions

Experiment 1 established that the age-related increase in S-R incompatibility costs is independent of both global slowing in cognitive processing speed with age (Salthouse, 1996) and other potential mediator variables that partially predicted the SRC effect. Experiment 2 demonstrated selective decreases in intrinsic FC between several brain regions that had previously been found to be associated with solving such incompatibility-induced response conflicts in the same task (cf. Cieslik et al., 2010). Further exploratory analyses revealed several regions of the default-mode network whose de-coupling from the SRC-related network was consistently diminished in advanced age. The behavioural data as well as the cognitive functions of the regions whose intrinsic FC strength decreased with age jointly suggest that healthy aging is selectively associated with deterioration in maintaining/monitoring relevant task schemata, ultimately leading to less efficient cognitive

control over action. Thus, our findings argue against an age-related decline in cognitive conflict resolution ability per se. They furthermore provide converging evidence against the notion of a uniform decline in the general efficiency of cognitive processes with age. On the contrary, the preserved intrinsic FC between many network nodes can be taken to indicate that the efficiency with which regions involved in top-down action control communicate with each other is, to a large degree, well maintained across the adult lifespan.

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References

Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., Lustig, C., Head, D., Raichle, M.E., Buckner, R.L., 2007. Disruption of large-scale brain systems in advanced aging. Neuron 56, 924-935. doi:10.1016/ j.neuron.2007.10.038.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. NeuroImage 26, 839-851.

Augustine, J.R., 1996. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res. Rev. 22, 229-244.

Behrwind, S.D., Dafotakis, M., Halfter, S., Hobusch, K., Berthold-Losleben, M., Cieslik, E.C., Eickhoff, S.B., 2011. Executive control in chronic schizophrenia: A perspective from manual stimulus-response compatibility task performance. Behav. Brain Res. 223, 24-29. doi:10.1016/j.bbr.2011.04.009.

Binder, J.R., Frost, J.A., Hammeke, T.A., Bellgowan, P.S., Rao, S.M., Cox, R.W., 1999. Conceptual processing during the conscious resting state: a functional MRI study. J. Cogn. Neurosci. 11, 80-93.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34, 537-541.

Bonin-Guillaume, S., Possamai, C.A., Blin, O., Hasbroucq, T., 2000. Stimulus preprocessing, response selection, and motor adjustment in the elderly: An additive factor analysis. Cah. Psychol. Cogn. 19, 245-255.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N. Y. Acad. Sci. 1124, 1-38. doi: 10.1196/annals.1440.011.

Bzdok, D., Langner, R., Schilbach, L., Engemann, D.A., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2013a. Segregation of the human medial prefrontal cortex in social cognition. Front. Hum. Neurosci. 7, 232. doi: 10.3389/fnhum.2013.00232.

Bzdok, D., Langner, R., Schilbach, L., Jakobs, O., Roski, C., Caspers, S., Laird, A.R., Fox, P.T., Zilles, K., Eickhoff, S.B., 2013b. Characterization of the temporo-parietal junction by combining data-driven parcellation, complementary connectivity analyses, and functional decoding. Neuroimage 81, 381-392.

Bzdok, D., Schilbach, L., Vogeley, K., Schneider, K., Laird, A.R., Langner, R., Eickhoff, S.B., 2012. Parsing the neural correlates of moral cognition: ALE meta-analysis on morality, theory of mind, and empathy. Brain Struct. Funct. 217, 783-796.

Cabeza, R., 2002. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol. Aging 17, 85-100.

Caspers, S., Geyer, S., Schleicher, A., Mohlberg, H., Amunts, K., Zilles, K., 2006. The human inferior parietal cortex: cytoarchitectonic parcellation and interindividual variability. NeuroImage 33, 430-448.

Chen, N.K., Chou, Y.H., Song, A.W., Madden, D.J., 2009. Measurement of spontaneous signal fluctuations in fMRI: adult age differences in intrinsic functional connectivity. Brain Struct. Funct. 213, 571-585. doi:10.1007/s00429-009-0218-4.

Cieslik, E.C., Müller, V.I., Kellermann, T.S., Grefkes, C., Halfter, S., Eickhoff, S.B., 2013a. Shifted neuronal balance during stimulus–response integration in schizophrenia: an fMRI study. Brain Struct. Funct. [Advance online publication]. doi: 10.1007/s00429-013-0652-1.

Cieslik, E.C., Zilles, K., Caspers, S., Roski, C., Kellermann, T.S., Jakobs, O., Langner, R., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2013b. Is there "one" DLPFC in cognitive action control? Evidence for heterogeneity from co-activation-based parcellation. Cereb. Cortex 23, 2677-2689. doi:10.1093/cercor/bhs256.

Cieslik, E.C., Zilles, K., Grefkes, C., Eickhoff, S.B., 2011. Dynamic interactions in the fronto-parietal network during a manual stimulus-response compatibility task. NeuroImage 58, 860-869. doi:10.1016/j.neuroimage.2011.05.089.

Cieslik, E.C., Zilles, K., Kurth, F., Eickhoff, S.B., 2010. Dissociating bottom-up and top-down processes in a manual stimulus-response compatibility task. J. Neurophysiol. 104, 1472-1483.

