



# Age-dependent changes in distribution of P3a/P3b amplitude and thickness of the cerebral cortex

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Received 8 June 2005; accepted 8 July 2005

With increasing age, the electrophysiological event-related potentials P3a/P3b tend to get a more frontal maximum. The cognitive significance of this so-called frontal shift is not known, but hypotheses have focused on changes in the integrity of the frontal lobes. The aim of the present study was to test how the thickness of the cerebral cortex is related to the frontal shift. Well screened elderly participants went through a visual three-stimuli oddball-task, a battery of neuropsychological tests, and magnetic resonance

imaging scans. It was found that participants with frontocentral maxima had a thicker cerebral cortex in distinct areas than participants with parietal maxima, both for P3a and for P3b, while the parietal P3b participants had a thicker cortex in the anterior cingulate. This is the first study to demonstrate that age-dependent changes in the scalp distribution of electrophysiological activity are related to differences in thickness of the cerebral cortex. *NeuroReport* 00:000–000 © 2005 Lippincott Williams & Wilkins.

**Key words:** Aging; Frontal lobe; Frontal shift; Neuropsychology; P3a; P3b; Thickness of the cerebral cortex

## INTRODUCTION

The distribution of cerebral neural activity has been found to change with age, but these changes have not consistently been mapped to information processing characteristics. The present study is focused on the relationship between cerebral cortical thickness and the amplitude of the electrophysiological event-related potentials (ERPs) P3a and P3b. These ERP components have a more frontal maximum in the elderly than in young adults [1], and have received much attention as a measure related to rapid cognitive functioning and aging [2,3]. As ERP recordings provide access to neural activity, the method can potentially detect minute differences in information processing between groups of comparable cognitive test performance. Thus, the frontal shift of the P3 complex in aging may prove to be related to changes in the thickness of the cerebral cortex. The present study aims at identifying neuroanatomical correlates of the frontal shift by comparing the thickness of the cerebral cortex of groups of the elderly with frontocentral versus parietal amplitude maximas.

Even though consensus has not been reached regarding the cognitive correlates of the frontal shift, changes in the efficiency of circuits involving the frontal lobes have been implied [4–6]. As both P3a and P3b index fundamental aspects of cognitive activity, one may speculate that shifts of these deflections are related to changes in the thickness of the cerebral cortex. It is known that P3b is associated with neural activity in a wide range of brain regions, while P3a is confined to a smaller area, involving frontal structures [7]. Further, relationships between brain volumes and P3 amplitude and/or latency in young or middle-aged healthy adults may exist ([8–11], but see [12]). A direct spatial

relationship between P3 and cortical volume underlying the recording electrode has not been established [11], however, and a recent study found that white matter conductivity between neural generators may influence P3b latency more than the generators themselves [13]. No previous study has focused on the relationship between the frontal shift and brain volumes, so the question is does the age-related frontal shift of the P3 reflect changes in the thickness of the cerebral cortex?

## MATERIALS AND METHODS

**Sample:** The sample consisted of 34 community dwellers (17 women and 17 men) in the age range 56–88 years (mean 70, SD=8), recruited from among employees of a local hospital, through charity organizations, activity centers for the elderly, and newspaper ads, who were given a moderate monetary compensation. Criteria for exclusion were self-reported neurological conditions, traumas or use of medication known to influence central nervous system functioning, IQ [Wechsler Adult Intelligence Scale (WAIS)] below 85, Mini Mental State Examination (MMSE) score below 26, or a score on Beck Depression Inventory (BDI) above 14. All participants were less than 2 SD from the population mean on three measures from the California Verbal Learning Test (CVLT) (Trial 1–5, 5 and 30 min recall), and were required to have normal or corrected-to-normal vision. The sample had a mean IQ of 114.4 (85–133), a BDI score of 5.8 (0–14), and an MMSE score of 28.6 (26–30). A general neuropsychological performance score was calculated: the mean (not age-corrected) *t*-score of 19 neuropsychologically well validated tests [verbal ability: vocabulary, similarities from WAIS;

nonverbal ability: block design, matrix reasoning from WAIS; executive function: Trail Making Test, Part B (TMT B), FAS, Stroop color/word, Controlled Word Association Test (COWAT), backward digit span; short term memory: digit span forward from WAIS, Corsi Block Tapping Test; memory function: CVLT learning and 30 min recall, CVMT learning and 20 min recognition; sensory-motor skills/cognitive efficiency: pegs, symbol substitution from WAIS-R]. The *t*-scores were based on a larger sample of well screened participants. An executive score based on the five executive tests (TMT B, FAS, Stroop color/word, COWAT, and backward digit span) was computed in the same manner. For specific references to the tests, see Lezak [14]. The sample is part of a larger sample described previously [1].

