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Contrasting neural effects of aging on proactive and reactive response inhibition

Mirjam Bloemendaal [a,*], Bram Zandbelt [a], Joost Wegman [a], Ondine van de Rest [b], Roshan Cools [a,c], Esther Aarts [a]

[a] Centre for Cognitive Neuroimaging, Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands
[b] Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands
[c] Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands

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ABSTRACT

Two distinct forms of response inhibition may underlie observed deficits in response inhibition in aging. We assessed whether age-related neurocognitive impairments in response inhibition reflect deficient reactive inhibition (outright stopping) or also deficient proactive inhibition (anticipatory response slowing), which might be particularly evident with high information load. We used functional magnetic resonance imaging in young (n = 25, age range 18–32) and older adults (n = 23, 61–74) with a stop-signal task. Relative to young adults, older adults exhibited impaired reactive inhibition (i.e., longer stop-signal reaction time) and increased blood oxygen level-dependent (BOLD) signal for successful versus unsuccessful inhibition in the left frontal cortex and cerebellum. Furthermore, older adults also exhibited impaired proactive slowing, but only as a function of information load. This load-dependent behavioral deficit was accompanied by a failure to increase blood oxygen level-dependent (BOLD) signal under high information load in lateral frontal cortex, presupplementary motor area and striatum. Our findings suggest that inhibitory deficits in older adults are caused both by reduced stopping abilities and by diminished preparation capacity during information overload.

1. Introduction

Older adults can have trouble stopping an action. Indeed, relative to young adults, older adults have been shown to exhibit impaired response inhibition in classic stop-signal paradigms; that is they need more time to stop a response when presented with a stop signal (Bedard et al., 2002; Kramer et al., 1994; van de Laar et al., 2011). At the neural level, older adults are known to exhibit attenuated blood oxygen level-dependent (BOLD) signal as well as reduced tract strength between brain regions involved in response inhibition (Coxon et al., 2012, 2014). However, the processes underlying these age-related behavioral and neural deficits in response inhibition are unclear. Two forms of response inhibition have been distinguished: reactive response inhibition is the process of canceling an ongoing response at the moment this is needed (i.e., outright stopping), whereas proactive response inhibition entails the preparation for stopping when this may become necessary. Experimental designs in previous studies on aging did not enable the separate investigation of reactive and proactive response inhibition. Thus, it remains unclear whether the effects of aging on response inhibition, both neurally and behaviorally, reflect deficient reactive or also altered proactive processing. This issue is particularly pertinent given recent proposals that an understanding of cognitive control deficits in aging requires taking into account dual—reactive and proactive—mechanisms of control (Braver et al., 2007) and evidence indicating deficient proactive but intact reactive control with age (Bugg, 2014; Jimura and Braver, 2010; Paxton et al., 2008).

Cautious response slowing in preparation for the possible upcoming need to stop increases the probability of successful stopping. Older adults might lack the cognitive capacity to process preparatory cues during information overload. Indeed, there is clear evidence for (load-dependent) reductions in working memory capacity due to deficits in prefrontal cortex functioning (Gazzaley et al., 2005; Nagel et al., 2009; Nyberg et al., 2010). By analogy, work with patients with schizophrenia has demonstrated an association between poor proactive response inhibition and low working memory capacity as well as reduced BOLD responses in frontal cortex (Zandbelt et al., 2011). Here, we investigated whether

* Corresponding author at: Centre for Cognitive Neuroimaging, Donders Institute for Brain, Behaviour and Cognition, Radboud University, Kapittelweg 29, 6525EN Nijmegen, The Netherlands. Tel.: +31 644 830 194; fax: +31 (0)24 36 10989.
E-mail address: mirjambloemendaal@gmail.com (M. Bloemendaal).

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diminished response inhibition in older adults is accompanied by altered behavioral and neural preparation for inhibition and whether this is particularly evident in situations of information overload.

To address these questions, young and older adults were scanned using event-related functional magnetic resonance imaging (fMRI) during the performance of an adapted version of a stop-signal task that allowed us to disentangle proactive and reactive response inhibition (Zandbelt and Vink., 2010). To assess whether response inhibition in aging varies as a function of information load, we manipulated the information processing demands required for interpreting the stop-signal probability cues.

A simple go task required a button press on every trial, unless a stop signal appeared indicating that the initiated button press had to be canceled. A measure of reactive response inhibition was obtained based on the race model (Logan and Cowan, 1984) by calculating the time needed to cancel an initiated response (i.e., the stop-signal reaction time [SSRT]). In addition, proactive slowing was indexed by the degree of preparatory response slowing of reaction times in response to cues signaling stop-signal probability (Chikazoe et al., 2009; Jahfari et al., 2010; Verbruggen and Logan, 2009c; Vink et al., 2005; Zandbelt and Vink, 2010). This stop-signal probability was manipulated parametrically, so that higher stop-signal likelihood would elicit greater proactive slowing. Critically, we also manipulated the information processing demands for interpreting these stop-signal probability cues, thus allowing us to assess our key hypothesis that besides behavioral and neural impairments during reactive response inhibition (as previously discussed), aging is accompanied also by deficits in proactive inhibition and associated prefrontal cortex signaling. Specifically, the effect of aging on proactive inhibition may vary as a function of information load because increased information load places greater weight on prefrontal resources that are vulnerable to aging.

2. Methods

2.1. Participants

Forty-eight participants were included in the analyses: 25 young (mean age: 22.7 years, range 18–29, 14 men) and 23 older adults (mean age: 67.6 years, range 61–74, 14 men). Participants met the following inclusion criteria: normal or corrected-to-normal vision, right handed, functioning within normal limits of general cognitive function with the mini-mental state examination (Folstein et al., 1975) (cutoff > 27 of 30), estimated verbal intelligence quotient (IQ) >85 (Schmand et al., 1991), no neurological or psychiatric disorders, no contraindications for MRI, and no use of psychotropic medication or medication influencing the BOLD signal, such as blood pressure–normalizing medication. Fifty-six participants were initially tested; 8 participants were excluded, of which 4 young and 4 older adults. Five participants were excluded before statistical data analysis: 2 due to technical problems (1 young and 1 older) and 3 participants (2 young and 1 older) were excluded due to excessive head movement (>4 mm translation). On data analysis of the behavioral effects, 3 participants were excluded due to task noncompliance (see in the following section) (1 young, 2 older). The experiment was approved by the local ethics committee (CMO 2001/095), and all participants gave written informed consent. Participants were matched on verbal IQ, Hospital Anxiety and Depression Scale (HADS) (Bjelland et al., 2002), and gender (Table 1). Participants also completed the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), immediate and delayed story recall (Wilson et al., 1985), digit span forward and backward (Wechsler, 1997), Stroop cards (Stroop, 1935), and verbal fluency (Tombaugh et al., 1999).

2.2. Experimental design: load-dependent stop-signal anticipation task

Participants performed a stop-signal anticipation task with blocks differing in information load. The paradigm was based on the stop-signal anticipation task (Zandbelt and Vink, 2010), which involved a modification of the classic stop-signal task (Verbruggen and Logan, 2008).

