Differential effects of age and executive functions on the resolution of the contingent negative variation: a reexamination of the frontal aging theory

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Abstract The “frontal aging theory” assumes the deterioration of executive/inhibitory functions as causal factors for the cognitive decline in human aging. The contingent negative variation resolution (CNV-R) is an electroencephalographic potential elicited after the second (informative) stimulus in warned Go/NoGo tasks requiring a response to one type of stimulus (Go) but not to the other (NoGo). Whereas the CNV-R across conditions is a measure of executive functions, the augmented potential in the NoGo condition is a specific measure of inhibitory processes. The aim was to examine the presumed linkage between executive processes and the CNV-R with special regard to inhibition in the NoGo condition, and to test whether any effects of age on this potential can be explained by a failure of (inhibitory) executive functions. Nineteen young and 15 elderly non-demented healthy volunteers were examined in a Go/NoGo CNV-R paradigm and on a test of executive functions focussed on set shifting

(Trail Making test). Results showed: (1) Better executive functions are associated with higher amplitudes of the CNV-R across conditions. (2) The CNV-R is higher for elderly than younger subjects; this increment is much stronger in the NoGo condition. In conclusion, the CNV-R across conditions reflects executive processes such as the shift of motor set. A higher CNV-R for elderly subjects (particularly of the inhibition-related NoGo CNV-R) indicates that this group is not impaired in the available amount of executive control but may exert such control for task demands where young subjects do not require it.

Keywords Age · Inhibition · Executive functions · Contingent negative variation resolution · Event-related potentials · EEG

Introduction

The human aging brain shows greater structural changes in the frontal lobes compared to other regions (Haug and Eggers 1991; Phillips and Della Sala 1999; Terry et al. 1987). The frontal lobes play a pivotal role for executive functions (Konishi et al. 1998; Rubia et al. 2001). Coincidentally, elderly subjects perform worse in executive tests such as Word Fluency, Trail Making and the Wisconsin Card Sorting test (Lezak 1995). This led to theories that a specific deterioration of frontal lobe functions is the relevant feature for human adult aging. Anatomical and functional imaging data

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suggests that mainly functions of dorsolateral frontal regions are impaired (Phillips and Della Sala 1999) which are essential for the exertion of switching and inhibitory control (Passingham 1993). This confirms observations that in higher age inhibitory control is more severely impaired than other executive functions such as working memory (Christ et al. 2001; Sweeney et al. 2001). Several authors have criticised this ‘frontal aging theory’, emphasizing that the frontal cortex is only one among a number of cerebral structures affected in the course of human aging (Braver et al. 2001; Greenwood 2000; Rubin 1999). According to these authors, an extensive connectionist approach is more valid to explain age-related deficits of cognition.

The contingent negative variation (CNV) is a slow surface-negative electroencephalographic (EEG) potential recorded in warned reaction time paradigms between an earlier warning stimulus and a later imperative stimulus. The CNV is followed by the CNV resolution (CNV-R), a positive-going potential elicited after the imperative stimulus (Tecce and Cattanaach 1993) which reflects executive functions such as set shifting and resetting of the current motor program (Jackson et al. 1999). If the CNV-R is recorded in Go/NoGo tasks where subjects are required to make some specific response to one type of stimulus (Go) but not to the other (NoGo) and full information about the correct response is exclusively provided with the imperative stimulus, it is larger and has a more anterior frontocentral maximum after NoGo stimuli (Roberts et al. 1994; Simson et al. 1977; Smith et al. 2008).¹ The unequal distribution suggests that different generators are active in the two conditions. In the NoGo condition any prepared motor or mental reaction cannot be exercised and has to be suppressed. Previous studies therefore assumed inhibitory processes as the relevant sources for the higher NoGo CNV-R (Kiefer et al. 1998; Pfefferbaum and Ford 1988; Roberts et al. 1994; Salisbury et al. 2004). In later intervals after the informative stimulus, inhibition is no longer needed to prevent imminent movement but might be relevant for the down-regulation of residual preparatory or cognitive activities. Recent data suggest that in fact inhibition

extends to cognitive and other non-motor domains (Smith et al. 2008).

By now there are no studies exploring effects of age on the CNV-R. Pfefferbaum and Ford (1988) examined effects of age in a similar electrophysiological paradigm, the continuous performance task. Because these authors focussed on other aspects of the CNV-R, in their statistical analysis the amplitude data was averaged across conditions. However, from visual inspection of their Figure 1 it is apparent that amplitudes of the NoGo CNV-R increase with higher age over frontal and perhaps central electrodes. Similar results were obtained by Wild-Wall and collaborators (2007) in a continuous performance task using a visual search paradigm, and by Vallesi and collaborators (2009) in two Go/NoGo experiments with either visual or auditory stimuli. Higher amplitudes of the NoGo CNV-R in elderly subjects contradict present concepts of reduced executive functions in higher age. However, the relationship of executive performance and the CNV-R has as well not been tested before.

The aim was to examine effects of age and executive functions on the amplitude of the CNV-R. We chose to examine preparation and inhibition in a very simple Go/NoGo task which all participants could perform with high accuracy. The reasoning was that any differences of CNV-R amplitudes between young and elderly subjects could thus be attributed to differences in the applied strategies rather than different performance levels. Particular emphasis was given to the NoGo CNV-R which is considered to reflect inhibitory processes best. According to our first hypothesis, if a general reduction of executive functions is the relevant feature of human aging (‘frontal aging theory’), then the CNV-R was predicted to be smaller for elderly compared to young subjects. In extension of the first hypothesis, if such a failure of executive control in higher age affects mainly inhibition, then we expected a specific attenuation of the NoGo CNV-R in the elderly. These effects were expected to be strongest over mid-frontocentral electrodes where differences associated with age and between Go and NoGo CNV-R are largest. According to our second hypothesis, if there is an association between the CNV-R and set shifting, then poorer executive functions should be associated with smaller amplitudes of the CNV-R across conditions. Again, this effect was expected to be maximal over mid-frontocentral electrodes.

