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ORIGINAL ARTICLE

Effects of aging on sequential cognitive flexibility are associated with fronto-parietal processing deficits

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Abstract

Albeit cognitive flexibility is well known to decline in aging, it has not been considered that this ability often requires sequential task control. That is, one may re-use tasks that have previously been abandoned in favor of another task. It is unclear whether sequential cognitive flexibility is affected in aging and what neurophysiological mechanisms and functional neuroanatomical structures are associated with these effects. We examined this question in a system neurophysiological study using EEG and source localization in healthy and elderly adults. We show that elderly people reveal deficient sequential cognitive flexibility. Elderly people encounter increased costs to overcome the inhibition of the lately abandoned task set that becomes relevant again and needs to be re-used. The neurophysiological (EEG) data show that differences in sequential cognitive flexibility between young and elderly people emerge as a consequence of two independent, dysfunctional processes: (i) the ability to suppress task-irrelevant information and (ii) the ability to re-implement a previously abandoned task set during response selection. These independent processes were associated with activation differences in inferior frontal and inferior parietal regions. The study reveals a new facet of cognitive flexibility dysfunctions in healthy elderlies.

Keywords Aging · Cognitive flexibility · EEG · Inhibition · Response selection · Parietal cortex · Inferior frontal cortex

Introduction

Cognitive flexibility or the ability to switch between different tasks is a core function of executive control and depends on the function of various prefrontal cortical structures (Diamond 2013). It allows us to flexibly control and adapt behavior to manage changing demands of our environment (Diamond 2013). As a central component of our daily life, cognitive flexibility and its developmental changes have been examined extensively on a neurophysiological as well as on a behavioral level (Diamond 2002, 2013; Davidson et al. 2006; Berry et al. 2016). Taking into account that cognitive flexibility is partly related to the changes in prefrontal cortical neuroanatomy, one consistent finding is that it declines with aging (for review: Gajewski et al. 2018; Verhaeghen and Cerella 2002). In many daily life situations, we re-encounter a task that has previously been abandoned in favor of another task. For example, this is the case in a situation where one switches from making a phone call to going to the door as the doorbell rings before going back to the phone. Thus, cognitive flexibility often refers to sequential task control (Hübner et al. 2003; Zink et al. 2019). Yet, it is elusive whether sequential cognitive flexibility is affected in aging and which neurophysiological mechanisms and associated functional neuroanatomical structures are associated with these effects.

Sequential cognitive flexibility is reflected by the backward inhibition (BI) effect (Allport et al. 1994; Allport and Wylie 1999). The BI effect emerges, because cognitive flexibility requires the activation of a new task set, which warrants the deactivation of the no longer needed, competing task through inhibitory processes (Mayr and Keele 2000; Klimesch 2011; Dajani and Uddin 2015). When switching back to a recently suppressed task set (e.g., task A) after another intermediate task set (B) has been used (e.g. ABA triplet/BI condition), the performance costs are higher

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compared to a task history without $n-2$ task repetitions in a sequence (e.g., DBA task triplet/BASE condition) (Mayr and Keele 2000). The BI effect refers to the time costs of overcoming the inhibition of the lately abandoned task set that becomes relevant again (Mayr and Keele 2000). Therefore, a strong BI effect suggests large costs during sequential cognitive flexibility (Allport et al. 1994; Allport and Wylie 1999). Formally, the BI effect concerns the interplay of the $n-2$ and $n-1$ trials and its effect on the nth trial (Zhang et al. 2016a, b).

From a neurobiological and functional neuroanatomical perspective, there is ample reason to assume that backward inhibition processes are altered in aging. One consistent reference is that the dopaminergic system becomes dysfunctional in aging (Bäckman et al. 2006, 2010; Li et al. 2010; Li and Rieckmann 2014). The catecholaminergic system, the dopaminergic system in particular, plays an important role in inhibitory control processes (Hershey et al. 2004; Bari and Robbins 2013; Albrecht et al. 2014). Inhibitory control processes are needed during backward inhibition to suppress the no longer needed, irrelevant task set (Mayr and Keele 2000; Klimesch 2011; Dajani and Uddin 2015), i.e., they represent a mechanism to suppress the effect of the $n-1$ trial on the $n-2$ trial (Wolff et al. 2018). This is reflected by the P1 event-related potential (ERP) component (Wolff et al. 2018). The P1 ERP component has been assumed to represent mechanisms related to the suppression of incoming, competing information (Klimesch 2011). It has been shown that a small BI effect (indicating efficient sequential cognitive flexibility) is associated with a larger P1 ERP component and that these modulations are associated with functions of the inferior frontal gyrus (rIFG) (Wolff et al. 2018). Notably, right inferior frontal regions have been associated with inhibitory processes (Aron et al. 2004a, b, 2014; Whitmer and Banich 2012; Wolff et al. 2017a, 2018). Several studies show that the rIFG (Hu et al. 2018) and inhibitory control are dysfunctional in elderly people (Hu and Li 2012; Coxon et al. 2016; Lee and Hsieh 2017).Therefore, we hypothesize that elderly people show an increased behavioral BI effect that is associated with a smaller P1 ERP component and diminished right inferior frontal gyrus activity, compared to a younger group.

However, it needs to be considered that aside from inhibitory control processes operating at the level of perceptual categorization, also response selection processes are important (Zhang et al. 2016a, b) and mediated via the anterior cingulate cortex (ACC) (BA24, BA32) and the right inferior parietal lobe (BA40) (Zhang et al. 2016a, b; Wolff et al. 2018). Likewise, they are modulated by the dopaminergic system (Zhang et al. 2016a, b). Since these areas and connections between them undergo declines during aging (Grady 2008; Hämmerer and Eppinger 2012; Lockhart and DeCarli 2014; Bubb et al. 2018), it is likely that dysfunctional response selection processes contribute to a stronger BI effect in elderly people. During backward inhibition, response selection processes are increasingly taxed and subjects need to increase response selection efforts (Zhang et al. 2016b). Considering age-related dysfunctional mechanisms associated with fronto-parietal cortices, it is possible that elderly people are not able to increase efforts for response selection in backward inhibition.

