The neural bases of proactive and reactive control processes in normal aging

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Abstract

Introduction. Research on cognitive control suggests an age-related decline in proactive control abilities (anticipatory control), whereas reactive control (following conflict detection) seems to remain intact. As proactive and reactive control abilities are associated with specific brain networks, this study investigated age-related effects on the neural substrates associated with each kind of control.

Methods. In an event-related fMRI study, a modified version of the Stroop task was administered to groups of 20 young and 20 older healthy adults. Based on the theory of dual mechanisms of control, the Stroop task has been built to induce proactive or reactive control depending on task context.

Results. Behavioral results ($p < .05$) indicated faster processing of interfering items in the mostly incongruent (MI) than the mostly congruent (MC) context in both young and older participants. fMRI results showed that reactive control is associated with increased activity in left frontal areas for older participants. For proactive control, decreased activity in the bilateral anterior cingulate cortex was associated with more activity in the right middle frontal gyrus in the older than the younger group**.**

Conclusion. These observations support the hypothesis that aging affects the neural networks associated with reactive and proactive cognitive control differentially. These age-related changes are very similar to those observed in young adults with low dopamine availability, suggesting that a general mechanism (prefrontal dopamine availability) may modulate brain networks associated with various kinds of cognitive control.

Keywords: aging – inhibition – cognitive control – fMRI – Stroop Task

1. Introduction

Cognitive control refers to a set of mental processes used to adjust and flexibly guide people's behavior in changing environmental circumstances, especially in situations where distracting information or a prepotent response tendency must be ignored in order to successfully act in a goal-directed manner [1-4]. The term of "cognitive control" encompasses the psychological concepts of executive control, goal maintenance, top-down processing, response selection and response inhibition [5]. Cognitive control processes are most often investigated with shifting and interference tasks, depending on whether the researcher is interested in the effect of changing environmental demands or the presence of competing alternative actions.

Several theoretical models have been proposed to explain how the control of cognition is achieved [1, 4, 6-9]. However, most of these models focus on the nature of the influence exerted by control (e.g., favoring the most relevant motor response regarding the context), rather than how the need for cognitive control is detected and how control processes are triggered (see [1] for a full discussion). To respond to that issue, Braver et al. [4] proposed, in their dual mechanism of control (DMC) account, that flexibility in cognitive control strategies may be achieved through reactive or proactive control, depending on situational demands or individual differences (see also [10]). Proactive control is a sustained, anticipatory form of control that allow us to respond rapidly and efficiently by actively maintaining all task-relevant information in mind (e.g., task instructions, identity of previous stimuli, cues for later behavior, etc.) in situations where one is able to anticipate upcoming stimuli. Reactive control, on the other hand, will intervene in situations in which anticipating the upcoming stimuli is not the most efficient strategy or is not possible at all, and where the most efficient response is to transiently reactivate required information following the occurrence of a critical event. In sum, with regard to interference tasks, the DMC model suggests that proactive control mechanisms specializes in interference prevention and anticipation, whereas reactive control detects and resolves interference when it occurs.

Consequently, the overall task context (i.e., task demands and characteristics) represents an important factor to modulate the proportion in which proactive or reactive strategies will contribute to task performance. Although both strategies are equally likely to lead to correct performance on a specific trial, the task context will encourage the adoption of one form of control over the other in some situations [4]. For example, the use of proactive control will be encouraged in conditions allowing the anticipation of interference effects, i.e. in high interference level conditions. However, reactive control mechanisms will dominate in situations in which interference is infrequent and unexpected.

Importantly, one of the key hypotheses within the DMC account is that the two control mechanisms are clearly dissociable according to the underlying brain regions and the temporal pattern of neural activity [4, 10, 11]. Proactive control is considered to be associated with sustained activation of the lateral prefrontal cortex, which reflects the active maintenance of task goals and instructions. For reactive control, the lateral prefrontal cortex should be engaged transiently when interference is detected, reflecting the reactivation of task goals. The anterior cingulate cortex (ACC), typically associated with conflict detection and monitoring, is also expected to play a crucial role in reactive control.

Few studies have focused on the neural substrates of proactive and reactive cognitive control processes using fMRI (see however [12, 13] for ERP studies on this topic). Burgess and Braver [14] compared with fMRI brain areas related to interference in low (few interfering items) and high (many interfering items) expectancy conditions using the recent probe task, which assesses sensitivity to interference in working memory. As expected, different patterns of brain activity were associated with proactive and reactive control mechanisms based on interference expectancy. More specifically, for interfering items in the low expectancy condition, the bilateral inferior prefrontal cortex exhibited a probe-triggered increase in activity, indicating the involvement of reactive control. By contrast, activity in the left middle frontal gyrus (MFG) increased in the high expectancy condition during the delay period, prior to probe onset; this effect occurred on both interfering and non-interfering trials, which is consistent with a proactive control strategy.

In a second study, these processes were investigated using the Stroop task [15] by varying the proportion of interfering and facilitating items across the task (with proportionally few and many interfering items in the reactive and proactive control conditions respectively). Reactive control engaged a frontoparietal network including the dorsolateral prefrontal cortex (DLPFC) and ACC, associated with the presentation of interfering items. However, in contradiction to the DMC model [4], proactive control was not associated with any sustained lateral prefrontal cortex activity. Because Braver et al. [4] also proposed that dopamine availability in PFC influences proactive (but not reactive) control abilities, we recently explored the effect of catechol-O-methyltransferase (*COMT*) Val158Met polymorphism on cognitive control using the same Stroop task [16]. This time, proactive control was in fact associated with sustained brain activity but in a genetic-dependent manner: increased activity was observed in the ACC in carriers of the Met allele (those with the most dopamine available in the PFC), while increased activity was observed in the MFG in carriers of the Val allele (with little dopamine available). When looking at brain activity in the reactive control condition, the presence of Val allele(s) was mainly related to higher activity in the right operculum. These observations were interpreted as reflecting less efficient conflict detection in *COMT* Val allele carriers and difficulties maintaining task goals in proactive control situations (supporting the proposal of Braver et al. [4]), while their increased transient activity in inferior frontal areas when reactive control is implemented would reflect a less efficient cortical response in areas related to cognitive control.

Individual differences in cognitive abilities also likely influences the selection of a control strategy. More particularly, the implementation of proactive control when required will be more efficient for individuals who have substantial cognitive resources available, because this kind of cognitive control is more resource-demanding [4, 10]. Accordingly, problems with proactive control implementation associated with intact reactive control strategies have been reported several times in healthy aging, notably using the AX-CPT task [17-19]. Braver et al. [18] found an age-related impairment when the task requires contextual representations to be maintained (and updated), but a preserved ability to transiently access contextual representations in order to use reactive control.

These authors therefore concluded that aging might be associated with a specific decline in proactive control. Recently, Manard, Carabin, Jaspar, and Collette [20], using a Sternberg recency task, also showed a selective age-related decline in high-interference situations requiring proactive control, in association with preserved reactive control abilities in low-interference conditions. Moreover, it was also observed that this effect of aging on the capacity to make efficient use of the proactive control strategy is modulated by the availability of cognitive resources (as assessed by processing speed and fluid intelligence level, two general cognitive processes both known to be affected by age; e.g., [21-26]).

2. Objectives of the study

Previous research on cognitive control suggests that (1) there is a specific age-related decline in proactive control abilities (e.g., [18, 20]); (2) specific cerebral areas are involved when proactive and reactive control strategies are implemented, and activity in these regions is modulated by the COMT gene [14-16]. However, no previous study has explored the neural substrates of these two kinds of control in healthy aging. Consequently, the objective of this study is to investigate age-related effects on the neural substrates of reactive control (comparison of interfering and neutral items in the mostly congruent condition of a Stroop task) and proactive control (comparison of all items in the mostly incongruent and mostly congruent contexts) processes.