¹ The CNV-R is therefore also known as Go/NoGo P3 or late positive component (Simson et al. 1977). Despite its similar name, the attentional P300 is not related to inhibitory processes but considered to represent processes of context update, and has a different scalp distribution than either Go and NoGo CNV-R.

Methods

Participants

Nineteen young healthy subjects (six males, 13 females) aged 18 to 29 years (mean $23 \pm \text{SD } 3$ years) and 15 elderly healthy subjects (four males, 11 females) aged 53 to 74 years (mean 66 ± 7 years) with an equivalent level of education (young: 13 ± 3 years; elderly: 12 ± 4 years) were recruited from our panel of volunteers. All were right-handed (Salmaso and Longoni 1985), had no history of psychiatric or neurological disease, normal hearing and normal or corrected-to-normal vision.

Neuropsychological assessment

The neuropsychological assessment took place before the EEG recording. The Mini-Mental State Examination (MMSE) is a 30-point screening test for dementia (Folstein et al. 1975). The short procedure tests various functions such as orientation, memory, arithmetic, language use and comprehension. A score of 27 or higher is considered normal (Crum et al. 1993) and was achieved by all participants.

The Trail Making test (Lezak 1995; Reitan 1958) is a visuomotor task that consists of two parts: in part A the participant must draw lines to connect consecutively numbered circles on one worksheet, and in part B then connect the same number of consecutively numbered and lettered circles by alternating between the two sets. The instruction for both parts is to perform the test as correct and as fast as possible. In case of any errors made by the subject, the examiner has to point out these as they occur so that the subject can always complete the test without errors and the scoring can be based on time alone (Lezak 1995). The time required to complete each task represents the relevant scores. In contrast to part A, part B involves frequent switching between two mental sets. Because visual search and general motor speed are relevant for both parts of the test, calculation of the difference score between parts A and B minimises these interfering effects. The $\text{TM}_{\text{B-A}}$ score is therefore well established as an instrument to assess executive functions with special emphasis on set shifting. While some researchers use the $\text{TM}_{\text{B/A}}$ ratio for the same purpose (Arbuthnott and Frank 2000), a large-scale ($n=285$) comparative assessment of the two scores observed better discriminatory power of the $\text{TM}_{\text{B-A}}$ score with respect to the detection of perfor-

mance differences between young and elderly subject (Drane et al. 2002).

Experimental design and procedure

Subjects performed a warned Go/NoGo task requiring a bilateral symmetric index finger to thumb opposition movement. A medium frequency warning tone (1,000 Hz, 200 ms) was first presented via a loudspeaker, and followed exactly 2 s later by an imperative stimulus consisting of either a high frequency (1,500 Hz, 200 ms) or low frequency tone (500 Hz, 200 ms) representing Go and NoGo signals, respectively. Upon hearing the high frequency Go signal, subjects were required to touch the index finger with the thumb simultaneously with both hands. Upon hearing the low frequency NoGo signal, subjects had to withhold responses. Go and NoGo stimuli were presented in a random order with the same probability. The interval between the imperative stimulus of the present trial and the warning stimulus for the subsequent trial varied randomly from 5.5 to 8.0 s. Subjects were comfortably seated with their arms supported by padded armrests. They wore a glove on their right hand with electrical contacts on the thumb and index finger. Subjects were instructed to perform the instructed movements as quick as possible. A total of 400 to 500 trials was recorded from each participant (duration about 70 min).

Recording of cortical potentials

EEG activity was recorded using Ag/AgCl electrodes from the sites F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, P7, P3, Pz, P4 and P8 (Chatrian et al. 1985), referenced to linked mastoids. The linked average was calculated so that unequal impedance at the two mastoids could not distort hemispheric symmetry. In addition, horizontal and vertical electrooculogram (EOG; electrode positions: above and below the left eye and adjacent to the outer canthus of each eye) and electromyographic activity (EMG) from left and right musculus flexor digitorum superficialis were recorded. Electrode impedance was kept below 5 k Ω .

EEG and EOG were recorded in DC mode, frequency band DC to 100 Hz (EEG) and DC to 41 Hz (EOG), respectively. EMG was recorded in AC mode. The analogue EMG signal was band pass filtered 0.1 to 300 Hz and the filtered signal then rectified (Lindinger et al. 1990). EEG, EOG and the envelope of the rectified

EMG were digitized on-line at a rate of 250 Hz and stored for subsequent analysis. The EEG was corrected for minor eye blink artefacts with an automatic blink correction algorithm (Lindinger et al. 1990). Trials with gross artefacts remaining after this correction were rejected manually after trial-by-trial visual inspection.

For all correct trials, event-related potentials were averaged time-locked to stimulus presentation and corrected to a baseline calculated from 250 ms before the imperative stimulus to the onset of this stimulus. Each subject's mean amplitude of the CNV-R was defined as the average amplitude in the interval from 300 to 600 ms after onset of the imperative stimulus (Jodo and Inoue 1990; Lai et al. 1997) and was calculated separately for each electrode and condition.

Recording of behavioural data

Reaction times were saved for subsequent analysis. The following boundaries were applied for error analysis: (1) reaction to the warning stimulus: 0.00 to 0.99 s after the warning stimulus; (2) anticipations: 1.00 s before to 0.09 s after the imperative stimulus; (3) Commission errors: 0.09 to 1.00 s after the imperative stimulus in NoGo trials; (4) Omission errors: no response in Go trials.

Data analysis

Amplitudes of the CNV-R were subject to a repeated measures analysis of covariance (ANCOVA) with CONDITION (Go vs. NoGo), lateral electrode position (LAT: left lateral, left medio-lateral, median, right medio-lateral, and right lateral) and coronal electrode position (COR: frontal, central, and parietal) as the within-subject factors, GROUP (young vs. elderly subjects) as the between-groups factor and TM_{B-A} (difference score of the Trail Making test) as the covariate. Following suggestions from one reviewer, the ANCOVA analysis was recalculated with the $TM_{B/A}$ ratio instead of the TM_{B-A} score as the covariate. The Kolmogorov–Smirnov test was used to test whether a Gaussian distribution could be assumed for these covariates. Where appropriate, Huynh–Feldt corrected univariate F values are reported. Only significant main or interaction effects are reported. Behavioural and neuropsychological data were analysed using non-parametric Mann–Whitney tests for between-groups comparisons. For all comparisons, the level of significance was set to $p \leq 0.05$.

