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# The effect of aging on fronto-striatal reactive and proactive inhibitory control

Iris Kleerekooper [a,1], Sanne J.H. van Rooij [b], Wery P.M. van den Wildenberg [c], Max de Leeuw [a], Rene S. Kahn [a], Matthijs Vink [a,d,*]

[a] Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Center Utrecht, Utrecht,The Netherlands
[b] Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine,Atlanta, GA, USA
[c] Amsterdam Brain and Cognition, Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands
[d] Departments of Experimental and Developmental Psychology, Faculty of Social Sciences, Utrecht University, Utrecht, The Netherlands

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ABSTRACT

Inhibitory control, like most cognitive processes, is subject to an age-related decline. The effect of age on neurofunctional inhibition processing remains uncertain, with age-related increases as well as decreases in activation being reported. This is possibly because reactive (i.e., outright stopping) and proactive inhibition (i.e., anticipation of stopping) have not been evaluated separately. Here, we investigate the effects of aging on reactive as well as proactive inhibition, using functional MRI in 73 healthy subjects aged 30–70 years.
We found reactive inhibition to slow down with advancing age, which was paralleled by increased activation in the motor cortex. Behaviorally, older adults did not exercise increased proactive inhibition strategies compared to younger adults. However, the pattern of activation in the right inferior frontal gyrus (rIFG) showed a clear age-effect on proactive inhibition: rather than flexibly engaging the rIFG in response to varying stop-signal probabilities, older subjects showed an overall hyperactivation. Whole-brain analyses revealed similar hyperactivations in various other frontal and parietal brain regions. These results are in line with the neural compensation hypothesis of aging: processing becomes less flexible and efficient with advancing age, which is compensated for by overall enhanced activation. Moreover, by disentangling reactive and proactive inhibition, we can show for the first time that the age-related increase in activation during inhibition that is reported generally by prior studies may be the result of compensation for reduced neural flexibility related to proactive control strategies.



## Introduction

Inhibitory control refers to the ability to suppress inappropriate impulses, a crucial proficiency in everyday life (Dempster and Brainerd, 1995; Lustig et al., 2007). Like most cognitive processes, inhibition performance over the life-span is typically represented by an inverted U-shape (Williams et al., 1999). During senescence, inhibitory control deteriorates with age, as illustrated by a decline in stopping accuracy and a slowing of the inhibitory process (Clapp et al., 2011; Bedard et al., 2002; Kramer et al., 1994; Coxon et al., 2014; Andrés et al., 2008; Healey et al., 2008; Hu et al., 2012). Although prior studies have focused on outright stopping, it has been suggested that inhibitory control can be divided into reactive and proactive inhibition (Vink et al., 2005).

Reactive inhibition describes the process of stopping a prepotent motor impulse in response to an external stop-signal. In healthy adults, this outright stopping depends upon suppression of the primary motor cortex (Aron and Poldrack, 2006; Coxon et al., 2006; Li et al., 2008; Robbins, 2007; van den Wildenberg et al., 2010; Vink et al., 2005; Zandbelt and Vink, 2010; Zandbelt et al., 2008), which is modulated by input from the right inferior frontal gyrus (rIFG), bilateral striatum, and the supplementary motor area (SMA) (Aron, 2011; Zandbelt et al., 2013a,b; Zandbelt and Vink, 2010; Vink et al. 2015b; Vink et al. 2014).

The second process, proactive inhibition, describes motor restraint in response to contextual cues indicating increased stop-signal probability. Specifically, healthy adults slow down their responses when expecting a stop-signal, hereby increasing chances of successful stopping when required (Chikazoe et al., 2009; Jahfari et al., 2010; Logan and Burkell, 1986; Verbruggen and Logan, 2008; Vink et al., 2005; Zandbelt and Vink, 2010; Zandbelt et al., 2011, Vink et al., 2014; Vink et al. 2015b). In the brain, the fronto-striatal system is believed to process cues indicating the probability of a stop-signal occurring (Aron, 2011; Chikazoe et al., 2009; Jahfari et al., 2010; Vink et al., 2005; Zandbelt and Vink, 2010; Zandbelt et al., 2011; Zandbelt et al., 2013a,

* Corresponding author at: Departments of Experimental and Developmental Psychology, Utrecht University, Room H.0.39, Heidelberglaan 1, NL-3584 CS Utrecht, The Netherlands.
*E-mail address:* m.vink2@uu.nl (M. Vink).
[1] medical student participating in the Honours program of the Faculty of Medicine, UMC Utrecht.

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b; Vink et al., 2015b; Van Belle et al., 2014). Specifically, activation in the rIFG, SMA, and right striatum increases as a function of stop-signal probability, illustrating their important role in contextual cue processing (Zandbelt and Vink, 2010; Vink et al., 2015b; Van Rooij et al., 2014).