3. Methods

3.1. Ethics statement

The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. In accordance with the Declaration of Helsinki, all participants gave their written informed consent prior to their inclusion in the study.

3.2. Participants

Twenty young (12 men; M age = 23.5 years; SD = 3.2; range = 21–30) and 20 healthy older adults (8 men; M = 65.1 years; SD = 3.8; range = 61–74), with no diagnosed psychological or neurological disorders, were recruited from the university community and seniors' associations and

received financial compensation for their participation. All were native French speakers and had normal color vision. The cognitive status of the older participants was examined with the Mattis Dementia Rating Scale [27] (see Table 1). All older participants had a total score greater than 130 (range 135–144), which constitutes the cut-off for distinguishing between healthy aging and dementia [28]. The younger and older groups of participants had the same educational level (t (38) = .76; p = .44) but their vocabulary level differed on the French adaptation of the Mill Hill test [29] (t (38) = 3.92; p < .0005) (see Table 1).

[Insert Table 1]

3.3. Materials and procedure

A modified form of the Stroop task [15] with four words presented on a white background (Red, Blue, Black, and Green; written in French: *Rouge, Bleu, Noir, Vert*) was used for this experiment. The congruency proportion was manipulated using three different contexts with 12 items each: the *mostly congruent context* (MC), the *mostly incongruent context* (MI), and the *mostly neutral context* (MN). Each MI block was composed of eight interfering items (e.g., the word "red" written in blue), two facilitating items (e.g., the word "blue" in blue), and two neutral items, which were nonverbal stimuli (i.e., strings of five percent signs %%%%%) presented in one of the four color possibilities. For the MC context, the proportions of facilitating and interfering items were reversed. Finally, eight neutral, two facilitating, and two interfering items were presented in the MN context. Importantly, the first four items in each block were representative of the current task context (e.g., four interfering trials at the beginning of each MI context) and served to induce the use of proactive or reactive control processes. The presentation order of the different blocks was pseudo-randomized, and three different presentation orders were used. Each of the three congruency conditions of 12 items (MI, MC, and MN) was presented 15 times, for a total of 45 blocks and 540 items.

The participants were instructed to indicate the color in which each item was printed by pressing the corresponding keyboard buttons. They were told that the items would be presented briefly and that they would have to respond as fast and accurately as possible. Color words were

presented on a screen that the participants lying in the fMRI scanner viewed through a mirror located on the scanner's head coil. Each trial consisted of the presentation of a word at the center of the screen, with four response possibilities at the bottom of the screen (corresponding to the four color possibilities, always in the same order). Each item was presented until the participant responded (with a maximum presentation time of 2000 ms). If the participant responded before the deadline, a white screen was presented for the remaining period. If no response was provided, a white screen appeared after 2000 ms. The interstimulus interval was set at 500 ms. A fixation cross was presented at the center of the screen for 8000 ms after every two contexts to provide breaks during the experiment.

Prior to the fMRI session, participants performed a practice session outside the scanner in which 40 items were presented to ensure that they understood the task instructions. In the fMRI scanner, four more examples were presented just before the test phase began. After the session, participants received a debriefing that explained the main objective of the experiment.

3.4. Behavioral data analysis

All behavioral data analyses were conducted with a statistical level set at $p < .05$. Repeated measures analyses of variance (ANOVAs) were run on the median response times (RTs) and accuracy data (correct responses), with task context (MC, MI, and MN contexts) and item type (incongruent, congruent, and neutral items) as repeated measures factors. The first four items of each context were removed from the analysis as they did not fully reflect the cognitive control strategy applied to the context in question (i.e., in the MI context, the first items served to establish the subsequent proactive control strategy by creating expectations associated with that context, and in the MC context, the first items created a low expectation of interfering trials). We also reported partial eta squared (η_p^2) as a measure of effect size. Finally, planned comparisons were performed, also with a $p < .05$, using univariate tests of significance. Our specific predictions were : (1) a slower performance for incongruent items by comparison to congruent and neutral ones; (2) faster response times in the MI than MC and MN conditions; (3) better processing of incongruent items in the MI than MC and MN contexts; (4) with regard to the specific effect of aging on proactive and reactive control processes, we

expected a selective age-related decline in task condition requiring proactive control (MI context), in association with preserved reactive control abilities in the MC context.

3.5. *fMRI acquisition and analyses*

Functional MRI time series were acquired on *a 3T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit-receive quadrature head coil.* Structural images were obtained using a high-resolution T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence, TR = 1960 ms, TE = 4.35 ms, inversion time (TI) = 1100 ms, FoV = 230 x 173 mm^2, matrix size = 256 x 192 x 176, voxel size = 0.9 x 0.9 x 0.9 mm^3). Multislice T2*-weighted functional images were acquired with a gradient-echo echo-planar imaging sequence using axial slice orientation and covering the whole brain or most of the brain (34 slices, FoV = 192 x 192 mm^2, voxel size 3 x 3 x 3 mm^3, 25% interslice gap, matrix size 64 x 64 x 34, TR = 2040 ms, TE = 30 ms, FA = 90°). In each session, between 760 and 800 functional volumes were obtained. The first three volumes were discarded to account for T1 saturation.

Data were preprocessed and analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.5.0 (Mathworks Inc., Sherborn, MA). Images of each individual participant were first realigned (motion corrected) to their own mean. After this realignment, we spatially coregistered the mean EPI image to the anatomical MRI image and coregistration parameters were applied to the realigned BOLD time series. Individual anatomical MRIs were spatially normalized into the MNI space (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca), and the normalization parameters were subsequently applied to the individually coregistered BOLD time series, which was then smoothed using an isotropic 10-mm full-width at half-maximum (FWHM) Gaussian kernel.

For each participant, BOLD responses were modeled at each voxel, using a general linear model with events convolved with the canonical hemodynamic response function as regressors. Events were divided according to the three contexts (MI, MC, or MN) and the type of item (interfering, facilitating, or neutral). These nine regressors were modeled as event-related responses. Event

durations corresponded to the presentation of the item until the participant's response, with a maximum duration of 2 s. Incorrect trials and no responses were also modeled as separate regressors. The design matrix also included the realignment parameters to account for any residual movement-related effect. In addition, the first four items for each context were modeled separately in the design matrix. The rationale for excluding those items was that they did not fully reflect the cognitive control strategy applied to the context in question (i.e., in the MI context, the first items served to establish the subsequent proactive control strategy by creating expectations associated with that context, and in the MC context, the first items created a low expectation of interfering trials). A high pass filter was implemented using a cut-off period of 128 s in order to remove the low-frequency drifts from the time series. Linear contrasts assessed the simple main effect of each trial type. The corresponding contrast images were entered into a second-level analysis, corresponding to a random-effect model.

At the second level (random-effect analysis), we used individual contrast images to examine the brain regions related to the comparisons of interest (i.e., general interference effect across the three contexts [I–N for MC, MI and MN], interference effect in the mostly congruent context [I–N in MC], and comparison of sustained brain activity between the mostly incongruent and mostly congruent contexts [MI–MC]). Based on the description of the DMC model [4, 14], these two last measures reflect the implementation of reactive (more transient activity following presentation of incongruent items by comparison to the other kind of items in the MC condition) and proactive (more sustained activity across the MI than MC blocks) cognitive control processes. First, these individual contrasts images were used to analyze neural activity common to the two groups (global effect and conjunction analyses), inclusively masked by the same contrast in the younger and older groups. In the second step, we focused on age-related differences in the neural correlates of reactive (comparison of interfering to neutral items in the MC context; I–N in MC) and proactive (comparison of activity associated to all items in the MI and MC contexts, MI–MC) control processes. T-test comparisons between young and older participants were performed. Finally, we performed regression analyses between RTs for interfering items and contrast images associated with reactive (I–N in MC) and

proactive (MI–MC) control conditions, and compared these regressions in our two groups of participants. All the analyses were conducted with a statistical voxel level threshold at p < .001 uncorrected and cluster extent threshold at p < .05 FWE corrected. Given the a priori hypothesis regarding specific anatomical loci of interest, we also adopted a small volume correction (SVC) approach to limit the scope of our analyses. These loci were the lateral prefrontal cortex (PFC) for the sustained response related to proactive control and the lateral prefrontal and ACC for the transient responses associated with reactive control [10, 15, 16].

