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ORIGINAL RESEARCH

Imaging the effects of age on proactive control in healthy adults

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Abstract

Previous research has reported reduced efficiency in reactive inhibition, along with reduced brain activations, in older adults. The current study investigated age-related behavioral and neural changes in proactive inhibition, and whether age may influence the relationship between proactive and reactive inhibition. One-hundred-and-forty-nine adults (18 to 72 years) underwent fMRI while performing a stop signal task (SST). Proactive inhibition was defined by the sequential effect, the correlation between the estimated probability of stop signal – p(Stop) – and go trial reaction time (goRT). P(Stop) was estimated trial by trial with a Bayesian belief model; reactive inhibition was defined by the stop signal reaction time (SSRT). Behaviorally the magnitude of sequential effect was not correlated with age, replicating earlier reports of spared proactive control in older adults. Age was associated with greater activations to p(Stop) in the lateral prefrontal cortex (PFC), paracentral lobule, superior parietal lobule, and cerebellum, and activations to goRT in the inferior occipital gyrus (IOG). Granger Causality analysis demonstrated that the PFC Granger caused IOG, with the PFC-IOG connectivity significantly correlated with p(Stop) in older but not younger adults. These findings suggest that the PFC and IOG activations and PFC-IOG connectivity may compensate for proactive control during aging. In contrast, while the activations of the ventromedial prefrontal cortex and caudate head to p(Stop) were negatively correlated with SSRT, relating proactive to reactive control, these activities did not vary with age. These findings highlighted distinct neural processes underlying proactive inhibition and limited neural plasticity to support cognitive control in the aging brain.

Keywords Proactive control · fMRI · Aging · Stop signal task · Prefrontal cortex

Introduction

Proactive and reactive control are important features of cognition. Proactive control allows restraint of behavior based on experience and anticipation, whereas reactive control facilitates inhibition of inappropriate responses based on environmental stimuli (Kenemans 2015; Jimura and Braver 2010; Jahanshahi et al. 2015; Wessel and Aron 2017; Aron 2011). As with other top-down and bottom-up processes, proactive and reactive control are often both involved but to different extents according to task demands. For example, in behavioral paradigms to examine conflict monitoring and resolution, such as the go/no-go, flanker, Stroop, and stop signal task (SST), participants not only adjust behavior according to the stimuli but also anticipate behavioral adjustment according to what they have learned from the tasks. We previously showed that the efficiency of reactive control in the SST diminished with age, as reflected by longer stop signal reaction time (SSRT), and was associated with reduced activations in the medial prefrontal cortex and right inferior frontal gyrus pars opercularis/anterior insula in older adults (Hu et al. 2018). The current work aimed to investigate age-related changes in proactive control and whether these changes may influence reactive control in the SST.

The SST has been widely used to investigate inhibitory control. Participants respond to a frequent go signal and

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withdraw their response occasionally when instructed by a stop signal. In previous studies of young adult individuals, we employed a Bayesian model to compute participant's trial-by-trial estimate of the likelihood of a stop signal, or p(Stop) (Hu et al. 2015; Ide et al. 2013). A higher p(Stop) reflects higher anticipation of the stop signal, which may prolong the go trial reaction time (goRT). The trial-by-trial correlation bewteen the goRT and p(Stop), termed the sequential effect, has been used as an index of proactive control. The sequential effect describes an individuals' ability to learn from recent trial history to predict future conflict and adjust their response accordingly (Yu and Cohen 2009). A stronger correlation between p(Stop) and goRT represents better proactive control. Similarly, in a variant SST with a color or auditory cue indicating the probability of the stop signal, proactive control could be measured by the relationship between RT and stop signal probability (Zandbelt et al. 2013; Hsieh and Lin 2017b; van de Laar et al. 2011). In the latter studies, both young and older adults showed positive correlations between RT and stop signal probability, and the slopes of linear regressions were not significantly different, indicating preserved proactive control in older adults (Bloemendaal et al. 2016; Hsieh and Lin 2017b; Kleerekooper et al. 2016; Smittenaar et al. 2015).

Imaging studies have examined the neural mechanisms of behavioral compensation during aging, and showed that older adults compensated by recruiting both task-related and non-related brain regions (Park and Reuter-Lorenz 2009; Cabeza et al. 2002). Two recent studies of the SST showed minimal age effects on proactive control as measured by the slope of go trial reaction time vs. stop signal probability (Kleerekooper et al. 2016; Bloemendaal et al. 2016). Further, the investigators reported increased cerebral activations especially in the frontal and parietal regions during proactive control, suggesting neural compensation to support this top-down process. Increased functional connectivity (FC) served as an additional mechanism to bolster behavioral performance (Phillips and Andres 2010). FC of the fronto-parietal/temporal network was greater in older compared to younger adults during the preparatory period of a selective attention task (Geerligs et al. 2012) and in the performance of orientation, attention, and calculation tasks (Wei et al. 2014). In addition, the prefrontal-temporal FC was in negative correlation with RT in older but not younger adults (Hakun et al. 2015). These studies highlighted the role of the fronto-parietal network in neural compensation during aging.

The goals of the current study are two-fold. First, we aimed to replicate preserved proactive control in aging using an SST with Bayesian modeling of stop signal anticipation. In particular, previous fMRI studies of the SST have not clearly established the neural mechanisms of behavioral compensation, and we characterized how changes in cerebral activities and FC supported performance in the old. Second, we investiageted the neural mechanisms relating proactive to reactive control and specifically how regional activations to conflict anticipation may influence the SSRT. As age was associated with longer SSRT (Hu et al. 2012; Hu et al. 2018) and cerebral responses to proactive control have been related to SSRT (Hu et al. 2016), we hypothesized that regional activations and FC in support of proactive control did not benefit reactive response inhibition, as indexed by SSRT, during aging.