One important aspect regarding the neurophysiological processes is that neurophysiological (ERP) methods can only yield accurate insights into the processes when there is little intra-individual variability (Ouyang et al. 2011, 2015a, b). Neurodevelopmental processes, however, are associated with high intra-individual variability (MacDonald et al. 2006; Garrett et al. 2013; Holtzer et al. 2014). Reliable age-related modulations in inhibitory control and response selection processes can only be detected when intra-individual variability in neurophysiological data is considered (Bodmer et al. 2018a, b). One means to do so is to apply a temporal EEG signal decomposition method—residue iteration decomposition (RIDE) (Ouyang et al. 2011, 2015a; Verleger et al. 2014). RIDE decomposes ERP data into several component clusters while accounting for intra-individual variability in the data. These clusters have different functional relevance: the S-cluster is related to early stimulus-related (gating) processes, the R-cluster reflects response-related processes (i.e., motor execution), and the C-cluster refers to intermediate processes between S and R (i.e., response selection) (Ouyang et al. 2011). We hypothesize that neurophysiological processes and functional neuroanatomical structures underlying age-related dysfunctions in backward inhibition cannot reliably be estimated using standard ERPs, but are evident when controlling for intra-individual variability and analyzing RIDE cluster components. We hypothesize that the S-cluster and the C-cluster reflect group differences in backward inhibition. Regarding the S-cluster, we hypothesize that the amplitude in the P1 time window in BI trials will be lower in elderly compared to younger adults. This will reflect deficient inhibitory control. Furthermore, these amplitude modulations arise from activity modulations in the right inferior frontal gyrus. Moreover, we hypothesize that there will be increases in C-cluster amplitudes in younger subjects in BI trials, compared to BASE trials. In elderly people, we hypothesize that there is no such increase in the C-cluster amplitude in BI trials. Since response selection processes during backward inhibition have been shown to be mediated via a fronto-parietal network (Zhang et al. 2016a, b), we hypothesize that these brain regions are associated with modulations in the C-cluster.

Materials and methods

Participants

For the a priori power calculation, we considered a mild-to-moderate effect size of $f=0.30$ to be detectable with a power of 95%. This corresponds to a partial eta squared in the hypothesized interaction "condition × group" of $\eta_p^2=0.08$–0.10. Accordingly, the power analysis recommended a total sample size of $N=40$ participants ($N=20$ per group). In total, $N=50$ healthy participants took part in the study ($N=25$ elderly and $N=25$ younger participants). $N=5$ elderly adults had to be excluded due to low EEG data quality (i.e., no reliable analysis was possible due to the high amount of artifacts). The remaining $N=20$ elderly adults (mean age 60.10 ± 1.24, 9 males, 11 females) and $N=25$ young adults (mean age 24.52 ± 0.75, 9 males, 16 females) were included in data analysis. The obtained effect sizes were in the range of $\eta_p^2=0.11$–0.14 and an analysis of the achieved power revealed a power greater than 98%. All subjects had normal or corrected-to-normal vision (self-report). Subjects' handedness was measured using the Edinburgh Handedness inventory (Oldfield 1971)—all participants were right-handed (LQ 90 ± 5). None of the participants had neurological or psychiatric diseases. None of the young adults was medicated. $N=11$ of the elderly adults were medicated, e.g., for hypertension or hyperthyroidism. The medication profile is shown in Table 1. Before the experiment started, written informed consent was obtained from all participants. The ethics committee of the TU Dresden approved the study.

Experimental setting and task

We used a backward inhibition paradigm introduced by Koch et al. (2004), as done in the previous studies by our group (Zhang et al. 2016a, b; Wolff et al. 2018). The paradigm is shown in Fig. 1.

The subjects were seated in front of a 19″ TFT screen and were instructed to respond using the left and right Ctrl buttons with the respective index finger. Each trial started with the presentation of one of three geometric forms, which served as cue stimuli and indicated the different task rules. Stimuli were coloured white and were presented on black background. A square indicated task A (odd or even). Here, participants had to indicate whether the target was odd (left index finger) or even (right index finger). A diamond cue indicated task B (smaller or larger), where the subjects decided whether the presented digit is smaller (left index finger) or larger (right index finger) than 5. Finally, a triangle indicated task D (double press), where the participants had to press both Ctrl buttons simultaneously and as fast as possible. Digits between one and nine (except five) were used as target stimuli and appeared 100 ms after cue onset inside the cue frame (= stimulus onset asynchrony, SOA). In task A and B, the stimuli remained on screen until a response was executed. In task D, the participants were requested to respond within 1000 ms. If this time interval was exceeded, a speed-up sign "Schneller!" (German word for "Faster!") appeared above the cue frame. If the response was given after the speed-up sign was shown, the subjects received the additional feedback "Zu langsam!" (German word for "Too slow!"). In this condition, too slow responses (> 1000 ms) were counted as errors. To ensure comparability between the tasks, the speed-up sign was also presented in task A and B whenever the responses exceeded the response deadline of 1000 ms. However, for these tasks, the response cut-off was defined at 2500 ms (i.e., responses > 2500 ms were counted as errors). In task D, a response had to be executed irrespective of the digit. Therefore, task D does not require complex response selection processes (in contrast to task A and B). Responses in task D can be regarded

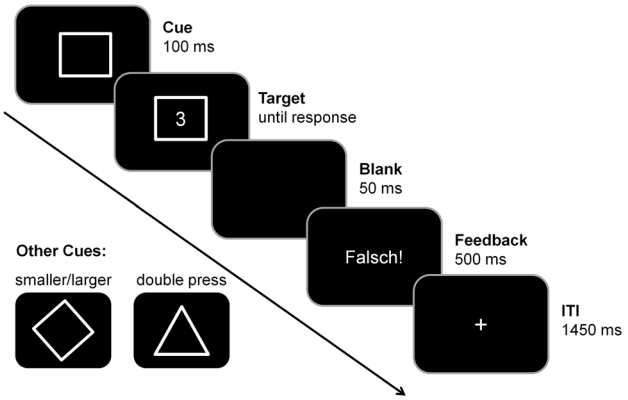

Fig. 1 Experimental task. Trials started with the presentation of one cue, indicating the odd or even rule (square cue, task A), the smaller or larger rule (diamond cue, task B) or the double-press rule (triangle cue, task D). A target (digit from 1 to 9, except 5) occurred centrally inside the cue stimulus 100 ms after cue onset. The target was shown until a key press was executed, except in the double-press task. The inter-trial interval ranged over 2000 ms. An error feedback was shown for 500 ms after incorrect trials

Table 1 Medication profile

Total	$N=11$
Multiple consumers (more than 1 drug)	$N=5$
High blood pressure medication	$N=6$
Hypothyroidism medication	$N=5$
Antidepressants	$N=1$
Dietary supplements	$N=2$
Statins	$N=1$
Proton pump inhibitors	$N=1$

as unconditional responses, making task D a rather simple task compared to the other two task rules (Koch et al. 2004). After a response was executed, the next trial (cue stimulus) was presented after a fixed time interval of 1500 ms (= response stimulus interval, RSI). During this interval, a fixation cross was shown in the center of the screen. Incorrect key presses, too slow responses, and non-simultaneous reactions in task D were counted as errors. In error trials, the feedback "Falsch!" (German word for "Wrong!") was presented for 500 ms before the RSI started. The instructions were given in written form and verbally. The subjects were requested to respond as accurately and as fast as possible. A practice was run before the main experiment started. The paradigm consisted of 768 trials, divided into eight equally sized blocks. Tasks A, B, and D were presented equally frequently in each block. Immediate repetitions of the cue or the target were not possible (e.g., trials with a diamond cue and a target stimulus 6 followed by a trial with a diamond cue and a target stimulus 7 could not occur. Likewise, two different cues including the same target or rather digit could not occur in two consecutive trials). Each trial (except for the first two trials in each block) formed a triplet with the last two preceding trials. There were 12 triplet combinations (ABA; ADA; BAB; BDB; DAD; DBD; DBA; BDA; DAB; ADB; BAD; ABD). Each triplet combination was categorized either to the backward switching or to the baseline condition. When the last trial n of a triplet had the same cue as the $n-2$ trial (e.g. ABA, BAB), this triplet represented the backward switching (BI) condition. Triplets without these $n-2$ cue repetition were categorized as baseline (BASE) condition. Considering the exclusion of the first two trials in each block, 380 triplets related to the BI and 372 triplets to the BASE condition.