4. Results

4.1. Behavioral results

We conducted a repeated 3 (context) x 3 (item) ANOVA on mean RTs for correct responses with group as an independent variable. We observed a significant group effect [$F(1,38) = 7.76$; $p < .01$; $\eta_p^2 = .17$, with slower RTs in the older group than in the younger one], a main effect of item [$F(2,76) = 156.30$; $p < .0001$; $\eta_p^2 = .80$] and a significant main effect of context [$F(2,76) = 13.59$; $p < .0001$; $\eta_p^2 = .26$]. Planned comparisons showed that the item effect was characterized by slower RTs for interfering than for facilitating [$F(1,38) = 199.44$; $p < .0001$] or neutral [$F(1,38) = 161.76$; $p < .0001$] items. The context effect was characterized by faster RTs in MI than in MC [$F(1,38) = 15.42$; $p < .0005$] and MN [$F(1,38) = 21$; $p < .0001$] contexts, but similar RTs in MC and MN contexts [$F(1,38) = 1.48$; $p > .1$]. An interaction effect between context and item was also observed [$F(4,152) = 17.07$; $p < .0001$; $\eta_p^2 = .31$]. The analysis of the interaction effect showed an interference effect in all three contexts (all *p*s < .001). However, RTs for interfering trials were faster in the MI context than the MC and MN contexts (all *p*s < .001), and also in the MC than the MN context ($p < .05$). No interaction effects between context and group, item and group, or context, item and group were observed (all *ps* > .1; see Figure 1A). These results remains similar when transforming RTs to z-scores to control for baseline RT differences between groups, which would artificially create group x condition interactions [30] : we observed main group [$F(1,38) = 86.36$; $p < .0001$; $\eta_p^2 = .69$], context [$F(2,76) = 4.77$; $p < .0001$; $\eta_p^2 = .29$] and items

[$F(2,76) = 505$; $p < .0001$; $\eta_p^2 = .93$] effects, as well as a significant interaction between context and item [$F(4,152) = 17.64$; $p < .0001$; $\eta_p^2 = .32$].

As we were particularly interested in the effect of age on the implementation of proactive and reactive control processes, we also performed planned comparisons in each group to specifically test these effects: the comparison of interfering and neutral items in the MC condition for reactive control and the comparison of interfering items in the MI versus MC conditions for proactive control. Z-scores controlling for baseline RT differences between groups were again used [30]. For reactive control, slower RTs for interfering than neutral items in the MC condition were observed in both young [$F(1,38) = 62.09$, $p < .0001$] and older [$F(1,38) = 35.46$, $p < .001$] participants. With regard to the proactive control condition, the comparison of interfering items in the MI versus MC contexts showed that both younger and older participants were slower at processing interfering items in the MC context [young: [$F(1,38) = 18.9950$; $p < .0001$; older $F(1,38) = 43.97$; $p = .0001$]. Finally, we computed index reflecting interference resolution in the reactive (MC_II – MC_IN) and proactive (MI_II – MC_II) cognitive control conditions, also on the basis of z-scores to control for baseline RTs differences. As previously observed, the index of both reactive control and proactive control revealed no group differences [reactive: $F(1,38) = 0.015$, $p = .90$; $\eta_p^2 = .0001$ (young: 1.46 (0.77); older: 1.10 (0.19)); proactive: $F(1,38) = 2.26$, $p = .14$; $\eta_p^2 = .006$] (see Figure 1B). On the basis of these results, we can consider that both groups of participants were actually implementing reactive and proactive control processes as required by the task context. Consequently, we are well positioned to explore age-related changes in the neural substrates underlying these processes

[Insert Figure 1]

As for RTs, a 3 (context) x 3 (item) ANOVA on item accuracy with group as an independent variable was performed (see Table 2). We observed a main effect of item [$F(2,76) = 12.13$; $p < .0001$; $\eta_p^2 = .24$] but no significant group [$F(1,38) = 2.30$; $p = .14$; $\eta_p^2 = .06$] or context [$F(2,76) = 2.94$; $p = .06$; $\eta_p^2 = .07$] effects. Planned comparisons showed that the item effect was characterized by more errors

for interfering than for facilitating [$F(1,38) = 17.43$; $p < .0005$] or neutral [$F(1,38) = 6.37$; $p < .05$] items, and also for neutral than facilitating items [$F(1,38) = 12.27$; $p < .001$].

[Insert Table 2]

4.2. fMRI results

4.2.1. General interference effect (interfering versus neutral items in MC, MI and MN contexts): transient activity

First of all, in our group of young and older participants, we replicated the classical network of brain areas associated with the general interference effect in the Stroop task (I–N in MI, MC and MN contexts). Indeed, we observed a large map of activation centered on the bilateral inferior frontal areas (extending to the insula) and the left inferior parietal areas across all participants (see Table S1). Similarly, a conjunction analysis on our two groups of participants showed increases in cerebral activity bilaterally in the inferior frontal operculum and insula, and in the left precentral, inferior parietal and superior occipital gyri.

Group comparisons indicated a greater increase in activity for interfering items by comparison to neutral ones in the young versus older participants in the left superior temporal gyrus. A larger difference between interfering and neutral items was found for older participants than for young ones in the left inferior frontal region (pars triangularis and pars opercularis), left inferior temporal gyrus and right anterior striatum (see Table 3 and Figure 2).

[Insert Table 3 and Figure 2]

4.2.2. Effect of aging on the brain regions associated with reactive control processes (I–N in MC)

Brain areas associated with the interference effect in the MC context (I–N) in the whole sample of young and older participants were located in mainly in the left inferior frontal and parietal areas (see Table S2). A conjunction analysis on the two groups of participants showed increased brain activity for interfering items in the left pars triangularis and opercularis inferior frontal areas.

Next, we compared the transient pattern of cerebral activity for interfering items (by comparison to neutral ones) in the MC context in the young and older groups of participants (see Table

4). Group comparisons indicated a proportionally larger transient increase in brain activity from neutral to interfering items for older participants by comparison to young ones in the left inferior frontal operculum and the left lateral orbitofrontal gyrus. The reverse contrast showed no location where brain activity was greater in young than older participants (see Figure 3).

[Insert Table 4 and Figure 3]

4.2.3. Effect of aging on the brain regions associated with proactive control processes (MI–MC)

Analysis of sustained brain activity during the MI condition (by comparison to the MC condition) in the whole sample of participants showed no common foci of activity, and this was confirmed by the conjunction analysis.

Sustained brain activity for all items in the MI condition (by comparison to the MC condition) was then directly compared in the young and older groups of participants (see Table 5). The older participants showed, by comparison to the younger ones, a decrease in sustained activity in the MI context in the ACC bilaterally and in the right lateral orbitofrontal gyrus. They also showed an increased sustained activity in the right MFG (see Figure 4).

[Insert Table 5 and Figure 4]

4.2.4. Correlation analyses between RTs for interfering items and neural substrates associated with reactive and proactive cognitive control processes

The comparison of regression analyses in young and older participants showed that RTs associated with the processing of incongruent items in the reactive control condition (I–N in MC) were more strongly (negatively) associated with activity in the left orbitofrontal area in older participants. Activity in the ACC was more strongly associated with interference resolution in the proactive condition in young participants (MI–MC) (see Table 6).

