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Event-related potentials in people at risk for vascular dementia

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Abstract

This study examined the relationship between the integrity of cerebrovascular microcirculation, neuropsychological testing and event-related potential indices of cognitive functioning in a nonclinical group of participants being at risk for vascular dementia. Sonographic measures, magnetic resonance (MR) scans and ERPs were recorded in 30 participants treated for arterial hypertension, with no report of neurological or psychiatric disorders. As a sonographic measure of cerebral microcirculation, the arteriorvenous cerebral transit time (cTT) was recorded. While neuropsychological measures of memory functions and general mental ability functions did not show systematic correlations with the cTT and other measures of vascular pathology, a pronounced correlation was obtained between P3a latency and cTT. Participants with long cTT showed a delayed P3a. These findings suggest that the P3a is a sensitive measure for reduced cognitive functions even at early stages of cerebrovascular pathology and by this may be a valuable tool for the early identification of cognitive deficits in individuals being at risk for vascular dementia.

Keywords: Hypertension; Arteriovenous cerebral transit time (cTT); Event-related potentials (ERP); P3a; P300; Vascular dementia; Old/new effect

1. Introduction

Vascular dementia refers to a reduction of cognitive functions due to widespread cortical and/or subcortical vascular originated brain parenchymal changes. A commonly used definition of dementia is a global cognitive decline to be recognized by impairments in more than one aspect of cognitive functioning and impairments in memory functions while the state of consciousness is awake and alert (Lezak, 1995). Predominantly, there are two vascular pathologies leading to dementia; one is the small vessel disease or microangiopathy with diffuse white matter changes and lacunar strokes, the other is the atherosclerosis of the large brain supplying arteries leading to larger ischemic strokes within the entire territory of such a vessel. An acute dementia with a believed but not proven vascular origin is the transient global amnesia, characterized by a sudden and reversible loss of memory functions.

High blood pressure (hypertension) is the major precursor of most types of cerebrovascular accidents. There is increasing evidence that hypertension together with diabetes, stroke and heart disease is one of the major risk factors for vascular dementia. A longitudinal study covering a 7 year period revealed that a history of hypertension was associated with an increased risk for vascular dementia, while there were no comparable associations between hypertension and Alzheimer's disease or general cognitive functions in normal individuals (Posner et al., 2002). Antihypertensive treatment over a period of 2.2 years reduced the incidence of vascular dementia but not for Alzheimer's disease in elderly people (Velt et al., 2001) and hypertension in elderly individuals is associated with smaller total brain volumes, more hyperintensities in MR-scans around the anterior horns of the lateral

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ventricles (i.e. the periventricular white matter) and a higher risk for periventricular lesions (Wiseman et al., 2004). A recent study using longitudinal measures of 5 year changes in regional brain volumes in healthy adults, found progressive shrinkage in the hippocampus only for hypertensive participants (Raz et al., 2005). Even though the functional characteristics of this selective shrinkage remains to be specified, the latter finding indicates that hypertension is not only a risk factor for cerebrovascular brain pathology but also for structural brain abnormalities. The identification and treatment of these vascular risk factors even in normal individuals is of high clinical relevance, as, in contrast to Alzheimer's dementia, the progression of vascular dementia can be stopped or at least delayed by the appropriate treatment of these factors (Hachinski, 2000; The 3C Study Group, 2003; Verleger, 2002).

1.1. Cerebrovascular microcirculation

Lacunar infarctions or diffuse white matter changes as a result of small vessel diseases due to hypertension or anoxic–ischemic episodes are frequently observed in vascular dementia. While for the identification of small vessel pathologies structural neuroimaging techniques, such as magnetic resonance (MR) diffusion imaging, cranial computed tomography (CT) or single photon emission computed tomography are common standards, cerebral duplex sonography was recently introduced as a new non-invasive and quickly to perform method to identify small vessel abnormalities in vascular dementia. By this approach the efficiency of cerebral microcirculation is measured by the time required for an ultrasound echo contrast agent to pass from the cerebral arteries to the veins. Based on the ability of the cerebral arteries to keep cerebral blood flow constant, the amount of the brain supplying blood flow is reduced by increasing the vascular resistance when high blood pressure brings a high amount of blood downstream to the brain. When blood pressure is low and, hence, the blood flow to the brain reduced, the arteries dilate to allow more blood to stream into the brain. Hypertension leads to a chronic state of high vascular resistance which will become irreversible at some point because the vessels loose their ability to dilate. Thus the injected ultrasound echo contrast agent will need a longer time to pass the microvascular bed when hypertension has caused a fixed high resistance compared to a vascular bed with a normal resistance. Using this arteriovenous cerebral transit time (cTT), Puls and colleagues (1999) found the cTT to be substantially prolonged in patients with vascular dementia as compared to controls and patients with degenerative (Alzheimer's) dementia. Moreover, cTT was correlated with the severity of the cognitive impairment in patients with vascular dementia and patients with cerebral microangiopathy had a longer cTT than healthy controls. This suggests that the cTT is a valuable tool in the diagnosis of dementia. Notably, the feasibility of the arteriovenous cerebral transit time for the identification of risk factors for vascular dementia in normal individuals has not been examined so far.