Methods

Participants and behavioral task

The same sample of 149 adults (83 women) between the age of 18 and 72 (31.6 ± 11.9; mean ± SD) years participated in the study (Hu et al. 2018). All participants were physically healthy with no major medical illnesses or current use of prescription medications. None of them reported having a history of head injury, neurological or psychiatric illness. All participants signed a written consent after given a detailed explanation of the study in accordance with a protocol approved by the Yale Human Investigation Committee.

Participants performed a stop signal task (SST) in which go and stop trials were randomly intermixed in presentation with an inter-trial interval of 2 s (Hu et al. 2012, 2014, 2016). Each trial started with the presentation of a fixation dot. After 1 to 5 s (the fore-period), the dot became a circle, which was the "go" signal. Participants were instructed to press a button quickly. The circle disappeared at button press or after 1 s if the participant failed to respond. In approximately one quarter of trials, the circle was followed by a "cross," the stop signal, prompting participants to withhold button press. The trial terminated at button press or after 1 s if the participant stopped successfully. The time between the go and stop signals, the stop signal delay (SSD), started at 200 ms and varied from one stop trial to the next according to a staircase procedure, increasing and decreasing by 67 ms each after a successful and failed stop trial (Levitt 1971). With the staircase procedure, we anticipated that participants would succeed in stopping half of the time. Participants were trained briefly on the task before imaging to ensure that they understood the task. They were instructed to press the button quickly when they saw the go signal while keeping in mind that a stop signal might come up in some trials. In the scanner, 146 participants completed four 10-min sessions of the task and 3 completed three sessions, with approximately 100 trials in each session.

Behavioral data analysis

We computed a critical SSD for each participant that represents the time delay required to withhold the response successfully in half of the stop trials, following a maximum likelihood

procedure (Wetherill et al. 1966). Briefly, SSDs across trials were grouped into runs, with each run being defined as a monotonically increasing or decreasing series. We derived a mid-run estimate by taking the median SSD of every second run. The critical SSD was computed by taking the mean of all median SSDs. It was reported that, except for experiments with a small number of trials (30), the measure was close to the maximum likelihood estimate of X_{50} (50% positive response; i.e., 50% SS in the SST; Wetherill et al. 1966). The stop signal reaction time (SSRT) was computed for each participant by subtracting the critical SSD from the median go trial reaction time (Logan et al. 1984). A longer SSRT suggests lesser capacity of reactive inhibitory control.

Trial-by-trial Bayesian estimate of the likelihood of a stop signal

As in our previous work (Ide et al. 2013; Hu et al. 2015), we used a dynamic Bayesian model (Yu et al. 2009) to estimate the prior belief of an impending stop signal on each trial, based on prior stimulus history. In the model subjects believe that stop signal frequency r_k on trial k has a probability α of being the same as r_{k-1}, and probability (1-α) of being re-sampled from a prior distribution $\pi(r_k)$. Subjects are also assumed to believe that trial k has probability r_k of being a stop trial, and probability 1- r_k of being a go trial. With these generative assumptions, subjects use Bayesian inference to update their prior belief of seeing a stop signal on trial k, $p(r_k|S_{k-1})$ based on the prior on the last trial $p(r_{k-1}|S_{k-1})$ and last trial's true category ($s_k = 1$ for stop trial, $s_k = 0$ for go trial), where S_k $\{s_1,. .., s_k\}$ is short-hand for all trials 1 through k. Specifically, given that the posterior distribution was $p(r_{k-1}|S_{k-1})$ on trial *k-1*, the prior distribution of stop signal in trial k is given by:

$$p(r_k|S_{k-1}) = \alpha p(r_{k-1}|S_{k-1}) + (1-\alpha)\,\pi(r_k),$$

where the prior distribution $\pi(r_k)$ is a beta distribution with prior mean *pm*, and shape parameter *scale*, and the posterior distribution is computed from the prior distribution and the outcome according to the Bayes' rule:

$$p(r_k|S_k) \propto P(s_k|r_k)p(r_k|S_{k-1}).$$

The Bayesian estimate of the probability of trial k being stop trial, which we colloquially call p(Stop) in this paper, given the predictive distribution $p(r_k|S_{k-1})$, is expressed by:

$$P(s_k = 1|S_{k-1}) = \int P(s_k = 1|r_k)P(r_k|S_{k-1})dr_k$$
$$= \int r_k P(r_k|S_{k-1})dr_k = \langle r_k|S_{k-1}\rangle$$

In other words, p(Stop) or the probability of a trial k being a stop trial is simply the mean of the predictive distribution $p(r_k|S_{k-1})$. The assumption that the predictive distribution is a mixture of the previous posterior distributions and a generic prior distribution is essentially equivalent to using a causal, exponential, linear filter to estimate the current rate of stop trials (Yu and Cohen 2009). In summary, for each subject, given a sequence of observed go/stop trials, and the three model parameters {α, *pm*, *scale*}, we estimated p(Stop) for each trial.