The paradigm consisted of Go trials and Stop trials. On every trial, a bar moved at a constant speed from a lower horizontal line toward an upper horizontal line, reaching a middle line (flanked by 2 vertical lines) in 800 ms. The horizontal and vertical lines were continuously present throughout the task (Fig. 1). The main Go task was to bring the bar to a halt as close to the middle line as possible, by pressing a button with the right thumb. A minority of trials were Stop trials. On these trials a stop signal appeared: the bar stopped moving automatically before reaching the middle line. This stop signal instructed the participants to withhold the planned Go response. The middle horizontal line and the 2 vertical lines represented cues that indicated stop-signal probability context by varying in color (see caption of Fig. 1). To manipulate information

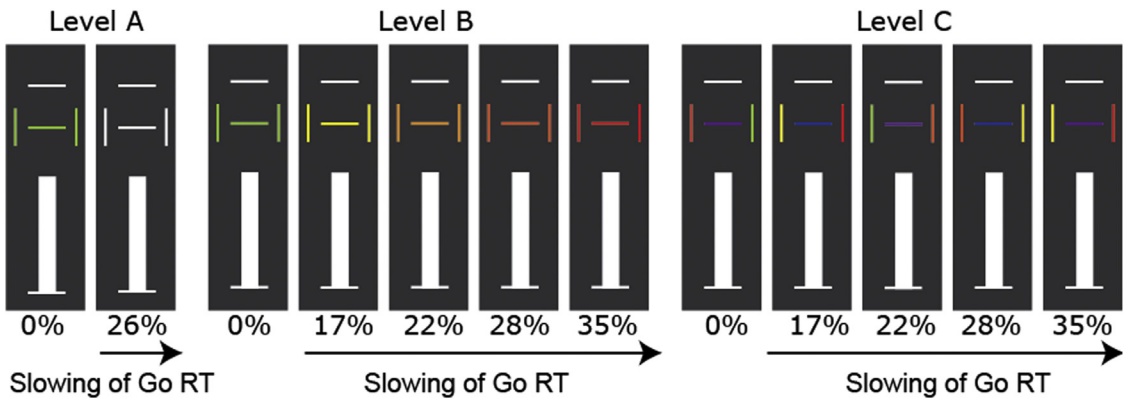

Fig. 1. Load-Dependent Stop-Signal Anticipation Task. Information load increased with level. Percentages reflect the probability a trial will be a Stop trial rather than a Go trial. For level B and C, stop-signal probability increased as a function of cue color. Every level contained 70 trials with 0% (green) and 270 trials with >0% (white) stop-signal probability. Of these 270 >0% trials, 70 were Stop trials, with a mean stop-signal probability of 26%. For Level B and C, each >0% trial type contained 50 Go trials, plus a varying amount of Stop trials per color resulting in varying stop-signal probabilities (in between brackets): 10 yellow (17%), 14 amber (22%), 19 orange (28%), and 27 red (35%). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

load, the task consisted of 3 levels that alternated in short blocks (see the following section). Between levels, stop-signal probability cues varied in amount as well as in complexity. The stop-signal probability could be anticipated based on the color of the cues (i.e., horizontal and vertical lines). Level A was the level with the least information load, with only white cues (stop probability of 26%) and green cues (stop probability of 0%). In Level B, there were 5 types of Go trials with varying stop-signal probability, using an intuitive color range for the cues (Zandbelt and Vink, 2010): green, 0%; yellow, 17%; amber, 22%; orange, 28%; and red, 35%, with a mean of 26% stop probability (caption Fig. 1). The nongreen trials are collectively called >0% trials. Level C consisted of the same types and numbers of stop-signal probability cues as Level B. However, in level C, only one of the vertical lines signaled the correct stop-signal probability context. The correct side could be identified by the color of the middle line: a blue middle line indicated that the left vertical line color was valid, whereas a purple middle line indicated that the right vertical line color was valid.

We instructed participants that going and stopping were equally important and that it would not always be possible to suppress a response when a stop signal occurred. Participants were not informed about the exact stop-signal probabilities, but they were told that stop signals in all levels would not occur on trials with a green cue and that stop signals in levels B and C were least likely in the context of a yellow cue and most likely in the context of a red cue, with the amber and orange cues coding intermediate, and respectively decreasing, stop-signal probabilities.

The stop-signal probability cues (i.e., colored horizontal middle line and vertical lines) were presented for 500 ms at the beginning of each trial before the bar started to move upward (relative to 0 ms in the original paradigm of the study reported by Zandbelt and Vink, 2010, thereby providing more time to process the stop-signal probability cues). On Stop trials, a stop signal was presented after some delay (stop-signal delay, SSD). SSD was initially set to 550 ms relative to moving bar onset (i.e., 250 ms before the target response time), equally for all stop-signal probability levels. During the experiment, SSD was adjusted depending on stopping performance, i.e., 25 ms decrease after a failed stop (StopFailure trial) and 25 ms increase after a successful stop (StopSuccess trial), for each level and stop-signal probability separately. This ensured roughly equal numbers of successful and unsuccessful Stop trials. In total, all trials had a fixed duration of 1500 ms. Levels were presented in 34 blocks, each lasting 27 seconds and consisting of 10 trials, with an intertrial interval of 1000 ms. Each block began with an instruction cue, displaying for 2000 ms which level would be presented in the coming block. The sequence of trials and blocks were pseudo randomized (ensuring that the first 3 blocks of the task were always in order of levels A, B, and C). In each level, 70 Go trials with 0% stop-probability, 200 Go trials with >0% stop-probability, and 70 Stop trials were presented (caption Fig. 1). Two rest blocks of 20 seconds each were implemented at one-third and two-thirds of the task, respectively. The total task duration was approximately 45 minutes.

2.3. Procedure

Older and young adults were trained for an equal number of practice trials on the stop-signal anticipation task before the actual fMRI experiment. Each level was explained and practiced separately for 48 trials (Level A) and 72 trials (Levels B and C). Participants were asked to repeat task instructions to ensure sufficient understanding. Then they practiced the task (levels were presented in alternating blocks) for 10 minutes. After the fMRI experiment, an exit questionnaire assessed the participants' strategy and understanding of the task instructions.

2.4. Behavioral data analysis

Data were tested for compliance with the main assumptions of the race model (Logan and Cowan, 1984). Inhibition functions were calculated, i.e., the probability of successfully inhibiting a response for every SSD, where the probability to inhibit decreases as the stop-signal is presented more closely to the moment that the response is made (Logan and Cowan, 1984). Specifically, for each level and age group separately, we assessed whether (1) mean response times (RTs) were faster on StopFailure versus >0% trials (paired *t*-test), (2) mean RTs were faster for StopFailure RTs for short versus long SSDs (paired *t*-test), and (3) individual inhibition functions represented the increasing probability of failed inhibition as a function of normalized SSD (as measured with a Weibull function fitted to the data). Reactive response inhibition was measured by calculating SSRT, according to the integration method (Verbruggen and Logan, 2009b). In short, >0% Go trials are sorted in ascending order. The Go RT corresponding to the percentage unsuccessful inhibitions is taken from this ranked list. Subsequently, the mean SSD is subtracted from this value. Hereby, SSRT represents the time needed to cancel an already initiated response (Logan and Cowan, 1984). An analysis of variance (ANOVA) of SSRTs was used with the within-participants factor Level (A, B, C) and the between-participants factor Age (young, older).

Previous studies have shown that participants slow down their responses in advance of a stop signal (Logan and Burkell, 1986; Verbruggen and Logan, 2009a; Vink et al., 2005; Zandbelt and Vink, 2010). RT slowing as a function of increasing stop-signal probability, indicated by the colored cues, indexed proactive response inhibition. For each level, the slope of RTs was calculated as a function of stop-signal probability using a general linear model, resulting in a beta value for the slowing slope. Hence, for level A, the slowing slope was calculated on the 2 proactive trial types (0% [green cues] and 26% [white]). For level B and C, the 5 proactive trial types were included in the slowing slope (0% [green cues], 17% [yellow], 22% [orange], 28% [amber], and 35% [red]). Level A consists of fewer cells than Levels B and C and was therefore not compared with the other levels. An ANOVA was performed using the within-participants factor Level (Level B, C) and the between-participants factor Age (young, older). The effect of Age on Level A was assessed using a separate 1-way ANOVA.