Studies investigating the effects of aging on inhibitory control have focused almost exclusively on reactive inhibition and yielded inconsistent results. Studies using go/no-go and Simon tasks generally report increased activation in core inhibition areas such as the rIFG and striatum in older relative to younger subjects (Heilbronner and Münte, 2013; Langenecker and Nielson, 2003; Nielson et al., 2002; Hong et al., 2014; Sebastian et al., 2013). In contrast, Sebastian et al. (2013) as well as Coxon et al. (2014) report age-related decreases of rIFG and SMA activation, when using more demanding stop-signal tasks. This may be in line with neural activation generally decreasing in concordance with performance when task demand exceeds compensatory abilities (Reuter-Lorenz and Cappell, 2008). Furthermore, the recently revised Scaffolding Theory of Aging and Cognition (STAC-r; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2014) states that older adults compensate for neural challenges that arise with aging by engaging supplementary neural circuits to preserve cognitive function. This can result in greater or additional activation of frontal or parietal brain regions, but also in bilateral recruitment, where younger adults show lateralized recruitment. Although tasks used in these studies focused on reactive inhibition, they likely evoked proactive inhibition as well. However, since reactive and proactive components were not disentangled, the reported age-related changes in inhibitory processing could reflect changes in both reactive and proactive inhibition. Regarding age-related changes in proactive inhibition, one study identified an increase in behavioral proactive inhibition, with elderly subjects responding more cautiously than their younger counterparts (Van de Laar et al., 2011). However, there are no studies reporting on age-related neurofunctional changes related to proactive inhibition. This information is particularly relevant in order to specify the neural correlates of reactive and proactive inhibition in relation to the observed age-related decline in inhibition proficiency.

Here, we investigate the effect of aging on fronto-striatal brain activation and performance during both reactive and proactive inhibition in a cross-sectional cohort of 73 healthy subjects aged 30–70 years. We obtained functional MRI data while participants performed the stop-signal anticipation task (SSAT) (Zandbelt and Vink, 2010). We investigated age-related changes on performance and fronto-striatal activation using regression analyses with age as a continuous factor. We used predefined regions of interest (ROI) that have been shown to be involved in inhibitory processing in prior research using a similar research paradigm (Zandbelt and Vink, 2010; Chikazoe et al., 2009; Jahfari et al., 2010; Li et al., 2008; Robbins, 2007; Vink et al., 2005), being the rIFG, the striatum and the SMA.

### *Hypotheses*

#### *Basic task execution*

Existing literature consistently reports a slowing of response speeds with increasing age (Williams et al., 1999; Bedard et al., 2002; Kramer et al., 1994). However, since our task requires timed rather than speeded responses, an age-related increase in response speed variability seems more likely than a general slowing. We do not expect activation in the primary motor cortex during basic task processing to be affected by age.

#### *Reactive inhibition*

We expect to find no age-related changes in stopping accuracy, as task difficulty is adjusted based on individual performance. We hypothesize that we will replicate the well-documented age-related slowing of inhibitory latencies (Williams et al., 1999; Bedard et al., 2002; Kramer et al., 1994; May and Hasher, 1998). We expect this slowing to be paralleled in the brain by an age-related increase in motor cortex activation. In line with the neural hypothesis of aging and the STAC-r model, we expect neural activation to be increased in older relative to younger adults. However, given the inconsistency of prior results relating the age-related changes in neurofunctional processing in the fronto-striatal system and the possible confounding of proactive inhibition, it is difficult to predict whether this hyper-activation will be more pronounced in reactive or proactive inhibition.

#### *Proactive inhibition*

We investigate proactive inhibition by measuring the effect of stop-signal probability on response latencies and fronto-striatal brain activation. Based on prior data, we expect an age-related increase in behavioral proactive inhibition (Van de Laar et al., 2011). Given that the older human brain is generally found to be less flexible and efficient (Eppinger et al., 2011; Vink et al. 2015a), we hypothesize that brain activation in older subjects is less related to contextual cues indicating stop-signal probability. This may be paralleled by an overall increase in activation levels, consistent with the hypothesis of neural compensation in aging and STAC-r (Reuter-Lorenz and Cappell, 2008; Grady, 2012; Reuter-Lorenz and Park, 2014; Sebastian et al., 2013).

## Materials and methods

### *Participants*

Seventy-three healthy participants aged 30–70 years (mean age: 49.2 y, SD: 10.68 y, 36 males) were included in the study. All subjects were right-handed, not colorblind, did not report a history of neurological or psychiatric illness, did not have a first-degree family member with a psychotic disorder, and did not use medication. None of the subjects reported alcoholism or recreational drug use.

The study protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht and all participants gave written informed consent after having received complete information on the study procedure. Subjects received a fixed monetary compensation after participation.

### *Stop-signal anticipation task*

Subjects performed the stop-signal anticipation task (Zandbelt and Vink, 2010; van Rooij et al., 2014; Vink et al., 2014), a modified version of the stop-signal task (Logan and Cowan, 1984) that allows separate evaluation of proactive and reactive inhibition. The task specifics are identical to those explained in detail earlier (Zandbelt and Vink, 2010). A brief description and visualization of the task are presented in Fig. 1. In the SSAT, three horizontal lines were displayed throughout the task and a moving bar had to be stopped at the middle colored line by pressing a button (go trial). In a minority of the trials, the bar stopped on its own before the middle colored line and the participant had to withhold their response (stop signal). This is taken as a measure of response inhibition. The time at which the bar stopped (i.e. stop-signal delay) was adapted dynamically in steps of 25 ms depending on stopping success and for each stop-signal probability separately. The color of the middle line indicated the probability that the bar stopped moving on its own: green 0%, yellow 17%, amber 20%, orange 25%, and red 33% (stop-signal probability; contextual cues). Subjects typically slow down their responses when they anticipate that the bar will stop (Zandbelt & Vink, 2010). This slowing is taken as a measure of proactive inhibition and contextual cue processing. The task lasted for 16 min and 36 s. A total of 234 go trials with stop-signal probability of 0%, 180 go trials with stop-signal probability >0%, and 60 stop trials were presented during the task. Each trial lasted 1000 ms with an intertrial interval of 1000 ms.