Cisek, P., 2006. Integrated neural processes for defining potential actions and deciding between them: a computational model. J. Neurosci. 26, 9761-9770. doi:10.1523/JNEUROSCI.5605-05.2006.

Clos, M., Amunts, K., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2013. Tackling the multifunctional nature of Broca's region meta-analytically: Co-activation-based parcellation of area 44. Neuroimage 83, 174-188. doi: 10.1016/j.neuroimage.2013.06.041.

Cole, M.W., Schneider, W., 2007. The cognitive control network: Integrated cortical regions with dissociable functions. NeuroImage 37, 343-360. doi:10.1016/j.neuroimage.2007.03.071.

Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: From environment to theory of mind. Neuron 58, 306-324. doi:10.1016/j.neuron.2008.04.017.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201-215. doi:10.1038/nrn755.

Craik, F.I.M., Salthouse, T.A., 2008. The handbook of aging and cognition. Psychology Press, New York, NY.

Dafotakis, M., Grefkes, C., Eickhoff, S.B., Karbe, H., Fink, G.R., Nowak, D.A., 2008. Effects of rTMS on grip force control following subcortical stroke. Exp. Neurol. 211, 407-412. doi:10.1016/ j.expneurol.2008.02.018.

Defer, G.L., Widner, H., Marie, R.M., Remy, P., Levivier, M., 1999. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov. Disord. 14, 572-584.

Dennis, N.A., Cabeza, R., 2008. Neuroimaging of healthy cognitive aging., in: Craik, F.I.M., Salthouse, T.A. (Eds.). The handbook of aging and cognition. Lawrence Erlbaum, London, UK, pp. 1-54.

Dosenbach, N.U., Fair, D.A., Miezin, F.M., Cohen, A.L., Wenger, K.K., Dosenbach, R.A., Fox, M.D., Snyder, A.Z., Vincent, J.L., Raichle, M.E., Schlaggar, B.L., Petersen, S.E., 2007. Distinct brain networks for adaptive and stable task control in humans. Proc. Natl. Acad. Sci. U.S.A. 104, 11073-11078. doi:10.1073/pnas.0704320104.

Dosenbach, N.U., Visscher, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.C., Burgund, E.D., Grimes, A.L., Schlaggar, B.L., Petersen, S.E., 2006. A core system for the implementation of task sets. Neuron 50, 799-812. doi:10.1016/j.neuron.2006.04.031.

Eickhoff, S.B., Bzdok, D., Laird, A.R., Roski, C., Caspers, S., Zilles, K., Fox, P.T., 2011a. Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. NeuroImage 57, 938-949.

Eickhoff, S.B., Pomjanski, W., Jakobs, O., Zilles, K., Langner, R., 2011b. Neural correlates of developing and adapting behavioural biases in speeded choice reactions: An fMRI study on predictive motor coding. Cereb. Cortex 21, 1178-1191. doi:10.1093/cercor/bhq188.

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

Fitts, P.M., Deininger, R.L., 1954. S-R compatibility: Correspondence among paired elements within stimulus and response codes. J. Exp. Psychol. 48, 483-492. doi:10.1037/H0054967.

Fox, M.D., Corbetta, M., Snyder, A.Z., Vincent, J.L., Raichle, M.E., 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc. Natl. Acad. Sci. U.S.A. 103, 10046-10051. doi:10.1073/pnas.0604187103.

Fox, M.D., Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat. Rev. Neurosci. 8, 700-711. doi:10.1038/nrn2201.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Raichle, M.E., 2007. Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. Neuron 56, 171-184. doi:10.1016/ j.neuron.2007.08.023.

Fox, M.D., Zhang, D., Snyder, A.Z., Raichle, M.E., 2009. The global signal and observed anticorrelated resting state brain networks. J. Neurophysiol. 101, 3270-3283. doi:10.1152/jn.90777.2008.

Fox, P.T., Laird, A.R., Fox, S.P., Fox, P.M., Uecker, A.M., Crank, M., Koenig, S.F., Lancaster, J.L., 2005. BrainMap taxonomy of experimental design: description and evaluation. Hum. Brain Mapp. 25, 185-198.

Geyer, S., 2004. The microstructural border between the motor and the cognitive domain in the human cerebral cortex. Adv. Anat. Embryol. Cell Biol. 174, 1-89.

Goh, J.O., 2011. Functional dedifferentiation and altered connectivity in older adults: Neural accounts of cognitive aging. Aging Dis. 2, 30-48.

Grady, C.L., 2005. Functional connectivity during memory tasks in healthy aging and dementia, in: Cabeza, R., Nyberg, L., Park, D.C. (Eds.). Cognitive neuroscience of aging: Linking cognitive and cerebral aging. Oxford University Press, Oxford, UK, pp. 286-308.

Grady, C.L., 2008. Cognitive neuroscience of aging. Ann. N. Y. Acad. Sci. 1124, 127-144. doi:10.1196/ annals.1440.009.