To assess the separate contributions of the information load manipulation on 0% and >0% stop-signal probability trials (present in all 3 levels), 2 ANOVA's were performed (using the factors Level [A, B, and C] and Age [Young, Older]) on the median RTs of 0% and >0% trials separately. Task instructions implied differential processing of 0% and >0% stop-signal probability trials, resulting in more slowing on >0% than 0% trials (i.e., a positive difference between these trial types). Task noncompliance was determined by a negative difference on median RTs between 0% (green) and >0% (white) trials during the lowest cognitive load (Level A). Three participants were excluded from analysis due to task noncompliance: negative slowing on Level A (1 young subject), not following the task instruction of timing the moving bar on the middle line (1 older subject) or failing to stop on every Stop trial (1 older subject).

Age differences between older and young adults on neuropsychological assessment (mini-mental state examination, Hospital Anxiety and Depression Scale, verbal IQ, BIS-11, Story recall, digit span, Stroop cards, and verbal fluency) were determined using 2-sampled *t*-tests. Categorical measures were tested using χ^2 tests.

2.5. MRI data acquisition and preprocessing

Whole-brain imaging was performed on a 3 Tesla MRI scanner (Magnetrom Skyra Tim, Siemens Medical Systems, Erlangen,

Germany). Functional data were obtained using a multi-echo gradient T2*-weighted echo-planar scanning sequence (Poser et al., 2006) with BOLD contrast (34 axial-oblique slices, repetition time, 2070 ms; echo-times, 9.0, 19.3, 30.0, and 40.0 ms; in plane resolution, 3.5 × 3.5 mm; slice thickness, 3 mm; distance factor, 0.17; field of view, 224 mm; flip angle, 90°). Visual stimuli were projected on a screen and were viewed through a mirror attached to the head coil. In addition, a high-resolution T1-weighted magnetization-prepared rapid-acquisition gradient echo anatomical scan was obtained from each subject (192 sagittal slices; repetition time, 2.3 seconds; echo time, 3.03 ms; voxel size 1.0 × 1.0 × 1.0 mm; field of view 256 mm).

Preprocessing and mass-univariate data analysis were performed using SPM8 software (Statistical Parametric Mapping; Wellcome Trust Centre for Cognitive Neuroimaging, London, UK). Realignment parameters were estimated for the images acquired at the first echo-time and subsequently applied to images resulting from the 3 other echoes. The echo images were combined by weighting with a parallel-acquired inhomogeneity-desensitized algorithm, assessing the signal-to-noise ratio as described by Poser et al. (2006). Thirty volumes, acquired before the task, were used as input for this algorithm. After data quality check (i.e., for signal intensity spikes), the echo combined and realigned images were slice time corrected to the middle slice. The functional images were coregistered to the T1 scan. A sample-specific template was created by segmenting each individual T1 and using diffeomorphic anatomical registration to place each subject's gray and white matter images in a study-specific space (Ashburner, 2007). Deformation parameters were stored in a subject-specific flow field. The coregistered fMRI images and anatomical T1 scan were nonlinearly normalized to the sample-specific anatomical template (using the subject-specific flow field), affine-aligned into a Montreal Neurological Institute template, and finally smoothed using an 8.0-mm full width at half maximum Gaussian filter.

2.6. FMRI task analysis

Twelve regressors of interest were included in a general linear model. For each Level, we included a regressor modeling all Go trials (i.e., containing 0% and >0% stop-signal probability trials) and a corresponding parametric regressor modeling stop-signal probability matching the behavioral slowing slope (6 regressors: Go Level A, Proactive Level A, Go Level B, Proactive Level B, Go Level C, Proactive Level C). In Level A, the parametric regressor consisted of 2 trial types (0% [green cues] and >0% [white cues]). In Levels B and C, the parametric regressors consisted of 5 trial types (0% [green cues], Go 17% [yellow], Go 22% [orange], Go 28% [amber], and Go 35% [red]). An actual stop-signal appeared on a proportion of >0% trials. These Stop trials were separately modeled as StopSuccess trials and StopFailure trials, based on whether or not the behavioral response was inhibited (6 regressors: StopSuccess level A, StopFailure level A, StopSuccess level B, StopFailure level B, StopSuccess level C, StopFailure level C). As regressors of noninterest, we included a regressor for missed trials across all levels (i.e., no button box response on a Go trial), as well as a regressor modeling task instructions at the beginning of each mini-block. Moreover, 24 realignment parameters were modeled as regressors of no interest (6 rigid-body movement parameters) plus Volterra expansion of these: first derivatives and quadratic derivatives of the original as well as first derivatives (Lund et al., 2005). Finally, to prevent contribution of global signal changes, we included signal from segmented out-of-brain voxels in the model as regressor of noninterest. All regressors of interest were modeled as delta functions at the onset of the trial and were convolved with a canonical hemodynamic response function. Time series were high-pass filtered (128-second cutoff), and serial correlations were corrected using an autoregressive 1 model during classical (ReML) parameter estimation. Parameter estimates for the regressors of interest, derived from the mean least-squares fit of the model to the data, were used to estimate contrasts on the first level.

At the subject-specific, first level we specified the reactive and proactive contrasts within, across, and between levels. The first level contrast images were subsequently used in a second level random effects analysis to assess consistent effects across participants as well as the effects of age. Reactive response inhibition can be assessed using 2 different contrasts: StopSuccess > StopFailure or StopSuccess > Go. The contrast StopSuccess > StopFailure provides optimal control for stimulus-driven processing (i.e., presentation of the stop signal). The contrast StopSuccess > Go provides optimal control for the timing of the Go responses (i.e., Go and StopSuccess RTs are both slower than StopFailure) and the outcome of the trial (i.e., both successful in Go and StopSuccess). In the main text, we focus on the StopSuccess > StopFailure contrast because we prioritized optimal control for stimulus-driven processing and because it is orthogonal by design to the proactive inhibition contrast (which also involves the Go trials). For completeness, we report the results of the contrast StopSuccess > Go in the Supplementary Materials.

At the group level, the main task effect of proactive response inhibition was assessed using a 1-sampled *t*-test of the parametric proactive regressors across Levels and Age. Task effects for reactive and proactive response inhibition were also tested using a 1-sampled *t*-test per Age group and per Level separately and are reported in the Supplementary Materials. In addition to the main task effects, Level × Age interactions were assessed using independent *t*-tests, comparing young and older age groups. For reactive response inhibition, this resulted in contrasts assessing Level × Age interactions for StopSuccess > StopFailure Level A versus Level B, Level C versus Level B, Level A versus Level C. For proactive response inhibition, a Level × Age interaction was assessed, comparing Level C versus Level B only, similar to the behavioral data analysis. This was done because the slope of Level A consists of an unequal number of cells compared with Levels B and C. On significant Level × Age interactions, we calculated simple effects of Level per age group or effects of Age per level.

To establish a relation between behavior and regions involved in the different types of response inhibition, whole brain-behavior correlations were assessed within age groups for the main reactive and proactive task contrasts across levels with mean SSRT and mean proactive slowing. On significant effects, we assessed the brain-behavior correlations per level. Statistical inference (pFWE < 0.05 [family-wise error corrected]) was performed at the cluster level, correcting for multiple comparisons over the whole brain. The intensity threshold necessary to determine the cluster-level threshold was set at $p < 0.001$, uncorrected.

3. Results

3.1. Behavioral results

Demographics and neuropsychological test scores from both age groups are presented in Table 1; an overview of task performance is given in Table 2. Response times of the participants followed the assumptions of the independent race model (Supplementary Materials 1.1, Table S1, and Fig. S1).