Prior to scanning, subjects were trained extensively on the task in a standardized setting to ensure that the task was well understood. In brief, during this practice session, subjects were first presented with 30 trials with a 0% stop-signal probability (green target cue), and

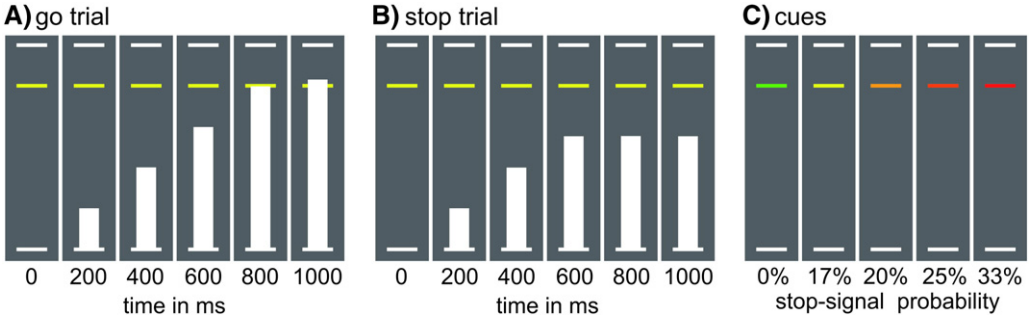


**Fig. 1.** Stop-signal anticipation task. Three horizontal lines formed the background displayed continuously during the task. A: In each trial, a bar moved at constant speed from the bottom up, reaching the middle line in 800 ms. The main task was to stop the bar as close to the middle line as possible by pressing a button with the right thumb. In other words, the target response time was 800 ms. These trials are referred to as go trials. B: In a minority of trials, the bar stopped moving automatically before reaching the middle line (i.e., the stop-signal), indicating that a response had to be withheld. These trials are referred to as stop trials. C: The probability that a stop-signal would occur was manipulated across trials and was indicated by the color of the target response line. There were five stop-signal probability levels: 0% (green), 17% (yellow), 20% (amber), 25% (orange), and 33% (red).

subjects were told that they had to respond on each trial. This way, subjects could familiarize themselves with the general task procedure. Next, 30 trials were presented with a yellow cue (17% stop-signal probability), and subjects were told that in some trials, the bar would stop moving. The purpose of this setup was to practice stopping. Then, all cues were presented (green to red) and subjects were asked to explain their meaning to the experimenter. All subjects were able to properly indicate the meaning of the cues. After a final standardized instruction on the task, the complete task (different sequence from the scanner sequence) was practiced in the presence of the experimenter.

*fMRI data acquisition*

The experiment was performed on a Philips Achieva 3.0 T MRI scanner at the UMCU. We collected 622 whole-brain, T2*-weighted echo planar images with blood oxygen-dependent contrast [repetition time 1600 ms, echo time 23.5 ms, flip angle 72.5, 4 mm 3 4 mm inplane resolution, 4 mm slice thickness, 30 slices per volume, SENSE factor, 2.4 (anterior–posterior)] in a single run, and a T1-weighted image for within-subject registration purposes [for details, see Zandbelt and Vink, 2010].

## Data analysis

*Behavioral data*

Basic response execution was measured by the response latency and variability (standard deviation) of correct responses on go trials with a 0% stop-signal probability.

Reactive inhibition was measured by the latency (SSRT) and accuracy of stopping on stop trials. SSRT was computed according to the integration method (Verbruggen and Logan, 2008) and calculated across all stop-signal probability levels. In line with the race-model paradigm (Logan and Cowan, 1984), the SSRT reflects the speed of the inhibitory process; with shorter SSRTs indicating a more proficient inhibition.

Proactive inhibition is the anticipation of inhibition based on contextual cues. It is measured as the effect of stop-signal probability on response time on go trials. Specifically, we calculated the slope at which reaction times slowed down as a function of stop-signal probability (17–33%). Adult subjects typically slow down their responses as stop-signal probability increases (Vink et al., 2005). For all measures, the effect of age was estimated using a regression analysis with age as a continuous regressor.