Grandjean, J., Collette, F., 2011. Influence of response prepotency strength, general working memory resources, and specific working memory load on the ability to inhibit predominant responses: a comparison of young and elderly participants. Brain Cogn. 77, 237-247. doi:10.1016/j.bandc.2011.08.004.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. U.S.A. 100, 253-258. doi:10.1073/pnas.0135058100.

Hommel, B., Prinz, W., 1997. Theoretical issues in stimulus–response compatibility. North-Holland, Amsterdam, The Netherlands.

Hoshi, E., Tanji, J., 2006. Differential involvement of neurons in the dorsal and ventral premotor cortex during processing of visual signals for action planning. J. Neurophysiol. 95, 3596-3616. doi:10.1152/jn.01126.2005.

Jakobs, O., Langner, R., Caspers, S., Roski, C., Cieslik, E.C., Zilles, K., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2012. Across-study and within-subject functional connectivity of a right temporo-parietal junction subregion involved in stimulus-context integration. NeuroImage 60, 2389-2398. doi:10.1016/ j.neuroimage.2012.02.037.

Kessler, J., Fast, K., Mielke, R., 1995. Zur Problematik der prämorbiden Intelligenzdiagnostik mit dem MWT-B bei Patienten mit Alzheimer-Erkrankung [Premorbid intelligence diagnosis with the MWT-B (Multiple-Choice Word Test–B) in patients with Alzheimer's disease]. Nervenarzt 66, 696-702.

Kiesel, A., Steinhauser, M., Wendt, M., Falkenstein, M., Jost, K., Philipp, A.M., Koch, I., 2010. Control and interference in task switching – a review. Psychol. Bull. 136, 849-874. doi: 10.1037/a0019842.

Kurth, F., Zilles, K., Fox, P.T., Laird, A.R., Eickhoff, S.B., 2010. A link between the systems: Functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct. Funct. 214, 519-534.

Laird, A.R., Eickhoff, S.B., Kurth, F., Fox, P.M., Uecker, A.M., Turner, J.A., Robinson, J.L., Lancaster, J.L., Fox, P.T., 2009. ALE meta-analysis workflows via the Brainmap database: progress towards a probabilistic functional brain atlas. Front. Neuroinformatics 3, 23. doi:10.3389/neuro.11.023.2009.

Langner, R., Eickhoff, S.B., 2013. Sustaining attention to simple tasks: A meta-analytic review of the neural mechanisms of vigilant attention. Psychol. Bull. 139, 870-900. doi:10.1037/a0030694.

Langner, R., Kellermann, T., Boers, F., Sturm, W., Willmes, K., Eickhoff, S.B., 2011. Modality-specific perceptual expectations selectively modulate baseline activity in auditory, somatosensory, and visual cortices. Cereb. Cortex 21, 2850-2862. doi:10.1093/cercor/bhr083.

Langner, R., Kellermann, T., Eickhoff, S.B., Boers, F., Chatterjee, A., Willmes, K., Sturm, W., 2012. Staying responsive to the world: Modality-specific and -nonspecific contributions to speeded auditory, tactile, and visual stimulus detection. Hum. Brain Mapp. 33, 398-418. doi:10.1002/hbm.21220.

Langner, R., Sternkopf, M.A., Kellermann, T.S., Grefkes, C., Kurth, F., Schneider, F., Zilles, K., Eickhoff, S.B., 2013. Translating working memory into action: Behavioral and neural evidence for using motor representations in encoding visuo-spatial sequences. Hum. Brain Mapp. doi: 10.1002/hbm.22415.

Lee, T.M., Zhang, J.X., Chan, C.C., Yuen, K.S., Chu, L.W., Cheung, R.T., Chan, Y.S., Fox, P.T., Gao, J.H., 2006. Age-related differences in response regulation as revealed by functional MRI. Brain Res. 1076, 171-176. doi:10.1016/j.brainres.2005.12.124.

Lehrl, S., 2005. Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) [Multiple-Choice Vocabulary Test–B] (5th ed.). Spitta-Verlag, Balingen, Germany.

Logan, G.D., 2007. What it costs to implement a plan: Plan-level and task-level contributions to switch costs. Mem. Cognit. 35, 591-602.

Los, S.A., 1996. On the origin of mixing costs: Exploring information processing in pure and mixed blocks of trials. Acta Psychol. 94, 145-188.

Madden, D.J., Costello, M.C., Dennis, N.A., Davis, S.W., Shepler, A.M., Spaniol, J., Bucur, B., Cabeza, R., 2010. Adult age differences in functional connectivity during executive control. NeuroImage 52, 643-657. doi:10.1016/j.neuroimage.2010.04.249.

Mason, M.F., Norton, M.I., Van Horn, J.D., Wegner, D.M., Grafton, S.T., Macrae, C.N., 2007. Wandering minds: the default network and stimulus-independent thought. Science 315, 393-395.

Matsumoto, E., Misaki, M., Miyauchi, S., 2004. Neural mechanisms of spatial stimulus-response compatibility: the effect of crossed-hand position. Exp. Brain Res. 158, 9-17. doi:10.1007/s00221-004-1872-7.