3.1.1. Reactive response inhibition

SSRTs are presented in Fig. 2 and Table 2 as a function of Level and Age. There was a main effect of Level on SSRT across Age

Table 1
Demographics and neuropsychological tests

Variable	Young (n = 25)	Older (n = 23)	*p*-value
Age (y)	22.7 (0.6)	67.6 (0.7)	**<0.001**
Sex (women/men)	W: 11, M:14	W: 9, M: 14	0.9
Verbal IQ (points)	107.4 (1.26)	112.4 (2.5)	0.1
HADS (points)	5.32 (0.9)	5.6 (0.8)	0.8
MMSE (points)	29.4 (0.1)	29.3 (0.16)	0.5
BIS-11 motor (points)	22.9 (0.8)	19.3 (0.6)	**0.01**
BIS-11cognitive (points)	14.9 (0.6)	14 (0.4)	0.2
BIS-11nonplanning (points)	22.5 (0.8)	22.2 (0.8)	0.8
BIS-11 total (points)	58.9 (2.2)	55.5 (1.2)	0.2
Story immediate recall (points)	11.3 (0.8)	8.8 (0.8)	**0.02**
Story-delayed recall (points)	10.5 (0.7)	7.7 (0.7)	**0.01**
Digit span forward (points)	9.8 (0.4)	8.7 (0.5)	**0.05**
Digit span backward (points)	9.5 (0.4)	8.6 (0.3)	0.06
Stroop effect (s)	20.9 (1.3)	31.4 (2.7)	**<0.001**
Stroop effect (errors)	0.3 (0.1)	0.2 (0.2)	0.6
Verbal fluency DAT (items)	50.1 (2.9)	48.4 (2.7)	0.7

All data in Young and Older columns represent mean (standard error of the mean) except for the variable Sex, for which data reflect frequencies. Verbal IQ is defined by scores on the Dutch Reading Test, mini-mental state examination (MMSE), Barratt Impulsiveness Scale (BIS-11) subscales, and total score. Immediate and delayed story recall, digit span forward and backward, Stroop cards (color naming: incongruent minus neutral cards), verbal fluency. Significant *p*-values are in bold.
Key: HADS, Hospital Anxiety and Depression Scale.

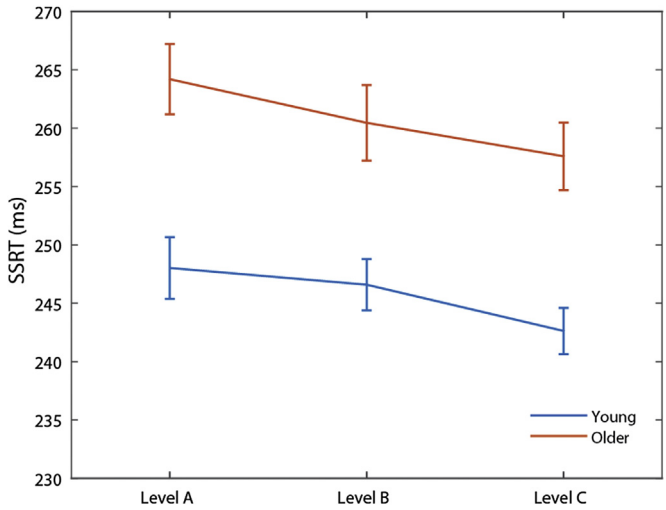

Fig. 2. Effects of Age and Level on reactive response inhibition, SSRT (ms). Error bars represent standard error of the mean. Abbreviation: SSRT, stop-signal reaction time.

groups (F[2, 92] = 5.30, $p = 0.007$), indicating that reactive inhibition became more efficient with increasing information load (Fig. 2). SSRTs in Level C were shorter compared with SSRTs in Level B (t[47] = 2.39, $p = 0.021$) and compared with SSRTs in Level A (t[47] = 2.90, $p = 0.006$). SSRTs did not differ between level A and B (t[47] = 1.32, $p = 0.19$). There was no Age × Level interaction (F[2,92] = 1.94, $p = 0.83$). However, critically, there was a main effect of Age: Older adults were on average 15 ms less efficient in stopping their initiated response than younger adults, irrespective of Level (F[1,46] = 23.18, $p < 0.001$) (Fig. 2).

3.1.2. Proactive response inhibition

The degree of proactive slowing (i.e., RT) with increasing stop-signal probability is presented as a function of Age and Level in Fig. 3 and Table 2. As shown in Fig. 3A (see also last column of Table 2), both older and young adults showed a significant decrease in the slowing slope from Level B to C (older adults: Level C < B, t[22] = 4.1, $p < 0.001$; young adults: Level C < B, t(24) = 4.5, $p < 0.001$). Thus, the degree to which proactive slowing increased with increasing stop-signal probability was reduced under high versus low information load. Critically, this decline in proactive slowing with increasing information load (i.e., Level) was greater in older than that in young adults (Fig. 3). This observation was substantiated by a Level (B, C) × Age (Young, Older) interaction (F[1,46] = 5.76, $p = 0.02$). There was no main effect of Age across Levels B and C (F[1,46] = 0.12, $p = 0.73$), and no simple main effects of Age per Level, although older adults tended to show more proactive slowing during level A than young adults (Level A, F[1,46] = 3.57, $p = 0.065$; Level B, F[1,46] = 1.69, $p = 0.2$; Level C, F[1,46] = 1.27, $p = 0.27$).

To investigate whether the effects of Age were driven by effects on the baseline 0% stop-signal probability condition or by the >0% conditions (Fig. 3B), we assessed simple interaction effects separately for the 0% stop-signal probability and >0% (grouped together) trial types. Level × Age interactions were found on 0% trials (F[2,92] = 3.86, $p = 0.025$) as well as on >0% trials (F[2,92] = 3.14, $p = 0.048$). Thus older adults exhibited a steeper Level-dependent increase of RTs for the 0% trial type, as well as a steeper Level-dependent decrease of RTs on the >0% trial types. Thus, the age-related decrease in slowing slope as a function of Level is driven by opposing effects on both trial types: relatively slower responding with increasing information load on the 0% trial type but relatively faster responding with increasing information load on the >0% trial type. As expected, older adults were slower in responding on all Go trial types compared with young adults (main effect of Age on 0% trial types: F[1,46] = 14.89, $p < 0.001$; and on >0% trial types: F[1,46] = 17.72, $p < 0.001$).

Table 2
RTs (in milliseconds) per trial type per level

Median RTs (ms) (SEM)	0% Green	>0% Other colors	17% Yellow	22% Amber	28% Orange	35% Red	Proactive slowing slope (beta)	SSRT (over levels)
Level A								
Young	811.5 (4.8)	834.2 (5.7)					0.96 (0.62)	248.0 (2.6)
Older	838.4 (6.8)	878.1 (7.7)					1.38 (0.90)	264.2 (3.0)
All	824.4 (4.5)	855.2 (5.7)					1.16 (0.79)	255.8 (2.3)
Level B								
Young	812.0 (4.3)	833.9 (5.8)	830.2 (5.5)	832.0 (6.0)	834.5 (6.1)	842.0 (6.8)	0.85 (0.62)	246.6 (2.2)
Older	838.3 (6.2)	871.7 (7.9)	864.7 (8.4)	868.6 (7.7)	873.4 (8.2)	878.6 (7.8)	1.11 (0.76)	260.5 (3.2)
All	824.6 (4.2)	852.2 (5.5)	846.7 (2.5)	849.5 (2.4)	853.2 (2.6)	859.5 (2.6)	0.98 (0.70)	253.2 (2.2)
Level C								
Young	824.0 (4.7)	834.0 (5.4)	829.9 (5.2)	832.0 (5.2)	834.0 (5.8)	844.5 (6.3)	0.58 (0.47)	242.6 (2.0)
Older	861.9 (8.1)	871.0 (8.1)	869.8 (7.4)	872.3 (8.0)	870.2 (8.3)	874.9 (7.8)	0.42 (0.49)	257.6 (3.0)
All	842.1 (5.3)	851.7 (5.4)	849.0 (5.3)	851.3 (2.5)	851.3 (5.6)	859.1 (2.4)	0.50 (0.48)	250.0 (2.0)

Median RTs for Go trails
Key: SEM, standard error of the mean; SSRT, stop-signal reaction time.