Results

Neuropsychological data

For the MMSE, the mean score was $29.4 \pm SD 0.8$ for young subjects and $28.8 \pm SD 0.8$ for elderly subjects. This difference between young and elderly subjects was not significant (Mann–Whitney test, $U=91$, $p=0.071$). For the Trail Making test, scores of part A were 27 ± 9 s for young subjects and 43 ± 9 s for elderly subjects. This difference between young and elderly subjects was significant (Mann–Whitney test, $U=26$, $p<0.001$). The TM_{B-A} scores were 29 ± 15 s for young subjects and 49 ± 23 s for elderly subjects. This difference was also significant (Mann–Whitney test, $U=66$, $p=0.007$). The $TM_{B/A}$ ratios were 2.2 ± 0.5 for young subjects and 2.1 ± 0.5 for elderly subjects, and this difference was not significant. The distribution of TM_{B-A} and $TM_{B/A}$ scores was tested for use in subsequent analyses. A Gaussian distribution could be assumed for both variables (Kolmogorov–Smirnov tests, all $p>0.200$).

Behavioural data

Reaction times were longer for elderly than young subjects (Table 1). Elderly subjects committed slightly more anticipations, commission errors and omission errors than young subjects. However, none of these differences was significant (Mann–Whitney test, all $U \geq 93$, all n.s.). Table 2 shows the behavioural data in relation to neuropsychological performance (a median split is applied here for illustrative purposes only). Subjects with poorer executive functions showed a non-significant tendency towards longer reaction times and more anticipations, commission errors and

Table 1 Behavioural data from the Go/NoGo task for young and elderly subjects

	Young subjects	Elderly subjects
Reaction time [ms]	546 ± 118	576 ± 152
Reactions to the warning stimulus [%]	0.10 ± 0.16	0.08 ± 0.26
Anticipations [%]	0.08 ± 0.17	0.27 ± 0.37
Commission errors [%]	0.47 ± 0.80	1.08 ± 1.42
Omission errors [%]	3.08 ± 1.89	4.18 ± 1.96

All values are given as mean $\pm$ standard deviation (SD)

Table 2 Behavioural data from the Go/NoGo task for subjects with better versus poorer executive functions

	Better Executive Functions	Poorer Executive Functions
Reaction time [ms]	519±126	598±131
Reactions to the warning stimulus [%]	0.17±0.26	0.02±0.05
Anticipations [%]	0.10±0.27	0.23±0.30
Commission errors [%]	0.49±0.83	0.98±1.36
Omission errors [%]	3.42±1.95	3.70±2.05

The Trail Making difference score (TM_{B-A}) was used to assess executive functions. In a median split (used for this illustrative purpose only), TM_{B-A} scores below 33.5 s were assigned to the subsample with better executive functions ($n=17$; 12 young, five elderly), and scores above 33.5 s to the subsample with poorer executive functions ($n=17$; seven young, ten elderly). All values are given as mean±standard deviation (SD)

omission errors than subjects with better executive functions (Mann–Whitney test, all $U \geq 90$, all n.s.).

Collinearity diagnostics

To test for potential problems of collinearity, we have calculated correlation analyses of variables age and the ANCOVA covariates. Results showed a moderate correlation of age with TM_{B-A} (Pearson's $r=0.48$,

$n=34$, $p=0.004$) for an analysis with two age groups, indicating that despite a significant association of these two variables collinearity is below the critical threshold usually assumed at $r>0.8$ (Goodwin 1998). The correlation between age and the TM_{B/A} ratio was even weaker (Pearson's $r=0.03$, $n=34$, $p=0.880$), again suspending collinearity.

Electrophysiological data

Figures 1 and 2 show the CNV-R for Go and NoGo trials, separately for each scalp location and for young and elderly subjects. For both groups, the most prominent component after the imperative stimulus is the CNV-R, a positive waveform with a latency of about 300 ms. The average amplitude of this potential is higher for the NoGo compared with the Go condition. For elderly subjects, however, the peak amplitude at frontal and central midline electrodes Fz and Cz is clearly higher than for young subjects, notably in the NoGo condition.

The results of the statistical analysis are given in Table 3. The main effect of GROUP is explained by more positive amplitudes for elderly compared to young subjects. The main effect of TM_{B-A} indicates a significant association of better frontal lobe function with higher amplitudes of the CNV-R. The main

Fig. 1 Grand average of the CNV-R for the Go condition, separately for young (*thin line*) and elderly (*thick line*) subjects. The *zero mark* on the time axis indicates the presentation of the imperative stimulus. Electrodes are indicated in the upper left of each diagram. Error bars indicate standard error

Fig. 2 Grand average of the CNV-R for the NoGo condition, separately for young (*thin line*) and elderly (*thick line*) subjects. The zero mark on the time axis indicates the presentation of the imperative stimulus. Electrodes are indicated in the upper left of each diagram. Error bars indicate standard error

Table 3 Comparison of the amplitude of the resolution of the contingent negative variation (CNV-R) using repeated measures analysis of covariance (ANCOVA)

	ANCOVA term		
	<i>df</i>	<i>F</i>	<i>p</i>
Main effects			
GROUP	1,30	5.22	0.030
Trail Making difference score [TM _{B-A}]	1,30	4.98	0.033
CONDITION	1,30	0.35	n.s.
Coronal electrode position [COR]	2,60	30.61	<0.001
Lateral electrode position [LAT]	4,120	12.73	<0.001
Interaction effects			
GROUP by LAT	4,120	3.30	0.043
TM _{B-A} by LAT	4,120	3.88	0.026
CONDITION by COR	2,60	7.18	0.003
CONDITION by LAT	4,120	5.67	0.004
COR by LAT	8,240	13.82	<0.001
GROUP by CONDITION by LAT	4,120	3.87	0.020
TM _{B-A} by COR by LAT	8,240	2.48	0.050
GROUP by CONDITION by COR by LAT	8,240	4.44	<0.001

The degree of freedom (*df*) and the *F* ratio are presented as actual values, whereas the *p* value is that associated with the conservative *df* after Huynh–Feldt correction

effect of COR indicates the most positive amplitudes for parietal, intermediate amplitudes for central, and the smallest amplitudes for frontal electrodes. The main effect of LAT is explained by a higher positivity over midline than mid-lateral and lateral electrodes. The main effect of CONDITION was not significant.