We followed our earlier work in specifying the parameters for Bayesian models (Ide et al. 2013; Hu et al. 2015). Specifically, we assumed a prior β distribution, β (3.5, 7.5), equivalent to a prior mean = 0.25, scale = 10, and a learning parameter $\alpha = 0.8$ for all participants. The mean of the prior distribution was set at 0.25 to reflect the frequency of stop trials. Although individual participant might present a different optimal set of parameters, individual model parameter estimates tended to be noisy, and we followed the standard of model-based fMRI analyses by keeping a fixed set of parameters across the group in characterizing behavior related to stop signal anticipation and regional responses to p(Stop) (Ide et al. 2013; O'Doherty et al. 2004; Daw et al. 2006). Our work also showed that the sequential effect, a positive correlation between p(Stop) and goRT, was not sensitive to the exact parametrization of the model; a significant correlation between p(stop) and goRT could be obtained for individual subjects for a wide range of parameters (r's > 0.92; Pearson regression) (Ide et al. 2013). The validity of the model was confirmed in a more recent work (Hu et al. 2015).

MRI protocol and spatial preprocessing of brain images

Conventional T1-weighted spin-echo sagittal anatomical images were acquired for slice localization using a 3-Tesla scanner (Siemens Trio, Erlangen, Germany). Anatomical images of the functional slice locations were obtained with spin-echo imaging in the axial plan parallel to the Anterior Commissure-Posterior Commissure (AC-PC) line with repetition time (TR) = 300 ms, echo time (TE) = 2.5 ms, bandwidth = 300 Hz/pixel, flip angle = 60°, field of view = 220 × 220 mm, matrix = 256 × 256, 32 slices with slice thickness = 4 mm and no gap. A single high-resolution T1-weighted gradient-echo scan was obtained. One hundred and seventy-six slices parallel to the AC-PC line covering the whole brain were acquired with TR = 2530 ms, TE = 3.66 ms, bandwidth = 181 Hz/pixel, flip angle = 7°, field of view = 256 × 256 mm, matrix = 256 × 256, 1 mm^3 isotropic voxels. Functional blood oxygenation level dependent (BOLD) signals were then acquired with a single-shot gradient-echo echo-planar imaging (EPI) sequence. Thirty-two axial slices parallel to the AC-PC line covering the whole brain were acquired with TR = 2000 ms, TE = 25 ms, bandwidth = 2004 Hz/pixel, flip angle = 85°, field of view = 220 × 220 mm, matrix = 64 × 64, 32 slices with slice thickness = 4 mm and no gap. There were three hundred images in each session.

Data were analyzed with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London, U.K.). In the pre-processing of BOLD data, images of each participant were realigned (motion-corrected) and corrected for slice timing. A mean functional image volume was constructed for each participant for each session from the realigned image volumes. These mean images were co-registered with the high-resolution structural image and then segmented for normalization to an MNI (Montreal Neurological Institute) EPI template with affine registration followed by nonlinear transformation (Ashburner and Friston 1999; Friston et al. 1995a). Finally, images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum. Images from the first five TRs at the beginning of each session were discarded so only signals with steady-state equilibrium between radio frequency pulsing and relaxation were included in data analyses.

General linear models and group analyses

Two general linear models were established with four trial outcomes, go success (GS), go error (GE), stop success (SS), and stop error (SE) distinguished for each model. In the first GLM, the F (i.e. fixation onset) model, we modeled BOLD signals by convolving the onsets of the fixation point (the beginning) of each trial with a canonical hemodynamic response function (HRF) and the temporal derivative of the canonical HRF (Hu et al. 2012; Friston et al. 1995b). Realignment parameters in all six dimensions were entered in the model. We included the following variables as parametric modulators in the model: p(Stop) of GS trials, SSD of SS trials, p(Stop) of SS trials, SSD of SE trials, and p(Stop) of SE trials, in that order. In the second GLM, the G (i.e., go onset) model, we modeled the BOLD signals by convolving go signal onsets of each trial with a canonical HRF and its temporal derivative. We included the following parametric modulators: p(Stop) of GS trials, RT of GS trials, SSD of SS trials, |1-p(Stop)| of SS trials, SSD of SE trials, |1-p(Stop)| of SE trials, and RT of SE trials, in that order (Ide et al. 2013; Hu et al. 2015). We placed p(Stop) before RT as a parametric modulator of GS trials so we were able to identify RT-related activities after the influence of p(Stop) was accounted for. Inclusion of these variables as parametric modulators improved model fit (Buchel et al. 1996, 1998; Cohen 1997; Hu et al. 2015). The parametric modulator of p(Stop) in the F model and the parametric modulator goRT in the G model each allowed us to examine the neural correlates of conflict anticipation and RT slowing. Serial autocorrelation of the time series was corrected by a first degree autoregressive or AR(1) model (Friston et al. 2000; Della-Maggiore et al. 2002). The data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts.

In the first-level analysis, we used a contrast "1" on the parametric modulator p(Stop) of GS trials in the F model to examine how deviations from the average BOLD amplitude were positively modulated by trial-by-trial estimate of the likelihood of a stop signal, and a contrast "1" on the goRT in the G model to identify activations to increasing go trial RT (Wilson et al. 2009; St Jacques et al. 2011). In the second-level analysis, we identified regional activations to p(Stop) and goRT respectively in one-sample t tests, and performed whole-brain regressions against age. Following current reporting standards, all results were examined for voxels meeting a threshold of voxel $p < 0.001$ uncorrected in combination with cluster $p < 0.05$, corrected for family-wise error (FWE), on the basis of Gaussian Random Field theory, as implemented in the SPM.

Granger causality analysis (GCA)

As stop signal anticipation takes place prior to RT slowing, we hypothesized that neural activities associated with stop signal anticipation Granger causes activities associated with RT slowing. To confirm this hypothesis, we employed a multivariate GCA to examine the direction of influence between the activation sites, referred to as the regions of interest (ROIs) (Deshpande et al. 2008; Duann et al. 2009; Deshpande et al. 2009; Ide and Li 2011; Stilla et al. 2007; Granger 1969).