EEG recordings and data processing

The EEG data were recorded utilizing a 72-channel QuickAmp amplifier (BrainAmp, Brain Products Inc.) and BrainVision Recorder software (Brain Products Inc.). An equidistant 60 Ag–AgCl-EEG setup was used in which the ground electrode was located at $\theta = 58$, $\phi = 78$, and the reference electrode at position Fpz. The sampling rate was set to 500 Hz and electrode impedances were kept below 5 kΩ. After recording, the data were down-sampled to 256 Hz and band-pass filtered (IIR filter: 0.5 Hz to 20 Hz, slope of 48 dB/oct each). By means of a manual raw data inspection, technical artifacts were eliminated (i.e., "offsets" in the EEG). Afterwards, an independent component analysis (ICA, infomax algorithm) was conducted to correct periodically reoccurring artifacts like blinks, vertical eye movements, and pulse artifacts. After these corrections, cue-locked segments were formed for all conditions separately. Only trials with correct responses were considered in the segmentation step. Segments started − 200 ms prior to cue onset and ended 1200 ms thereafter. Furthermore, an automated artifact rejection procedure was conducted in these segments, using amplitude differences above 200 µV in a 200 ms time interval as well as activity below 0.5 µV in a 100 ms time span as rejection criteria. To ensure a reference-free evaluation of the electrophysiological data, a current source density (CSD) transformation was run (Kayser and Tenke 2015). CSD transformation has been used in the previous studies of our work group using the same task and, therefore, fosters comparability across studies and examined populations (Zhang et al. 2016a, b; Wolff et al. 2018). Following the CSD transformation, a baseline correction was performed to a pre-stimulus interval of − 200 to 0 ms before cue onset and segments were averaged for each subject and condition. The following ERP components were quantified on the single subject level: The P1 component following the cue was quantified at electrodes P7 and P8 in the time interval from 80 to 100 ms for both groups. The cue N1 mean amplitude was quantified at electrode P8 in an interval from 130 to 160 ms for both groups. The visual inspection of the data showed latency delays between young and elderly adults. The previous studies showed that this observation is very common examining developmental changes (Kok 2000; Zanto et al. 2010; Bourisly 2016). Thus, the P1 evoked by the target stimulus was quantified at electrode P8 in an interval from 200 to 220 ms for both groups. At electrode P7, the amplitudes were quantified between 200 and 220 ms for elderly adults and between 230 and 270 ms for younger adults. The quantification of the target N1 was conducted at electrode P8 in a time window from 240 to 270 ms for both groups. At electrode P7, the mean amplitudes were quantified from 250 to 270 ms for elderly adults and from 340 to 365 ms for young adults. The target P1 at electrode PO1 and PO2 was quantified in an interval between 230 and 240 ms for young adults and between 250 and 260 ms for elderly adults. The P3 component at electrode Pz was quantified in a time window from 550 to 600 ms in both groups.

The choice of electrodes and search intervals for data quantification was based on the inspection of scalp topographies with a subsequent statistical validation of this choice. This validation has been introduced before (Mückschel et al. 2014) and revealed the same electrodes as identified in the visual inspection of the data. For the source localization, sLORETA was conducted using standardized low-resolution brain electromagnetic tomography (Pascual-Marqui 2002) (for details, see "Source localization analysis (sLORETA)".

It may be argued that the short cue-stimulus interval of 100 ms causes problems in EEG data quantifications. However, this is note case for the following reasons. To quote: "The reason for this is that when analyzing the BI effect in the last trial of a triplet, one does not directly compare different conditions or trials as there are no differences in the

conditions of the last trial the triplets used to compare the BASE and BI conditions. The BI condition comprises the two triplets ABA and BAB, so that ERPs obtained from both A and B trials will be averaged to form the BI condition. The BASE condition comprises the two triplets DBA and DAB, so that, again, EEG data obtained from both A and B trials will again be averaged to form the BASE condition. Therefore, comparing the BI and BASE conditions means comparing an average of A&B trials to an average of A&B trials. When investigating the BI effect, we are interested in the interplay of the $n-2$ and $n-1$ trials and its effect on the nth trial. Due to the sufficiently long RSI of 1500 ms, there can be no overlap between the ERPs evoked by the $n-1$ or $n-2$ trial and the trial which we quantified for analyses. Aside from this, the experimental paradigms used in both groups were absolutely identical. Hence, it is entirely impossible that any of the reported effects caused by either group or BI condition are caused by an overlap of ERP components" (Zhang et al. 2016a).

Residue iteration decomposition (RIDE)

As outlined, ERPs consist of various components with variable inter-component delays (Ouyang et al. 2015b). Traditionally, they are calculated by averaging the data across a number of single trials (Ouyang et al. 2015b), but this procedure barely considers the trial-to-trial variability of brain activity patterns (Ouyang et al. 2011, 2015a). As done previously by our work group (Chmielewski et al. 2017; Mückschel et al. 2017; Bodmer et al. 2018b), we applied the RIDE analysis utilizing the toolbox package and manual of RIDE available on http://cns.hkbu.edu.hk/RIDE.htm using MATLAB (MATLAB 12.0; Mathworks Inc.). RIDE analysis is based on an iteration procedure of residues of the averaged ERPs, decomposing ERP components by utilizing an *L1*-norm minimization (Ouyang et al. 2011, 2015a). The decomposition is conducted for each electrode separately. RIDE decomposes the ERP signals into clusters that are either associated with the stimulus onset (S-cluster) or with the response time (R-cluster). Moreover, there is a central component (C-cluster) with variable latency, which is neither locked to the stimulus onset nor to the response time (Ouyang et al. 2011, 2015a). The time markers to derive the C-cluster are estimated and iteratively improved. This scheme improves timing using the time markers of stimulus onsets and RTs. Full mathematical details on the RIDE method can be found in various methodological papers (Ouyang et al. 2011, 2015a). For the calculation of the components (S-, R-, and C-clusters), RIDE uses a time window function, which is assumed to cover the time span in which each component occurs (Ouyang et al. 2011, 2015a). In the present study, the S-cluster window was timed between −200 and 600 ms, the search interval for the C-cluster was defined from 0 to 900 ms, and the R-cluster window was timed ± 300 ms around the response trigger (Ouyang et al. 2015b). Each cluster was quantified on the single subject level. The S-cluster mean amplitudes were quantified at electrodes P7, P8, PO1, and PO2. The same time intervals as for the standard ERPs served as search intervals for the S-cluster quantification. Equally, the quantification of the C-cluster was conducted at electrode Pz in the same time interval that we used at electrode Pz for the standard ERP component quantification. As done previously by our work group, the R-Cluster mean amplitudes were quantified at electrodes C3 and C4 in an interval from 800 to 1000 ms for both conditions and groups (Wolff et al. 2017b; Bodmer et al. 2018b). Details on the standard ERP-component time windows can be gathered from the supplementary material.