[Insert Table 6]

5. Discussion

The objective of this study was to explore age-related neural changes underlying the implementation of proactive and reactive cognitive control processes using a Stroop task. Less efficient

proactive control strategies had been reported in healthy aging [18, 20] but, to the best of our knowledge, there was no information on the neural counterparts of these difficulties. As expected, older participants were as efficient as young ones in implementing reactive control in low-interference condition. Contrary to previous behavioral studies, no significant group difference was found in the implementation of proactive control. This pattern of behavioral results means that we can discuss age-related changes in the neural substrates of cognitive control with the confidence that each kind of cognitive control was implemented according to the task context (namely the presence of a low or high interference level).

From a neuroimaging viewpoint, we found that, in our whole group of participants, the classical network of frontoparietal areas associated with the general interference effect in the Stroop task was activated (e.g., [15, 31-33]). Moreover, age-related differences in patterns of brain activity were observed both for the general interference effect and for the two kinds of cognitive control processes: (1) Resolution of interference (whatever the task context) was associated with increased activity in the left superior temporal gyrus for younger participants and in the left inferior frontal and temporal areas for older adults. (2) In reactive control condition, processing of interfering items was associated with increased activity in the left inferior frontal areas for older participants. (3) The implementation of proactive control in older participants led simultaneously to greater sustained recruitment of the right MFG and decreased activity in the ACC and right lateral orbitofrontal gyrus. As a whole, these results appear particularly valuable for understanding age-related changes in cognitive control.

5.1. The neural substrates of interference resolution in normal aging

Few previous studies had investigated whether normal aging is associated with changes in brain activity when subjects must suppress irrelevant information or resolve interference. The first such studies showed that problems with interference resolution in working memory were associated with increased activity in the left lateral prefrontal areas (e.g., [34]). When only successfully inhibited items were included in the analyses, increased activity was observed in the prefrontal and parietal

areas activated by young adults, as well as in additional contralateral areas (e.g., [35, 36]). The increase in activity or the recruitment of supplementary areas has generally been interpreted as a compensatory process enabling older adults to perform at a similar level to younger ones.

Similarly, we observed increased activity in inferior frontal areas in our older participants; these areas were previously associated with inhibitory recruitment (see for example the review by Aron and colleagues [37]). It should, however, be noted that the right inferior frontal gyrus was reported by Aron et al., while we observed an age-related effect in a left-hemisphere area. We consider that this change in laterality can be explained by the material used. Tasks that are particularly dependent on verbal mechanisms, such as verbal interference tasks (e.g., Stroop), typically rely on prefrontal activation on the left side (for a meta-analysis, see [32]), while tasks involving motor inhibition (as discussed in the Aron et al. review) are mainly right-lateralized (e.g., [38]). Because greater recruitment of the left inferior frontal cortex was observed for items associated with the successful inhibition of irrelevant information in our older participants, we consider activity in this region to reflect the use of compensatory processes.

We also observed that the older group relied more on anterior striatal activity. The activation of frontostriatal loops has frequently been observed during inhibition in both normal and pathological groups [39-41]. Like activation in the left inferior frontal gyrus, greater striatal activity can also be considered as a compensatory mechanism. Indeed, Lorenz et al. [42] found that increased activity in that area was associated with better inhibition abilities during a Stop Signal task. Because striatal dopamine has previously been found to be associated with the ability to update goal representations (see [43]), our results might suggest that older adults find it more difficult than younger ones to reactivate the goal task when confronted with interfering items, independently of the level of interference induced by the task context.

Interestingly, the greater recruitment of frontostriatal loops by our older participants is associated with both increased activity in the left inferior temporal area and decreased activity in the left posterior superior temporal area. The simultaneous observation of these activity peaks suggests

that the interplay between regions responsible for control and language processes differs in younger and older people. For instance, the left posterior superior temporal area is activated in the same way for interfering and neutral items in older participants, while it is less activated (particularly for interfering items) in young participants (see beta estimates in Figure 2A). As this area was previously found to be associated with phonological processes [44, 45], this result suggests that older people may have difficulties actively inhibiting automatic access to phonological information. With regard to the inferior temporal region (previously associated with lexico-semantic access [46, 47]), brain activity for neutral items is generally similar in the two groups, while older participants experienced greater activity for interfering items, suggesting that lexico-semantic access to the words is also highly activated (see beta estimates in Figure 2B). As a whole, these results suggest that older participants find it difficult to suppress the automatic language processes (phonological and lexico-semantic) associated with the Stroop task and must recruit more control areas (here, the left inferior frontal region) to produce the correct (less automatic) response. To specifically assess this interpretation, further studies using, for example, magnetoencephalography will be necessary to identify the temporal course of the frontal and temporal areas identified here according to the status of the items (interfering versus neutral) and age group (young versus older).

5.2. Age-related changes in cognitive control

To date, few studies have examined the changes in the neural substrates associated with different cognitive control strategies during normal aging. By contrasting the activity dynamics of younger and older adults in an AX-CPT task, Paxton et al. [19] obtained results supporting the hypothesis that age-related impairments in goal maintenance abilities cause a compensatory shift in older adults from a proactive to a reactive cognitive control strategy. They identified a large region of the right DLPFC that showed a selective reduction in sustained brain activity associated with the presentation of B-cues (associated with proactive control) among older adults. With regard to transient probe-related activity specific to BX trials (associated with reactive control), older adults showed significantly enhanced activation in several lateral PFC regions including the dorsolateral and

ventrolateral prefrontal cortex and bilateral premotor and supplementary motor cortex. The authors interpreted the cue-related sustained activity as indicating that older adults had more difficulty maintaining general task goals with the need to activate additional regions to maintain global task information. Using the Stroop task, we also observed age-related changes in the neural substrates of proactive and reactive control.

5.2.1. Reactive control

In the reactive control condition (inducing a low-level of interference), we observed that older participants recruited the left inferior frontal operculum more than younger subjects for the transient processing of interfering items in comparison with neutral ones. That region is associated with inhibitory processes (for reviews, see [31, 33]) and is very close to the region we observed to be associated with interference resolution in the whole task. In a previous study using the Stroop task [15], increased brain activity in the left inferior frontal area was also observed in young participants processing interfering items in conditions inducing reactive control. Similar results were found with an interference resolution task in working memory [14]. Thus, the results observed here seem to indicate at first glance that our older participants need to recruit their inhibitory abilities, associated to the left inferior frontal gyrus, more intensively to overcome the irrelevant processing (word naming) when (infrequent) interfering items are presented. However, we did not observe increased activity in the middle frontal and parietal areas, as Grandjean et al. [15] and Burgess and Braver [14] did, in association with the implementation of reactive control processes.

A series of arguments led researchers to consider the inferior frontal gyrus to be involved in the implementation of reactive control processes, supplementing its role in interference resolution. Novick, Trueswell, and Thompson-Schill [48] proposed that the left inferior frontal gyrus is part of a network of frontal lobe subsystems that are generally responsible for detecting and resolving incompatible stimulus representations (rather than response-based conflict) in the verbal domain. More specifically, according to these authors, this area is involved in implementing the control processes necessary to resolve conflicts that arise among the distinct representational subsystems

necessary for language use (i.e., phonological, syntactic, and semantic subsystems), as is the case when resolving interference in the Stroop task. Indirect evidence for the role of the inferior frontal gyrus in reactive control also comes from studies on motor inhibition that showed involvement of the right inferior frontal gyrus when there is a need for a transient recruitment of control processes: that area is involved in detecting task-relevant salient cues [49] and in reactivating the relevant task rules that link relevant stimulus features and nondominant responses in a task-specific manner [31]. On basis of these arguments, we consider that a specific subregion of the inferior frontal gyrus (the left frontal operculum) may be involved in implementing reactive cognitive control processes, when the global level of interference is low. Consequently, we suggest that older participants have difficulties reactivating the nondominant but relevant stimulus-response mapping as opposed to the automatic but inappropriate response that must be inhibited, when (relatively infrequent) interfering items are presented. Because our analyses were performed on correct trials only, the increased activity in the inferior frontal operculum indicates that such reactivation is in fact possible, but at a higher brain cost.