The interaction COR by LAT confirms that across conditions the highest amplitudes of the CNV-R are found at parietal midline electrodes. The interactions CONDITION by COR and CONDITION by LAT indicate that the increase of amplitude in the NoGo condition is strongest at frontal and central midline electrodes. The interaction GROUP by LAT indicates that for elderly subjects amplitudes are higher over midline compared with left and right lateral electrodes whereas for young subjects this difference is very small and not significant (see also Fig. 3).

The interactions GROUP by CONDITION by LAT and GROUP by CONDITION by COR by LAT indicate that for elderly compared to young subjects, the CNV-R in the NoGo condition is higher (more positive) at frontal and central midline electrodes (Fig. 3). This was shown in a post hoc analysis revealing that the simpler interaction effects GROUP by LAT and GROUP by COR by LAT are significant in the NoGo condition ($F_{4,120}=6.24$; $p=0.005$; $F_{8,240}=3.90$; $p=0.005$) but not in the Go condition ($F_{4,120}=0.94$, n.s.; $F_{8,240}=1.32$, n.s.). Further

Fig. 3 Amplitude of the CNV-R after the imperative stimulus, separately for young (*broken line*) and elderly (*solid line*) subjects. Data from the Go condition are shown in the left diagram, and data from the NoGo condition are shown in the right diagram. For elderly subjects, amplitudes of the CNV-R at frontal and central (*arrow*) electrodes are higher at midline than lateral electrodes. *Error bars* indicate standard error

analysis of amplitudes in the NoGo condition revealed that the main effect of GROUP is strongest over midline electrodes (from left to right: $F_{1,30}=3.07, 5.50, 5.72, 5.12, 0.05$; n.s., $p=0.026, p=0.023, p=0.031$, n.s.); the interaction GROUP by COR is also strongest at midline and, in addition, left lateral electrodes (from left to right: $F_{2,60}=4.60, 2.40, 3.25, 1.22, 1.04$; $p=0.032$, n.s., $p=0.050$, n.s., n.s.). Finally, amplitudes over midline electrodes in the NoGo condition show the strongest effect of GROUP at frontal and central ($F_{1,30}=10.57, 5.96$; $p=0.003, 0.021$) as compared with parietal electrodes ($F_{1,30}=1.48$; n.s.).

The interactions TM_{B-A} by LAT and TM_{B-A} by COR by LAT are explained by a significant association of better frontal lobe function (lower scores of TM_{B-A}) with more positive amplitudes of the CNV-R. These effects were strongest at central midline electro-

des (Fig. 4). If these interactions are broken down into simpler effects, the main effect of TM_{B-A} is stronger over midline electrodes compared to lateral electrodes (from left to right: $F_{1,30}=3.21, 5.67, 6.95, 3.51, 0.92$; n.s., $p=0.024, p=0.013$, n.s., n.s.). In accordance, the interaction TM_{B-A} by LAT is strongest at central electrodes (from frontal to parietal: $F_{4,120}=1.26, 4.57, 3.67$; n.s., $p=0.013, p=0.036$), and at central sites the main effect of TM_{B-A} is stronger over midline than lateral electrodes (left to right: $F_{1,30}=3.66, 7.40, 8.32, 4.60, 0.93$; n.s., $p=0.011, p=0.007, p=0.040$, n.s.).

Supplementary analyses

A separate ANCOVA analysis with the same within-subject and between-group factors but the $TM_{B/A}$ ratio as the covariate revealed that a main effect of $TM_{B/A}$ is

Fig. 4 Amplitude of the CNV-R separately for subjects with better (*broken line*) and poorer (*solid line*) frontal executive functions as assessed with the Trail Making difference score (TM_{B-A}). In a median split only applied for the illustrative purpose of this figure, TM_{B-A} scores below 33.5 s were assigned to the subsample with better executive functions ($n=17$; 12 young, five elderly), and scores above 33.5 s to the subsample with worse executive functions ($n=17$; seven young, ten elderly). Amplitudes of the CNV-R at central midline electrodes are higher for subjects with better executive functions (*arrow*). *Error bars* indicate standard error

not significant ($F_{1,30}=1.44$; n.s.) whereas the interactions $TM_{B/A}$ by LAT ($F_{4,120}=3.60$; $p=0.026$) and $TM_{B/A}$ by COR by LAT ($F_{8,240}=2.23$; $p=0.050$) remained significant. In analogy to our original analysis, there were no further significant interaction effects of $TM_{B/A}$ with other factors. In summary, an analysis with the $TM_{B/A}$ ratio instead of the TM_{B-A} difference score lead to almost identical results.²

Discussion

To summarize the main results: (1) The CNV-R at frontal and central midline electrodes is higher (more positive) in the NoGo compared with the Go condition. (2) Better inhibitory/executive functions are associated with higher amplitudes of the CNV-R across conditions. This effect is also strongest at central midline electrodes. (3) The amplitude of the CNV-R is higher in elderly compared to young subjects. This increment is strongest in the NoGo condition and again most pronounced at frontal and central midline electrodes. (4) As expected, executive functions (Trail Making TM_{B-A} scores) in young subjects are higher than those in the elderly.