Source localization analysis (sLORETA)

Standardized low-resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui 2002) was applied for source localization using the RIDE data. sLORETA provides a unique linear solution to the inverse problem without a localization bias (Marco-Pallarés et al. 2005; Sekihara et al. 2005). The validity of source localization by sLORETA is supported by several findings of EEG/fMRI and EEG/TMS studies (Sekihara et al. 2005; Dippel and Beste 2015). For the localization, the intracerebral volume is partitioned into 6239 voxels at 5 mm spatial resolution. The standardized current density at each voxel was computed in a realistic head model utilizing the MNI152 template (a realistic head model). In the current study, the images of the intracerebral volume were contrasted between younger and elderly adults as well as between the BI and BASE condition. This comparison was done using the sLORETA-built-in-voxel-wise randomization tests with 3000 permutations, based on statistical nonparametric mapping (SnPM). Voxels holding significant differences between the contrasted groups were located in the MNI brain (www.unizh.ch/keyinst/NewLORETA/sLORETA/sLORETA.htm).

Statistics

Before analyzing the behavioral and neurophysiological data, the first two trials of each of the eight blocks, error trials and the two subsequent trials were excluded. Likewise, trials with RTs higher than 2500 ms or lower than 100 ms were not considered for data analysis. For the calculation of the BI effect, we analyzed the data as done in recent studies by our research group (Zhang et al. 2016a, b). First, to obtain a measurement for BI and BASE condition, we averaged the two backward switching and the two respective baseline triplets, which only differed in the $n-2$ cue. Afterwards, the magnitude of the "BI effect" was calculated using the

RT difference between the BI and BASE conditions [BI effect = mean (ABA, BAB)—mean (DBA, DAB)]. There were eight more possible triplet combinations (ADA, BDB, DAD, DBD, BDA, ADB, BAD, and ABD). These triplet combinations were not considered for the present study, since they were stated by Koch et al. (2004) to examine not only the basic BI effect. Rather, these conditions examine response-related factors and response mode settings (i.e., response selection vs. simple response) in backward inhibition in particular. As outlined in former sections, the aim of this study is to investigate modulatory effects of aging on the magnitude of the BI effect at the behavioral and the neurophysiological levels. Because it is important to consider the signal-to-noise ratio for reliable effects in the neurophysiological data, it is essential to have strong BI effects. This is even more important considering changes of intra-individual variability over the lifespan. As shown in recent studies, the eight above-mentioned triplets did not ensure the occurrence of a robust BI effect (Koch et al. 2004). Considering this, and to keep data analysis and results comparable to the previous published studies using the BI paradigm (Zhang et al. 2016a, b; Wolff et al. 2018; Giller et al. 2019), those triplets were not included in the statistical analysis.

The behavioral and neurophysiological data were analyzed, applying mixed-effects ANOVAs including within-subject factors "condition" (BI vs. BASE) and "electrode". The factor "group" served as between-subject factor. Considering an imbalance regarding the gender ratio between the two groups, no significant main or interaction effects were shown while inspecting the behavioral data (all $F < 0.893$, $p > 0.350$) when taking the factor "gender" into account. Therefore, we did not include this factor in the analysis of the neurophysiological data. Greenhouse–Geisser corrections were applied and post hoc tests were Bonferroni-corrected whenever necessary. To increase the readability of the following section, we focus on reporting effects which are immediately relevant to our research, i.e., interaction effects of "condition" and "group". Other main or interaction effects are shown in the supplementary material.

Results

Behavioral data

The results of the behavioral analysis are shown in Fig. 2.

The mixed-effects ANOVA on reaction times (RTs) revealed an interaction of "condition × group" ($F[1,43] = 5.13$, $p = 0.029$, $\eta_p^2 = 0.106$), which indicated a larger difference between BI and BASE condition in the elderly group (1021 ± 30 ms vs. 940 ± 31 ms; difference: 81 ± 12 ms), compared to younger adults (812 ± 27 ms vs. 755 ± 27 ms; difference: 57 ± 1 ms). A post hoc test revealed that the difference between BI and BASE condition (i.e., the BI effect) was larger in elderly adults than in younger adults ($t(43) = -2.26$, $p = 0.015$). Further tests show that the difference between the BI and the BASE condition was significant in both groups (OA: $t(19) = 6.84$, $p < 0.001$; YA: $t(43) = 86.29$, $p < 0.001$).

For accuracy measures, the mixed-effects ANOVA revealed a significant interaction of "condition × group" ($F[1,43] = 5.50$, $p = 0.024$, $\eta_p^2 = 0.113$), showing decreased percentage of hits in the BASE versus BI condition in the elderly group (BI: 70 ± 4% vs. BASE: 66 ± 3%) ($t(19) = 1.19$, $p = 0.034$), but not in younger adults (73 ± 3% vs. 75 ± 3%) ($t(24) = -1.12$, $p = 0.137$). Analyzing the BI effect in accuracy measures, elderly adults revealed a greater BI effect (4 ± 2%) compared to younger adults (− 1 ± 1%) ($t(43) = -2.23$, $p = 0.033$), Post hoc tests showed that this difference was driven by the BASE condition, since young adults differed from elderly adults in the BASE condition

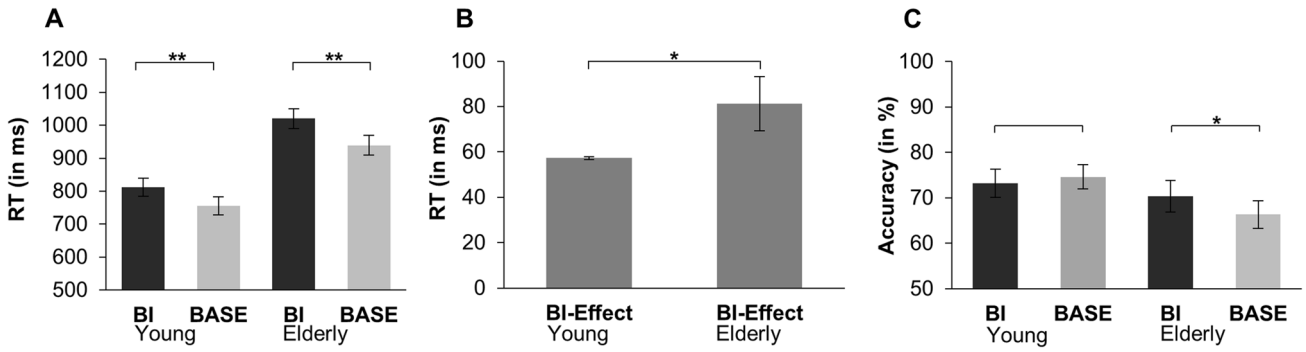

Fig. 2 **a** Mean reaction times for the BI and the BASE condition in young adults (= young) and elderly adults (= elderly). **b** The magnitude of the BI effect (i.e. BI minus BASE) in each group. **c** Percentage of hits (accuracy) for the BI and the BASE condition in young adults and elderly adults is shown on the right. Means and SEMs are given. Stars represent significant differences between conditions or groups