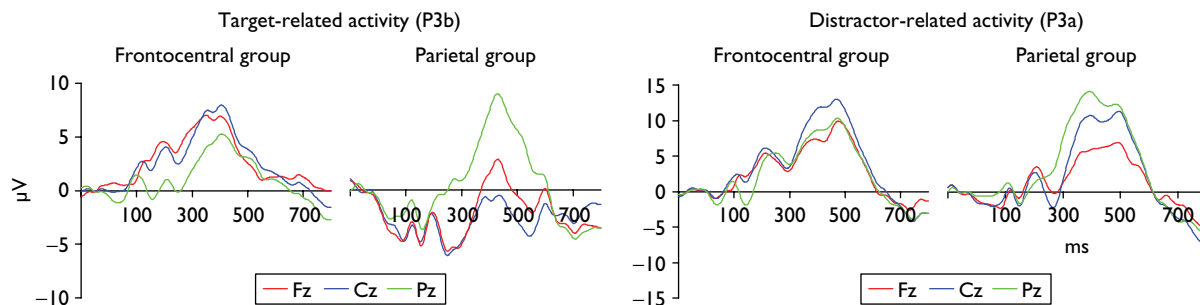
**Event-related potential task, recording procedures, and bootstrapping:** A three-stimuli visual oddball task, with 210 stimuli, 0.10 target and 0.10 distractor probability, was used. The standard and target stimuli were blue ellipses,  $15 \times 12.5$  cm and  $17.5 \times 14.5$  cm, and the distractor stimuli were rectangles of  $21 \times 17$  cm. The targets required button press, and other stimuli were to be ignored. The stimuli were presented on a 21-inch screen with black background, with a viewing distance of 100 cm, and a visual field of about  $9^\circ \times 7^\circ$ ,  $10^\circ \times 8^\circ$ , and  $12^\circ \times 10^\circ$  for the standard, target, and distractor stimuli, respectively. The small target-standard difference and the large target-distractor difference were chosen to maximize the P3a [15]. Presentation time was 0.5 and interstimulus interval was 1.5 s. Cutoff criteria were set to  $\geq 20\%$  target misses, 20% responses to standards, or 25% responses to distractors. Mean reaction time after cut-off criteria were applied was 520 ms and mean target hit rate was 96%. Before recording, an example task with 11 standard and target stimuli was presented to prime the participants for the task.

The electrodes (Ag/AgCl) were placed in accordance with the International 10-20 System (Fz, Cz, Pz), referred to the left mastoid. A vertical ocular motor channel was obtained by electrodes above and below the left eye, and ground was placed anteriorly (right). Interelectrode impedance was generally less than 10 k $\Omega$ . A/D rate was 500 Hz and filter setting 0.10 Hz (high pass) and 70 Hz (low pass), in addition to a 50 Hz notch filter. Signals were amplified by a SynAmp DC (Neuroscan Inc., Texas, USA). Epochs were rejected if amplitude exceeded  $\pm 110 \mu\text{V}$ ; eye blinks were corrected [16] and average files were baseline-corrected and filtered (15 Hz low pass). Single-sweep analysis was conducted, using the average activity between 250 and 600 ms to avoid latency jitter.