*Activation*

Image data were analyzed using SPM 5 (http://www.fil.ion.ucl.ac.uk/spm5). Methods of preprocessing and first-level statistical analysis were identical to those described by Zandbelt and Vink (2010). In short, preprocessing involved correction for slice timing differences, realignment to correct for head motion, spatial normalization, and spatial smoothing to accommodate interindividual differences in neuroanatomy. The fMRI data were modeled voxelwise using a general linear model, in which the following events were included as regressors: successful stop trials, failed stop trials, and go trials with stop-signal probability >0% (i.e., 17, 20, 25, and 33%). Rest blocks were also modeled so that go trials with a 0% stop-signal probability served as baseline. For go trials with a stop-signal probability >0%, we also included two parametric regressors modeling response time and stop-signal probability level. The response time regressor was included to control for variation in response speed independent from stop-signal probability effects. The stop-signal probability regressor modeled brain activation related to changes in the level of stop-signal probability. That is, lower values for go-trials with a low stop-signal probability, and higher values for go trials with a higher stop-signal probability. The realignment parameters were included to account for residual effects of head motion during scanning. A high-pass filter was included to correct for low-frequency drifts. For each participant, we computed five contrast images: (1) activation during go trials with a 0% stop-signal probability versus rest (to assess potential baseline differences in motor cortex processing), (2) activation during successful stop trials versus failed stop trials (to assess reactive inhibition), (3) activation during successful stop trials versus go trials in the 0% stop-signal probability context (also to assess reactive inhibition), (4) the effect of stop-signal probability on go trial activation (to assess proactive inhibition), and (5) the activation during go trials with a stop-signal probability >0% versus go trials with a 0% stop-signal probability (to assess proactive inhibition). We computed two contrasts for reactive inhibition because there is no consensus on which contrast is most appropriate for investigating reactive inhibition, and these contrasts may provide complementary information. Next, we examined the effect of age on brain activation in predefined ROI. ROIs were defined using data from a previous experiment [for details, see Zandbelt and Vink, 2010], in which a sample of 24 healthy volunteers performed the same task. These ROIs were defined using a cluster-level threshold (cluster-defining threshold $p < 0.001$, cluster probability of $p < 0.05$, family-wise error corrected for multiple comparisons) and include the right striatum, the SMA, the rIFG, and the motor cortex [for details, see Zandbelt and Vink, 2010]. From these ROIs, we extracted for each participant the mean activation level (i.e., parameter estimate) for the five contrasts of interest. Mean activation levels of all ROIs were analyzed using a regression analysis with age as predictor. Finally, to investigate potential age-related effects in regions outside the predefined ROI, whole-brain analyses with age as covariate were performed. Maps resulting from this analysis were tested for significance using cluster-level inference (cluster-defining threshold, $p < 0.001$, cluster probability of $p < 0.05$, family-wise error

corrected for multiple comparisons). These parameters were determined using SPM and a script (CorrClusTh.m, http://www2.warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/scripts/spm), which uses estimated smoothness (estimated full width at half maximum: 3.56 3 3.65 3 3.46 voxels) and random field theory to find these corrected thresholds.

## Results

### *Basic task execution*

#### *Performance*

Basic task execution data are presented in Fig. 2. Response latency on baseline go trials with a 0% stop-signal probability tended to increase with age but not significantly [$F(1,72) = 2.80$; $r = 0.19$; $p = 0.099$]. The effect of aging on baseline response speed may have been attenuated by the fact that our task requires timed rather than speeded responses. We did identify an age-related increase in reaction time variability on go trials with a 0% stop-signal probability [$F(1,72) = 29.61$; $r = 0.54$; $p < 0.001$], indicating that older subjects were less consistent in timing their responses. Responses on baseline go trials were given in time in about 97% of the trials for all subjects and there was no effect of age ($F(1,72) = 1.11$, $p = 0.296$).

#### *Activation*

Activation in the primary motor cortex during basic task processing (go trials with a 0% stop-signal probability versus rest) did not to differ across age [$F(1,72) = 0.16$; $r = -0.05$; $p = 0.694$].

### Reactive inhibition

#### *Performance*

Behavioral reactive inhibition data are presented in Fig. 3. We found reactive inhibition latencies (as expressed by the stop-signal reaction time, SSRT) to increase with advancing age [$F(1,72) = 10.79$; $r = 0.36$; $p = 0.002$], reflecting a slowing of inhibitory processing. Stopping accuracy was not affected by age [$F(1,72) = 0.9103$; $r = -0.11$; $p = 0.343$]. This indicates that the dynamic adaptation of stop-signal delay based on individual stopping performance was successful (see Materials and methods).

#### *Activation*

An age-related increase of motor cortex activation ($F(1,72) = 3.98$; $r = 0.23$; $p = 0.050$) was observed when contrasting successfully stopped versus failed stop trials, suggesting less efficient suppression of the motor cortex during reactive inhibition in older subjects. Analyses of successful stop versus go trials with 0% stop-signal probability did not reveal age-related effects ($F(1,72) = 1.73$; $r = 0.15$; $p = 0.193$).

Activation in other predefined regions of interest was not related to age (left striatum: $F(1,72) = 0.27$; $r = 0.06$; $p = 0.605$; right striatum: $F(1,72) = 1.67$; $r = 0.15$; $p = 0.200$; rIFG: $F(1,72) = 2.07$; $r = -0.17$; $p = 0.154$; and SMA: $F(1,72) = 0.35$; $r = -0.07$; $p = 0.559$). Results of the ROI analyses are shown in Fig. 4.

Finally, we investigated potential age-related effects outside the predefined regions using a whole-brain approach, which did not yield significant results.

### Proactive inhibition

#### *Performance*

Proactive inhibition data are presented in Fig. 5. A regression analysis with age as predictor revealed that proactive inhibition, calculated as the slope of response slowing as a function of stop-signal probability, was unaffected by age [$F(1,72) = 0.71$; $r = -0.10$; $p = 0.399$]. To investigate for an overall age-related slowing on all go trials in which a stop-signal could occur, we compared reaction times on trials with a >0% stop-signal probability to baseline trials with a 0% stop-signal probability. Analysis revealed that this measure was also not related to age [$F(1,72) = 0.84$; $r = 0.11$; $p = 0.361$]. Taken together, there was no effect of age on the behavioral proactive inhibition measures.