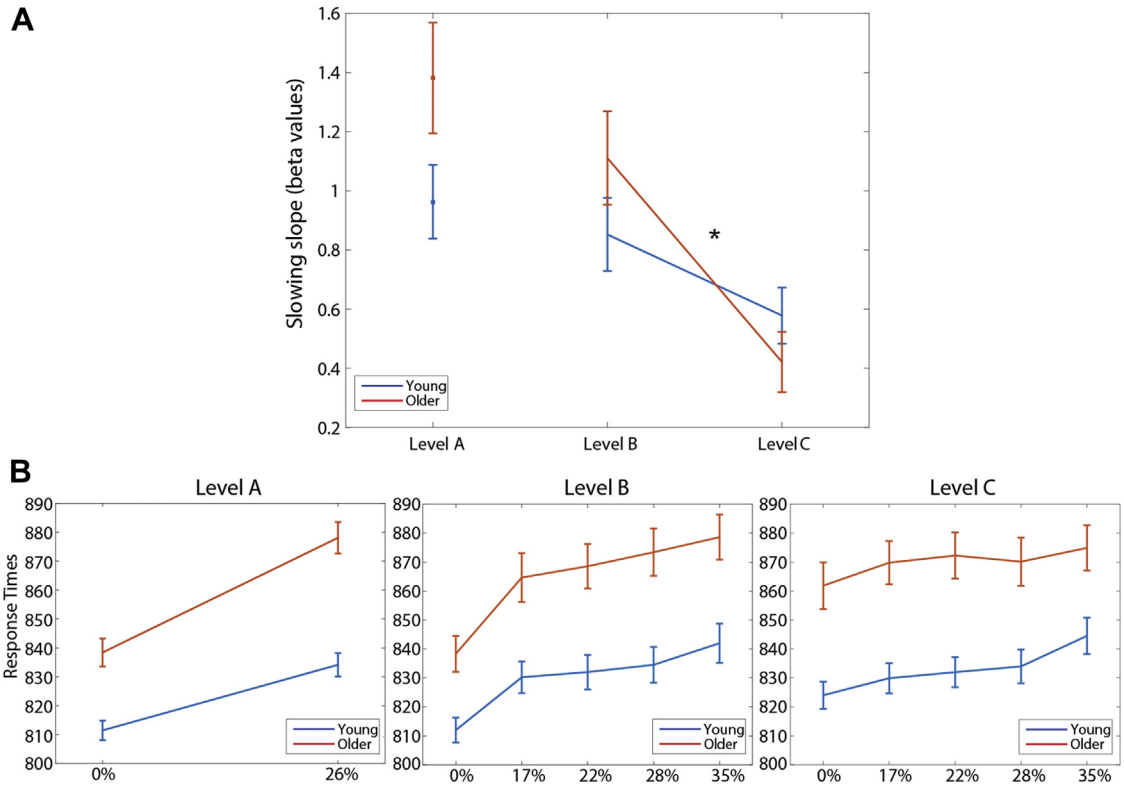

Fig. 3. (A) Slowing slope, that is, the degree to which participants slowed their responses with increasing stop-signal probability, plotted as a function of age and level. (B) Proactive slowing per level as a function of proactive cues for young and older adults in median RTs (ms). The slopes of the lines plotted in panel (B) are presented on the y-axis in panel (A). Error bars represent standard error of the mean. *$p < 0.05$.

In sum, relative to young adults, older adults showed decreased reactive response inhibition (i.e., longer SSRTs), as previously observed (Bedard et al., 2002; Kramer et al., 1994; van de Laar et al., 2011), across all load levels. In addition, as hypothesized, the degree of proactive slowing depended on information load and age: relative to young adults, older adults exhibited relatively decreased proactive slowing under high versus low information load.

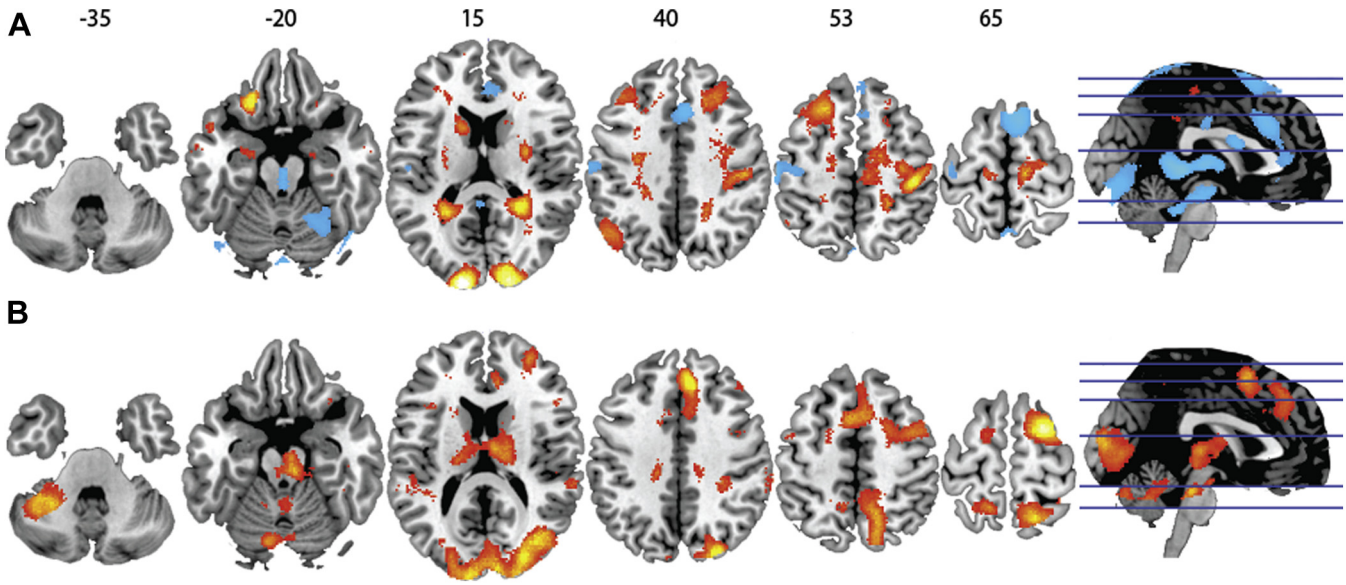

Fig. 4. (A) Main task effects for reactive response inhibition (StopSuccess > StopFailure). Images are thresholded at $p < 0.001$ uncorrected, and cluster-level significant clusters (pFWE < 0.05) are presented in Supplementary Table S2. (B) Main task effects for proactive response inhibition (parametric regressors of Go) plotted across levels and age groups. Images are thresholded at $p < 0.001$ uncorrected, and cluster-level significant clusters (pFWE < 0.05) are presented in Supplementary Table S3. The position of the slices is labeled with the Z coordinates of the MNI atlas. Task activation is plotted in hot colors, deactivation in cold colors. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.2. FMRI results

3.2.1. Reactive and proactive inhibition activate frontoparietal networks and basal ganglia

At our whole-brain corrected threshold of pFWE < 0.05 (cluster-level), main task effects revealed responses in a frontoparietal and striatal task network for reactive and proactive response inhibition (Fig. 4, Supplementary Tables S2 and S3), and deactivation of, for example, motor cortex in the reactive response inhibition network, as shown previously (Aron, 2011; Chikazoe et al., 2009; Jahfari et al., 2010; Swann et al., 2013; Zandbelt and Vink, 2010). Task effects of the StopSuccess > Go reactive response inhibition contrast are presented in the Supplementary Materials (Figure S2 and Table S4), as are simple task effects per Level and per Age group (Supplementary Figs. S3, S4 and S5).

3.2.2. Effect of age during reactive response inhibition (StopSuccess > StopFailure)

During reactive inhibition, BOLD signal was increased in older relative to younger adults in the right middle cingulate gyrus, the right cuneus, left middle frontal gyrus orbital part, and left cerebellum (Fig. 5 and Supplementary Table S5). Concurring with the behavioral pattern, these Age effects did not differ between levels: there were no Level × Age interactions during reactive response inhibition.