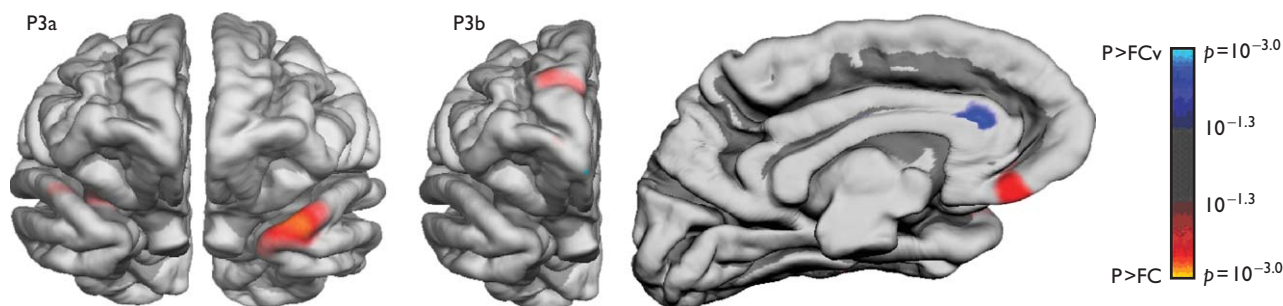
The bootstrap procedure was chosen to assess the reliability of differences in scalp distribution on an individual basis, modeled on the approach of Fabiani *et al.* [6]. In short, three steps were conducted: First, a large number of averages of equal sample size were calculated per study participant, which constitutes the bootstrap replications. In all, 10 000 bootstrap samples of 24 trials were randomly selected (with replacement) from the pool of trials of a given participant. Second, the electrode location with maximum activity for each bootstrap replication was determined. Finally, the frequency distributions of this sample statistic across bootstrap replications were derived. The frequency distribution is an index of the probability that

a participant will be classified with the same P3 maxima if the task had been repeated. Thus, the participants were grouped on the basis of where on the scalp their P3s were of maximum amplitude, and contrasted by use of a general linear model approach point by point across the entire cortical mantle, both for P3a and for P3b. As a result of the well known problems of inferring localization of ERP sources from scalp recordings, a close mapping correspondence was not expected. Participants with more than 5000 bootstrap replications of maximum amplitude at Fz/Cz versus Pz were characterized as frontocentral versus parietal. The same criterion was used for both P3a and P3b. For P3b, 90.9% of the bootstrap replications for the frontocentral groups peaked on Fz or Cz, while the parietal group had 85.3% of the peaks on Pz. For P3a, the numbers were 89.6% and 74.1%. Twenty of the participants were characterized as either frontocentral or parietal both for P3a and for P3b, while 14 changed status from P3a to P3b. For the P3a, the frontocentral and parietal groups consisted of 24 and 10 participants, respectively, comparable with respect to age (68.2 vs. 72.9 years,  $t=-1.7$ ,  $df=32$ , NS), general neuropsychological (48.7 vs. 48.3,  $t=0.289$ ,  $df=32$ , NS), and executive (47.7 vs. 45.4,  $t=0.94$ ,  $df=32$ , NS) function. For P3b, the groups each consisted of 17 participants, also here comparable with respect to age (68.6 vs. 70.1 years,  $t=-0.51$ ,  $df=32$ , NS), general neuropsychological (48.8 vs. 48.7,  $t=0.016$ ,  $df=32$ , NS), and executive (48.1 vs. 45.9,  $t=1.04$ ,  $df=32$ , NS) function. The sex distribution was equal across groups ( $p > 0.70$ ).

**Magnetic resonance image scanning and volumetric analyses:** A Siemens Symphony Quantum 1.5 T magnetic resonance scanner with a conventional head coil was used. The pulse sequences used for analysis were as follows: two three-dimensional magnetization prepared gradient echo, T1-weighted sequences in succession (TR/TE/TI/FA=2730 ms/4 ms/1000 ms/ $7^\circ$ , matrix=192  $\times$  256, FOV=256 mm), with a scan time of 8.5 min per volume. Each volume consisted of 128 sagittal slices with slice thickness of 1.33 mm, and in-plane pixel size of 1 mm  $\times$  1 mm. Automated procedures for thickness measurement of cortex were used, reconstructing representations of the gray/white matter boundary [17] and the cortical surface, and then calculating the distance between those surfaces at each point across the cortical mantle. The technique has been validated via histological and manual measurements. The maps produced are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. They are not restricted to the voxel resolution of the original data and thus are capable of detecting submillimeter differences between groups [18]. Maps were smoothed by a circularly symmetric Gaussian kernel across the surface with a SD of 12.6 mm and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns [19]. Individual hemispheres are inflated to a sphere and warped along the spherical surface to a spherical template, using Talairach coordinates. As discrete surface models from different participants are often not topologically equivalent, the analysis of interparticipant data requires data interpolation onto a common mesh. Statistical comparisons of global data and surface maps were generated by computing a general linear model at each vertex. The total



**Fig. 1.** Grand average event-related potential curves for the old groups with reliable frontocentral versus parietal maxima defined by the bootstrap procedure.