#### *Activation*

Activation data are presented in Fig. 6. First, we investigated the parametric effect of stop-signal probability on brain activation. In healthy adults activation is generally positively related to stop-signal probability. In the rIFG, this effect of stop-signal probability on activation decreased with age ($F(1,72) = 8.27$; $r = -0.32$; $p = 0.005$), indicating that in this region contextual cue processing declines with advancing age. In contrast, the effect of stop-signal probability on activation in the striatum and SMA did not change with age (striatum: $F(1,72) = 0.63$; $r = -0.09$; $p = 0.431$; SMA: $F(1,72) = 2.59$; $r = -0.19$; $p = 0.112$). A whole-brain analysis revealed a significant cluster in the rIFG (also partly overlapping the insular region) to be negatively related to age, thereby replicating our ROI results (see Supplemental Table 1).

Second, we compared activation during go trials with a stop-signal probability >0% to activation during baseline go trials with 0% stop-signal probability. In this way, we could test for general differences in activation levels apart from parametric effects. We found a significant age-related activation increase in the rIFG [$F(1,72) = 5.10$; $r = 0.26$; $p = 0.027$] and the SMA [$F(1,72) = 5.54$; $r = 0.27$; $p = 0.021$]. Activation in the striatum was not related to age [$F(1,72) = 0.53$; $r = 0.09$; $p = 0.469$].

A whole-brain analysis replicated these ROI results, by revealing a significant age-related increase in rIFG and SMA activation, as well as in right superior temporal lobe, left precuneus/superior parietal lobe,

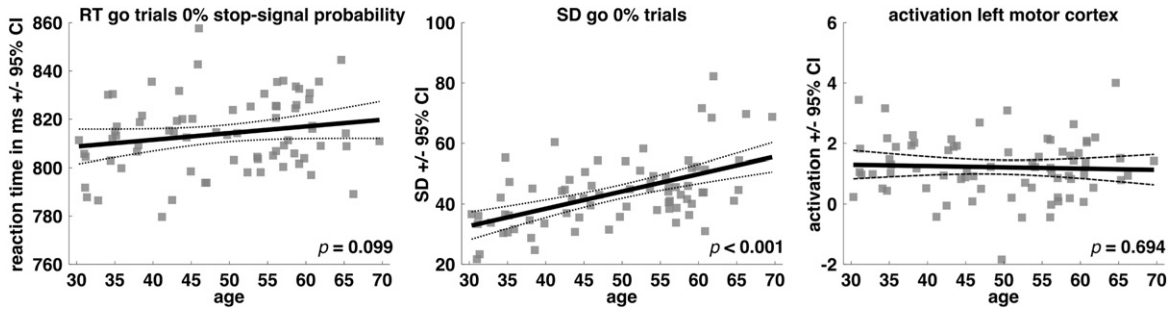


**Fig. 2.** Basic response execution. Scatter plots of reaction times (RT), standard deviations (SD), and left motor cortex activation for go trials with a 0% stop-signal probability versus rest as a function of age (with linear trend line and 95% confidence interval).

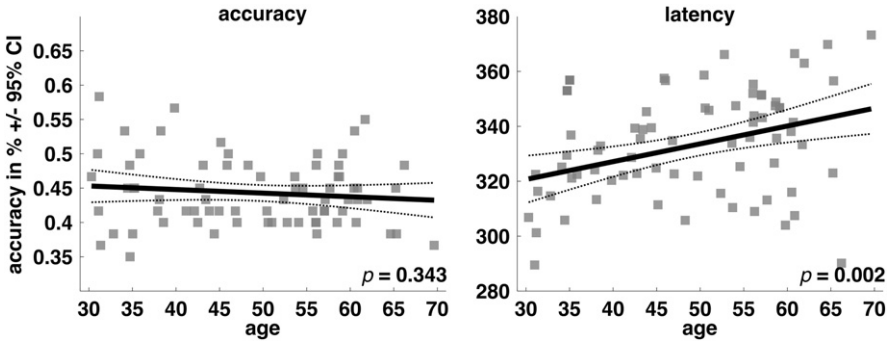


**Fig. 3.** Reactive inhibition performance data. Scatter plots of inhibition accuracy (in percent) and stop-signal reaction time (SSRT in milliseconds) as a function of age (with linear trend line and 95% confidence interval).

left thalamus, right middle and superior frontal lobe, and left inferior frontal gyrus (for details see Supplemental Table 1).

To further illustrate the effect of age on brain activation related to proactive inhibition, we subdivided the sample into four 10-year age bins (SPECS) and performed a repeated-measures regression analysis (see Fig. 7). For this analysis, we used parameter estimates (regression-coefficients or b-values) for both the main effect as well as the parametric effect of stop-signal probability in trials with a stop-signal probability >0%. For the rIFG, this analysis revealed a main effect of stop-signal probability ($F(1,67) = 27.99$; $p < 0.001$), indicating an increase in activation with increasing stop-signal probability (i.e., proactive inhibition). The age-group by stop-signal probability interaction was also significant ($F(3,64) = 3.41$; $p = 0.020$), with the older group showing less proactive activation increase than the younger group. Finally, the main effect of age-group was significant ($F(3,64) = 3.03$; $p = 0.035$), indicating an overall increase in activation levels in the older versus younger age groups.

Taken together, these results suggest that with advancing age, inhibitory processing becomes less efficient: we observed an age-related decline in the parametric effect of stop-signal probability, particularly in the rIFG, paralleled by a general increase in activation.