On further inspection, some of the age-related effects showed remarkable overlap with the deactivations observed for the StopSuccess > StopFailure contrast (as plotted in Fig. 4A). Indeed, in middle and anterior cingulate gyrus, the age effect on reactive inhibition was driven by more activation of the reverse contrast StopFailure > StopSuccess for young than that for older adults. However, in left middle frontal gyrus and bilateral cerebellum, the age effect represented over-recruitment during reactive stopping (StopSuccess > StopFailure) by older versus young adults (encircled regions in Fig. 5, further visualized in Supplementary Fig. S6).

No whole brain-behavior correlations were observed within older or young adults between BOLD responses during reactive response inhibition and SSRT. For completeness, we report the effects of reactive response inhibition as defined by the StopSuccess > Go contrast (see Section 2) in the Supplementary Materials, Figure S7 and text.

3.2.3. Effect of information load during reactive response inhibition (StopSuccess > StopFailure)

Similar to the behavioral results, Level effects irrespective of age were observed on reactive response inhibition (StopSuccess > StopFailure), Fig. 6. Specifically, BOLD signal for StopSuccess > StopFailure in the left superior frontal gyrus (encircled) was increased during level B relative to level C, (Montreal Neurological Institute (MNI) coordinates [−9 66 18], $p = 0.003$, k = 359).

3.2.4. Effects of age for high versus low information load during proactive response inhibition

As predicted and in accordance with the behavioral results, effects of Age during proactive response inhibition varied as a function of information load, as evidenced by Age × Level interaction effects in terms of the parametric proactive regressors. These were observed in frontal, temporal, and occipital areas: left inferior frontal gyrus extending into middle frontal gyrus and insula, right superior frontal gyrus extending into right anterior cingulate gyrus, vermis and bilateral calcarine gyri, left thalamus and right middle temporal gyrus (Fig. 7A). When breaking down this interaction into simple effects, increased signal was revealed for older adults relative to young adults during Level B in occipital and frontal regions (Fig. 7B in green). In contrast, decreased signal was found for older compared with young adults during Level C (Fig. 7B in violet) in medial and lateral frontal regions as well as a region extending into the right caudate nucleus. No cluster-level significant regions were observed when comparing level C with level B per age group. Cluster-level (pFWE < 0.05) significant clusters are listed in Supplementary Table S6. When assessing an age effect in Level A separately, we observed increased right precentral gyrus and postcentral gyrus in older compared with young adults (Fig. 7C in green).

Within older adults, we found a whole brain negative correlation between proactive BOLD signal across levels in the right middle occipital gyrus extending into angular gyrus (MNI coordinates [40 −72 28] and [42 − 73 39], $p = 0.008$, k = 318) and behavioral slowing across levels (Fig. 8A). This correlation was driven by the low and intermediate information load levels (level A: r = −0.520, $p = 0.011$; level B: r = −0.49, $p = 0.017$) and not by the high load level (level C: r = 0.088, $p = 0.69$; Fig. 8B). Within young adults, no whole brain correlation during proactive response inhibition with behavioral slowing was observed.

4. Discussion

We investigated how aging and information load impact inhibitory control. To this end, older and young individuals performed a stop-signal task designed to measure reactive inhibition (outright stopping) and proactive inhibition (anticipatory response slowing) across low, intermediate, and high levels of information load while being scanned with fMRI. We report 3 main findings.

First, reactive stopping was slower in older than young adults and was accompanied by more age-related activation of left middle frontal gyrus and bilateral cerebellum. We replicate the long-standing finding that aging is associated with slowing of the SSRT (Coxon et al., 2014; Kramer et al., 1994; Smittenaar et al., 2015; Williams et al., 1999; van de Laar et al., 2011) as well as

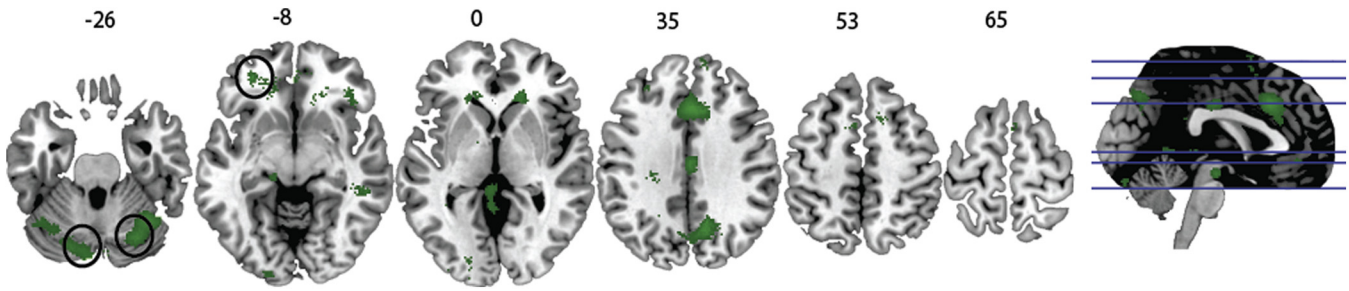

Fig. 5. Increased blood oxygen level–dependent signal for older versus young adults during reactive response inhibition (StopSuccess > StopFailure). Cluster-level significant regions in which the age effect was driven by an over-recruitment of StopSuccess > StopFailure for older > young adults are encircled. Other regions are driven by the reverse effect: more activation by young > older adults for the reverse contrast StopFailure > StopSuccess. The reverse contrast young > older adults did not yield any significant clusters. The position of the slices is labeled with the Z coordinates of the MNI atlas. Images thresholded at $p < 0.001$ uncorrected, cluster-level (pFWE < 0.05) significant clusters are listed in Supplementary Table S5.

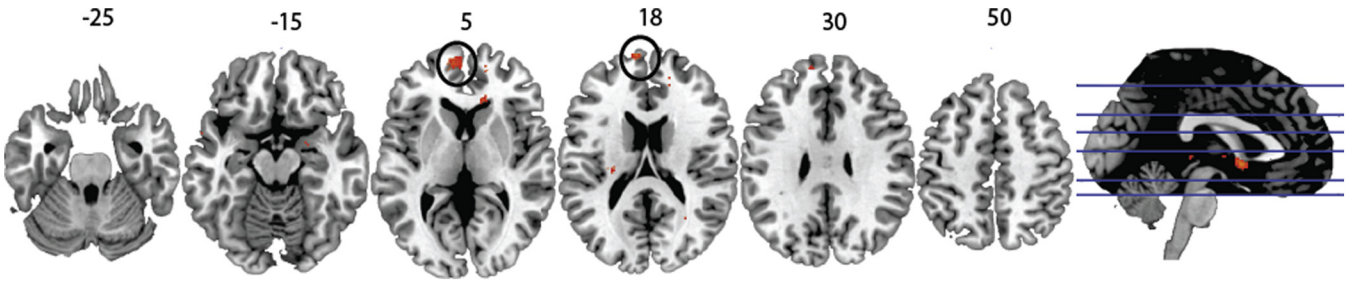

Fig. 6. Level effects for reactive inhibition (StopSuccess > StopFailure), Level B > Level C across age groups, thresholded at $p < 0.001$ uncorrected. Left superior frontal gyrus is cluster level significant (MNI coordinates [−9 66 18], $p = 0.003$).

differences in the neural correlate of this effect (Coxon et al., 2014). At first glance, our finding of more activation of left prefrontal and bilateral cerebellar cortex seems at odds with a previous study of response inhibition in aging (Coxon et al., 2014), reporting that slower reactive stopping in older adults was accompanied by less activation of regions more commonly associated with reactive stopping, including bilateral anterior insula, supramarginal gyrus, right inferior frontal cortex, and pre-supplementary motor cortex (SMA). Closer inspection reveals that this discrepancy is likely due to a difference in the way reactive inhibition was measured: we contrasted successful stop trials with failed stop trials, whereas these authors contrasted successful stop trials with go trials. Indeed, when we assessed reactive stopping by contrasting successful stop trials with go trials, we found similar activation patterns (see Supplementary Fig. S7). Both contrasts have previously been used to assess reactive inhibition (e.g., Aron and Poldrack, 2006; Boehler et al., 2010; Zandbelt and Vink, 2010), and each has different strengths: the former (StopSuccess > StopFail) is better at filtering out activation related to perceptual and attentional processes triggered by the presentation of the stop-signal, the latter (StopSuccess > Go) is better at controlling for response outcome and performance monitoring. We speculate that greater activation in left prefrontal and cerebellar cortex in older adults seen when contrasting successful stop trials with failed stop trials reflects an attempt to compensate for the diminished activation in regions associated with reactive stopping seen when contrasting successful stop trials with go trials.