The multivariate GCA was performed for individual participants. For each subject and each ROI, a summary time series was computed by averaging across voxels of the ROI. The average time series were concatenated across sessions, after detrending and normalization (Ding et al. 2000). The pre-processed time series were used for multivariate GCA. We used Akaike Information Criterion (AIC), which imposes a complexity penalty on the number of parameters and avoids over-fitting of the data (Akaike 1974). The model order (lag) was 2.35 ± 0.71 (mean ± SD). The multivariate GCA required that each ROI time series was covariance stationary, which we confirmed with the Augmented Dickey Fuller (ADF) test (Hamilton 1994). The ADF test verified that there was no unit root in the modeled time series. The residuals were used to compute the Granger causality measures (F values) of each possible connection between ROIs. Alternatively, connectivity strength could be measured by using the variance of the residual other than the sum of square of the variable (Goebel et al. 2003; Geweke 1982), which we referred to as the Geweke test. As multivariate GCA often involves interdependent residuals (Deshpande et al. 2009), we used permutation resampling (Seth 2010; Hesterberg et al. 2005) to obtain an empirical null distribution of *no causality*, as suggested in Roebroeck et al. (2005), in order to estimate the F_{critical}, and assess the statistical significance of Granger causalities. With resampling, we produced surrogate data by randomly generating time series with the same

mean, variance, autocorrelation function, and spectrum as the original data (Theiler et al. 1992), as implemented in previous EEG (Kaminski et al. 2001; Kus et al. 2004), and fMRI studies (Deshpande et al. 2009). We used the Geweke test to assess statistical significance in group analysis (Duann et al. 2009; Uddin et al. 2014), and reported the connections with F value $> F_{critical}$ as estimated by permutation resampling (Seth 2010). Multiple comparisons were corrected for false discovery rate or FDR (Genovese et al. 2002).

Results

Behavioral performance

Participants averaged 0.98 ± 0.03 (mean ± SD) in go response rate and 0.51 ± 0.03 in stop success rate, suggesting the success of SSD staircase in tracking the performance, 628 ± 119 ms in median go trial RT (goRT), and 215 ± 45 ms in SSRT. As reported earlier, goRT and SSRT were both positively correlated with age ($r = 0.1671$, $p = 0.0176$; and $r = 0.2271$, $p = 0.0001$, respectively), suggesting an effect of age on response speed and reactive inhibitory control (Hu et al. 2018). To investigate the effect of age on proactive control, we performed a linear regression and observed that age did not correlate with the magnitude of sequential effect ($r = -0.0510$, $p = 0.5366$, Fig. 1a). On the other hand, the magnitude of sequential effect was negatively correlated with SSRT ($r = -0.3654$, $p < 0.0001$), even after controlling for age ($r = -0.3637$, $p < 0.0001$) (Fig. 1b). The latter finding suggests that the behavioral measures of proactive and reactive control are related regardless of age. The results also suggest a potential for age-related neural processes of proactive control to influence the SSRT.

Age and regional activations to proactive control

All imaging results reported satisfied a threshold of voxel $p < 0.001$ uncorrected in combination with cluster $p < 0.05$ corrected for family-wise error (FWE). We performed one-sample t-tests each on "p(Stop) > 0" in the F model and "goRT>0" in the G model (Fig. 2a) (Hu et al. 2015). The anterior pre-SMA showed increased activation to higher p(Stop), and the posterior pre-SMA, right inferior frontal gyrus pars operculum/anterior insula, and left anterior insula showed higher activation to prolonged RT. These four clusters would serve as regions of interest for Granger causality analyses (next section).

To examine age-related changes in the functional correlates of proactive control, we performed linear regressions of the contrast "p(Stop) > 0" in the F model and "goRT>0" in the G model on age. The left lateral prefrontal cortex (PFC), paracentral lobule (PCL), superior parietal lobule (SPL), and cerebellum (CBL) showed greater age-related activation during stop signal anticipation, and right inferior occipital gyrus (IOG) showed greater age-related activations during prolonged RT (Fig. 2b; Table 1). No voxels showed activities in negative correlation with age for either contrast.

In the linear regression of "p(Stop) > 0" on stop signal reaction time (SSRT), the right caudate head and ventromedial prefrontal cortex (VMPFC) showed higher activation to shorter SSRT (Fig. 2c; Table 1). The activity (beta weight) of neither region was significantly correlated with age (caudate head: $r = -0.0718$, $p = 0.1466$; VMPFC: $r = 0.3861$, $p = 0.0754$).