Mayr, U., Liebscher, T., 2001. Is there an age deficit in the selection of mental sets? Eur. J Cognit. Psychol. 13, 47-69.

Onoda, K., Ishihara, M., Yamaguchi, S., 2012. Decreased functional connectivity by aging is associated with cognitive decline. J. Cogn. Neurosci. 24, 2186-2198.

Park, D.C., Reuter-Lorenz, P., 2009. The adaptive brain: aging and neurocognitive scaffolding. Annu. Rev. Psychol. 60, 173-196. doi:10.1146/annurev.psych.59.103006.093656.

Park, D.C., Schwarz, N., 2000. Cognitive aging: A primer. Psychology Press, Philadelphia, PA.

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

Proctor, R.W., Vu, K.P., Pick, D.F., 2005. Aging and response selection in spatial choice tasks. Hum. Factors 47, 250-270.

Reitan, R.M., 1955. The relation of the trail making test to organic brain damage. J. Consult. Psychol. 19, 393-394.

Reuter-Lorenz, P.A., Cappell, K.A., 2008. Neurocognitive aging and the compensation hypothesis. Curr. Dir. Psychol. Sci. 17, 177-182. doi:10.1111/j.1467-8721.2008.00570.x.

Roski, C., Caspers, S., Langner, R., Laird, A.R., Fox, P.T., Zilles, K., Amunts, K., Eickhoff, S.B., 2013a. Adult age-dependent differences in resting-state connectivity within and between visual-attention and sensorimotor networks. Front. Aging Neurosci. 5, 67. doi: 10.3389/fnagi.2013.00067.

Roski, C., Caspers, S., Lux, S., Hoffstaedter, F., Bergs, R., Amunts, K., and Eickhoff, S.B., 2013b. Activation shift in elderly subjects across functional systems: an fMRI study. Brain Struct. Funct. [Advance online publication]. doi: 10.1007/s00429-013-0530-x.

Rottschy, C., Caspers, S., Roski, C., Reetz, K., Dogan, I., Schulz, J.B., Zilles, K., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2013. Differentiated parietal connectivity of frontal regions for "what" and "where" memory. Brain Struct. Funct. 218, 1551-1567. doi: 10.1007/s00429-012-0476-4.

Salthouse, T.A., 1991. Theoretical perspectives on cognitive aging. Erlbaum, Hillsdale, NJ.

Salthouse, T.A., 1996. The processing-speed theory of adult age differences in cognition. Psychol. Rev. 103, 403-428.

Sánchez-Cubillo, I., Perianez, J.A., Adrover-Roig, D., Rodriguez-Sánchez, J.M., Rios-Lago, M., Tirapu, J., Barcelo, F., 2009. Construct validity of the Trail Making Test: Role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. J. Int. Neuropsychol. Soc. 15, 438-450. doi:10.1017/S1355617709090626.

Satterthwaite, T.D., Elliott, M.A., Gerraty, R.T., Ruparel, K., Loughead, J., Calkins, M.E., Eickhoff, S.B., Hakonarson, H., Gur, R.C., Gur, R.E., Wolf, D.H., 2013. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. NeuroImage 64, 240-256. doi:10.1016/j.neuroimage.2012.08.052.

Scheperjans, F., Hermann, K., Eickhoff, S.B., Amunts, K., Schleicher, A., Zilles, K., 2008. Observer-independent cytoarchitectonic mapping of the human superior parietal cortex. Cereb. Cortex 18, 846-867.

Schilbach, L., Bzdok, D., Timmermans, B., Fox, P.T., Laird, A.R., Vogeley, K., Eickhoff, S.B., 2012. Introspective minds: using ALE meta-analyses to study commonalities in the neural correlates of emotional processing, social & unconstrained cognition. PLoS One 7, e30920.

Schulte, T., Müller-Oehring, E.M., Chanraud, S., Rosenbloom, M.J., Pfefferbaum, A., Sullivan, E.V., 2011. Age-related reorganization of functional networks for successful conflict resolution: A combined functional and structural MRI study. Neurobiol. Aging 32, 2075-2090. doi:10.1016/ j.neurobiolaging.2009.12.002.

Schumacher, E.H., Elston, P.A., D'Esposito, M., 2003. Neural evidence for representation-specific response selection. J. Cogn. Neurosci. 15, 1111-1121. doi:10.1162/089892903322598085.

Shallice, T., Stuss, D.T., Alexander, M.P., Picton, T.W., Derkzen, D., 2008. The multiple dimensions of sustained attention. Cortex 44, 794-805. doi:10.1016/j.cortex.2007.04.002.

Shulman, G.L., Fiez, J.A., Corbetta, M., Buckner, R.L., Miezin, F.M., Raichle, M.E., Petersen, S.E., 1997. Common blood flow changes across visual tasks. 2. Decreases in cerebral cortex. J. Cogn. Neurosci. 9, 648-663.

Simon, J.R., Wolf, J.D., 1963. Choice reaction-time as a function of angular stimulus–response correspondence and age. Ergonomics 6, 99-105. doi:10.1080/00140136308930679.

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., Beckmann, C.F., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U.S.A. 106, 13040-13045. doi:10.1073/pnas.0905267106.