($t(43) = 0.617$, $p = 0.540$), but not in the BI condition ($t(43) = 2.06$, $p = 0.045$). There were no other significant main effects or interactions (all $F < 1.77$, $p > 0.191$).

Neurophysiological data

Standard event-related potentials (ERP)

The standard ERP component is shown in Fig. 3.

For the P1 component elicited by the cue, the mixed-effects ANOVA revealed an interaction effect of "condition × group" ($F[1,43] = 5.06$, $p = 0.030$, $\eta_p^2 = 0.105$), showing a larger difference between the two conditions in younger adults (BI: 21.36 ± 2.65 µV/m^2; BASE: 24.42 ± 2.95 µV/m^2) than in elderly adults (BI: 21.78 ± 2.96 µV/m^2; BASE: 21.19 ± 3.30 µV/m^2). Post hoc tests showed that this difference was significant in younger adults ($t(24) = -2.53$, $p = 0.010$) but not in elderly adults ($t(19) = 0.59$, $p = 0.280$). Thus, the BI effect in the cue P1 was bigger in younger adults (-3.06 ± 1.21 µV/m^2) compared to elderly participants (0.59 ± 1.00 µV/m^2) ($t(43) = -2.25$, $p = 0.015$). There were no more main or interaction effects (all $F < 2.31$; $p > 0.136$). Please note that this interaction cannot explain the behavioral effects, since the cue does not carry information about whether a BI or a BASE stimulus is presented as a target.

Analyzing the N1 component following the cue stimulus, the mixed-effects ANOVA showed no significant interaction of "condition" and "group" ($F[1,43] = 0.65$, $p = 0.426$, $\eta_p^2 = 0.015$). Further results are reported in the supplementary

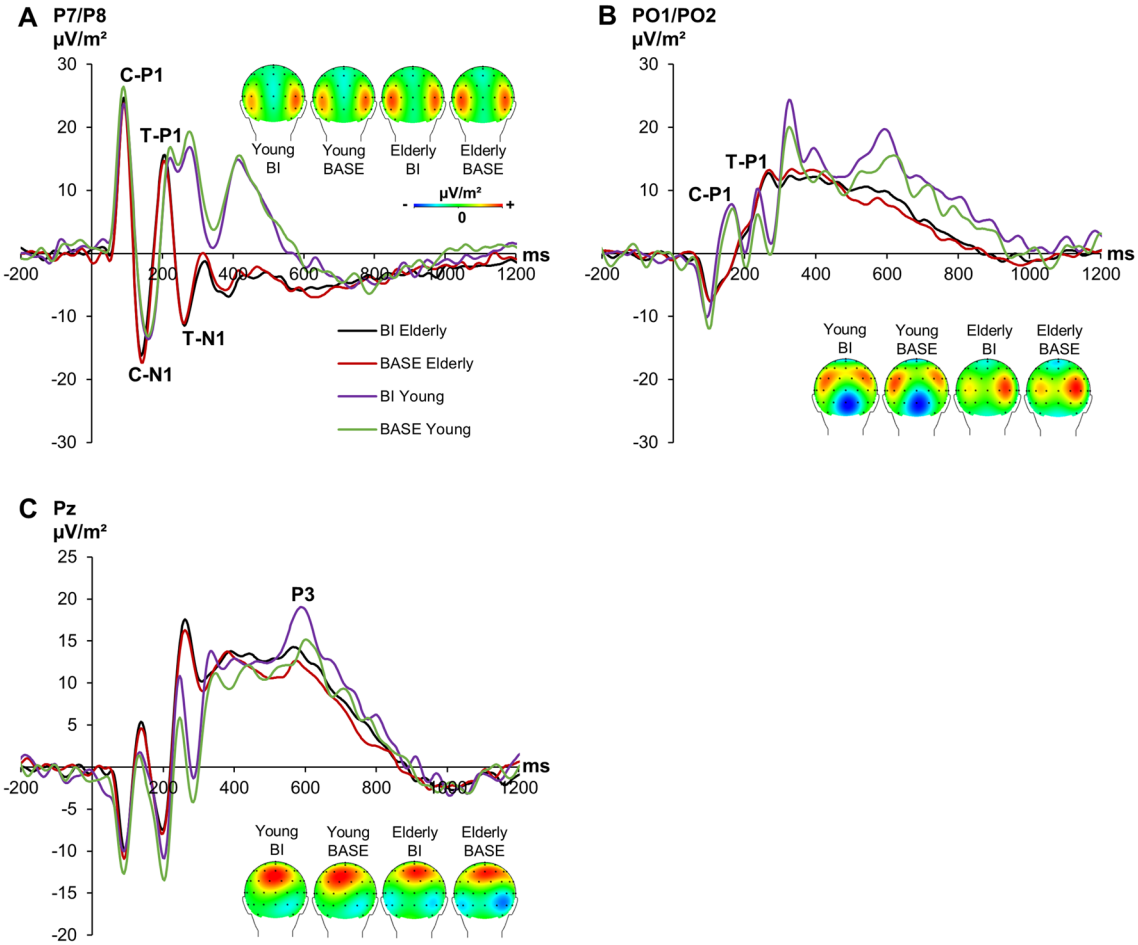

Fig. 3 Standard event-related potential (ERP) components. Time point zero represents the cue onset. The target appeared 100 ms later. **a** P1 and N1 components on the cue and target pooled across electrodes P7/P8. P1 and N1 evoked by the cue (C-P1 and C-N1) are shown in the first two peaks with the corresponding scalp topography maps for C-P1 (at 90 ms). Red colours denote positivity and blue colours negativity. The target P1 and N1 (T-P1 and T-N1) are represented by the following two peaks. **b** The target P1 pooled across the electrodes PO1/PO2 including the corresponding scalp topography for the T-P1 (at 235 ms in young adults and at 205 ms in elderly adults). **c** The P3 ERP was quantified at electrode Pz with the corresponding scalp topography (at 586 ms) for the time point of the P3 peak