Age and functional connectivity for proactive control

Our previous research identified directional relationship between regional activities of stop signal anticipation and prolonged RT (Hu et al. 2015). In Granger causality analysis (GCA), the anterior pre-SMA Granger caused activations of the posterior pre-SMA and bilateral anterior insula, indicating a directional link to support proactive control. Here, we performed GCA on three different age groups (≤30; 30 < age < 50; and ≥ 50 years). Three of the 149 participants were excluded because of one missing session, and 7 participants failed the Augmented Dickey Fuller test (i.e., not covariance

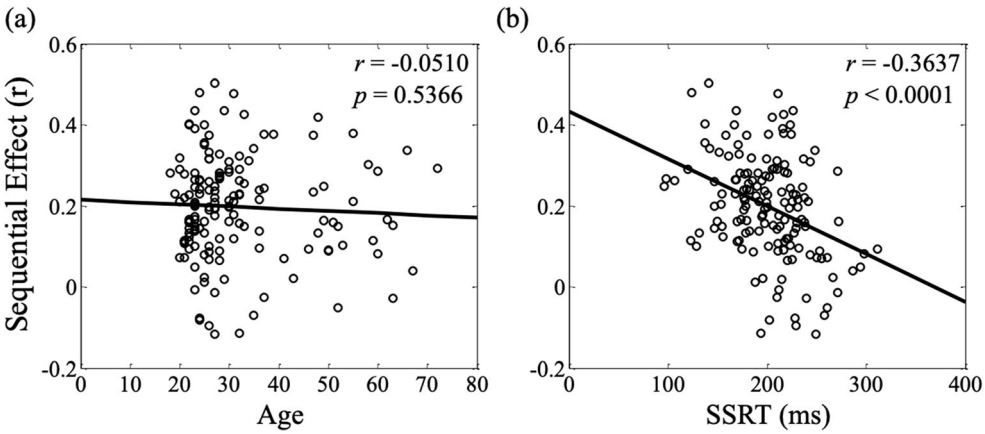

Fig. 1 Correlations between the magnitude of sequential effect and (**a**) age ($r = -0.0510$, $p = 0.5366$); and (**b**) SSRT ($r = -0.3637$, $p < 0.0001$)

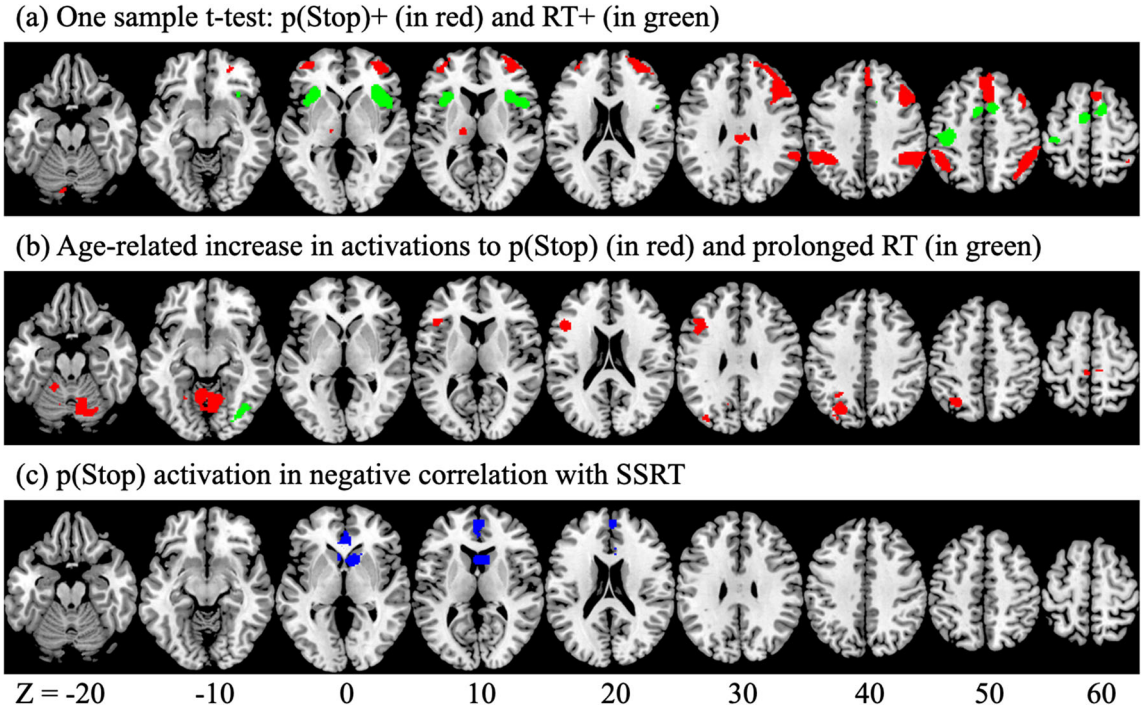

Fig. 2 **a** Regional activations in one sample t-test of positive p(Stop) (in red) and RT (in green) modulation; **b** Greater age-related activations to p(Stop) (in red) and prolonged RT (in green); and (**c**) regional activations to p(Stop) in negative correlation with the SSRT

stationary), resulting in a total of 139 subjects (≤30: $n = 91$; 30 < age < 50, $n = 30$; and ≥ 50 years, $n = 18$) for GCA. Geweke tests showed that the effective connectivities were largely intact in older adults (Fig. 3). We also correlated age with the F values of Geweke tests on directional connectivities. No significant correlations were found for the majority of connections (ant. Pre-SMA ➔ R IFGpo/AI; $r = -0.0489$, $p = 0.5674$; ant. Pre-SMA ➔ L insula; $r = -0.0362$, $p = 0.6726$; ant. Pre-SMA ➔ post. Pre-SMA: $r = -0.0490$, $p = 0.5666$; post. Pre-SMA ➔ L Insula; $r = 0.0238$, $p = 0.7809$) with the exception of the connection post. Pre-SMA ➔ R IFGpo/AI ($r = 0.1764$, $p = 0.0378$). These findings were consistent with indistinguishable sequential effect between young and older adults.