Second, across age groups, reactive stopping was faster under high versus low information load, and this was associated with diminished activation in left superior frontal gyrus. The behavioral effect size was remarkably small (5 ms in young people, 7 ms in older people), but more importantly, it differed in direction from previous studies, showing that information load had no effect on reactive stopping (Huizenga et al., 2012) or resulted in SSRT slowing

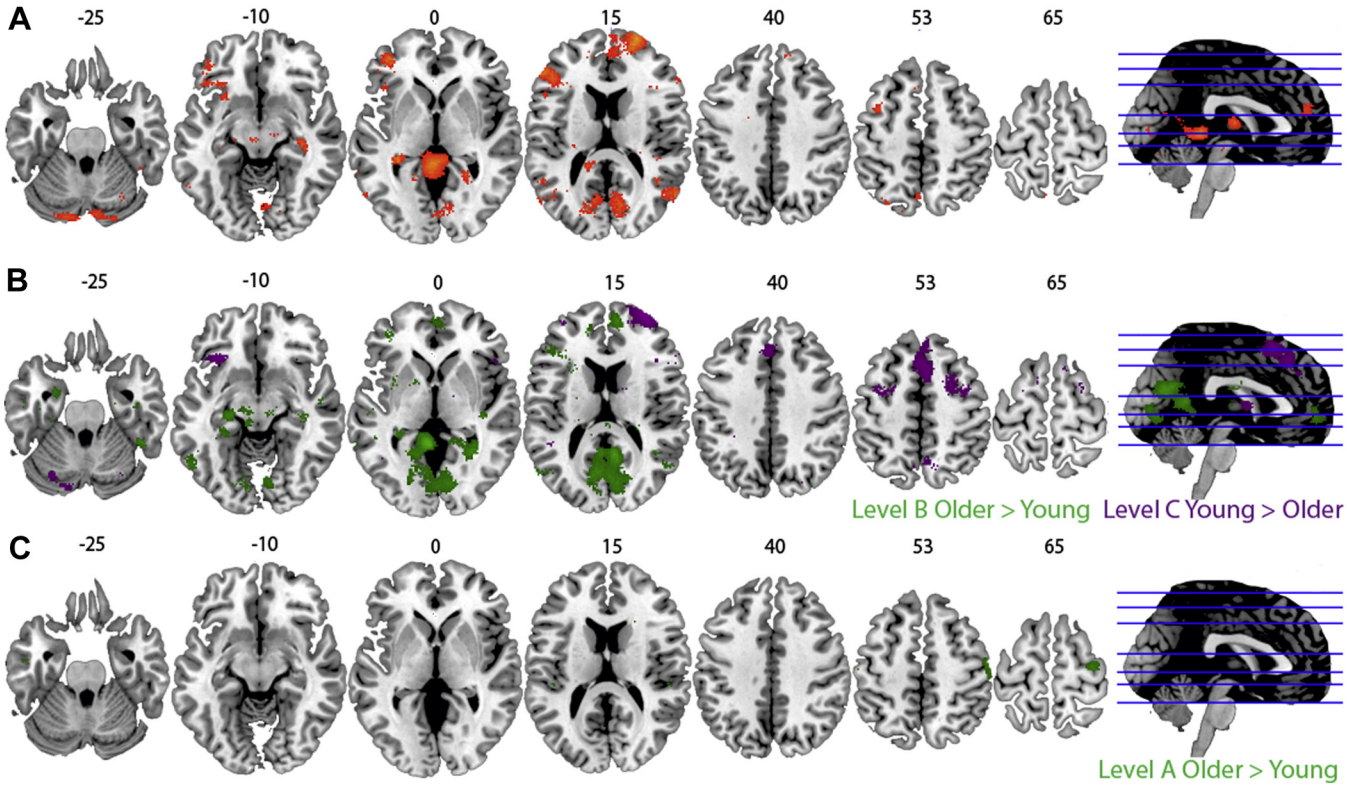

Fig. 7. (A) Level × Age interaction for Level C > B, Young > Older adults during proactive response inhibition (parametric proactive regressor). (B) Significant simple effects, signal for Older > Young adults Level B in green, for Young > Older adults Level C in violet. (C) Age effect for Older > Young adults during Level A in green. The position of the slices is labeled with the Z coordinates of the MNI atlas. Images are thresholded at $p < 0.001$ uncorrected. Cluster-level (pFWE < 0.05) significant clusters are listed in Supplementary Table S6. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

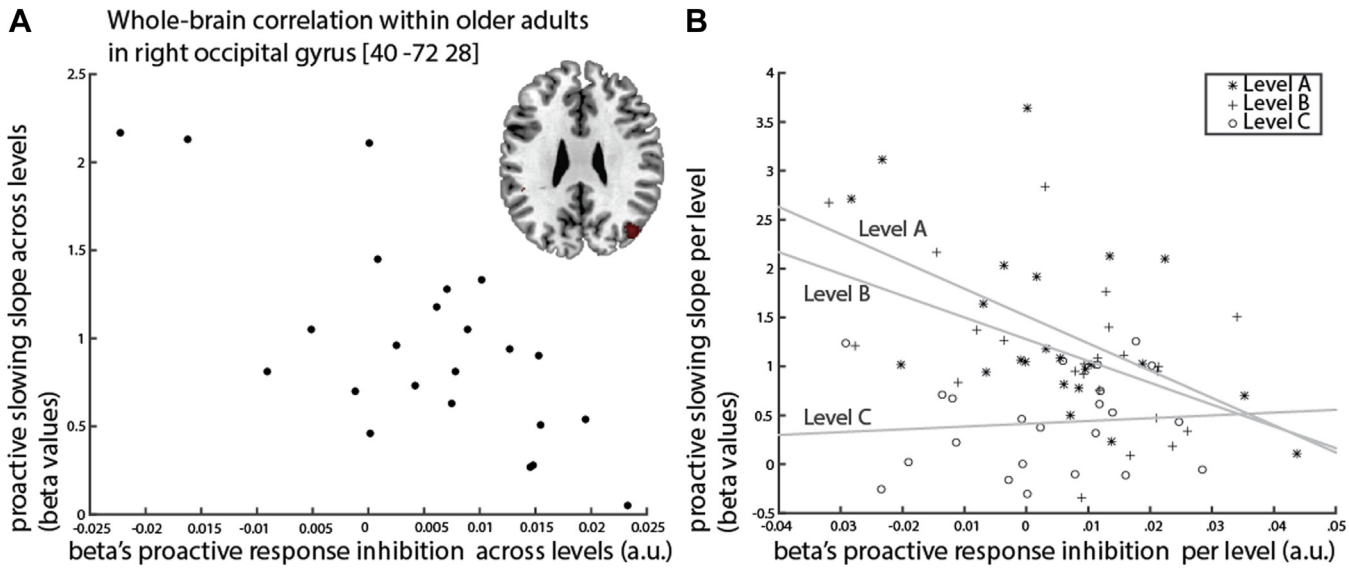

Fig. 8. (A) Whole-brain negative correlation within older adults between proactive response inhibition signal in right occipital gyrus and behavioral response slowing across levels (scatter plot for illustration purposes). (B) The correlation is driven by blood oxygen level–dependent signal and slowing slopes in the low (Level A) and intermediate (Level B) information load levels, not the high (Level C) load level. Abbreviation: a.u., arbitrary units.