Smulders, F.T., Kenemans, J.L., Schmidt, W.F., Kok, A., 1999. Effects of task complexity in young and old adults: Reaction time and P300 latency are not always dissociated. Psychophysiology 36, 118-125.

Sridharan, D., Levitin, D.J., Menon, V., 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc. Natl. Acad. Sci. U.S.A. 105, 12569-12574. doi:10.1073/pnas.0800005105.

Stevens, M.C., 2009. The developmental cognitive neuroscience of functional connectivity. Brain Cogn. 70, 1-12. doi:10.1016/j.bandc.2008.12.009.

Stuss, D.T., Shallice, T., Alexander, M.P., Picton, T.W., 1995. A multidisciplinary approach to anterior attentional functions. Ann. N. Y. Acad. Sci. 769, 191-211.

Sylvester, C.Y., Wager, T.D., Lacey, S.C., Hernandez, L., Nichols, T.E., Smith, E.E., Jonides, J., 2003. Switching attention and resolving interference: fMRI measures of executive functions. Neuropsychologia 41, 357-370.

Taylor, K.S., Seminowicz, D.A., Davis, K.D., 2009. Two systems of resting state connectivity between the insula and cingulate cortex. Hum. Brain Mapp. 30, 2731-2745. doi:10.1002/hbm.20705.

Toro, R., Fox, P.T., Paus, T., 2008. Functional coactivation map of the human brain. Cereb. Cortex 18, 2553-2559. doi: 10.1093/cercor/bhn014.

Turner, G.R., Spreng, R.N., 2012. Executive functions and neurocognitive aging: dissociable patterns of brain activity. Neurobiol. Aging 33, 826 e821-813. doi:10.1016/j.neurobiolaging.2011.06.005.

Verhaeghen, P., 2011. Aging and executive control: Reports of a demise greatly exaggerated. Curr. Dir. Psychol. Sci. 20, 174-180. doi:Doi 10.1177/0963721411408772.

Verhaeghen, P., Steitz, D.W., Sliwinski, M.J., Cerella, J., 2003. Aging and dual-task performance: a meta-analysis. Psychol. Aging 18, 443-460. doi:10.1037/0882-7974.18.3.443.

Vu, K.P., Proctor, R.W., 2008. Age differences in response selection for pure and mixed stimulus–response mappings and tasks. Acta Psychol. 129, 49-60. doi: 10.1016/j.actpsy.2008.04.006.

Wasylyshyn, C., Verhaeghen, P., Sliwinski, M.J., 2011. Aging and task switching: a meta-analysis. Psychol. Aging 26, 15-20. doi:10.1037/a0020912.

Weinrich, M., Wise, S.P., 1982. The premotor cortex of the monkey. J. Neurosci. 2, 1329-1345.

Weissenbacher, A., Kasess, C., Gerstl, F., Lanzenberger, R., Moser, E., Windischberger, C., 2009. Correlations and anticorrelations in resting-state functional connectivity MRI: A quantitative comparison of preprocessing strategies. NeuroImage 47, 1408-1416. doi:10.1016/j.neuroimage.2009.05.005.

Weissman, D.H., Roberts, K.C., Visscher, K.M., Woldorff, M.G., 2006. The neural bases of momentary lapses in attention. Nat. Neurosci. 9, 971-978.

Wu, T., Zang, Y., Wang, L., Long, X., Hallett, M., Chen, Y., Li, K., Chan, P., 2007. Aging influence on functional connectivity of the motor network in the resting state. Neurosci. Lett. 422, 164-168. doi:10.1016/j.neulet.2007.06.011.

Zhang, D., Raichle, M.E., 2010. Disease and the brain's dark energy. Nat. Rev. Neurol. 6, 15-28. doi:10.1038/nrneurol.2009.198.

Zuo, X.N., Kelly, C., Di Martino, A., Mennes, M., Margulies, D.S., Bangaru, S., Grzadzinski, R., Evans, A.C., Zang, Y.F., Castellanos, F.X., Milham, M.P., 2010. Growing together and

growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. J. Neurosci. 30, 15034-15043. doi: 10.1523/JNEUROSCI.2612-10.2010.