5.2.2. Proactive control

In the proactive control condition, we observed, in our older participants, a decrease in sustained activity in the bilateral ACC associated with higher activity in the right MFG. Activity in cingulate areas is associated with very specific role in conflict detection and monitoring [1, 50, 51]. Otherwise, the right MFG is associated in the DMC model with active maintenance of general task goals and contextual information [4, 10]. Overall, these results indicate that successful inhibition of information in a condition characterized by a high level of interference is associated with a different trade-off between conflict monitoring and maintenance of contextual information in younger and older participants. We propose that, as older participants find it more difficult to keep conflict monitoring processes constantly and efficiently activated in situations where proactive control is implemented (i.e., resource-demanding situations [4]), they need to keep general task goals and contextual information more highly activated (in the middle frontal cortex) so they can react correctly at each presentation of an interfering item. Consequently, according to the DMC model, maintenance

of contextual task information (associated with the middle frontal cortex) is the main determinant of performance in proactive control situations in older people. An indirect argument in favor of that interpretation is the presence of a stronger association between activity in the ACC and interference resolution (measured with RTs on interfering items) in the proactive condition in young than in older participants, indicating that processes associated with the ACC have less of an impact on the performance of our older participants.

Interestingly, the observation of beta estimates (see Figure 4B) showed that the ACC is already highly activated in a sustained way in the MC context in older participants, indicating that they need to recruit many resources to deal with conflict processing even in situations where the interference level is low. Such high recruitment in a relatively easy task condition, in association with behavioral performance similar to that of younger participants, can be considered as compensatory [52]. However, this compensatory process leads to cerebral overload in more resource-demanding contexts, and thus to a decrease in brain activity and behavioral performance. There is considerable evidence that older brains engage more neural resources to accomplish cognitive tasks completed with fewer resources by younger brains; this situation was formalized by Reuter-Lorenz and Cappell [52] in the CRUNCH model. For example, in the working memory domain, Cappell, Gmeindl, and Reuter-Lorenz [53] observed age-related over-activation in the right DLPFC with lower memory loads despite equivalent performance accuracy across age groups. In contrast, with the highest memory load, older adults were significantly less accurate and showed less DLPFC activation than their younger counterparts. In our study, we observed that the low level of interference associated with the reactive control condition already induced very high activity in the ACC, so that when participants had to implement proactive control, the ACC was no longer able to manage interference resolution efficiently. Simultaneously, activity in the right middle frontal area increased in the proactive condition for older participants although it remained stable in the younger group (see beta estimates in Figure 4A). That pattern of results led us to suggest that activity in the right middle frontal area offset the depletion in the ACC by reinforcing the active maintenance of general task goals and contextual information.

5.3. The function of orbitofrontal areas in cognitive control

We observed an involvement of the lateral orbitofrontal areas in both reactive and proactive control conditions (left and right hemisphere, respectively). Moreover, activity in the left orbitofrontal region correlated more with RTs for interfering items in older than younger participants in the contrast emphasizing reactive control processes (I–N in MC). Although increased activity in the orbitofrontal cortex has sometimes been reported in fMRI studies using inhibition tasks [54, 55], this area is commonly associated with reversal learning processes – that is, when a previously learned rule has to be inhibited to respond efficiently to a new one – and with the regulation of behavioral responses in the context of changing reinforcement contingencies [56, 57]. So we can tentatively propose that, whatever the level of context-related interference, older participants find it more difficult to inhibit the rule that prevailed for the previous facilitating items (*reading the word will also lead to the correct answer*) in order to implement the rule associated with the rare interfering items (*stop reading the word or the answer will be false*).

5.4. Relationship between cognitive control, aging and prefrontal dopamine level

To summarize, the following age-related changes in the neural substrates of cognitive control were observed: (1) in the reactive control condition, a transient increase in activity for interfering items in the left inferior operculum; (2) in the proactive condition, a sustained decrease in activity in the ACC and an increase in activity in the right MFG. In a recent study that also used a Stroop task, Jaspar et al. [16] showed that the level of dopamine availability in prefrontal areas influences the patterns of brain activity associated with cognitive control in a young healthy population. Indeed, for proactive control, increased activity was observed in the ACC in people with the most prefrontal dopamine (carriers of the Met allele of the COMT gene), while increased activity was observed in the MFG in carriers of the Val allele (with less dopamine available). In reactive control, the presence of Val allele(s) was mainly related to greater brain activity in the right inferior frontal operculum.

The striking parallel between the results obtained in these two studies led us to question whether frontal dopamine level plays a major role in cognitive control in normal aging, as our older

participants showed patterns of brain activity that were generally similar to those of young Val allele carriers. Indeed, normal aging had previously been found to be associated with a depletion of dopamine function in the striatum and PFC, including reductions in dopamine concentration, receptor density and transporter availability [58]. Moreover, some authors have suggested that frontal atrophy and white matter integrity could be influenced by the COMT polymorphism (e.g., [59, 60]) and a few studies found an effect of COMT on the neural substrates of certain cognitive processes (e.g., working memory) in normal aging (e.g., [61-64]). Consequently, the observation of very similar context-related changes in the neural patterns of older adults and young adults with low dopamine availability could indicate that a more general mechanism (prefrontal dopamine availability) modulates the brain networks associated with cognitive control mechanisms. However, some very recent data [65] suggest that the age-related effects of *COMT* polymorphism on cognitive control are complex and do not exactly correspond to a magnification of the effects reported in young participants. Indeed, an age-related difference for both cognitive control conditions was evidenced only in older Met carriers, and only old Val/Val individuals showed neural over-recruitment allowing them to achieve a similar performance as young Val/Val, suggesting efficient compensatory mechanisms associated with the Val allele. As a whole, these results seem to indicate that Val allele carriers could have greater behavioral and brain plasticity to cope with the effect of aging on cognitive control.

Some recent models of cognitive aging have explicitly considered dopamine availability as a factor that can enrich or deplete neural resources (e.g., the STAC and STAC-r models proposed by Reuter-Lorenz's team [66, 67]). According to these models, a low level of prefrontal dopamine availability constitutes a neural challenge that stimulates the use of compensatory processes (here evidenced by specific changes in activity of brain areas in situations inducing high or low interference). The STAC and STAC-r models also suggest that the strategies used by the brain when faced with cognitive and behavioral challenges are very general (i.e., they will be used by young people subjected to sleep deprivation or greater task demands). Because our older participants' results are similar to those obtained in young subjects faced with the challenge of a low level of prefrontal dopamine

availability [16], we could hypothesize that the changes in brain activity in normal aging we observed when proactive or reactive control strategies have to be implemented are not specifically age-related but reflect normal responses to a challenging environment (i.e., little dopamine available [66, 67]).

5.5. Limitation of the study

Finally, it appears important to discuss some point that seems puzzling at first sight. At a behavioral level, we did not observe significant condition effects on accuracy data. Such effects were not systematically observed in fMRI data (i.e., [15]). Here, performance was high for each group and condition, confirming that our participants are able to maintain task-goal related information and that the task context effects can only expressed by a differential slowing down (see Bélanger et al. [68] for a similar interpretation in the domain of normal and pathological ageing). This also explain why we did not observe a significant age-related group difference in implementation of proactive control. However, as indicated previously, this absence of difference means that we can be confident that each kind of cognitive control was implemented according to the task context when discussing age-related changes in the neural substrates of cognitive control.

Our measure of proactive control includes list-based proportion congruent effects, which could influence performance in the sense that a previous face-off with a congruent item will influence the processing of the written information the next time that word appears (see [69-71]). As we do not have a condition with a number of critical items that are equally congruent in each list, we can't control for this confound. However, works by Bugg and colleagues [72, 73] have provided evidence against a pure item-specific proportion congruent effect, by clearly demonstrating the involvement of a list-level control mechanism minimizing the influence of word-reading processes when item specific influences were controlled for (see also Hutchison [74] for a demonstration of a list-wide congruency effect not confounded with item-specific effects). So, even if further studies are necessary to clearly disentangle these two effect, we can be relatively confident that observed effects are driven (at least in part) by list-wide control mechanisms.