material. Likewise, there was no significant interaction effect of "condition" and "group" ($F[1,43] = 1.94$, $p = 0.171$, $\eta_p^2 = 0.043$) when analyzing the P1 evoked by the target stimulus. For other main or interaction effects please refer to the supplementary material. Finally, the mixed-effects ANOVA for the N1 elicited by the target revealed no significant interaction effect of "condition" and "group" ($F[1,43] = 3.53$, $p = 0.067$, $\eta_p^2 = 0.076$). Further effects are reported in the supplementary material. Examining the target P1 on electrodes PO1 and PO2, the mixed-effects ANOVA revealed no significant main or interaction effects (all $F < 2.09$, $p > 0.286$). For the P3 component examined at electrode Pz, the mixed-effects ANOVA showed a significant interaction effect of "condition x group" ($F[1,43] = 7.02$, $p = 0.011$, $\eta_p^2 = 0.140$). This interaction indicates a larger difference between BI and BASE condition in younger adults (BI: 18.06 ± 2.11 μV/m^2; BASE: 13.66 ± 1.88 μV/m^2) in comparison to elderly adults (BI: 11.67 ± 2.36 μV/m^2; BASE: 11.34 ± 2.11 μV/m^2).

Post hoc tests showed that this difference was significant in younger adults ($t(24) = 3.58$, $p = 0.001$) but not in elderly adults ($t(19) = 0.44$, $p = 0.333$).Thus, the BI effect (BI minus BASE) was larger in younger adults (4.40 ± 1.23 μV/m^2) in comparison to elderly participants (0.33 ± 0.76 μV/m^2) ($t(43) = 2.65$, $p = 0.006$). Post hoc tests showed that the group difference in the BI effect was driven by the BI condition, since younger adults differed from elderly adults in the BI condition ($t(43) = 2.02$, $p = 0.025$) but not in the BASE condition ($t(43) = 0.82$, $p = 0.208$). Further main or interaction effects are reported in the supplementary material.

Residue iteration decomposition (RIDE)

S-cluster The S-cluster data are shown in Fig. 4a, b.

The mixed-effects ANOVA in the P1 time window following the cue at electrode P7/P8 revealed a significant interaction of "condition × group" ($F[1,43] = 5.27$, $p = 0.027$, $\eta_p^2 = 0.109$). This interaction showed a larger difference between BI and BASE condition in younger adults (BI: 21.40 ± 2.59 μV/m^2; BASE: 24.71 ± 2.86 μV/m^2) compared to elderly adults (BI: 21.06 ± 2.89 μV/m^2; BASE: 20.69 ± 3.20 μV/m^2). Post hoc tests showed that this difference was significant in younger adults ($t(24) = -2.91$, $p = 0.004$) but not in elderly adults ($t(19) = 0.34$, $p = 0.369$). Thus, the BI effect in the cue P1 was bigger in younger adults (-3.30 ± 1.37 μV/m^2) compared to elderly participants (0.37 ± 1.08 μV/m^2) ($t(43) = -2.30$, $p = 0.014$). There were no further main or interaction effects (all $F < 3.36$; $p > 0.074$).

The mixed-effects ANOVA for the N1 following the cue stimulus revealed no significant main or interaction effects (all $F < 3.69$; $p > 0.061$). For the P1 evoked by the target stimulus at electrodes P7/P8, the mixed-effects ANOVA showed no significant main or interaction effects (all $F < 3.08$, $p > 0.086$). However, previous studies have shown that the P1 on the target stimulus shows differential effects at centro-parietal or parieto-occipital electrode sites (Wolff et al. 2018). The same was the case in the current study, as shown in Fig. 4. The P1 at these more central electrode sites likely reflects a propagation of the P1 signal from parietal electrodes P7/P8 to these electrodes. When analyzing the P1 following the target stimulus at electrodes PO1/PO2, there was a significant interaction between "condition" and "group" ($F[1,43] = 5.38$, $p = 0.025$, $\eta_p^2 = 0.111$), indicating a larger difference between the BI and the BASE condition in younger adults (BI: 9.71 ± 3.50 μV/m^2; BASE: 4.32 ± 3.42 μV/m^2) compared to elderly participants (BI: 8.18 ± 3.91 μV/m^2; BASE: 7.75 ± 3.82 μV/m^2). Post hoc tests showed that this difference between the BI and BASE condition was significant in younger adults ($t(24) = 3.49$, $p = 0.001$) but not in the elderly group ($t(19) = 0.31$, $p = 0.380$). Consequently, it was shown that the BI effect (i.e., BI minus BASE) was larger in younger adults (5.40 ± 1.55 μV/m^2) than in elderly adults (-0.44 ± 1.41 μV/m^2) ($t(43) = 2.32$, $p = 0.013$). The source localization analyses using sLORETA showed that activation differences in the right inferior frontal gyrus (BA47) are associated with this effect.

The mixed-effects ANOVA for the target N1 at electrodes P7/P8 showed no significant interaction effect of "condition" and "group" ($F[1,43] = 0.01$, $p = 0.943$, $\eta_p^2 = 0.000$). More details on other main or interaction effects can be found in the supplementary material.

C-cluster The C-cluster data are shown in Fig. 4c. The mixed-effects ANOVA in the P3 time interval at electrode Pz revealed a significant interaction effect of "condition × group" ($F[1,43] = 6.42$, $p = 0.015$, $\eta_p^2 = 0.130$). This interaction indicates a larger difference between BI and BASE condition in younger adults (BI: 18.08 ± 2.14 μV/m^2; BASE: 14.11 ± 1.81 μV/m^2) in comparison to elderly adults (BI: 11.91 ± 2.40 μV/m^2; BASE: 12.46 ± 2.02 μV/m^2).

Post hoc tests showed that this difference was significant in younger adults ($t(24) = 2.76$, $p = 0.006$) but not in the elderly group ($t(19) = -0.64$, $p = 0.264$). Hence, the BI effect (BI minus BASE) was larger in younger adults (3.96 ± 1.44 μV/m^2) compared to elderly participants (-0.55 ± 0.85 μV/m^2) ($t(43) = 2.53$, $p = 0.008$). Moreover, post hoc tests revealed that the group difference in the BI effect was driven by the BI condition, since younger adults differed from elderly adults in the BI condition ($t(43) = 1.92$, $p = 0.031$) but not in the BASE condition ($t(43) = 0.61$, $p = 0.273$). There were no further significant main effects (all $F < 3.68$, $p > 0.064$). The source localization analyses using sLORETA showed that activation differences in the