Because age was not correlated with the magnitude of sequential effect, we hypothesized that greater PFC activation to p(Stop) and IOG activation to RT slowing (Fig. 2b) served to support performance in older people. To confirm, the results of GCA showed that PFC Granger caused IOG ($p < .0001$, permutation test). Further, in linear regression of the sequential effect vs. PFC-IOG connectivity (the F value in Geweke test of GCA) for the three age groups (≤30, 30 < age < 50 and ≥ 50 years), older adults demonstrated a significantly positive correlation ($r = 0.5696$, $p = 0.0136$), which was absent in the younger and middle-aged groups (Age ≤ 30: $r = 0.0315$, $p = 0.7669$; 30 < Age < 50: $r = 0.2498$, $p = 0.1831$). In addition, slope tests (Zar 1999) showed no differences between the younger and middle-aged groups ($t = 0.6910$, $p = 0.2306$), a marginal difference between the middle-aged and older groups ($t = 1.6246$, $p = 0.0557$), and a significant difference between the younger and older groups ($t = 2.0183$, $p = 0.0231$). These results together suggest that PFC and IOG activations and PFC-IOG connectivity served to support proactive control during aging (Fig. 4).

Discussions

Age was not significantly correlated with the sequential effect, suggesting preserved proactive control during aging. Meanwhile, greater age-related activations to p(Stop) were found in the left lateral prefrontal cortex, left superior parietal cortex, paracentral gyrus, as well as cerebellum, and greater age-related activations to prolonged RT were found in the right inferior occipital gyrus. Such age-sensitive differences may suggest compensatory mechanisms to support behavioral performance in older adults, as demonstrated in functional connectivity. First, the circuits of proactive control as shown by Granger causality analysis appeared to be similar in old and young individuals. Second, the sequential effect and Granger causality measures of age-related circuits of proactive control were positively correlated in older but not younger adults. Thus, changes in functional activities and connectivities support proactive control during aging in the stop signal task.

Age-related activations to proactive control

We replicated preserved proactive control in aging (Bloemendaal et al. 2016; Hsieh and Lin 2017b;

Table 1 Brain regions showing age-related activation to stop signal anticipation or p(Stop) and goRT, and activation to p(Stop) in negative correlation with SSRT

Contrast	Region	Cluster Size	Corrected *P* Value	Peak Voxel Z Value	MNI Coordinate (mm)		
					X	Y	Z
p(Stop) > 0 pos. With Age	CBL	454	0.000	4.91	6	−67	−14
	PCL	104	0.046	4.16	9	−28	70
	L SPL	160	0.011	3.89	−33	−61	52
	L PFC	136	0.020	3.80	−42	23	10
goRT>0 pos. With Age	R IOG	51	0.049^	4.44	36	−76	−11
p(Stop) > 0 neg. With SSRT	R Caudate	156	0.013	4.16	9	14	1
	VMPFC	147	0.016	3.79	0	53	10

CBL cerebellum; *PCL* paracentral lobule; *SPL* superior parietal lobule; *PFC* prefrontal cortex; *IOG* inferior occipital gyrus; *VMPFC* ventromedial prefrontal cortex

^ peak voxel p value. L = Left; R = Right

Kleerekooper et al. 2016; Smittenaar et al. 2015). For instance, in an SST with both unprepared and prepared go responses, old and younger adults showed no differences in proactive control, measured as the difference in SSRT between unprepared and prepared conditions (Smittenaar et al. 2015). Using a probabilistic SST with different levels of cue validity, Bloemendaal et al. (2016) investigated proactive control as measured by the slope of RT vs. stop signal probability. Older adults performed significantly worse than younger adults at the high but not at the low or intermediate levels of cue validity. Greater responses to proactive control were observed for low and intermediate loads in the cerebellum, cuneus, left and medial PFC, and occipital gyrus in older as compared to young adults. On the other hand, older as compared to young adults showed decreased activation in the pre-SMA and right dorsolateral PFC to high loads. These findings suggested that older adults were able to maintain proactive control at lower but not high load levels with compensatory neural processes. In a similar study, Kleerekooper et al. (2016) reported no age effects on the slope of RT as a linear function of stop signal probability. Neural activations of proactive control were examined by the difference between go trials with >0 vs. 0 stop signal probability. The contrast revealed higher age-related activations in bilateral middle/superior frontal gyrus extending to the anterior cingulate cortex, left superior parietal gyrus, and subcortical regions including the thalamus and pallidus. The authors interpreted the overall age-related increases in frontal parietal activation as a compensatory process. The current finding of higher age-related PFC response to proactive control is therefore consistent with these previous studies.

In another work, proactive control was quantified by differences in RT and error rates across a choice reaction time task (CRT), SST, and selective SST, each requiring an increased degree of proactive control: CRT < SST < selective SST (Hsieh and Lin 2017b). In general, older adults reacted slower than younger adults in all tasks. However, the interaction between age and task was not significant and older adults did not produce significantly more choice errors than younger adults, suggesting that aging did not involve additional costs in proactive control. In an event-related potential study of the same paradigms, preserved proactive control was reflected by a similar extent of RT slowing in the SST and CRT, as well as increased frontal potentials during the SST, potentially suggesting a compensatory process during aging (Hsieh and Lin 2017a).

Studies of other behavioral paradigms similarly highlighted limited age-related declines in proactive control. In an interference task, a subliminal prime appeared only briefly and immediately before the target, and participants responded promptly to the target according to stimulus-response mapping in alternating blocks with mostly congruent (MC) and mostly incongruent (MI) trials (Xiang et al. 2016). Participants responded faster and more accurately to target during congruent than incongruent trials (a priming effect), as a result of learning prime-target congruency (Rybash and Osborne 1991). Both the young and old groups showed equitable proactive control, as quantified by the magnitude of priming effect in MI versus MC, suggesting that proactive control may be spared during aging.