Young and elderly subjects were well matched in terms of education, and both groups did not show any evidence of cognitive deficit. The reaction times in Go trials were slightly slower in elderly than young subjects, and some types of error were committed more often by the elderly. However, these small differences were not significant for any of the behavioural measures. For both groups, reaction times and error scores are most similar to those reported in previous studies (Bruin and Wijers 2002; Roberts et al. 1994). Scores of the Trail Making test were in the normal range of the respective age cohort (Drane et al. 2002; Goul and Brown 1970), confirming poorer performance of the elderly. As expected, the TM_{B-A} score had better discriminatory power than the $TM_{B/A}$ score (Drane et al. 2002). In agreement with previous studies, amplitudes of the CNV-R were higher and the maximum was more anterior in the NoGo compared with the Go condition (Bruin and Wijers 2002; Salisbury et al. 2004; Simson et al. 1977).

² The same applies to a $TM_{(B-A)/A}$ ratio; results with this covariate were numerically identical to the results obtained with the $TM_{B/A}$ covariate owing to the linear dependency of the two ratios (Perianez et al. 2007).

Relation of the CNV-R to preceding preparatory activity

An alternative explanation for the between-group differences would be carryover effects which arise from group differences in the late CNV (the baseline interval in our experiment). It could be argued that the amplitude of the CNV-R is higher (more positive) whenever the preceding late CNV had higher (more negative) amplitude. However, previous studies confute this interpretation. Studies exploring effects of age on the CNV found larger age differences for early to intermediate CNV intervals. Amplitudes of the late CNV were often quite similar, and if the differences were significant, larger amplitudes were typically found for young subjects (Dimberger et al. 2000; Loveless and Sanford 1974; Michalewski et al. 1980; Zappoli et al. 1988; see Wild-Wall et al. 2007 for a longer discussion). A simple rebound or return of CNV-negativity to more positive values therefore cannot explain our results as the CNV-R was higher for elderly subjects, i.e. the group with a smaller late CNV. Further arguments against dominant carryover effects are the different scalp distribution of the late CNV and the CNV-R (Roberts et al. 1994) and regression analyses made by Oddy et al. (2005) who found that the amplitude of the late CNV was not a significant predictor of the NoGo CNV-R. Similarly, Segalowitz et al. (1992) examined the relationship of the CNV amplitude and various tests of executive functions including the Trail Making test. They found significant associations only for the early but not the late CNV, so consequently there are no effects of executive functions on the late CNV that could be carried over to the subsequent CNV-R.

In extension of the classic conception of a frontocentral early CNV followed by a centroparietal later CNV (Gomez et al. 2003), the latter component according to our results is followed by a CNV-R with again a frontocentral maximum. Interestingly, effects of age and executive functions were strongest for the early CNV and the CNV-R, the only two components with mid-frontocentral maximum.

Alternative concepts for the CNV-R

The sources contributing to the NoGo CNV-R and its relation to inhibitory processes have been controversial (Bruin and Wijers 2002; Kiefer et al. 1998; Pfefferbaum

and Ford 1988; Roberts et al. 1994; Salisbury et al. 2004; Smith et al. 2008). Although the vast number of contributions to this topic does not allow us to summarise this entire debate, we discuss here theories with particular reference to the contexts of the present study, aging and executive functions.

The P300 is a positive scalp-recorded potential generated some 300 ms after the detection of a target stimulus which differs in some dimension from a sequence of irrelevant stimuli (Polich and Kok 1995). Because polarity and latency of the P300 are similar to the CNV-R, a contribution of the P300 to the higher amplitude of the CNV-R in the NoGo condition was considered: Performance in NoGo trials might be more difficult than in Go trials and therefore evoke the higher potential. However, several features of the CNV-R are dissimilar to the P300. If subjects perform the same CNV task but the information is provided with the first of two successive stimuli (S1-choice paradigm), the amplitude of the potential is equivalent for Go and NoGo condition (McCallum and Curry 1981). This suggests that motor or cognitive preparation and information update are important for the formation of the higher NoGo potential. Moreover, the scalp distribution of the NoGo CNV-R is more anterior than the one elicited in classical P300 oddball paradigms (Friedman et al. 1998; Roberts et al. 1994; Smith et al. 2008). Finally, the amplitude of the P300 attenuates with increasing age (Polich 1996) whereas in the present experiments amplitudes of the NoGo CNV-R were higher for elderly compared with young subjects.

Another concept seeks to explain the higher amplitude of the NoGo CNV-R by movement-related negativity in the Go condition. This negativity is proposed to add up and reduce the CNV-R in the Go condition so that the remaining net positivity in the Go condition is lower than in the NoGo condition. The same effect can explain the larger amplitude of the NoGo CNV-R contralateral to the side of movement (Lai et al. 1997; Roberts et al. 1994; Smith et al. 2008). However, although such an effect may contribute to the higher NoGo resolution, this concept does not explain the effects of different Go/NoGo probabilities on the CNV-R (Smith et al. 2008). It is also in variance with observations that the amplitude of the CNV decreases or remains unaffected in higher age (Dimberger et al. 2000; Michalewski et al. 1980; Zappoli et al. 1988) whereas the amplitude of the NoGo resolution in our study increased.

The CNV-R and set shifting

The Trail Making test is an established instrument to assess set shifting (Lezak 1995). A recent construct validation study showed that in a multivariate analysis set shifting was the only significant regressor for the TM_{B-A} difference score whereas other executive functions such as visuomotor speed, working memory, the ability to maintain a goal and inhibition were not significant (Sanchez-Cubillo et al. 2009). Our results showed that better executive functions (lower TM_{B-A} scores) are associated with higher amplitudes of the CNV-R. It is therefore likely that the observed associations between Trail Making scores and the amplitude of the CNV-R are mainly attributable to set shifting. Across conditions this may comprise down-regulation of activity related to the previous trial and resetting of the current motor program.

Age and strategy

The effects of age on the amplitude of the CNV-R can be explained by subjective task difficulty and differences in the strategy used. A decline of abilities associated with higher age might compel elderly subjects to prepare tasks with more efforts and to spend additional activity if the prepared task is called off later (i.e. in NoGo trials). This additional activity might be required for the reorganisation and the re-sequencing of reactions required in the ongoing or forthcoming trial. According to this reasoning, higher age would not be characterised by reduced inhibitory functions but by greater planning and sequencing requirements possibly associated with higher subjective task difficulty for the elderly. Because planning and sequencing are executive functions as well, this explanation is in accordance with the frontal maximum of the augmented CNV-R of elderly subjects observed in this experiment.

