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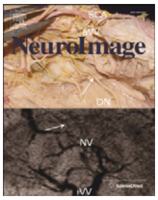

A multivariate analysis of age-related differences in functional networks supporting conflict resolution

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ABSTRACT

Functional neuroimaging studies demonstrate age-related differences in recruitment of a large-scale attentional network during interference resolution, especially within dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). These alterations in functional responses have been frequently observed despite equivalent task performance, suggesting age-related reallocation of neural resources, although direct evidence for a facilitating effect in aging is sparse. We used the multi-source interference task and multivariate partial-least-squares to investigate age-related differences in the neuronal signature of conflict resolution, and their behavioral implications in younger and older adults. There were interference-related increases in activity, involving fronto-parietal and basal ganglia networks that generalized across age. In addition an age-by-task interaction was observed within a distributed network, including DLPFC and ACC, with greater activity during interference in the old. Next, we combined brain–behavior and functional connectivity analyses to investigate whether compensatory brain changes were present in older adults, using DLPFC and ACC as regions of interest (i.e. seed regions). This analysis revealed two networks differentially related to performance across age groups. A structural analysis revealed age-related gray-matter losses in regions facilitating performance in the young, suggesting that functional reorganization may partly reflect structural alterations in aging. Collectively, these findings suggest that age-related structural changes contribute to reductions in the efficient recruitment of a youth-like interference network, which cascades into instantiation of a different network facilitating conflict resolution in elderly people.

Introduction

Humans have access to information that originates from available external stimuli or can be retrieved from stored experiences. However, prepotent but task-irrelevant information may interfere with relevant information and impair performance. The ability to ignore irrelevant information has been investigated in several paradigms, with participants responding to stimuli in the presence or absence of distracting items (Bush et al., 2003; Eriksen and Eriksen, 1974; Simon and Berbaum, 1990; Stroop, 1935). Each paradigm relies on different methods for inducing cognitive conflict (for review, see Nee et al., 2007). For instance, the Stroop effect represents cognitive interference produced by color incongruence between a word depicting a color with the color of the ink (i.e. stimulus conflict), whereas the Simon effect denotes cognitive interference through spatial incongruence between the target and response (i.e. response conflict). The type of conflict resolution targeted in this research declines with age. Elderly persons have fewer resources available during a task conflict to inhibit irrelevant information (Gazzaley et al., 2008; Madden et al., 2004). Imaging studies have linked age-related deficits in conflict resolution to alterations in the anterior control network that involves DLPFC (Langenecker et al., 2004; Thomsen et al., 2004) and dorsal ACC (Milham et al., 2002), as well as the posterior attention network, including superior parietal cortex (Schulte et al., 2009). For example, Langenecker and colleagues reported similar brain activation patterns for younger and older adults during a Stroop task, along with age-related over-recruitment in frontal regions. The authors suggested that greater frontal activity among elderly people promotes successful inhibition. By contrast, Milham et al. found that older adults exhibited reduced DLPFC activity and greater ACC activity compared to younger adults during interference. Reduced DLPFC activity may reflect age-related impairment in attentional control, whereas increased ACC activity may indicate heightened potential for error.

Complex cognitive processes, such as interference resolution, may not be localized to discrete brain regions such as ACC and DLPFC, but rather be mediated by interactions among a set of functionally related areas (McIntosh, 1999). Functional connectivity (Friston et al., 1993; McIntosh, 1999) is an approach to directly assess interactions among

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network nodes for a specific cognitive process and their alterations in aging, which in turn might affect behavior (e.g. Clapp et al., 2011; Grady et al., 2010; Nagel et al., 2011). For example, Clapp and colleagues reported age-related working memory deficits for scenes during a delayed matching-to-sample task along with disruption of functional connectivity between PFC and the parahippocampal place area. Despite increasing interest in understanding covarying activity within a network for determining the neural underpinnings of cognitive functions (Bressler and Menon, 2010; McIntosh, 1999), direct evidence regarding age-related differences in connectivity of critical nodes for conflict resolution (i.e., ACC, DLPFC) and concomitant behavioral implications is lacking. To date, few studies have reported how brain responses during interference are modulated by performance (Zysset et al., 2007), and no study has examined whole-brain patterns of activity in relation to performance (for review, see Grady, 2012). Similarly, past research on this topic has examined regional effects of age on conflict resolution and not reported data at the network level. Thus, although past research suggests age-related differences in functional activation of critical nodes for conflict resolution, they do not provide direct evidence as to whether unique brain networks promote interference resolution across different age groups.

In the context of possible functional alterations in aging, an important question is how age-related functional alterations relate to other factors that are also affected by aging and influence brain function, such as brain structure. There is robust evidence for age-related decline in brain volumes, particularly in the frontal lobes (Good et al., 2001; Raz et al., 2005). Age-related differences in gray-matter (GM) volume may locally account for regional alterations in functional responses (e.g. Kalpouzos et al., 2011; Salami et al., 2012). However, an examination of the full set of brain regions also reflecting potential distal associations is lacking (e.g. Calhoun et al., 2006; Stevens et al., 2009).