To complement our results, it would have been very interesting to analyze fMRI data by separately accounting for brain activity during the preparatory period (before stimulus presentation) as measure of proactive control and for brain activity associated with post-incongruent stimulus onset as measure of reactive control. Then these could be compared across MC, MN, and MI lists to disentangle brain areas associated with reactive and proactive cognitive control processes (for a presentation of the method, see [11]). Unfortunately, as the interstimulus interval was inferior to 3 seconds in our experimental design, valid measures of brain activity during the preparatory period were not possible, and the overlap in BOLD response for preparatory and post-stimulus period was too large to allow informative statistical inferences. We nevertheless consider that these alternative measures of proactive and reactive cognitive control will help to a better understanding of age-related changes in the neural substrates of these processes.

6. Conclusion

In this study, we explored the age-related neural changes associated with the implementation of reactive and proactive cognitive control processes. In the reactive control condition, we observed increased activity in the right inferior frontal operculum, which we interpreted as a successful compensatory process in an inhibition-related area. In proactive control situations, we observed changes in the balance between areas involved in conflict detection (decreased activity in the ACC) and maintenance of task goals or contextual information (increased activity in the middle frontal cortex) to attempt to deal with the high level of interference. Moreover, these age-related changes in neural patterns are very similar to the changes observed in young adults with low dopamine availability. On this basis, we proposed that a general mechanism (prefrontal dopamine availability) may modulate the brain networks associated with various kinds of cognitive control, and that changes in brain activity associated with normal aging reflect normal responses to a challenging environment (see also [65, 66]). Future studies are needed to confirm and/or refine this proposal, for example by

comparing groups of older participants with different levels of available dopamine (using genetic variants or direct measures of dopamine concentration).

Acknowledgments

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Figure 1

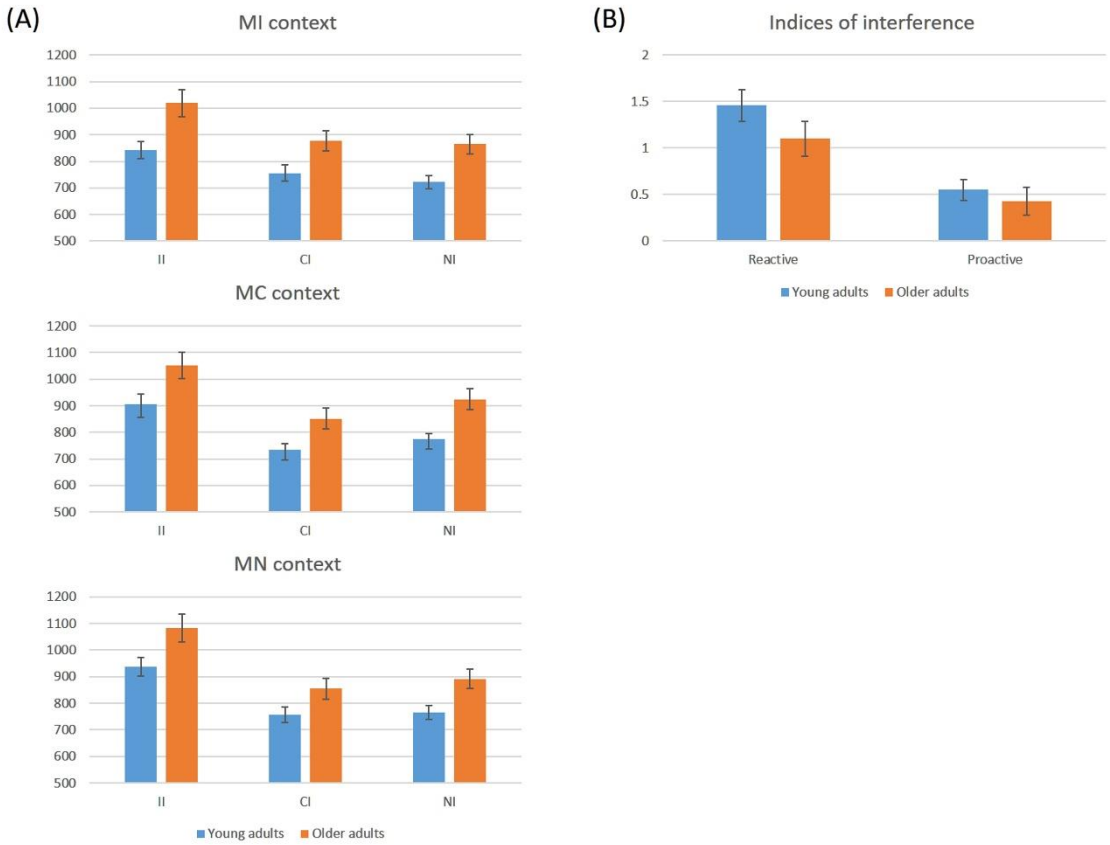

Figure 1. Behavioral results. **(A)** Response times (ms) in the proactive (top), reactive (middle) and neutral (bottom) contexts. II = interferent items; CI = congruent items; NI = neutral items. Main effects of group, item and context; item * context Interaction: MI_II < MC_II and MN_II. **(B)**. Indices of interference in the reactive and proactive conditions (Z-scores controlling for baseline RT differences between groups). Reactive interference index: (MC_II – MC_IN) ; Proactive interference index: (MI_II – MC_II). Bars represent standard errors.

Figure 2

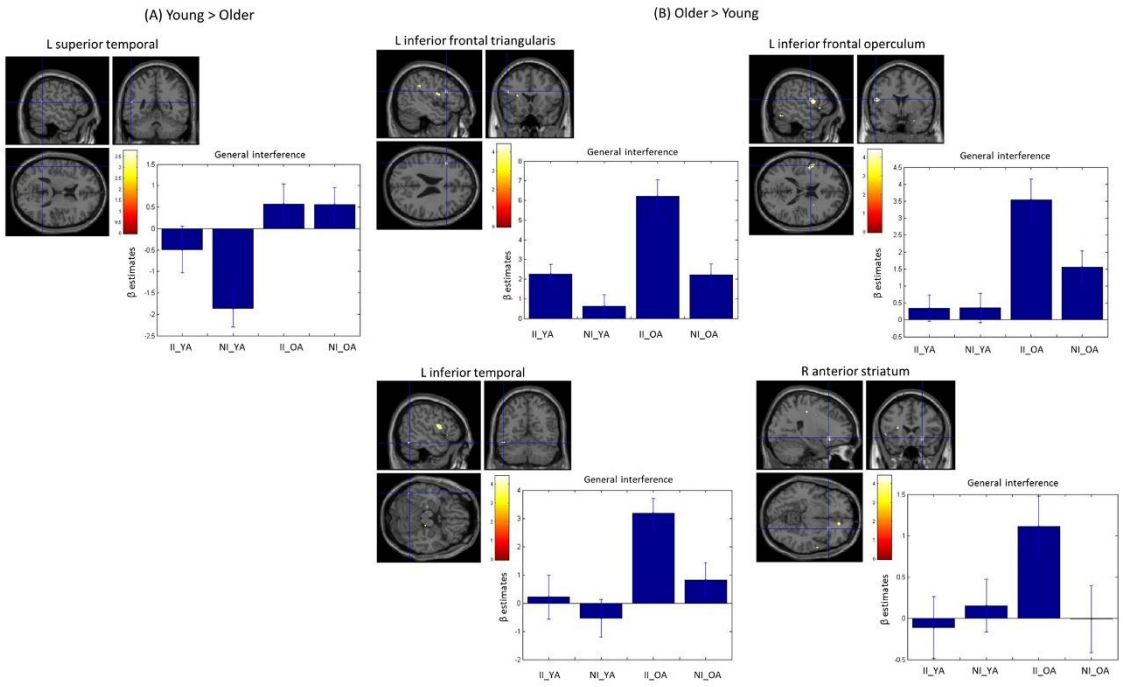

Figure 2. Brain areas associated with the general interference effect (I–N in MC, MI and MN contexts). **(A)** Brain areas showing increased brain activity in young by comparison to older participants; **(B)** Brain areas showing increased brain activity in older by comparison to young participants. The regions are displayed on the MNI template. See Table 3 for coordinates. II_YA: beta estimates for interfering items in young adults; NI_YA: beta estimates for neutral items in young adults; II-OA: beta estimates for interfering items in older adults; NI_OA: beta estimates for neutral items in young adults.