## Discussion

This study investigated age-related changes in performance and fronto-striatal activation during reactive (i.e., outright stopping) and proactive inhibition (i.e., anticipation of stopping). Seventy-three healthy participants aged 30–70 years performed a modified stop-signal task in which stop-signal probability was indicated by a visual cue, while functional MRI data were obtained.

We found no significant effects of age on baseline response latencies and cortical motor activation (Fig. 2). In line with literature, we found an age-related slowing of inhibition speed (Fig. 3). In the brain, this was paralleled by decreased suppression of the primary motor cortex (Fig. 4), while activation levels in the rIFG, SMA, and the striatum were not affected by age. On a behavioral level, proactive inhibition was observed (i.e., subjects slowed down responding when stop-signal probability increased), but did not change with advancing age. However, both whole-brain and ROI analyses revealed that the dynamic effect of stop-signal probability on brain activation in the rIFG declined with age (Fig. 5). This was coupled with an overall increase in activation in the rIFG and SMA (Fig. 6), and other frontal and parietal regions (Supplemental Table 1).

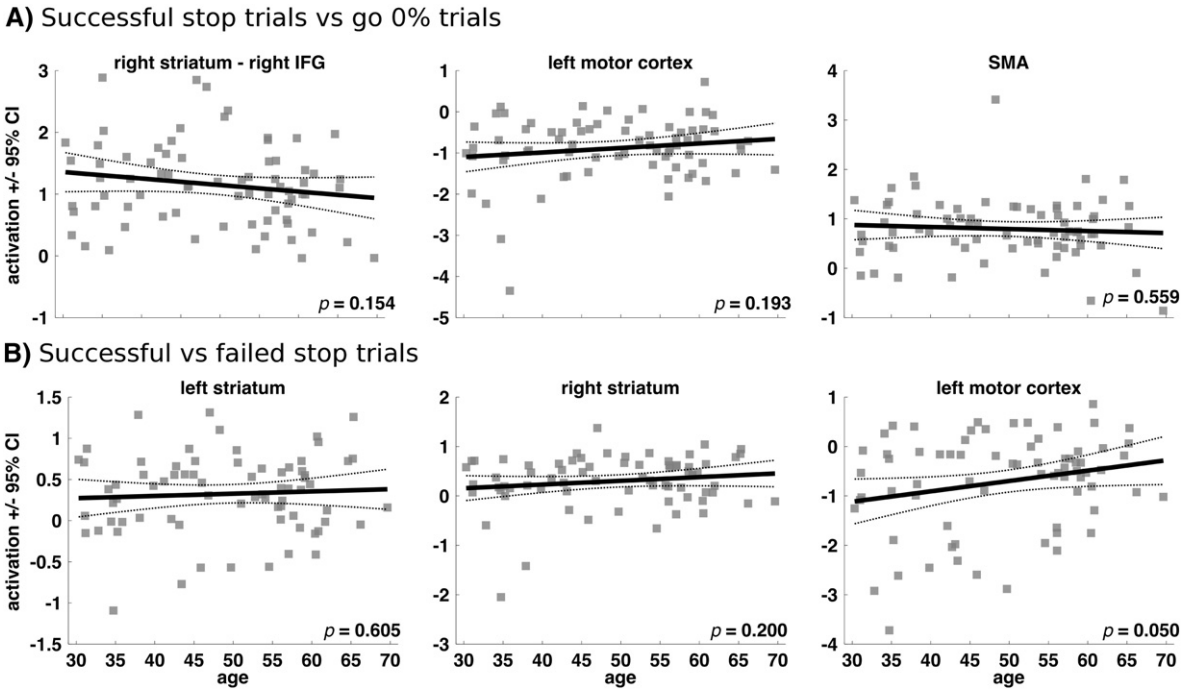


**Fig. 4.** Reactive inhibition activation data. Scatter plots of brain activation (regression coefficients) as a function of age (with linear trend line and 95% confidence interval). Abbreviations: IFG, inferior frontal gyrus; SMA, supplementary motor area.

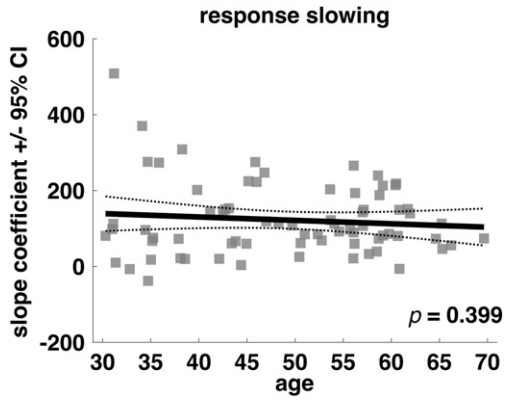


**Fig. 5.** Proactive inhibition performance data. Scatter plot of the level of response slowing (regression coefficient of the slope of response slowing) as a function of age (with linear trend line and 95% confidence interval).

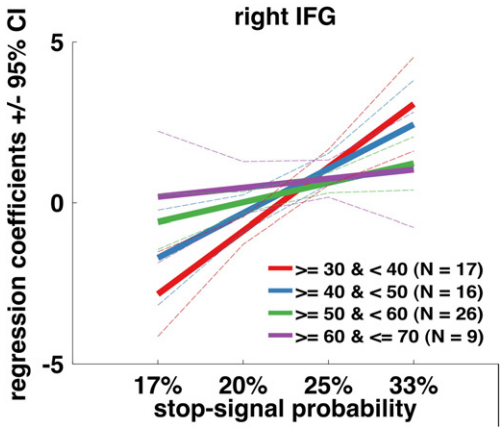


**Fig. 7.** Repeated-measures plot for the regression coefficients of rIFG activation with the subjects divided in four 10-year age bins (with linear trend line and 95% confidence interval. Abbreviation: IFG, inferior frontal gyrus.