Supplementary Material

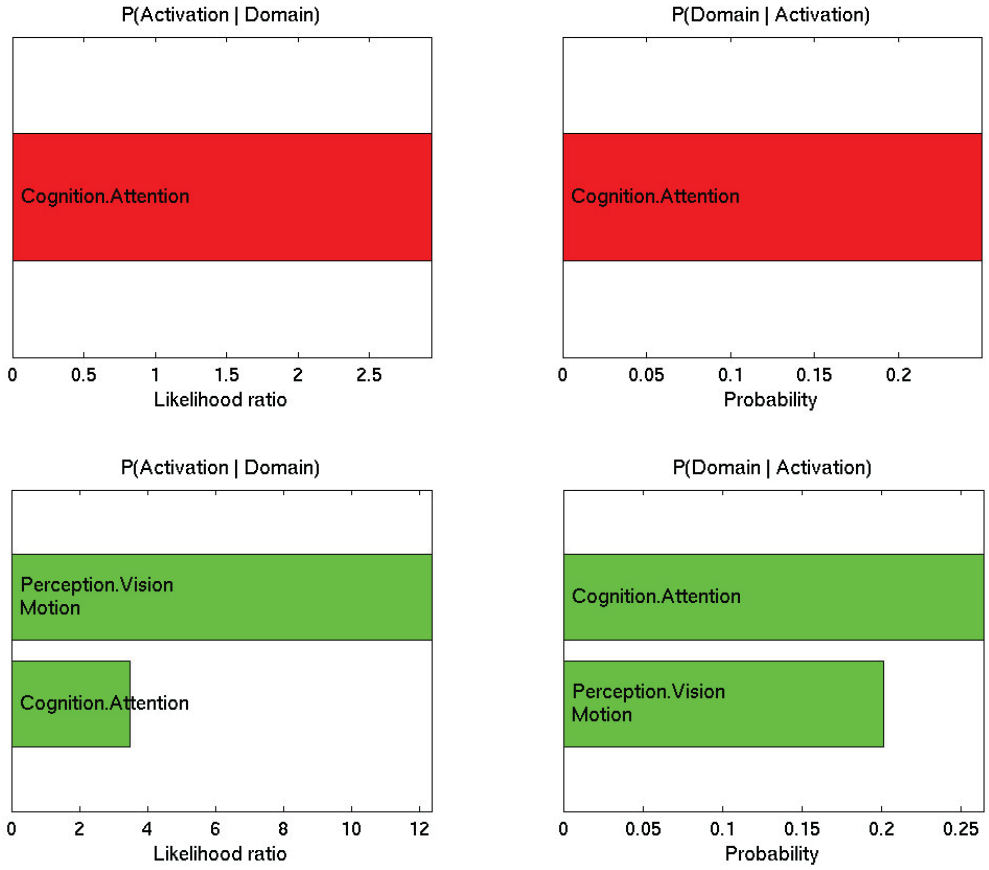

Figure S1 | Significant associations of the age-sensitive (red) and age-insensitive (green) sets of seed regions with behavioural domains of the BrainMap database. Left panels: forward inference (significant probability of activating either set of seeds given a particular behavioural domain). Right panels: reverse inference (significant probability of domain presence given activation of either set of seeds).

Table S1 | Control Seed Regions Used in Experiment 2 and Correlations Between Their Pairwise (Interhemispheric) Functional Connectivity and Age (n = 399).

Seed Region	x, y, z	Correlation with Age (r_s)
L fusiform gyrus	**–39 –51 –21**	**–.19**
R fusiform gyrus	**39 –60 –17**	
L auditory cortex	**–56 –20 5**	**–.24**
R auditory cortex	**60 –21 5**	
L amygdala	**–20 –3 –21**	**–.15**
R amygdala	**20 –3 –21**	
L superior temporal sulcus	–48 –39 12	.03
R superior temporal sulcus	48 –53 8	

Note. Seed regions showing a significant (p < .05, uncorrected for multiple comparisons) correlation between age and the resting-state functional connectivity with their contralateral homotopic region are set in bold. Coordinates indicate the centre of the seed region (5-mm sphere around the centre) in MNI space. L, left; R, right.

Supplementary methods: Exploratory whole-brain functional connectivity (FC) analysis

For each of our nine seeds, we performed a whole-brain FC analysis to explore whether there was significant FC with brain regions outside the a priori specified, incompatibility-related network. As with the network-based analysis, these seed-based analyses were performed using conjunctions across the FC main effect (separately for positive and negative FC) and the correlation between FC and age. However, we only tested for age-related decreases in positive FC (i.e., reduced neural coupling) and increases in negative FC (i.e., reduced neural de-coupling), given that these changes should be the most relevant ones for driving behavioral changes with age. For these exploratory analyses to be sufficiently sensitive, we did not use an effect-size criterion but rather considered each cluster significant for which the conjunction analysis survived a cluster-level threshold of $p < .05$ (FWE-corrected; cluster-forming threshold at voxel level: $p < .001$).

Subsequently, the resulting statistical maps were overlaid with each other to identify regions outside the a priori defined set of seed regions whose FC with the incompatibility-related network was consistently affected by age. More specifically, we looked for additional regions that showed significant age modulations of their FC with more than half (i.e., > 4) of the original seed regions. This approach was based on the notion that additional regions that potentially contribute to the observed age effects on SRC task performance should show an age-sensitive neural coupling with, or de-coupling from, a substantial number (i.e., > 50%) of nodes of our incompatibility-related network.

Discussion

The three studies at hand investigated age-related differences of task-dependent regional brain activity and intrinsic functional connectivity within and between brain networks. Study 1 examined task-dependent age differences in activity of the sensorimotor system and the visual attention system, focusing on the dedifferentiation of task-evoked activity across both underlying networks. In Study 2, the neural underpinnings of this phenomenon in terms of resting-state functional connectivity were analyzed, thereby illuminating the putative relation of age-related connectivity differences to common behavioral changes in older adults. Finally, Study 3 focused on age-related differences in cognitive action control and connectivity changes within a distinct functional network associated with that process.