Figure 3

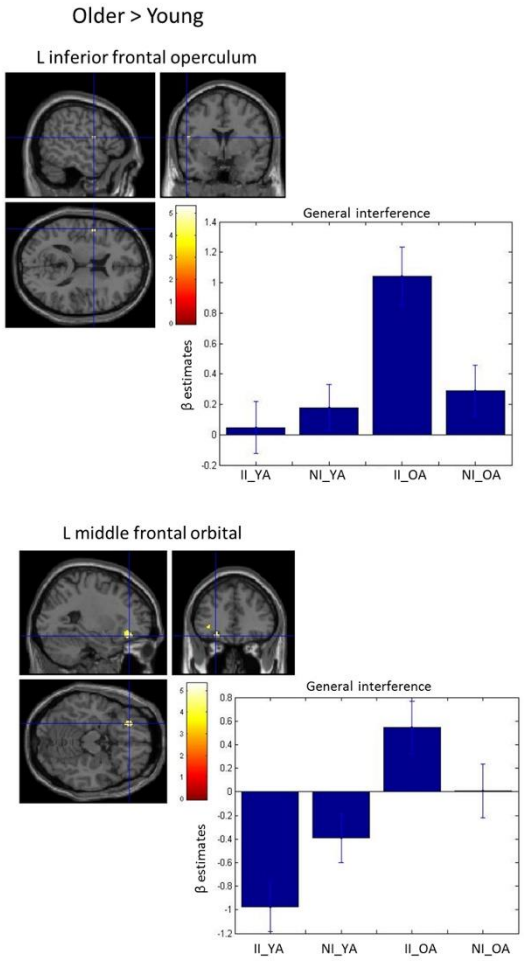

Figure 3. Changes in brain activity between young and older participants in the reactive control condition. Brain areas more active in older than younger participants. The regions are displayed on the MNI template. See Table 4 for coordinates. II_YA: beta estimates for interfering items in young adults, NI_YA: beta estimates for neutral items in young adults; II-OA: beta estimates for interfering items in old adults; NI_OA: beta estimates for neutral items in young adults.

Figure 4

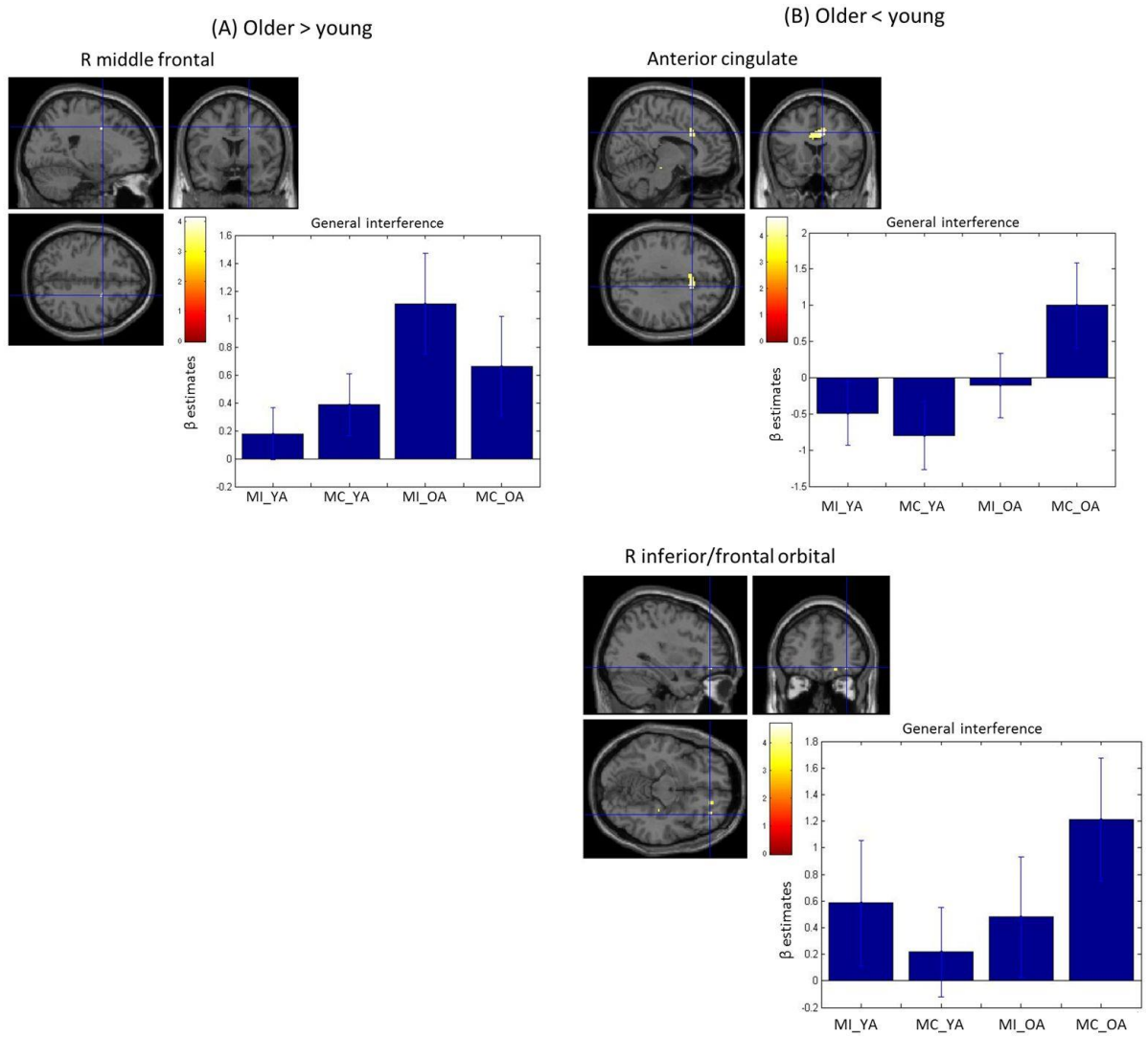

Figure 4. Changes in brain activity between young and older participants in the proactive control condition. **(A)** Brain areas more active in older than younger participants; **(B)** brain areas more active in younger than older participants. The regions are displayed on the MNI template. See Table 5 for coordinates. MI_YA: beta estimates for all items in the MI condition in young adults; MC_YA: beta estimates for all items in the MC condition in young adults; MI_OA: beta estimates for all items in the MI condition in older adults; MC_OA: beta estimates for all items in the MC condition in older adults.

Table 1. Demographic variables. Mean (standard deviation) age and intelligence level (Raven's advanced progressive matrices test); number of males and females in each group.

