



# Stability of brain potentials, mental abilities, and cortical thickness

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The purpose of the study was to test whether trial-to-trial variation in amplitude of the brain potentials P3a and P3b is related to age, intelligence (verbal and performance abilities), and brain volumetry. One hundred and thirty-three participants underwent neuropsychological testing and an event-related potential task, whereas a subgroup ( $n=72$ ) also had magnetic resonance scans. Trial-to-trial variation in P3a amplitude correlated positively with age, and negatively with verbal and performance intelligence.

Trial-to-trial variation in amplitude also correlated negatively with thickness in temporoparietal junction and the precentral gyrus of the cerebral cortex, but these relationships were dependent on the influence of age. The results indicate that intraindividual variability should be used as a variable in the study of control nervous system function. *NeuroReport* 00:000–000 © 2007 Lippincott Williams & Wilkins.

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## Introduction

Intraindividual variability refers to transient, within-person change in behavioral performance [1]. This is often treated as noise, and analysis is based on mean scores across trials, tests, or occasions. Several lines of evidence, however, link intraindividual variability in reaction time to general mental abilities, e.g., the psychometric  $g$  [2] or measures of fluid intelligence [3]. Hultsch *et al.* [4] have shown that greater intraindividual variability is associated with poorer cognitive performance, aging, and neurological deficits. Other studies [1,5] present converging evidence, and Hultsch *et al.* [6] have drawn the conclusion that intraindividual variability predicts cognitive performance independently of mean scores.

It is not known which neuropsychological processes underlie intraindividual variability. This will likely depend on the type of cognitive performance measured. The focus has been on choice reaction time tasks involving attentional and executive capacities. Intraindividual variability may be related to attentional lapses [4,7], regulation of responses [8], information processing instability [1,3], and physiological arousal rhythms [9]. In a recent review, MacDonald *et al.* ([1], p. 474), argued that 'Despite frequent reports of intraindividual variability, there is little synthesis, and no direct examination of the neural underpinnings.' Few studies have related intraindividual variability in healthy persons to physiological measures. An exception is a recent study presenting a correlation between intraindividual variability of reaction time and white matter volume (Walhovd and Fjell, submitted). White matter consists of myelinated neural connections, and a high degree of

myelination may yield better isolation and hence more stable flow of electrical currents in dendrites and axons.

Even though intraindividual variability is a predictor of intellectual function, the biological foundation is poorly understood. In this study, the aim was to shed light on this by measuring trial-to-trial variability in the amplitude of the enterprise resource planning (ERP) components P3a and P3b. These were chosen because they are related to cognitive function [10], aging [11], neurological conditions [12], and brain morphometry [10]. It has been demonstrated that variability of these component is related to neuropsychiatric conditions [13]. In addition, P3 is the largest cognitive ERP, making it easier to quantify in single trials.

The main hypothesis is that increased intraindividual variability in P3 amplitude will be related to lower cognitive function and smaller brain volumes. On the basis of studies of average ERPs from the same task [10] we expect larger correlations for P3a than P3b. Furthermore, we speculate that negative correlations between amplitude variability and cortical thickness may be found in left posterior cingulate, the temporoparietal junction, precentral gyrus, and superior frontal gyrus. This is based on a previous study of the same sample, showing correlations between average P3a amplitude and cortical thickness. In addition to the region of interest (ROI) analyses, an unbiased approach was taken, where the relationship between variability and cortical thickness at all vertexes of the brain surface was tested. It has previously been shown that hippocampus [14] and white matter volume [15] are important for P3 generation, so the relationship between these structures and P3 variability will be tested. Furthermore, a special role of striatal dopaminergic systems in intraindividual variability

has been proposed [16], so the relationship between striatal volume and P3 variability will be investigated.

## Methods

### Sample

The original sample consisted of 137 healthy volunteers (70 females) evenly distributed from 20 to 89 years (mean 51 years, SD 21 years), screened for diseases and traumas known to affect central nervous system (CNS)-functioning by a set of health-related questions. Seventy-two participants had magnetic resonance (MR) scans. All participants were examined with the Wechsler Abbreviated Scale of Intelligence (WASI: [17]), and excluded if  $IQ < 85$ . One participant was excluded owing to low IQ, and four were excluded owing to low performance on the ERP task (see below), reducing the sample to 133. WASI consists of two verbal (vocabulary, similarities) and two performance (matrix reasoning, block design) tests, which were used to calculate an age-adjusted IQ score (sample mean 114, SD=10, range 85–136), which did not correlate with age ( $r=0.05$ , n.s.). The raw scores for each of the subtests were used for the statistical analyses. One of the 133 persons in the final sample did not complete the matrix-reasoning test. IQ score for this person was calculated based on the other three tests.