Dedifferentiation – a global age-related phenomenon

In the first study, two tasks engaging two distinct sets of brain regions (i.e., a sensorimotor task and a visual attention task) were analyzed in terms of their associated hemodynamic activity pattern and its change with age. The principal finding was a significant age-by-task interaction within specific regions in both networks reflecting a loss of neural specificity across brain systems. In detail, these regions showed a decrease of neural activity during the primarily associated task and increased activation during the other task with increasing age. These regions encompass the superior parietal area 7A and a sub-region within the dorsal pre-motor cortex bilaterally as nodes associated with the visual attention task and a sub-region within the parietal opercular cortex bilaterally (predominantly area OP4), which is associated with the sensorimotor task. Importantly, the here observed loss of neural specificity thus seems to span multiple brain systems, mirroring a more global phenomenon during healthy aging as suggested previously (Grady et al., 1994; Carp et al., 2011). In particular, dedifferentiation has already been demonstrated within several functional systems (Grady et

al., 1994; Townsend et al., 2006) as well as across different tasks within a distinct functional system. However, the present results suggest that dedifferentiation in older adults comprises even brain regions that are associated with a functional system not engaged by the task at hand in younger adults. In terms of functional specialization, this finding emphasizes a substantial plasticity throughout the human life span, as the mapping between regional processes (local brain activity) and experimental tasks seems to vary with age. As elaborated on in the discussion of the first study, all regions in question feature a broad functional variety, playing a role in several cognitive and motor processes. To successfully perform a given task, these processes may be differentially recruited in the elderly, as compared with younger adults, leading to the observed modulation of neural specificity. In other words, the functional specificity of a brain region, reflected by its neural process, has not to be restricted to a distinct task and could even adapt its integration in neural networks. Consequently, the investigation of functional activity patterns throughout the life span may profit from comparing activation patterns from different tasks (engaging different brain systems).

Dedifferentiation across systems - intrinsic changes

The results of the second study highlight the intrinsic properties that may give rise to age-related dedifferentiation across functional systems, as observed in Study 1. In particular, the resting-state FC analysis points to a diminished anti-correlation of intrinsic FC between the sensorimotor related and visual-attention-related regions (i.e., the task-specific regions). As these regions are anti-correlated with each other in the young subsample, their less distinct connectivity with age suggests a deterioration of mechanisms supporting task switching or mutual suppression in older adults. In line with this assumption, executive control processes, such as attention switching between tasks (Mayr et al., 2001) or inhibitory control (Hasher and Zacks, 1988) are proposed to be age sensitive. Correspondingly, the intrinsic

characteristics between the task-general regions, which feature interactions with all task-specific regions, also point to this assumption. In particular, the communication between the rostral part of the supplementary motor cortex (SMAr) and the anterior insular cortex (AIC) bilaterally seems to decrease with increasing age. Both regions are known to be associated with the initiation and maintenance of mental task-sets (Dosenbach et al., 2006) and are assumed to contribute to the processing of one`s personal salience (Craig, 2002; Kerns et al., 2004). The observed reduction in RS-FC between nodes of this network (SMAr and AIC) may hence affect task-switching (Wasylyshyn et al., 2011) and dual-tasking performance (Verhaeghen et al., 2003; Just et al., 2008) in older adults. Next, reduced intrinsic communication between the task-general SMAr and the sensorimotor-related area OP4 as well as the visual-attention-related area 7A was observed, reflecting again common difficulties for older adults during "top down" modulation (Gazzaley and D'Esposito, 2007). As mentioned previously, the SMA is known to play a role within the "salience network" (Craig, 2002;Kerns et al., 2004) and represents a node within a "core network" involved in the control of mental task sets (Dosenbach et al., 2006). An age-related decrease of communication between task-specific regions and such a cognitive "core-region" likewise indicates a putative neural substrate of common difficulties in older adults during executive control processes (for review see Braver and West, 2007).

Importantly, deteriorated mechanisms during task-switching or mutual suppression between both the visual attention and the sensorimotor networks and the less precisely controlled interplay of both systems may potentially drive a loss of neural distinctiveness across both systems with increasing age, corroborating the effect described in Study 1 (i.e., the dedifferentiation across systems). That is, the observed age-related RS-FC pattern reflect the previously demonstrated task-dependent activation pattern, thereby prompting

considerations on the potential predictive character of intrinsic FC for task-dependent activation.