Studies have reported age-related decreases in occipital activation during working memory, visual attention, language, and emotion tasks (Li et al. 2015; Spreng et al. 2010). According to the proposition of Posterior-Anterior Shift with Aging or PASA, increased PFC activation was accompanied with decreased occipital activation in the aging brain, with over-recruitment of the PFC compensating for behavioral performance (Davis et al. 2008). On the other hand, increases in occipital activation were found in older adults performing a semantic matching task at a comparable level as younger adults (Peelle et al. 2013). In an electroencephalographic study of visual attention task, increased parieto-occipital coupling in beta frequency band predicted better performance during "pop-out" target detection in older adults (Li and

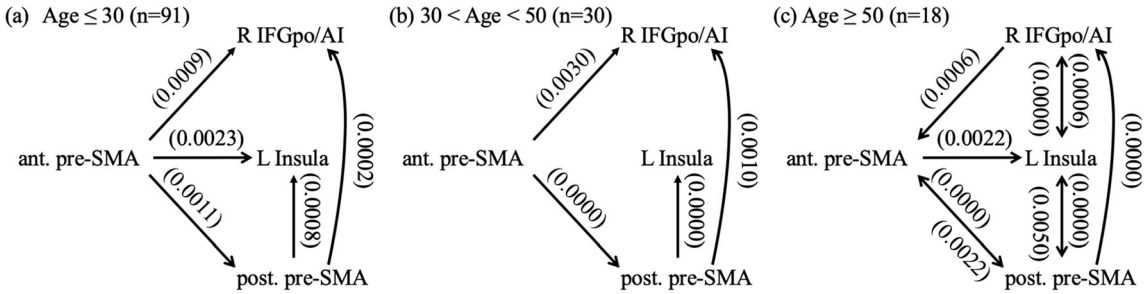

Fig. 3 GCA demonstrated how time series of the anterior pre-SMA (stop signal anticipation) and right IFGpo/AI, left insula, and posterior pre-SMA (prolonged RT) were directionally connected in Geweke tests. The results are shown for individuals (**a**) age ≤ 30 years, (**b**) age between 30 and 50 years; and (**c**) age ≥ 50 years. Connectivity *p* value in parenthesis. The effective connectivity appeared to be largely intact in the oldest group

Zhao 2015). Together, although an occipital cortical mechanism does not appear to be typically implicated in behavioral compensation during proactive cognitive processes, the current findings along with these earlier studies suggest that the role of the occipital cortices need to be more carefully examined for age-related changes in the neural processes across different paradigms.

Age and functional connectivity for proactive control

Our previous study revealed a directional link between conflict anticipation (anterior pre-SMA) and RT slowing (posterior pre-SMA and bilateral IFGpo/insula) to support proactive control (Hu et al. 2015). Here, the Granger causal connections were mostly replicated, except that there were more bidirectional links and the direction from anterior pre-SMA to right IFGpo/insula was reversed in adults over 50 years of age. Importantly, the functional coupling between the PFC and LOG, each showing higher age-related response to p(Stop) and goRT, was positively correlated with the magnitude of sequential effect, suggesting a potential compensatory mechanism.

Although task-related and resting state connectivities generally decreased with age (Sala-Llonch et al. 2015), greater connectivities have been reported to support behavioral performance in older adults (Reuter-Lorenz and Park 2010). For example, in a word matching task, two words were presented on the same side (unilateral condition) or opposite sides (bilateral condition) of the screen, and participants were to decide if the words were semantically related (Davis et al. 2012). Analysis of variance showed no main effect of age group or condition but a significant age group by condition interaction, with young but not older participants demonstrating better sensitivity (d′ score) in the unilateral than in the bilateral condition. Compared to young adults, older adults showed greater functional connectivity (FC) between left and right PFC in the bilateral condition, suggesting that enhanced connectivity helped older adults maintain performance. Greater FC between bilateral PFC and the hippocampus was also found in older adults performing a scene recognition task (Dennis et al. 2008). Older adults showed greater FC of bilateral PFC and the amygdala when viewing pictures with negative valence, potentially reflecting enhanced emotion regulation (St Jacques et al. 2009) in support of the "positivity effect" (Charles et al. 2003). Less pronounced decreases in connectivity between the SMA and bilateral premotor as well as primary motor cortex were observed in older versus younger adults to support performance in a simple reaction time task (Michely et al. 2018). Similar findings were obtained in a face-matching task where stronger connectivity between the orbital frontal cortex and fusiform gyrus was observed in link with lower error rates in older adults (Burianova et al. 2013). In sum, the current findings add to the literature of increased FC as a compensatory mechanism in the aging brain.

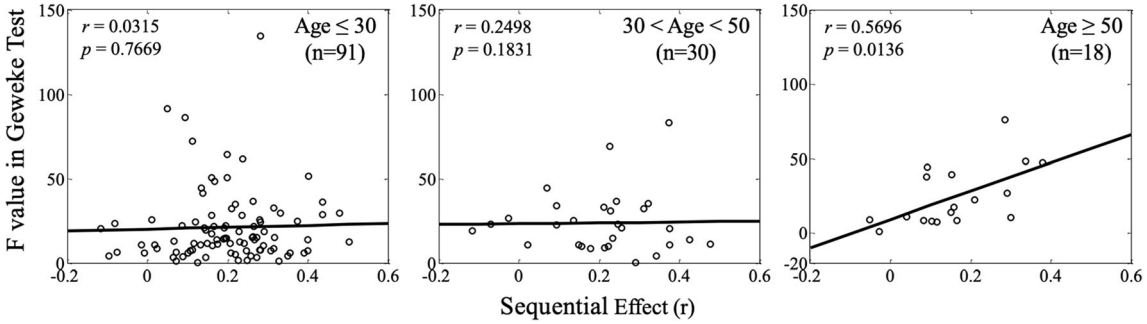

Fig. 4 Correlation between sequential effect and Granger causality of prefrontal cortex (PFC) on inferior occipital gyrus (IOG) in groups of age ≤ 30 years ($r = 0.0315$, $p = 0.7669$), 30 < age < 50 years ($r = 0.2498$, $p = 0.1831$), and age ≥ 50 years ($r = 0.5696$, $p = 0.0136$)