### Enterprise resource planning task and recording

A three-stimuli visual oddball task with 210 stimuli, 0.10 target and 0.10 distractor probability was used. Stimuli were blue ellipses (standard:  $15 \times 12.5$  cm; target:  $17.5 \times 14.5$  cm) and rectangles (distractor:  $21 \times 17$  cm), presented on a 21-in. screen with black background, viewing distance of 100 cm, and visual field of about  $9 \times 7^\circ$ ,  $10 \times 8^\circ$ , and  $12 \times 10^\circ$  for standard, target, and distractor stimuli, respectively. Targets required button press, and other stimuli were to be ignored. Presentation time was 0.5 and ISI 1.5 s. Cut-off criteria were set to  $\geq 20\%$  target misses/ $20\%$  responses to standards/ $25\%$  distractor responses. Mean target hit rate was 96%. An example task was presented to introduce the participants to the task.

Twenty electrodes (Ag/AgCl) were placed in accordance with the international 10–20 system (Cz, Pz used for analyses), referred to the left mastoid. A vertical electro-oculogram (VEOG) channel was obtained by electrodes above and below the left eye, and ground was placed anteriorly (right). Inter-electrode impedance was generally measured to be 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.). Epochs were rejected if amplitude exceeded  $\pm 75 \mu\text{V}$ , eye blinks were corrected [18], and files were baseline-corrected and filtered (3 Hz low pass). A harsh low-pass filter was used as the analyses were performed on single trials, with more noise to be removed from the data [19]. The average activity between 250 and 600 ms was entered into statistical analyses.

### Magnetic Resonance Imaging scanning and volumetric analyses

A Siemens Symphony Quantum 1.5 T MR scanner with a conventional head coil was used. The pulse sequences were two 3D magnetization prepared gradient echo (MP-RAGE), 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 isotropic pixel size of 1 mm. Automated procedures for thickness measurement of cortex were used [20,21]. Maps were smoothed by a circularly symmetric Gaussian kernel across the surface with a standard deviation of 12.6 mm and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns [22]. All scans were also run through the whole brain segmentation procedure as described in Ref. [23], which automatically assigns a neuroanatomical label to each voxel based on probabilistic information estimated from a manually labeled training set. Intracranial volume (ICV) was calculated based on proton density (PD) weighted lowflip angle FLASH scans. A deformable template procedure ('shrink wrapping') [24] was used to obtain an estimate of the smooth surface surrounding the intracranial space (containing brain, CSF, and meninges). Subcortical structures were regressed on ICV, and the statistics analysis carried out on the residuals.

### Statistical analyses

The standard deviation (SD) of the single trial amplitudes for each participant and each stimulus class was calculated. A version of the coefficient of variation (CV) [5] was obtained by dividing SD with the mean (to remove negative values from rare negative amplitudes in the P3 window, the square root of the square of this number was used in the analyses). This will hereafter be referred to as intraindividual variability. To test the relationship between intraindividual variability and neuropsychological performance, Pearson correlations were calculated. To avoid multiple comparison problems, analyses were restricted to Cz for P3a and Pz for P3b. All *P*-values were Bonferroni-corrected (by a factor of 10; four neuropsychological tests and age for each component). The volume of striatum (defined as the sum of putamen, pallidum, and caudate), hippocampus, and white matter were correlated with intraindividual variability, as was the mean thickness in four ROIs (see Fig. 3). Bonferroni-corrections were used. Finally, an unbiased general linear model (GLM) analysis with a false discovery rate (FDR) threshold of 0.05 was carried out. Here, thickness at each point of the cortical surface was correlated with intraindividual variability. All statistical analyses were performed with outliers excluded (deleted Studentized residual value of  $\geq 2.0$ ). The number of outliers in each analysis was small, typically  $< 3$ . SPSS 12.0.1 and Freesurfer were used.