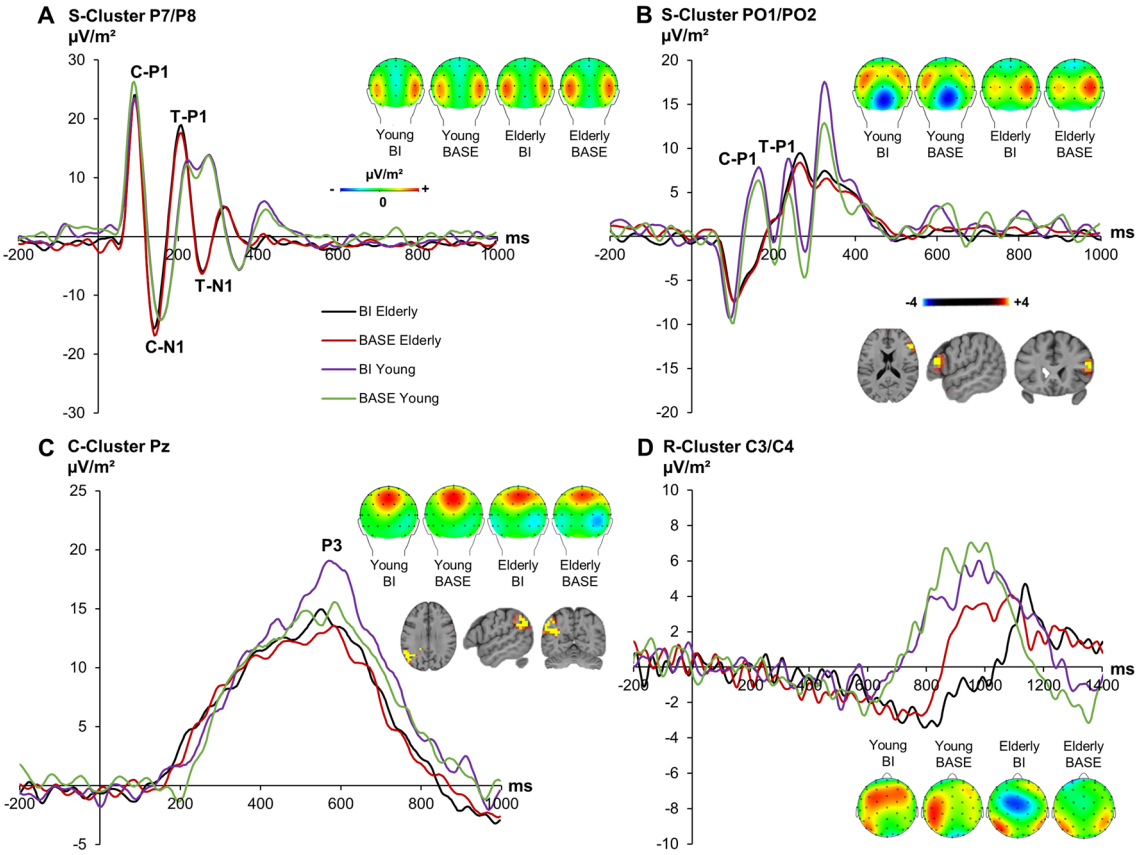

Fig. 4 RIDE cluster. **a** The S-cluster at electrodes P7/P8 is shown for young adults (=young) and elderly adults (=elderly) in the BI and BASE condition. Time point zero represents the beginning of the cue presentation. The target stimulus presentation started 100 ms later. Depiction of the P1 and N1 ERPs as reflected in the S-cluster elicited by the cue and target stimuli pooled across electrode P7 and P8. P1 and N1 elicited by the cue (C-P1 and C-N1) are shown in the first two peaks. The target P1 and N1 (T-P1 and T-N1) are represented by the following two peaks. The scalp topography maps given for the C-P1 (at 90 ms). Red colours denote positivity and blue colours negativity. **b** The P1 ERP as reflected in the S-cluster pooled across electrode PO1 and PO2, including the corresponding scalp topography maps for the T-P1 (at 235 ms in young adults and at 205 ms in elderly adults). The sLORETA plots show a source of difference in the right inferior frontal gyrus (BA47) (corrected for multiple comparisons). **c** The P3 as reflected in the C-cluster at electrode Pz with the corresponding scalp topography map (at 586 ms). Activation differences in the left inferior parietal cortex (BA40) including the temporo-parietal junction (TPJ) can be seen in the corresponding sLORETA plots (corrected for multiple comparisons). **d** The R-cluster pooled across the electrode C3 and C4 including the corresponding scalp topography maps (at 902 ms)

left inferior parietal cortex (BA40) including the temporo-parietal junction (TPJ) are associated with modulations in the C-cluster amplitudes.

A regression analysis was calculated to examine whether modulations of the BI effects observed in the C-cluster depend on the modulations in prior processing stages (i.e., the target P1 in the S-cluster). To this end, the BI effect was calculated for the C-cluster and the P1 time window in the S-cluster. The BI effect in the C-cluster was used as dependent variable in the regression model, which included the BI effect in S-cluster and age group as predictors. The regression model was significant ($F[2,42]=3.26$; $p=0.048$), only the factor "group" was a significant predictor ($\beta=-0.388$; $p=0.016$). The BI effect in the S-cluster did not predict the BI effect in the C-cluster ($\beta=-0.072$; $p=0.643$). Modulations in the C-cluster were, therefore, independent from modulations in the S-cluster.

R-Cluster The R-cluster is shown in Fig. 4d. The mixed-effects ANOVA at electrodes C3 and C4 revealed no significant interaction between "condition" and "group" ($F[1,43]=2.09$, $p=0.155$, $\eta_p^2=0.046$). Other main or interaction effects are reported in the supplementary material.

Discussion

Using a backward inhibition task, we examined neurophysiological processes associated with changes in sequential cognitive flexibility in elderly people compared to younger people.

The behavioral data (reaction time, RT) show that the BI effect was larger in elderly compared to younger participants. While RTs were generally prolonged in elderlies, the increase in RTs in BI, compared to BASE trials, was stronger in elderly than younger participants. The BI effect refers to the time costs of overcoming the inhibition of the lately abandoned task set that becomes relevant again (Mayr and Keele 2000). A strong BI effect indicates large costs during sequential cognitive flexibility (Allport et al. 1994; Allport and Wylie 1999). Thus, the behavioral data show that elderly people have deficits in sequential cognitive flexibility. This has, until now, not been shown before. The results of a behavioral study by Schuch (2016) did not show differential backward inhibition effects between elderly and younger participants. However, the backward inhibition paradigm by Schuch (2016) is hardly comparable to the paradigm used in the present study. In the study of Schuch (2016), the subjects were instructed to respond to facial expression and to evaluate them regarding gender, emotional expressions, and age. Moreover, the experiment used in the present study contained three-times more trials, which leads to a better signal-to-noise ratio and power to detect effects between groups.