**Fig. 2.** The thickness of the cerebral cortex and P3. General linear model contrasting participants whose P3s reached frontocentral (FC) versus parietal maxima (P). P3a: Frontal view. P3b: frontal (left) and medial (right) views.

brain size may have an influence on anatomical data [20], but the focus in this paper is limited to the thickness of the cerebral cortex, which probably is most directly related to scalp ERPs.

## RESULTS

The P3a groups differed in that the frontocentral group had a thicker cortex in parts of the right superior planum polare of the temporal gyrus, and the gyrus and sulcus of the insula (Figs 1 and 2). In the left hemisphere, differences were found in the temporal pole. For P3b, the frontocentral group had a thicker cortex in the junction of the right middle, superior frontal, and transversal frontopolar gyrus in the right hemisphere. In the left hemisphere, a part of the gyrus rectus differed in thickness between the groups. In addition, the parietal group showed a thicker cortex in a part of the anterior cingulate gyrus and a small area of the pericallosal sulcus.

## DISCUSSION

The present results indicate that the scalp distribution of neural activity, as indexed by P3a and P3b, is related to the thickness of the cerebral cortex in distinct areas. This finding is intriguing because the groups with frontocentral versus parietal amplitude maxima showed comparable cognitive function on a battery of neuropsychological tests. Neuropsychological results are limited to behaviorally executed responses, but electrophysiological potentials are probably related to human cognition at a more basic level. Thus, ERPs may potentially identify subtle changes in neuroanatomical structures not yet detectable by standardized cognitive tests.

The results were dependent on whether P3a or P3b was used for group classification. This may relate to findings reviewed above, pointing to nonoverlapping brain areas responsible for the generation of P3a and P3b. The areas of difference were a little more widespread for P3b than for P3a, which may be associated with more widespread neural origins. It is possible that partly different processes may be responsible for the frontal shift of P3a versus P3b. The frontal shift in P3b is caused mainly by a reduction in parietal amplitude, while the shift in P3a is caused by a central reduction [1]. Thus, it is not given that the frontal shift is related to the same processes for P3a as for P3b.

The cognitive significance of the differences in the thickness of the cerebral cortex cannot yet be decided with certainty, because the groups had the same neuropsychological function. Thus, age-dependent changes in where on the scalp P3 amplitude reaches its maximum cannot from the present data be related to compensation or inefficiency in cognitive processing. Recent functional imaging studies indicate that changes in neuronal activity with age signify compensation, and thus are associated with higher cognitive function [21]. The reasoning is that when the efficiency of brain structures normally supporting a cognitive process declines, cognitive function may be preserved by inclusion of other brain structures to compensate for the reduced efficiency of the original ones. Evidence, however, is conflicting. Friedman [22] found that a frontal shift of late negative ERP activity along the posterior–anterior axis in aging was associated with superior cognitive performance, while Fabiani *et al.* [6] reached the opposite conclusion for P3. In the latter study, a bootstrap procedure very similar to the one in the present study was used, and the results showed that participants with a frontal distribution of the

P3b had lower performance on parts of the Wisconsin Card Sort Test. In the present study, the groups showed the same level of cognitive function.

Still, the results may be taken to support a view of the frontal shift as involving recruitment of alternative or additional cortical areas. Neural activity can increase the volume of specific brain structures in a few months [23]. Thus, systematic changes in the distribution of neural activity may have the potential to change the thickness of the cerebral cortex. Such changes may be almost impossible to detect with standard psychometric instruments, because increased involvement of alternative processing resources may serve to keep cognitive function at a satisfactory level. Thus, it cannot be ruled out that changes in where on the scalp P3 reaches maximum affect the thickness of the cerebral cortex. This is in line with possible effects of training on the size and composition of the attentional network responsible for P3 generation.

## CONCLUSION

The present study is the first to demonstrate that the thickness of the cerebral cortex is related to systematic changes in the distribution of cerebral neural activity. Further research should use a longitudinal design to monitor parallel or divergent changes in ERP, thickness of the cerebral cortex, and cognitive function.

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**Acknowledgement:** Support for this research was provided by the Norwegian Research Council and the Institute of Psychology at the University of Oslo. We thank Christopher Nielsen for development of Readpeak software used to determine ERPs, and Ole J. Røgeberg for implementing the bootstrap procedures in Mathematica, Stine E. Vogt for assisting in making the graphics, and Bruce Fischl, Anders Dale, David Salat, and Brian T. Quinn for advice, assistance and help during various parts of the project.

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