Taken together, these results indicate that neural processing underlying inhibitory control becomes less efficient with advancing age. In older subjects, the rIFG responds less flexibly to contextual cues, which is paralleled by a global and extensive increase in activation.

## Behavior

Basic task execution declined slightly with advancing age, as evidenced by an increase in reaction time variability (standard deviation of response times on go trials with a 0% stop-signal probability). Reaction times on baseline go-trials were not subject to an age effect, likely because the task required timed rather than speeded responses. Stopping accuracy also did not change with age, probably due to the individual and trial-to-trial adjustment of stop-signal delay to attain 50% stopping success in all subjects [see Zandbelt and Vink, 2010]. In line with literature, we identified an age-related slowing of reactive inhibition, as measured by an increase in stop-signal reaction times (SSRT) with advancing age (Williams et al., 1999; Bedard et al., 2002; Kramer et al., 1994; Coxon et al., 2014).

Across the entire sample, we replicated earlier findings on proactive inhibition, by finding subjects to slow down their responses when anticipating a stop-signal (Chikazoe et al., 2009; Jahfari et al., 2010; Logan and Burkell, 1986; Verbruggen and Logan, 2008; Vink et al., 2005, 2014; Zandbelt and Vink, 2010; Zandbelt et al., 2011). However, we did not observe an age-related effect. In contrast, Van de Laar et al. (2011) did find that elderly subjects exercised more proactive control compared to their younger counterparts. It is plausible that our task evoked proactive slowing to a lesser degree, because it required timed rather than speeded responses.

## Neuroimaging

Prior research shows that activation in the primary motor cortex is generally found to be negative during reactive inhibition, indicating that successfully stopping a motor impulse may rely on suppression of this area (Chikazoe et al., 2009; Vink et al., 2005; Vink et al., 2014; Zandbelt and Vink, 2010). We found this suppression to decrease with

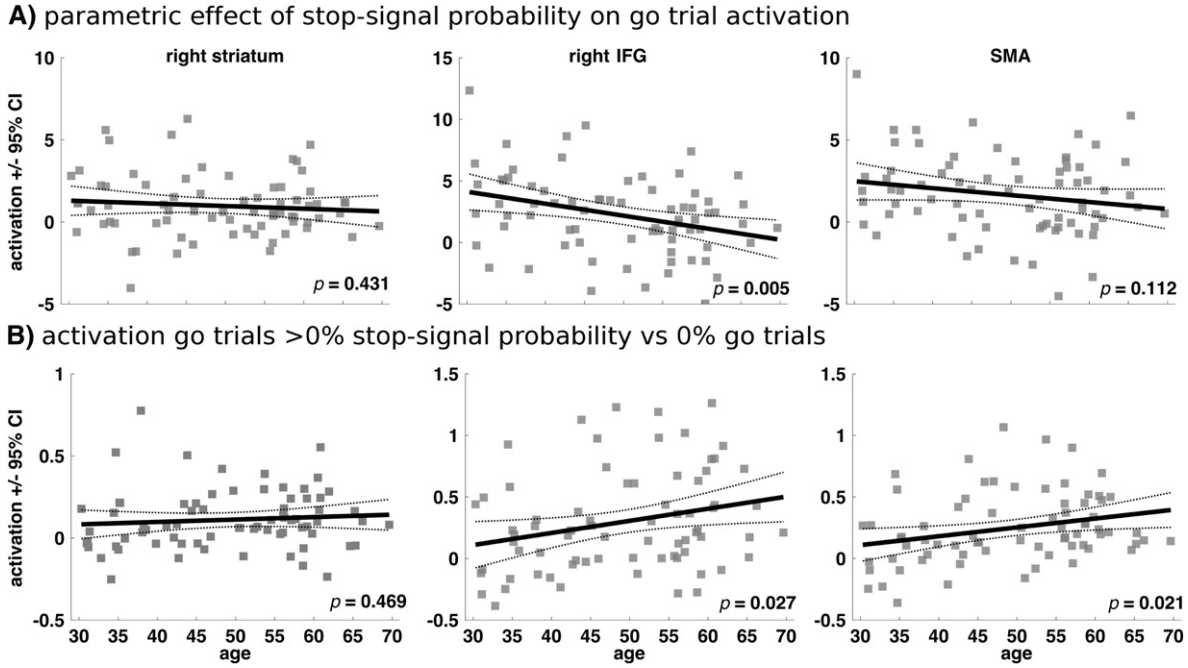


**Fig. 6.** Proactive inhibition activation data. Scatter plots of brain activation (regression coefficients) as a function of age (with linear trend line and 95% confidence interval). Abbreviations: IFG, inferior frontal gyrus; SMA, supplementary motor area.

advancing age when successful inhibition was compared with failed inhibition. This suggests that motor inhibition becomes less efficient with advancing age, which is in line with the age-related increase in SSRTs. This age-related decrease in motor cortex suppression is in direct opposition to the increase in motor cortex suppression that has been found to accompany the speeding of reactive inhibition during adolescent development (Vink et al., 2015a). In contrast, we found no effect of age in the second contrast for reactive inhibition (i.e., successful inhibition versus go 0%), indicating that processing of go trials with a 0% stop-signal probability may be less affected by aging than processing of failed inhibition. This is in line with our results on basic task performance revealing no age effect on activation during go 0% trials versus rest.