Most important are the results from the EEG analyses. We observed neurophysiological effects paralleling the behavioral data when analyzing the standard ERPs, when evaluating the cue P1 and the P3 effects in particular. Effect patterns were replicated after RIDE application. Regarding the target P1 results at electrodes PO1 and PO2, no reliable effects were obtained before RIDE conduction. Considering that not all effects become evident when solely analyzing the standard ERPs, this likely reflects an effect of the known increase in intra-individual variability of neural processes with increasing age variability (Williams et al. 2005; MacDonald et al. 2006; Hultsch et al. 2008; Garrett et al. 2013; Holtzer et al. 2014). With respect to this interpretation and to previous results indicating detraction of neurophysiological effects due to intra-individual variability (Bodmer et al. 2018a, b), more reliable effects were obtained after accounting for intra-individual variability in the neurophysiological signal, i.e., analyzing the RIDE clusters. The R-cluster, reflecting processes of motor activation and response execution (Ouyang et al. 2011, 2015a, b), did not show significant differences between groups and experimental conditions. This suggests that basic motor processes do not explain differences in sequential cognitive flexibility between age groups. Yet, differential effects in the degree of BI effects were obtained for the S-cluster and the C-cluster. Since the S-cluster and C-cluster data were not correlated, modulations of response selection processes seen in the C-cluster are unlikely to reflect a direct consequence of altered inhibitory gating mechanisms seen in the S-cluster. Rather, there are two distinct processes contributing to age-related differences in sequential cognitive flexibility:

The BI effect concerns the interplay of the $n-2$ and $n-1$ trials and its effect on the nth trial (Zhang et al. 2016b). If the impact of the $n-1$ trial is weakened, it becomes easier to re-use the previously abandoned $n-2$ trial task set in the nth trial. The previous findings suggest that this can be accomplished by suppressing the $n-1$ task representation (Wolff et al. 2018). In line with that, the S-cluster data showed a higher amplitude in the target P1 time window during BI trials in younger participants compared to the elderly group. Modulations of amplitudes in the P1 time window likely reflect processes related to the filtering of relevant stimulus features in task relevant networks and with processes that block irrelevant information (Klimesch 2011; Wolff et al. 2017c). Possibly, the larger P1 in the nth trial likely reflects the suppression of the blocking effect of $n-1$ task set to be re-used $n-2$ trial task set. Within the elderly group, no differences between the BI and the BASE conditions were evident. This suggests that elderly people are not able to intensify inhibitory gating mechanisms to suppress the blocking effect of the $n-1$ task sets to be re-used $n-2$ trial task set. The source localization analysis shows that modulations of activity in the right inferior frontal gyrus (rIFG and BA47) are associated with these effects. Since the rIFG has frequently been shown to mediate inhibitory control processes (e.g., Aron et al. 2004a; Dippel and Beste 2015; Stock et al. 2016; Chmielewski et al. 2017; Bodmer and Beste 2017), the source localization results corroborate the interpretation that elderly people show deficits to suppress the adverse effect of the n-1 trial to re-use the $n-2$ trial task set. The obtained results fit to findings reporting deficient inhibitory control processes associated with decreased right inferior frontal gyrus activity in elderly (Hu and Li 2012; Coxon et al. 2016; Lee and Hsieh 2017; Hu et al. 2018). Importantly, the current results put deficits in inhibitory control as one important mechanism contributing to deficits in sequential cognitive flexibility.

The C-cluster also revealed differential effects between condition (BI vs. BASE) and group (young vs. elderly). The results show that the C-cluster at parietal electrode sites was larger in BI trials than BASE trials in the younger group. In the elderly group, no such differences between trial types were evident and the C-cluster amplitude was generally smaller. According to the RIDE concept, the C-cluster reflects intermediate processes between stimulus evaluation

and responding, i.e., response selection processes (Ouyang et al. 2011, 2015a; Verleger et al. 2014). Therefore, the C-cluster data suggest that also response selection deficits contribute to backward inhibition deficits in elderlies. It seems that younger participants intensify response selection processes in BI trials, compared to BASE trials. The previous studies have shown that the C-cluster is modulated during task switching (Wolff et al. 2017a, 2018). In these studies the C-cluster was smaller during task switch than repetition trials. While this may seem to be at odds with the current findings, it is important to consider that BI trials do not only contain a switch from the $n-1$ trial to the nth trial. Rather, BI trials include the reactivation or repetition of the $n-2$ trial task set in the nth trial. The source localization results show that these modulations in the C-cluster amplitude are due to activation differences in left inferior parietal cortex (BA40) including the temporo-parietal junction (TPJ). Theoretical accounts on TPJ function suggest that this brain area plays a key role in processes necessary to generate appropriate actions once internal representations have been updated (Geng and Vossel 2013). It seems that younger participants are better able to re-use the $n-2$ trials task set in the nth trial in a sense that they are better able to implement the recently abandoned $n-2$ trial task set during response selection in the nth trial. Interestingly, previous findings suggest that elderly people have problems to implement sequential behavior, e.g., when they have to interrupt an ongoing response and change to an alternative response (Stock et al. 2016). These problems in elderly participants to implement response selection processes were also related to inferior parietal regions and the TPJ (Stock et al. 2016).

Notably, the functional neuroanatomical regions found to be associated with group differences in sequential cognitive flexibility (i.e., the inferior parietal cortex and the right inferior frontal gyrus) are part of the multiple-demand system (Duncan 2010). The multiple-demand fronto-parietal control network has been shown to implement task rule/sets during goal-directed behavior (Fedorenko et al. 2013; Tschentscher et al. 2017). Large-scale data suggest that particularly regions in the multiple-demand network are subject to age-related changes (Kievit et al. 2014). Therefore, the current findings on sequential cognitive flexibility seem to reflect a major aspect of brain aging. Since age-related alterations in the multiple-demand system are associated with declines in fluid intelligence performance (Kievit et al. 2014), future studies shall investigate the interrelation of sequential cognitive flexibility and fluid intelligence in aging. This is crucial, since both aspects are central to cope with daily life requirements.

A limitation of the study is that the medication profile in the elderly group was quite heterogeneous. Due to the sample size and the heterogeneous profile, it was not possible to examine whether this may have biased the results. However, drugs taken by the elderly group do not directly affect central nervous system function. Therefore, we consider this as a limitation of minor importance. Nevertheless, this may be addressed in future research.

In summary, the study examined age-related differences in sequential cognitive flexibility using a backward inhibition paradigm. Elderly people show deficient backward inhibition (sequential cognitive flexibility). The BI effect was larger in the elderly group, showing that elderly people encounter increased costs to overcome the inhibition of the lately abandoned task set that becomes relevant again. The neurophysiological data pattern suggests that differences in sequential cognitive flexibility between young and elderly people emerge as a consequence of two independent processes: (i) ability to suppress task-irrelevant information and (ii) the ability to re-implement a previously abandoned task set during response selection. These processes were associated with differences in the activation of inferior frontal and inferior parietal regions.

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Compliance with ethical standards

Ethical statement The research involved young (mean age 24.52, all > 18 years) and elderly (mean age 60.10 years) human participants. Before any of the study's procedures started, written informed consent was obtained from all subjects. All participants were treated according to the Declaration of Helsinki. The ethics committee of the TU Dresden approved the study. There were no conflicts of interest. The present study was supported by a Grant from the BMBF 01GL1741C and partly by SFB 940 project B8.

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