A decline of executive functions with higher age is not necessarily linked to performance deterioration. Previous studies suggested different behavioural strategies in young and elderly subjects for a large variety of memory and executive tasks. An age-related increase in frontal activity may constitute functional compensation (Cabeza et al. 1997; Reuter-Lorenz 2002). Neuroimaging studies of healthy aging revealed higher activation of frontal regions in elderly subjects for a similar level of performance (Friedman et al. 2008; Velanova et al. 2007). It was subsequently

suggested that older adults permanently recruit pre-frontal resources for executive task demands which young subjects can perform with lower levels of activation (Friedman et al. 2008). Although some authors emphasised inhibition among the most relevant features of human aging, it is possible to take a broader view and generalise this theory to other executive functions.

Time estimation and monitoring in young and elderly subjects

Warned and unwarned reaction times become slower with advanced age (Fozard et al. 1994; Welford 1977). Likewise, elderly subjects perform worse in tasks involving time estimation over intervals similar to those tested in the present experiment (Nichelli et al. 1993; Schaie and Syndulko 1978). Loveless and Sanford (1974) hypothesized that older persons may have ‘difficult[ies] in controlling a sequence of operations so as to initiate preparation at an appropriate time.’ Elderly subjects may consequently need to prepare responses a longer time beforehand than young subjects to pertain the same level of performance.

The frontal lobes are essential for accurate processing of temporal intervals (Nichelli et al. 1995; Jones et al. 2004). Imaging studies, intracranial recordings and surface EEG recordings in humans showed that structures of the cortical midline such as the anterior cingulate and the supplementary motor area are strongly activated during time perception and reproduction tasks compared to simpler control conditions (Hamano et al. 1997; Johannes et al. 1997; Macar et al. 1999; Rao et al. 2001). Impaired time estimation in elderly subjects may therefore contribute to the suggested impairment of sequencing. It is also conceivable that the observed age-related differences in executive functions reflect monitoring related to some other subsequent steps of processing. The anterior cingulate is known as a relevant neuroanatomical structure for the self-monitoring of willed actions in the framework of temporal processing (Lejeune et al. 1997; Pouthas et al. 2005), and neural activity within this structure is sensitive to aging (Cabeza et al. 1997; Sharp et al. 2006).

The frontal aging theory

According to Horn and Cattell’s (1967) theory of intelligence, ‘fluid’ cognitive functions such as figural

classifications, word fluency and word analogies require flexibility whereas ‘crystallized’ functions such as retrieval from episodic memory predominantly rely on acquired knowledge. Whereas fluid abilities decline with advancing age, crystallized abilities remained largely intact (Horn and Cattell 1967). In more modern terminology, fluid abilities demand a higher level of executive control. This decline of executive functions with advancing age (Lezak 1995) is accompanied by anatomical changes predominantly in the frontal lobes (Haug and Eggers 1991; Terry et al. 1987) and in the striatum (Hedden and Gabrieli 2004; Rubin 1999; Umegaki et al. 2008). The striatum is intimately connected to the frontal lobes (Passingham 1993), and both structures are pivotal for executive functions (Lezak 1995). In conjunction with modern network concepts of cognition, this led to the proposition of the frontal aging theory (Moscovitch and Winocur 1995; West 1996). According to this hypothesis, an age-related decline of frontal structures is responsible for the diminished ability of elderly adults to monitor and control processes subserved by other brain regions which may be less affected by aging (Hedden and Gabrieli 2004).

Inhibition is one specific executive function essential, for example, to control a sequence of actions or reactions (Gade and Koch 2005). It allows us to reject a predominant but inappropriate response so that a more suitable response (or, no response at all) can be selected. Behavioural and functional imaging studies demonstrated that with advancing age inhibition is among the most severely reduced executive functions. For example, the ability to inhibit a prepotent response and generate a compatible response is worse for children and older adults than for young adults (Christ et al. 2001). Importantly, only for elderly subjects the slower reactions were explained by a lack of inhibitory control rather than insufficient preparation. Similarly, elderly subjects demonstrated a reduced ability to voluntarily inhibit eye movements toward targets in an antisaccade task whereas their memory for spatial location was as accurate as in young adults (Sweeney et al. 2001).

Reconsidering the frontal aging theory

The frontal aging theory assumes a specific deterioration of frontal lobe functions as the relevant characteristic of human adult aging. The observation

that amplitudes of the CNV-R were generally higher for elderly than young subjects is in variance with a pronounced reduction of inhibitory/executive functions in higher age. However, this theory could be modified so that it assumes dysregulation instead of failure of frontal executive functions with advancing age. Likewise, a modified theory could envisage an increased demand of executive control in the elderly for tasks which younger subjects perform with a lower level of control. This higher level of executive control would be paralleled by increased frontal activation. The findings of the present study would be in agreement with these modified concepts.

Significant effects of age on the CNV-R were found in addition and in parallel to significant effects of executive functions, and the two variables did not show any simple or higher-order interactions. This indicates that some effects of executive functions on the CNV-R are independent of age. The validity of the present study is, however, limited by the sample size and the restricted number of neuropsychological measures. We propose that future studies examine larger randomized samples of young and elderly subjects in a CNV-R paradigm together with a broader battery of executive tests.