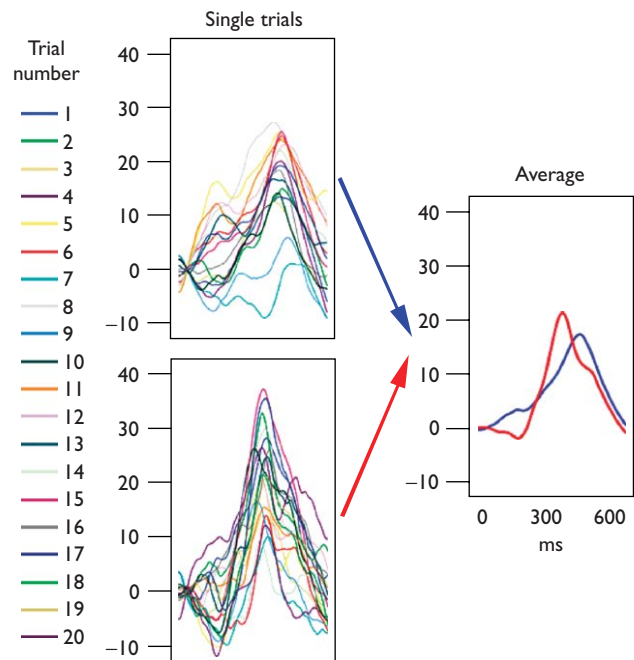
## Results

Examples of ERP activity are shown in Fig. 1. P3a is expected to be more frontocentral than P3b. To test this, an analysis of variance with two components (P3a, P3b)  $\times$  3 electrodes (Fz, Cz, Pz) was carried out, yielding a significant component  $\times$  electrode interaction [ $F(1.87, 241.73) = 33.17$ ,  $P < 0.0001$ , Greenhouse–Geisser-corrected]. In this analysis, mean amplitude across all single trials was used. Inspections of the data revealed that the interaction was due to maximum amplitude at Cz for P3a and Pz for P3b, indicating that the paradigm elicited physiologically distinct components.

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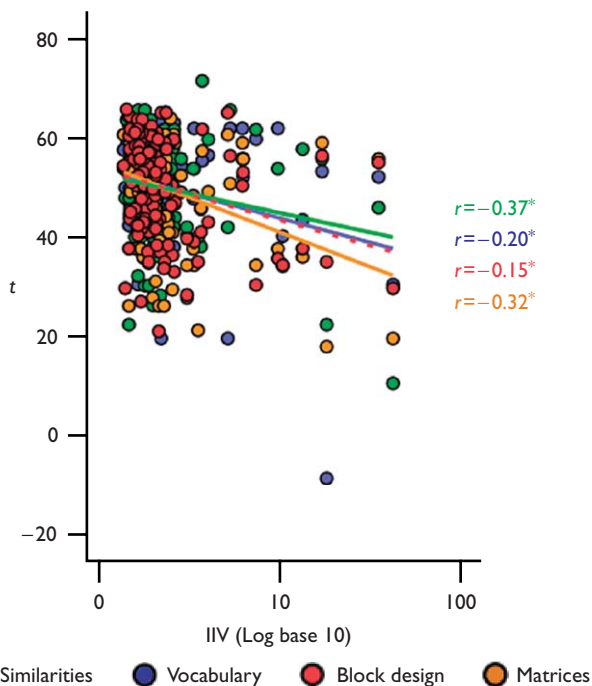
AQ3



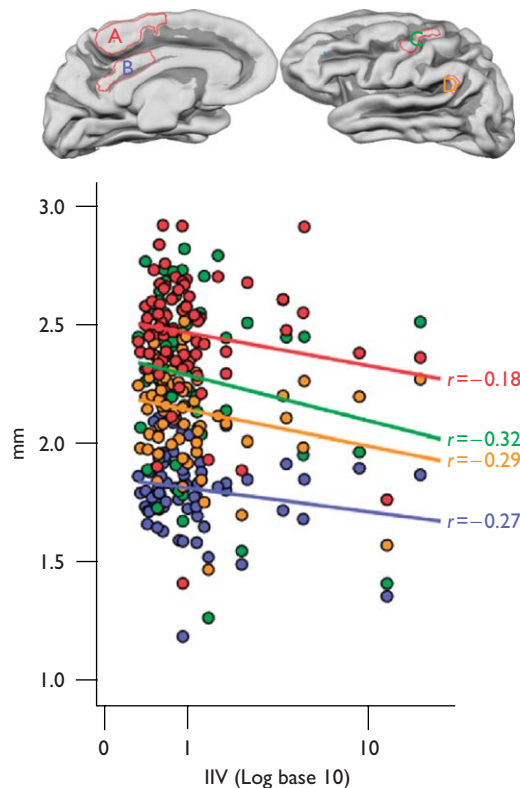
**Fig. 1** Single subject event-related potentials. Left column: single sweeps to the distractor at Cz for two representative participants, showing a considerable variance in the amplitude from trial-to-trial. Right column: average event-related potentials for these participants.

Intraindividual variability correlated with mean Cz P3a amplitude ( $r=-0.51, P<10^{-6}, n=129$ ), similarities ( $r=-0.30, P<0.01, n=131$ ), vocabulary ( $r=-0.31, P<0.01, n=129$ ), matrix reasoning ( $r=-0.38, P<0.0001, n=132$ ) and block design ( $r=-0.27, P<0.05, n=131$ ), but not age ( $r=0.15, n.s., n=133$ ) (Fig. 2). Partial correlations controlling for age and mean P3a amplitude showed that correlations with similarities ( $r=-0.28, P<0.01, DF=127$ ), vocabulary ( $r=-0.30, P<0.005, DF=127$ ) and matrix reasoning ( $r=-0.33, P<0.01, DF=124$ ) were still significant, whereas block design was not ( $r=-0.12, n.s., DF=127$ ).