Proactive vs. reactive control during aging

As a measure of reactive control, the SSRT represents the time required to stop the motor response since the appearance of the stop signal. A shorter SSRT indicates better reactive control. The SSRT was negatively correlated with the magnitute of sequential effect even after controlling for age, suggesting that proacive and reactive control may be inter-related. Our previous study showed that age was associated with diminished regional activations during reactive control (Fig. 3c and d in Hu et al. 2018). Here, whole-brain linear regression showed greater activations of the VMPFC and caudate head during stop signal anticipation in association with shorter SSRT. However, these regional activities were not correlated with age. Further, age-related regional processes appear to be distinct for proactive control (current study) and reactive control (Hu et al. 2018). Together, these findings suggest that the neural processes of proactive and reactive control are not influenced in parallel by age and that the compensatory processes for proactive control did not translate to support reactive control during aging.

Other behavioral paradigms

Studies of other behavioral tasks have presented evidence of impaired proactive control during aging. In the AX-continuous performance task (AX-CPT) a sequence of letters appeared one at a time, with the letter A (a valid cue) instructing a target response to the valid probe X (~70% of trials), and other combinations such as BX, AY, and BY instructing a non-target response (Braver 2012). Because correct response required maintenance of information across time (i.e., working memory for proactive control), individuals typically showed a higher error rate in AY than in BX trials. Compared to younger adults, older adults showed lower error rates and comparable RT in AY trials but increased error rates and RT in BX trials, suggesting impaired proactive control but intact reactive control (Jimura and Braver 2010; Braver et al. 2005). Likewise, in a working memory task where proactive interference was measured by the RT and error rates based on the temporal distance of the lure and target (Samrani et al. 2017), older as compared to young adults showed greater interference effects, with higher error rates and longer RT during increased memory loads. Thus, it appeared that proactive control that requires extensive working memory would decline with aging, in contrast to the findings obtained of the stop signal task. These considerations suggest the importance in considering the psychological constructs required of behavioral performance to thoroughly evaluate age-related changes in cognition.

Limitations and conclusions

This study has several limitations. First, we used a convenience sample of participants with a small number of older adults. In particular, the skewed age distribution may account for the lack of a significant correlation between age and the magnitude of sequential effect. Moreover, the three age groups were defined arbitrarily for the correlation between sequential effect and PFC-IOC connectivity. The current findings are thus preliminary and need to be replicated with a larger sample size of the elderly. Second, it is important to note that the results of Granger causality analysis describe the temporal relationship between two time series and "Granger causality" does not characterize biological causality. More broadly, the validity of the application of GCA to fMRI data continues to be debated, particularly with respect to the requirement of the time series being stationary and the difficulty in interpreting GC at the neural level (Wen et al. 2013b). A recent study suggested that the average GC computed for each session for an individual participant is a more sensitive measure for studies involving multiple sessions (Wen et al. 2013a). On the other hand, this approach resulted in a greater number of participants with non-stationary time series in our data. We thus employed the "classical GCA" by concatenating time series across sessions so they were covariance stationary (Seth et al. 2015). Further, studies have suggested that the GC might be affected by the potentially distinct HRF in different brain regions, smaller TR and noise during data acquisition (Seth et al. 2015; Wen et al. 2013b). Wen et al. (2013b) varied the latency of HRF, TR and noise level, and found that the GC of neural and fMRI signals maintained a monotonic relationship, supporting the validity of GCA of fMRI data. For instance, the GC from the dorsal to ventral attention network was positively correlated with better top-down performance, and vice versa, in a spatial attention task (Wen et al. 2012). Using the same task, the GC from the task control to the default mode network was also associated with better performance (Wen et al. 2013a). It thus appears that GCA can be fruitfully applied to fMRI data when all assumptions are met.

In sum, we replicated earlier findings of spared proactive control, quantified by the sequential effect, in older adults performing a stop signal task. Proactive control in older adults was accompanied by greater prefrontal, paracentral cortical, and cerebellar activation during stop signal anticipation and stronger prefrontal and inferior occipital cortical connectivity, supporting a neural compensatory mechanism in the aging brain. Further, the caudate head and ventromedial prefrontal cortex showed greater activations during conflict anticipation in negative correlation with SSRT. However, these regional activities did not vary with age, suggesting that these neural processes for proactive control did not translate to influence reactive control. These new findings highlight the neural plasticity, albeit limited, of the aging brain.

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Compliance with ethical standards

Conflict of interest Author C-S.R. Li has received research grants from NIH (DA023248, AA021449, and MH113134) and he declares no conflict of interest. Author H.H. Chao has received research grants from the NIH (CA218501) and VA (VA Merit Award CX001301) and she declares no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All participants signed a written consent after given a detailed explanation of the study in accordance with a protocol approved by the Yale Human Investigation Committee.

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