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References

Arbuthnott K, Frank J (2000) Trail Making test part B as a measure of executive control: validation using a set-switching paradigm. *J Clin Exp Neuropsychol* 22:518–28

Braver TS, Barch DM, Keys BA, Carter CS, Cohen JD, Kaye JA, Janowsky JS, Taylor SF, Yesavage JA, Mumuthaler MS, Jagust W, Reed BR (2001) Context processing in older adults: evidence for a theory of relating cognitive control to neurobiology in healthy aging. *J Exp Psychol Gen* 130:746–763

Bruin KJ, Wijers AA (2002) Inhibition, response mode, and stimulus probability: a comparative event-related potential study. *Clin Neurophysiol* 113:1172–1182

Cabeza R, Grady CL, Nyberg L, McIntosh AR, Tulving EK, Jennings J, Houle S, Craik F (1997) Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *J Neurosci* 17:391–400

Chatrian G, Lettich E, Nelson P (1985) Ten percent electrode system for topographic studies of spontaneous and evoked EEG activities. *Am J EEG Technol* 25:83–92

Christ SE, White DA, Mandernach T, Keys BA (2001) Inhibitory control across the life span. *Dev Neuropsychol* 20:653–669

Crum RM, Anthony JC, Bassett SS, Folstein MF (1993) Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA* 269:2386–2391

Dimberger G, Lalouschek W, Lindinger G, Egkher A, Deecke L, Lang W (2000) Reduced activation of midline frontal areas in human elderly subjects: a contingent negative variation study. *Neurosci Lett* 280:61–64

Drane DL, Yuspeh R, Huthwaite J, Klingler L (2002) Demographic characteristics and normative observations for derived Trail Making test indices. *Neuropsychiatry Neuropsychol Behav Neurol* 15:39–43

Folstein M, Folstein S, McHugh P (1975) ‘Mini-Mental State’: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198

Fozard J, Verccryssen M, Reynolds S, Hancock P, Quilter R (1994) Age differences and changes in reaction time: the Baltimore longitudinal study of aging. *J Gerontol* 49:179–189

Friedman D, Kazmerski V, Cycowicz Y (1998) Effects of aging on the novelty P3 during attend and ignore oddball tasks. *Psychophysiology* 35:508–520

Friedman D, Nessler D, Johnson R, Ritter W, Bersick M (2008) Age-related changes in executive function: an event-related potential (ERP) investigation of task-switching. *Neuropsychol Dev Cogn B Aging* 15:95–128

Gade M, Koch I (2005) Linking inhibition to activation in the control of task sequences. *Psychon Bull Rev* 12:530–534

Gomez CM, Marco J, Grau C (2003) Preparatory visuo-motor cortical network of the contingent negative variation estimated by current density. *Neuroimage* 20:216–224

Goodwin CJ (1998) Research in psychology: methods and design. Wiley, New York

Goul WR, Brown M (1970) Effects of age and intelligence on Trail Making test performance and validity. *Percept Mot Skills* 30:319–326

Greenwood P (2000) The frontal ageing hypothesis evaluated. *J Int Neuropsychol Soc* 6:705–726

Hamano T, Lüders H, Ikeda A, Collura T, Comair Y, Shibasaki H (1997) The cortical generators of the contingent negative variation in humans: a study with subdural electrodes. *Electroencephalogr Clin Neurophysiol* 104:257–268

Haug H, Eggers R (1991) Morphometry of the human cortex cerebri and corpus striatum during aging. *Neurobiol Aging* 12:336–338

Hedden T, Gabrieli JD (2004) Insights into the ageing mind. *Nat Rev Neurosci* 5:87–96

Horn J, Cattell R (1967) Age differences in fluid and crystallized intelligence. *Acta Psychol* 26:107–129

Jackson S, Jackson G, Roberts M (1999) The selection and suppression of action: ERP correlates of executive control in humans. *Neuroreport* 10:861–865