(Ridderinkhof et al., 1999). This discrepancy may be due to a difference in tasks. Although previous studies used a standard stop-signal task in which fast reactive stopping is emphasized and response slowing is discouraged, we used a task that promotes not only fast reactive stopping but also proactive slowing. This may have shifted the balance between proactive and reactive control toward proactive control, leaving more room for SSRT improvement than in previous studies. Supporting this explanation, SSRT of young adults in our low information load condition (245 ms) is much slower than SSRT of young adults in a corresponding condition reported by Huizenga et al., (Huizenga et al., 2012) and Ridderinkhof et al., (Ridderinkhof et al., 1999) (190 ms and 182 ms, respectively). Increased recruitment of the left superior frontal gyrus during reactive inhibition in level B versus C is in line with the observed increases in SSRT in level B versus C and might reflect difficulty when engaging in both reactive and proactive response inhibition. The right inferior frontal gyrus is suggested to be the main locus of inhibition, by actively braking a motor plan (Aron et al., 2014). Other frontal regions, as among others the left superior frontal region, might be involved in different processes that contribute to successful inhibition, for example attention to object features such as motion and color.

Third, proactive slowing decreased as information load increased but more so in older than young adults. Under low information load, we found slightly more proactive slowing in older than young adults, replicating previous findings obtained under similar information loads (van de Laar et al., 2011). Response slowing in aging has been shown to reflect a cautious attitude, indicated by response patterns favoring accuracy over speed even despite instructions directed toward speed (Forstmann et al., 2011; Rabbit, 1979; Starns and Ratcliff, 2010). In keeping with this idea, we found that older adults had lower levels of motor impulsivity than young adults, as measured with the BIS-11 motor subscale (see Table 1). In addition to slightly more age-related proactive slowing in level A, we found increased precentral and postcentral gyrus activation at this low information load in older versus young adults. This concurs with a previous observation that right precentral and postcentral gyrus activation is increased during proactive response inhibition (Zandbelt and Vink, 2010). Under intermediate information load, older adults were still able to maintain proactive slowing levels similar to young adults, yet expressed greater activation in visual cortex and prefrontal cortex than young adults. This could mean that older adults, to maintain adequate levels of proactive slowing, resorted to enhanced visual processing of stimuli, such as the moving bar and color cues. Under high information load, when older adults were less able to maintain the proactive slowing levels seen with intermediate information load compared with their younger peers, we saw a reduction of activation in regions commonly associated with both proactive and reactive inhibition, including dorsolateral prefrontal cortex, pre-SMA, and striatum (van Belle et al., 2014; Vink et al., 2015; Zandbelt et al., 2013). Thus, the tendency of older people to respond more cautiously collapses in situations of information overload and is associated with a failure to sustain activation in brain regions implicated in proactive inhibition. This conclusion is further strengthened by a negative correlation within older adults between the right middle occipital gyrus, involved in proactive inhibition across levels (see Fig. 4B) and proactive behavioral slowing. This correlation may reflect unsuccessful recruitment of this region by older adults, attempting to engage in proactive response preparation. It was driven by low and intermediate information load levels but was not present in the high information load level. This again indicates disengagement of older adults in the proactive part of the task under high information load. Our age-related comparisons confirm our hypothesis that aging affects proactive response inhibition as a function of information load due to failure of recruiting frontal regions. Moreover, our brain-behavior correlation within older adults shows that occipital gyrus signal is unsuccessfully recruited in lower load levels and not recruited during high information load.

Taken together, aging and information load appear to have opposing effects on the balance between proactive and reactive inhibition. Aging shifts the balance toward proactive inhibition, resulting in longer SSRT and a tendency toward more proactive slowing (under low information load), whereas information load shifts the balance toward reactive inhibition, resulting in shorter SSRT and less proactive slowing, with the latter being more pronounced in older than young adults.

The impact of information load on proactive inhibition and reactive inhibition fits well with the dual mechanisms of control (DMC) framework (Braver, 2012; Braver et al., 2007) that puts

forward the idea that cognitive control operates via proactive and reactive modes. According to this framework, proactive control is metabolically costly, and capacity demanding, so that proactive control is preferred primarily under low levels of information load. In contrast, the effect of aging on proactive slowing and reactive inhibition we observed differs from predictions of the DMC framework. The DMC framework predicts that aging, like information load, produces a shift from proactive toward reactive control and subsequent studies confirmed this idea (Bugg, 2014; Jimura and Braver, 2010; Paxton et al., 2008). In fact, we replicate previous behavioral findings showing excessive posterror slowing in older versus younger adults, which can also be viewed as a measure of proactive response inhibition (van de Laar et al., 2011). Therefore, it is possible that this discrepancy results from differences in the concepts of proactive and reactive control between the domain of response inhibition (e.g., Aron, 2011; Jahanshahi et al., 2015) and other cognitive control domains from which the DCM originates (Braver, 2012; Braver et al., 2007). First, different measures are used: the response inhibition domain uses response time measures, whereas other domains tend to use accuracy measures (but see Bugg, 2014). Second, different brain structures appear to be involved: in the response inhibition domain primary regions of interest are the ventrolateral prefrontal cortex (e.g., right inferior frontal cortex [rIFC]), dorsomedial frontal cortex (e.g., pre-SMA), and basal ganglia (e.g., striatum, subthalamic nucleus), whereas other cognitive control domains appear to focus mainly on dorsolateral frontal and parietal cortex. These discrepancies highlight the need for future research to examine the domain specificity and generality of the constructs of proactive and reactive control.

Several measures were taken to account for differences in the 2 age cohorts that are likely unrelated to the cognitive processes studied. A bias due to anatomical differences between age groups (e.g., cortical shrinkage) was minimized by normalizing participants to a sample-specific anatomical template (Ashburner, 2007) before normalizing to MNI space. Furthermore, as recommended when studying aging using neuroimaging (D'Esposito et al., 2003; Samanez-Larkin & D'Esposito, 2008), the task compared different conditions and different levels. This experimental design allowed assessment of level- and condition-specific age-related effects that are unlikely explained by a general physiological effect such as parenchymal volumetric differences and differences in BOLD signal evolution. These general cross-sectional differences would affect all task conditions in the same or nearby region equally. Indeed, we observed both hyper- and hypo-activation, accompanied by impairments in behavior, for different conditions, that is reactive and proactive inhibition respectively. Thus, our age-related effects seem to reflect task- (i.e., type of response inhibition) specific effects instead of general physiological effects. Another possible caveat could be an age-related difference in discrimination of the colors. However, this is unlikely given that both age groups showed color-(i.e., stop-probability) related slowing within levels B and C. Moreover, both during practice and the exit interview, the participants repeated the task instructions using the colors.

In summary, this study investigated whether diminished response inhibition in older adults is accompanied by altered behavioral and neural preparation for inhibition, and whether this is particularly evident in situations of information overload. We demonstrate that under low information load diminished reactive stopping in older adults is accompanied by slightly increased proactive response slowing. Under high information load, this putative compensatory mechanism collapses in older adults, resulting in reduced inhibitory control more generally. Our neuroimaging findings indicate that this behavioral deficit reflects a failure to recruit a network of cortico-basal ganglia areas known to be involved in proactive and reactive control, including prefrontal cortex, pre-SMA, and striatum. Thus, in line with our hypothesis, aging is not only accompanied by deficits in outright stopping but also impaired preparation for stopping during information overload.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.neurobiolaging.2016.06.007.

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