Intrinsic functional connectivity – selective changes

The second study indicated a relation between intrinsic variations of FC and local task-dependent activity changes with increasing age. Importantly, not all analyzed intrinsic connections showed age-related changes. A loss of intrinsic FC seems to occur rather selectively, arguing against a general and unspecific age-related decline in the functional coupling between brain regions. Moreover, is appears that in particular higher-order cognitive brain regions, relevant for top-down control, are affected. This, in turn, leads to a reduced efficiency in maintaining and controlling multiple task sets (Verhaeghen et al., 2003; Wasylyshyn et al., 2011). Consistent with these assumptions, Study 3 also reported intrinsic functional connections to be selectively affected by age between nodes of a network associated with incompatibility-induced stimulus–response conflicts. These nodes predominantly comprised prefrontal brain regions, including the dorsolateral prefrontal cortex, pre-SMA, and AIC. Notably, the latter two regions closely correspond to the task-general regions of the second study. Moreover, they showed similar intrinsic properties to these task-general regions, thereby fortifying the consistency of these RS-FC findings. Prior to the intrinsic FC analysis it was demonstrated in Study 3 that performance in a stimulus-response incompatibility task is deteriorated in older adults beyond a global slowing of cognitive processing. In particular, it was shown that mediator variables (i.e., performance accuracy, motor speed, speeded visuomotor coordination, and cognitive flexibility) were unable to fully explain the observed differences related to aging. Hence, a deficit in cognitive action control based on selectively affected connections can be assumed. Supporting this

view, the subsequent analysis of intrinsic FC highlighted, similarly to the second study, a reduced intrinsic coupling between pre-SMA and AIC bilaterally. In accordance with the second study, a reduced ability of older adults for implementing task sets, is hypothesized.

Taken together, Study 2 and 3 consistently yielded selective age-related changes in intrinsic coupling, which were predominantly observed between brain regions related to higher cognitive action control (i.e., activation and control of task-sets). It may hence be argued that these interregional variations might generally contribute to common age-related deficits in dual-tasking and task-switching performance.

Summary

An age-related loss of neural specificity might not be system- or task-specific but rather appears to span multiple brain systems, mirroring neuronal dedifferentiation within a particular system and suggesting that this may be a more global phenomenon than has been assumed up to now. In terms of functional specialization, the age-related differences in the mapping between neural activity and experimental tasks indicate functional plasticity throughout the human life span. The observed task-dependent loss of specificity across the visual-attention and sensorimotor system is accompanied by changes in intrinsic interregional FC. In particular, the interregional integration of a network strongly associated with the initiation and control of mental task sets (Dosenbach et al., 2006) seems to be deteriorated in advanced age, potentially triggering the observed less differentiated activation pattern. Moreover, this task-independent less efficient “top-down” control in older adults may also contribute to common age-related performance deficits across tasks that require managing several distinct task-sets, in turn reflecting the reduced ability of older adults to efficiently inhibit prepotent but irrelevant response tendencies. These assumptions, however, need to be addressed more directly in future research. In conclusion, the intrinsic state of the human

brain, and in particular age-related changes of this state, may predict changes of task-dependent activation with age, thereby providing evidence that spontaneous brain activity (as observable in the "resting" state) is critical to cognitive functioning in older adults and has a fundamental relevance for understanding the human aging brain.

References

Braver, T.S., and West, R. (2007). "Working memory, executive control, and aging," in *The handbook of cognition,* eds. T.A. Salthouse & A.D. Craig. (New York and Hove: Psychology Press).

Carp, J., Park, J., Hebrank, A., Park, D.C., and Polk, T.A. (2011). Age-related neural dedifferentiation in the motor system. *PLoS One* 6**,** e29411.

Craig, A.D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 3**,** 655-666.

Dosenbach, N.U.F., Visscher, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.S.C., Burgund, E.D., Grimes, A.L., Schlaggar, B.L., and Petersen, S.E. (2006). A core system for the implementation of task sets. *Neuron* 50**,** 799-812.

Gazzaley, A., and D'esposito, M. (2007). Top-down modulation and normal aging. *Ann N Y Acad Sci* 1097**,** 67-83.

Grady, C.L., Maisog, J.M., Horwitz, B., Ungerleider, L.G., Mentis, M.J., Salerno, J.A., Pietrini, P., Wagner, E., and Haxby, J.V. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. *J Neurosci* 14**,** 1450-1462.

Hasher, L., and Zacks, R.T. (1988). "Working memory, comprehension, and aging: A review and a new view," in *The psychology of learning and motivation,* ed. G.H. Bower. (New York: Academic Press).

Just, M.A., Keller, T.A., and Cynkar, J. (2008). A decrease in brain activation associated with driving when listening to someone speak. *Brain Res* 1205**,** 70-80.

Mayr, U., Spieler, D.H., and Kliegl, R. (2001). *Aging and executive control.* New York: NY: Routledge.

Salthouse, T.A. (1996). The processing-speed theory of adult age differences in cognition. *Psychol Rev* 103**,** 403-428.

Townsend, J., Adamo, M., and Haist, F. (2006). Changing channels: an fMRI study of aging and cross-modal attention shifts. *Neuroimage* 31**,** 1682-1692.

Verhaeghen, P., Steitz, D.W., Sliwinski, M.J., and Cerella, J. (2003). Aging and dual-task performance: a meta-analysis. *Psychol Aging* 18**,** 443-460.

Wasylyshyn, C., Verhaeghen, P., and Sliwinski, M.J. (2011). Aging and task switching: a meta-analysis. *Psychol Aging* 26**,** 15-20.

Kerns, J.G., Cohen, J.D., Macdonald, A.W., 3rd, Cho, R.Y., Stenger, V.A., and Carter, C.S. (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science* 303**,** 1023-1026.

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