- Jodo E, Inoue K (1990) Effects of practice on the P300 in a Go/NoGo task. *Electroencephalogr Clin Neurophysiol* 76:249–257
- Johannes S, Kube C, Wieringa B, Matzke M, Munte T (1997) Brain potentials and time estimation in humans. *Neurosci Lett* 231:63–66
- Jones CR, Rosenkranz K, Rothwell JC, Jahanshahi M (2004) The right dorsolateral prefrontal cortex is essential in time reproduction: an investigation with repetitive transcranial magnetic stimulation. *Exp Brain Res* 158:366–372
- Kiefer M, Marzinzik F, Weisbrod M, Scherg M, Spitzer M (1998) The time course of brain activations during response inhibition: evidence from event-related potentials in a go/no go task. *Neuroreport* 9:765–770
- Konishi S, Nakajima K, Uchida I, Sekihara K, Miyashita Y (1998) No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. *Eur J Neurosci* 10:1209–1213
- Lai C, Ikeda A, Terada K, Nagamine T, Honda M, Xu X, Yoshimura N, Hwong S, Barrett G, Shibasaki H (1997) Event-related potentials associated with judgement: comparison of S1- and S2-choice conditions in a contingent negative variation (CNV) paradigm. *J Clin Neurophysiol* 14:394–405
- Lejeune H, Maquet P, Bonnet M, Casini L, Ferrara A, Macar F, Pouthas V, Timsit-Berthier M, Vidal F (1997) The basic pattern of activation in motor and sensory temporal tasks: positron emission tomography data. *Neurosci Lett* 235:21–24
- Lezak M (1995) *Neuropsychological assessment*. Oxford University Press, New York
- Lindinger G, Svasek P, Urban G, Lang W, Deecke L (1990) Microcomputer-assisted 64-channel EEG amplifier (DC–2 kHz) with digital filter and 16 bit resolution. *Biomed Tech (Berl)* 35(Suppl 2):88–89
- Loveless NE, Sanford A (1974) Effects of age on the contingent negative variation and preparatory set in a reaction-time task. *J Gerontol* 29:52–63
- Macar F, Vidal F, Casini L (1999) The supplementary motor area in motor and sensory timing: evidence from slow brain potential changes. *Exp Brain Res* 125:271–280
- McCallum W, Curry S (1981) Late slow wave components of auditory evoked potentials: their cognitive significance and interaction. *Electroencephalogr Clin Neurophysiol* 51:123–137
- Michalewski HJ, Thompson LW, Smith DB, Patterson JV, Bowman TE, Litzelman D, Brent G (1980) Age differences in the contingent negative variation (CNV): reduced frontal activity in the elderly. *J Gerontol* 35:542–549
- Moscovitch M, Winocur G (1995) Frontal lobes, memory, and aging. *Ann N Y Acad Sci* 769:119–150
- Nichelli P, Vermneri A, Molinari M, Tavani F, Grafman J (1993) Precision and accuracy of subjective time estimation in different memory disorders. *Cogn Brain Res* 1:87–93
- Nichelli P, Clark K, Hollnagel C, Grafman J (1995) Duration processing after frontal lobe lesions. *Ann N Y Acad Sci* 769:183–190
- Oddy B, Barry R, Johnstone S, Clarke A (2005) Removal of CNV effects from the N2 and P3 ERP components in a visual Go/NoGo task. *J Psychophysiol* 19:24–34
- Passingham R (1993) *The frontal lobes and voluntary action*. Oxford University Press, Oxford
- Perianez JA, Rios-Lago M, Rodriguez-Sanchez J, Adrover-Roig D, Sanchez-Cubillo I, Crespo-Facorro B, Quemada J, Barcelo F (2007) Trail Making test in traumatic brain injury, schizophrenia, and normal ageing: sample comparisons and normative data. *Arch Clin Neuropsychol* 22:433–447
- Pfefferbaum A, Ford J (1988) ERPs to stimuli requiring response production and inhibition: effects of age, probability and visual noise. *Electroencephalogr Clin Neurophysiol* 71:55–63
- Phillips LH, Della Sala S (1999) Aging, intelligence, and anatomical segregation in the frontal lobes. *Learn Individ Differ* 10:217–243
- Polich J (1996) Meta-analysis of P300 normative aging studies. *Psychophysiology* 33:334–353
- Polich J, Kok A (1995) Cognitive and biological determinants of P300: an integrative review. *Biol Psychol* 41:103–146
- Pouthas V, George N, Poline J, Pfeuty M, Vandemoortele P, Hugueville L, Ferrandez AM, Lehericy S, Lebihan D, Renault B (2005) Neural network involved in time perception. *Hum Brain Mapp* 25:433–441
- Rao SM, Mayer AR, Harrington DL (2001) The evolution of brain activation during temporal processing. *Nat Neurosci* 4:317–323
- Reitan RM (1958) Validity of the Trail Making test as an indicator of organic brain damage. *Percept Mot Skills* 8:271–276
- Reuter-Lorenz P (2002) New visions of the aging mind and brain. *Trends Cogn Sci* 6:394–400
- Roberts LE, Rau H, Lutzenberger W, Birbaumer N (1994) Mapping P300 waves onto inhibition: Go/NoGo discrimination. *Electroencephalogr Clin Neurophysiol* 92:44–55
- Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, Simmons A, Williams SC, Giampietro V, Andrew CM, Taylor E (2001) Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage* 13:250–261
- Rubin DC (1999) Frontal-striatal circuits in cognitive aging: evidence for caudate involvement. *Aging Neuropsychol Cognit* 6:241–259
- Salisbury DF, Griggs CB, Shenton ME, McCarley RW (2004) The NoGo P300 ‘anteriorization’ effect and response inhibition. *Clin Neurophysiol* 115:1550–1558
- Salmaso D, Longoni A (1985) Problems in the assessment of hand preference. *Cortex* 21:533–549
- Sanchez-Cubillo I, Perianez J, Adrover D, Rodriguez J, Rios M, Tirapu J, Barcelo F (2009) Construct validity of the Trail Making test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *J Int Neuropsychol Soc* 15:438–450
- Schiaie JP, Syndulko K (1978) Age differences in cortical activity associated with preparation to respond. *Int J Behav Dev* 1:255–261
- Segalowitz SJ, Unsal A, Dywan J (1992) CNV evidence for the distinctiveness of frontal and posterior neural processes in a traumatic brain-injured population. *J Clin Exp Neuropsychol* 14:545–565
- Sharp D, Scott S, Mehta M, Wise R (2006) The neural correlates of declining performance with age: evidence

- for age-related changes in cognitive control. *Cereb Cortex* 16:1739–1749
- Simson R, Vaughan H, Ritter W (1977) The scalp topography of potentials in auditory and visual Go/NoGo tasks. *Electroencephalogr Clin Neurophysiol* 43:864–875
- Smith J, Johnstone S, Barry R (2008) Movement-related potentials in the Go/NoGo task: the P3 reflects both cognitive and motor inhibition. *Clin Neurophysiol* 119:704–714
- Sweeney J, Rosano C, Berman R, Luna B (2001) Inhibitory control of attention declines more than working memory during normal aging. *Neurobiol Aging* 22:39–47
- Tecce JJ, Cattanach L (1993) Contingent negative variation. In: Niedermeyer E, Lopes da Silva F (eds) *Electroencephalography: basic principles, clinical applications, and related fields*. William & Wilkins, Baltimore, pp 887–910
- Terry RD, de Teresa R, Hansen LA (1987) Neocortical cell counts in normal adult aging. *Ann Neurol* 21:530–539
- Umegaki H, Roth G, Ingram D (2008) Aging of the striatum: mechanisms and interventions. *Age* 30:251–261
- Vallesi A, Stuss DT, McIntosh AR, Picton TW (2009) Age-related differences in processing irrelevant information: evidence from event-related potentials. *Neuropsychologia* 47:577–586
- Velanova K, Lustig C, Jacoby LL, Buckner RL (2007) Evidence for frontally mediated controlled processing differences in older adults. *Cereb Cortex* 17:1033–1046
- Welford A (1977) Motor performance. In: Birren J, Schaie K (eds) *Handbook of the psychology of aging*. Van Nostrand Reinhold, New York, pp 450–496
- West RL (1996) An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull* 120:272–292
- Wild-Wall N, Hohnsbein J, Falkenstein M (2007) Effects of ageing on cognitive task preparation as reflected by event-related potentials. *Clin Neurophysiol* 118:558–569
- Zappoli R, Versari A, Paganini M, Arnetoli G, Roma V, Battaglia A, Porcù S (1988) Age differences in contingent negative variation activity of healthy young adults and presenile subjects. *Ital J Neurol Sci* 9:219–230