	Young (N = 20)	**Older (N = 20)**	**t(38)**
Age (years)	23.5 (3.22)	65.1 (3.8)	
Gender (M/F)	12/8	8/12	
Education (years)	14.80 (1.82)	15.45 (3.3)	0.76
Mill-Hill	25.50 (3.59)	29.45 (2.72)	3.92*
Mattis	/	142.54 (2.65)	

Table 2. Accuracy performance [Percentage], response times (mean) and index of interference of young and older participants on the different conditions of the Stroop task. Standard errors are in brackets

	Young adults			Older adults		
	MI	**MC**	**MN**	**MI**	**MC**	**MN**
			Accuracy			
I items	95.42 (1.23)	98.67 (0.80)	96.67 (1.06)	93.67 (1.23)	95 (1.40)	94.17 (1.39)
C items	96.17 (1.40)	98.58 (0.85)	97.83 (0.93)	96.17 (0.80)	97.33 (0.85)	96 (0.86)
N items	95.67 (1.39)	98.67 (0.85)	97.58 (0.97)	95.33 (1.05)	96.17 (0.93)	95.42 (0.97)
			Response times			
I items	841 (43)	905 (44)	937 (44)	1019 (43)	1052 (44)	1083 (44)
C items	756 (34)	733 (32)	757 (35)	877 (34)	852 (32)	855 (35)
N items	722 (32)	774 (31)	765 (31)	865 (32)	925 (31)	891 (32)
			Index			
Reactive		1.46 (0.17)			1.10 (0.19)	
Proactive		0.55 (0.11)			0.43 (0.11	

MI = mostly incongruent condition; MC = mostly congruent condition; MN = mostly neutral condition. I items = incongruent items; C items = congruent items; N items = neutral items.

Table 3: General interference effect – group comparisons. Local maxima of brain areas showing more activity for the interfering than neutral items in the MI, MC and MN contexts at a voxel p value < .001 uncorrected [I–N in MI, MC and MN].

Hemisphere	Anatomical region	MNI coordinates			Z score	P value
		x	y	z		
Younger > older participants						
L	Posterior superior temporal	–52	–48	14	3.44	.029*§
Older > younger participants						
L	Inferior frontal triangularis	–46	18	24	3.45	.029*§
L	Inferior frontal operculum	–52	2	18	3.83	.001
		–54	10	14	3.62	.001
L	Inferior temporal	–50	–58	–18	3.68	.015*§
R	Anterior striatum	24	22	–8	3.95	.006*§

L/R = left/right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). Cluster size min = 139; *p < .05 corrected; §with SVC (10 mm) from Grandjean et al. (2012)

Table 4. Transient brain activity during reactive control – group differences (I–N in MC context).
Local maxima of brain regions showing more activity for interfering than neutral items in the mostly congruent condition [I–N in MC] at a voxel p value < .001 uncorrected.

Hemisphere	Anatomical region	MNI coordinates			Z score	P value
		x	y	z		
Younger > older participants						
	Nil					
Older > younger participants						
L	Inferior frontal operculum	–52	2	14	3.51	.024*[†]
L	Lateral orbitofrontal	–26	36	–16	4.58	.001
		–20	26	–12	3.69	.001

L/R = left/right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). Cluster size min = 141; *p < .05 corrected; [§]with SVC (10 mm) from Grandjean et al. (2012); [†]with SVC (10 mm) from Jaspar et al. (2014), vv > vm and mm

Table 5. Sustained brain activity during proactive control – Group differences. Local maxima of brain regions showing more activation for interfering, facilitating and neutral items in the mostly incongruent condition than in the mostly congruent condition [MI–MC] at a voxel p value < .001 uncorrected.

Hemisphere	Anatomical region	MNI coordinates			Z score	P value
		x	y	z		
Younger > older participants						
R	Anterior cingulate	10	18	32	4.13	.001
L		–4	16	28	4.09	.001
R	Lateral orbitofrontal gyrus	34	42	–12	3.33	.035*†
Older > younger participants						
R	Middle frontal gyrus	22	6	40	3.73	.011*†

L/R = left/right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). Cluster size min = 160; *p < .05 corrected; †with SVC (10 mm) from Jaspar et al. (2014), vv > vm and mm for older and MM and VM > VV for young (note that the regions were left-sided in Jaspar et al., 2014)

Table 6. Correlation between RTs for interfering items and (A) transient patterns of brain activation in the MC context and (B) sustained patterns of brain activation in the MI context.

Hemisphere	Anatomical region	MNI coordinates			Z score	P value
		x	y	z		
(A) Processing of interfering items in the MC context (reactive control; I–N in MC contrast)						
Regression older > younger participants						
L	Middle frontal orbital	–26	36	–16	4.95	.05*
Regression younger > older participants						
	Nil					
(B) Processing of interfering items in the MI context (proactive control; MI–MC contrast)						
MI I: Regression older > younger participants						
	Nil					
MI I: Regression younger > older participants						
R	Anterior cingulate	8	20	30	4.05	.001
L		–4	18	28	3.76	.001

L/R = left/right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). (A) cluster size min = 141, (B) cluster size min = 160. *p < .05 corrected

Table S1: General interference effect in the whole sample of participants. Local maxima of brain areas showing more activity for interfering than neutral items in the MI, MC and MN contexts [I–N in MI, MC and MN] at a voxel p value < .001 uncorrected.

Hemisphere	Anatomical region	MNI coordinates			Z score	P value
		x	y	z		
(A) All subjects						
L	Inferior frontal triangularis and operculum	–44	18	26	6.64	.0001*
		–36	10	22	6.45	.0001*
		–38	44	6	5.22	.008*
L	Insula	–34	24	–2	6.41	.0001*
R	Insula	42	14	–6	6.25	.0001*
		32	22	6	4.96	.025*
L	Precentral	–38	–2	34	4.88	.035*
L	Inferior parietal	–32	–56	56	5.79	.0001*
		–42	–30	38	5.19	.009*
		–40	–40	34	5.00	.021*
R	Inferior parietal	48	–40	44	5.24	.023*
L	Superior parietal	–22	–68	52	5.22	.008*
		–46	–46	50	4.98	.001*
		–50	–38	42	5.60	.001*
L	Precuneus	–12	–68	48	5.17	.010*
L	Middle temporal	–58	–54	10	4.81	.047*
L	Inferior temporal	–48	–56	–16	5.71	.001*
L	Superior occipital	–26	–70	34	5.10	.014*
L	Inferior occipital	–44	–80	–10	5.74	.001*
R	Calcarine	14	–72	8	5.22	.007*
(B) Conjunction on younger and older groups, with inclusive mask at p < .001						
L	Inferior frontal operculum	–46	8	26	4.48	.001*
		–42	18	28	4.11	.001*
		–54	12	0	4.24	.001
R	Inferior frontal operculum	58	18	0	3.52	.001
L	Insula	–34	24	–2	5.03	.018*
R		42	14	–6	4.84	.041*
		60	20	14	3.19	.001
L	Precentral	–50	2	38	3.89	.001
L	Inferior parietal	–32	–56	46	4.48	.001
		–48	–38	46	3.73	.001
L	Superior occipital	–26	–70	34	3.70	.001

L/R = left/right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). Cluster size min = 139; *p < .05 corrected

Table S2. Transient brain activity during reactive control in the whole sample of participants. Local maxima of brain regions showing more activation for interfering than neutral items in the mostly congruent condition [I–N in MC] at a voxel p value < .001 uncorrected.

Hemisphere	Anatomical region	MNI coordinates			Z score	P value
		x	y	z		
(A) All subjects						
L	Inferior frontal operculum	–44	6	26	4.82	.05*
L	Inferior frontal triangularis	–42	20	22	4.72	.001
		–38	24	16	4.63	.001
R	Insula	38	18	–10	3.88	.001
L	Postcentral	–40	–32	48	4.02	.001
L	Superior parietal	–18	–56	58	3.99	.001
		–20	–68	52	3.86	.001
L	Inferior parietal	–40	–40	50	4.01	.001
L		–52	–34	46	4.32	.001
L	Precuneus	–8	–58	62	3.82	.001
R	Superior temporal pole	52	16	–10	3.94	.001
(B) Conjunction analysis on younger and older groups, with inclusive mask at p < .001						
L	Inferior frontal triangularis	–38	22	–2	3.21	.001†
L	Inferior frontal operculum	–44	6	26	3.62	.05*

L/R = left/right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). Cluster size min = 141; *p < .05 corrected; † with SVC (10 mm) from Jaspar et al. (2014), vv > vm and mm