Thickness in temporoparietal junction ( $r=-0.30, P<0.05, n=71$ ) and precentral gyrus ( $r=-0.29, P=0.05, n=71$ ) correlated with intraindividual variability (Fig. 3), whereas the two other ROIs did not. When controlling for the effect of age, the correlations with intraindividual variability did not survive the Bonferroni correction (both  $r=-0.26, P=0.12, n=68$  and  $67$ , respectively). No relationships survived an unbiased general linear modeling with intraindividual variability on thickness across the entire cortical mantle ( $FDR<0.05$ ), and none of the subcortical structures correlated with intraindividual variability (striatum:  $r=-0.24, n=70$ ; hippocampus:  $r=-0.20, n=69$ ; white matter:  $r=-0.12, n=70$ ). The scatterplots revealed some large intraindividual variability scores not defined as statistical outliers. The intraindividual variability–age correlation was thus re-run with a nonparametric method less sensitive to extreme



**Fig. 2** Cognitive function and P3a amplitude variations. The relationship between cognitive function and intraindividual variability in P3a amplitude. The amplitude variability (intraindividual variability) is the standard deviation divided by the mean. Cognitive test scores are shown as t-scores (mean of 50, SD of 10), standardized to the sample. The colored numbers are Pearson correlations (green, similarities, blue, vocabulary, red, block design, yellow, matrix reasoning).  $* < P < 0.05$ , Bonferroni corrected.



**Fig. 3** P3a amplitude variations and cortical thickness. The relationship between the intraindividual variability in P3a amplitude (intraindividual variability) and cortical thickness. Four region of interests were defined. The amplitude variability (intraindividual variability) is the standard deviation divided by the mean. The colored numbers are Pearson correlations [red=posterior part of the superior frontal gyrus (a), blue=posterior cingulate cortex (b), green=precentral gyrus (c), yellow=temporoparietal junction (d)].  $* < P < 0.05$ , Bonferroni corrected.

values (Spearman's  $\rho$ ), and this yielded a significant relationship ( $r=0.24$ ,  $P<0.05$ ).

The analyses performed for P3a were repeated for P3b. Mean Pz P3b amplitude and intraindividual variability correlated significantly ( $r=-0.49$ ,  $P<10^{-6}$ ,  $n=129$ ). Intraindividual variability did not correlate with age ( $r=0.17$ ,  $n=132$ ) or neuropsychological tests (similarities:  $r=0.10$ ,  $n=130$ ; vocabulary:  $r=0.07$ ,  $n=129$ ; block design:  $r=-0.08$ ,  $n=129$ ; matrix reasoning:  $r=-0.03$ ,  $n=130$ ) or the subcortical (striatum:  $r=-0.17$ ,  $n=68$ ; hippocampus:  $r=-0.08$ ,  $n=68$ ; white matter:  $r=-0.13$ ,  $n=69$ ) or cortical brain structures (superior frontal gyrus:  $r=0.12$ ,  $n=71$ ; temporoparietal junction:  $r=0.20$ ,  $n=71$ ; precentral gyrus:  $r=0.12$ ,  $n=71$ ; posterior cingulate:  $r=0.06$ ,  $n=70$ ).

## Discussion

Theory and research has indicated that intraindividual variability is negatively related to general cognitive ability [2], positively related to neurological injury and disease [5], and negatively related to white matter volume (Walhovd and Fjell, submitted). This paper presents three additional findings. The first is that the variability in the brain's electrical responses (P3a) is related to general intellectual functioning. Thus, intraindividual variability at the level of CNS activity validates previous findings at the behavioral level. An implication is that cognitive variability exists before behavioral responses. As seen from the scatterplots, whereas most participants showed low variability ( $<1$ ), effects were created by participants with large variability ( $>2$ ), indicating that this measure may be sensitive to deviant CNS function.

The second main finding is that intraindividual variability correlates with cortical thickness in two areas. As expected, more variability meant thinner cortex. The correlations, specific to P3a, were found in areas assumed to contain P3a generators: the temporoparietal junction and precentral gyrus. These areas correlate with P3a amplitude in elderly [10], and activation in these areas have been found in functional magnetic resonance imaging studies [25]. Owing to the large age-variance, however, Bonferroni corrected results did not survive controlling for age. No correlations with subcortical structures were found.

Finally, age correlated positively with intraindividual variability when Spearman's  $\rho$  was used. This suggests that the CNS of elderly persons works in a less stable way, which fits well with findings of increased intraindividual variability in behavioral tests in aging [5], and may explain part of the cognitive decrements that follows increased age.

## Conclusion

Variability in P3a amplitude correlated with cognitive abilities, neuroanatomical volumes, and age, indicating that intraindividual variability-analyses of fast psychophysiological responses represent a promising tool in the study of CNS function.

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