In contrast to prior studies that reported age-related changes in fronto-striatal regions, we did not find age-related changes in activation during reactive inhibition in the striatum, supplementary motor area (SMA), or right inferior frontal gyrus (rIFG). A majority of studies observed increased fronto-striatal activation during successful inhibition in older relative to younger subjects (Sebastian et al., 2013; Heilbronner and Münte, 2013; Vallesi et al., 2011; Langenecker and Nielson, 2003; Nielson et al., 2002; Hong et al., 2014). In contrast, Sebastian et al. (2013) and Coxon et al. (2014) found activation in the rIFG to decrease with advancing age. An important difference between our study and prior studies is that our task design allowed us to disentangle reactive and proactive inhibition. As we found that proactive inhibition is affected by aging, these alterations may well have confounded the findings of prior studies. To illustrate, healthy adults show increased activation of the striatum and right inferior frontal cortex during go trials in which a stop-signal is anticipated (>0% stop-signal probability) (Vink et al., 2005; Zandbelt and Vink, 2010; Zandbelt et al., 2013a). These regions also activate during successful stop trials. Therefore, the contrast of successful stop trials versus go trials, as used in these studies, will not show activation in these regions, as these networks activate during proactive as well as reactive inhibition. Taken together, the reported age effects in prior research may well be the consequence of changes in proactive inhibition instead of reactive inhibition.

When investigating proactive inhibition, we found activation in the rIFG to become less related to stop-signal probability with advancing age. In healthy young adults, activation in the rIFG generally increases as a function of stop-signal probability, implicating its important role in the flexible adaptation to different stop-signal probabilities. With increasing age, the rIFG becomes more rigid and less efficient in reacting to contextual cues. This suggests less efficient contextual cue processing in old age.

Furthermore, we found overall activation levels during proactive inhibition (i.e., go trials with a stop-signal probability >0% versus go trials with a 0% stop-signal probability) to increase in a number of frontal brain regions such as the rIFG and SMA, as well as the bilateral striatum and parietal regions. We take this overall increase in activation to indicate a form of compensation for the loss of flexibility in contextual cue processing: whereas younger subjects are able to flexibly engage the rIFG depending on the level of stop-signal probability, older subjects seem to go 'all-in' already at low levels of stop-signal probability (Fig. 7). This compensation appears to be adequate in that, on a behavioral level, proactive inhibitory control in older subjects equaled the level of younger subjects. Our findings seem to fit the neural compensation hypothesis and the STAC-r model, which state that older adults mobilize brain regions to a higher level and engage additional brain regions to compensate for impaired cerebral functioning and maintain adequate performance (Reuter-Lorenz and Cappell, 2008; Sebastian et al., 2013; Reuter-Lorenz and Park, 2014). This compensatory activation was already evident in frontal brain regions (Gutchess et al., 2005; Davis et al., 2008) and has more recently been documented in parietal regions as well (Angel et al., 2011). In our study, we identify these effects in both frontal brain regions as well as parietal regions.

## Limitations

There are several limitations that need to be discussed. Firstly, future studies could improve upon our results by using a longitudinal design instead of a cross-sectional design. Furthermore, cognitive functioning was screened globally by self-developed questionnaires and screening by the interviewer. However, we did not use standardized questionnaires, which would possibly give a more accurate depiction of global cognitive functioning. Future studies might benefit from including these questionnaires. The use of fMRI poses a possible limitation, since it measures cerebral activity indirectly, through the blood-oxygen-level-dependent (BOLD) response. Old age is associated with an increased prevalence of hypertension, hyperlipidemia, and clinically silent cerebral or vascular pathology, which could hypothetically alter the BOLD-response (Raemaekers et al. 2006). An age-related decrease in BOLD-response is generally reported (Ances et al. 2009; Buckner et al. 2000), although some studies report no age-effect (Huettel et al. 2001; Aizenstein et al. 2004). Since our data mainly show age-related increases in activation, the bias presented by age-related hemodynamic changes appears limited.

## Summary and conclusion

In summary, we found behavior regarding proactive inhibition (i.e., response slowing in relation to higher stop-signal probabilities) to be unaffected by age. In the brain, this was paralleled by a marked age-related decrease of flexibility specifically in the right inferior frontal gyrus (rIFG). This region is typically associated with contextual cue processing, with higher levels of stop-signal probability being associated with increased activation. In addition to this loss of contextual processing, older subjects showed hyperactivation of the rIFG, as well as other frontal and parietal regions, irrespective of cue context. This age-related increase in activation seems to be in line with the compensation hypothesis of aging; with hyperactivation during proactive inhibition compensating for the age-related decline in contextual cue processing. Furthermore, we replicated prior research by finding inhibitory latencies to increase with age. This was paralleled in the brain by less efficient suppression of the motor cortex in older participants. No other age effects were identified regarding reactive inhibition. By using a task that allows for the separate evaluation of reactive and proactive inhibition, we can now, for the first time, show that the age-related increase in activation during inhibition that is generally reported by prior studies may be the result of compensation for reduced neural flexibility related to proactive control strategies.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2016.02.031.

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