To assess age differences in conflict resolution and associated brain systems, multivariate spatial–temporal partial-least-squares (PLS; McIntosh et al., 1996, 2004) was applied to data from younger and older adults. Participants were scanned with functional magnetic resonance imaging (fMRI) while they performed the Multi-Source Interference Task (MSIT; Bush and Shin, 2006; Bush et al., 2003), which involves control and interference trials and the critical contrast concerns differences in accuracy and/or response latency between the two conditions. This task combines multiple dimensions of cognitive interference. Specifically, the MSIT contains elements of flanker interference (i.e. distracting items flanking the target; Eriksen and Eriksen, 1974) and Simon interference (i.e. incongruity between the position of the target and the position of the response; Simon and Berbaum, 1990). The MSIT engages the cingulo-fronto-parietal attentional network (Bush and Shin, 2006; Bush et al., 2003). To identify whole-brain activity during the two MSIT conditions for each age group, we initially applied task PLS analysis. As opposed to traditional analysis which largely rests on cognitive subtraction, PLS is able to use all conditions in an experiment at once, and thus provides an additional dimension to data by simultaneously considering indices of both similarities and differences across all grouping/experimental variables. If young and older adults engage many similar brain regions differentiating the two task conditions, task PLS analysis reveals an age-common network. Alternatively and/or in addition, if some brain regions exhibit age-differential activation between conditions, PLS analysis reveals group-specific networks. Another way in which interference resolution might be compromised in aging is that regions supporting interference resolution may remain relatively similar, although the functional connectivity within the network is altered. On this view, less proficient interference resolution in elderly people may be related to less efficient recruitment of the network promoting interference resolution in the young. Specifically, interference resolution might be compromised in older adults due to less efficient interaction within the anterior control network or the posterior attention network. Using seed PLS, we first examined whether functional connectivity among those network nodes reflecting the most reliable group differences varied between age groups and was modulated by performance. If younger and older adults alike engage the same network to support performance, the seed PLS should reveal a common circuitry with possible quantitative differences across age. Alternatively, if younger and older persons recruit distinct networks to support performance, the seed PLS should reveal networks differentially correlated with performance across age. This analysis allows us to verify whether the functional network supporting interference resolution in old age is similar to that recruited by the young, or constitutes a different network that may not facilitate interference resolution in younger adults. Finally, relationships between brain activity and GM volume were explored to investigate whether age-related differences in structural integrity are associated with age-related alterations in functional networks during interference resolution.

Methods

Participants

29 young (20–31 years of age, 16 females) and 29 old (65–74 years of age, 16 females) participants from Stockholm, Sweden participated. There were no significant age differences in years of education (Young: 14.7 ± 2.1; Old: 14.3 ± 3.7) or on a test of mental status (Mini Mental Status Examination, Folstein et al., 1975) (Young: 29.2 ± 0.7; Old: 28.9 ± 0.8). From the initial sample of 58 participants, four (three old, one young) were excluded due to low task performance (below chance level). Two older subjects were excluded due to not performing the task at all. Finally, one young subject was excluded due to technical error. All remaining participants (27 young and 24 old) were right-handed, native Swedish-speakers, had normal or corrected to normal vision, and had no history of neurological illness. In addition, participants neither reported nor were diagnosed with cognitive impairment (e.g. dementia, mild cognitive impairment). The ethics committee at the Karolinska Institute approved the protocol; informed consent was obtained from all participants.

fMRI activation task

The MSIT (Bush et al., 2003) consists of a total of 16 blocks of control and interference trials, alternating during the scanning session. Within each control and interference block (8 each), 12 stimuli were presented for 2 s each. Participants were given a button-press and instructed that the keypad buttons represented one, two, and three from left to right (Fig. 1A). They were informed that sets of three numbers (1 and/or 2 and/or 3) and/or the distracter number (0) would appear in the center of the screen and that one number would always be different from the other two numbers. During the control task, distracters were always the number zero, and the target number (1 or 2 or 3) was always placed congruently with its position on the button press (e.g. the number 3 always appeared at the rightmost position). In contrast, during the interference task, distracters were other numbers (1 or 2 or 3), and the target never matched its spatial position. Participants were asked to report the identity of the number that was different from the other two numbers, regardless of its position. They were also instructed to respond as accurately and quickly as possible (Fig. 1A).

Image acquisition

fMRI data were collected on a 3 T Siemens Magnetom TrioTim scanner at Huddinge Hospital, Stockholm, Sweden, with a 32-channel head coil. Scanner parameters for the gradient-echo EPI sequence were as follows: TR = 2.5 s, 39 slices (3.0 mm thick), voxel size 3 × 3 × 3 mm, FOV = 230 mm, flip angle = 90°, TE = 40 ms. Four dummy scans were collected to allow for equilibration of the fMRI signal. Stimuli