The main goal of the present study was to investigate whether the efficiency of cerebral microcirculation (as measured by cTT) in clinical asymptomatic individuals is correlated with neuropsychological tests and event-related potential indices of cognitive functions. In more detail it was investigated whether individuals with prolonged cTT show a predisposition for vascular dementia. To address theses issues, we examined 30 individuals with arterial hypertension and used neuropsychological testing and event-related potentials to assess their attention and memory processes.

1.2. Event-related potentials and cerebrovascular brain lesions

In recent years, event-related potentials (ERPs) are more frequently used in the diagnosis of neuropsychological disorders resulting from neurological diseases (see Verleger, 2002 and Reinvang, 1999 for overviews). ERP abnormalities are commonly found in patients with dementia of different aetiologies. A consistent finding is a prolongation of the P300, a positive deflection between 300 and 600 ms elicited by task-relevant stimuli with low probability (Polich et al., 1990; Yokoyama et al., 1995). The P300 is assumed to index brain activity required to update or modify the contents of working memory (Polich, 2004). The latency of the P300 is considered to be a measure of stimulus classification speed, that is independent from overt responses. The prolongation of the P300 in patients with dementia may suggest that it reflects the poorer mental status of these patients (Goodin and Aminoff, 1987). This view is also supported by the observation that prolonged P300 latencies are not selectively diagnostic for dementia but are also observed in various other disorders that lead to dementia, like Huntington's disease or Progressive Supranuclear Palsy (PSP), or in patients with Multiple Sclerosis (Verleger, 2002). Using a longitudinal study in which the P300 was examined in relation to the functional status of patients with dementia 4 years after the initial assessment, Cohen et al. (1995) showed that P300 latency is one of the best predictors of the functional outcome in dementia. A recent P300 study with patients with transient global ischemia revealed not only prolonged P300 latencies but also a selective reduction of the P300 to visual stimuli over posterior recording sites (Ullsperger et al., 2000). This latter finding suggests that the P300 may index selective pathologies in the parieto-occipital cortex after anoxic–ischemic encephathology even in patients who did not show pathological changes on structural (MR) images. A recent fMRI study (Bledowski et al., 2004a) showed that regions around the temporo-parietal junction, the ventral prefrontal cortex, in the insula and the frontal operculum contribute to the P300. These regions are part of a fronto-parietal network that is involved in goal-directed stimulus-response selection and the generation and application of attentional sets (Corbetta and Shulman, 2002).

While a large number of studies have used the P300 as a diagnostic tool in neurological diseases, only few studies examined the P3a in patient groups. The P3a can be recorded

in so-called three-stimulus paradigms in which rare targets have to be discriminated from frequent standards and rare "distractor" events. In these tasks, the target stimuli elicit a parietal P300 component and for "distractor" events a fronto-centrally distributed P3a is obtained. The P3a has a shorter peak latency than the P300 and can be elicited by distractor events of different kinds and modalities. When novel events (e.g. dog barks, breaking glass, etc.) are used as distractors a so-called novel P3 is obtained (Knight, 1996; Mecklinger et al., 1997; Mecklinger and Ullsperger, 1995). Recent studies confirmed that the P3a and the novel P3 are the same components (Simons et al., 2001). Thus, the term P3a will be used in the present report for the component elicited by distractor events in threee-stimulus paradigms. Polich and Comerchero (2003) showed that the main factor driving the amplitude of the P3a is the difficulty of target/standard discrimination, i.e. the less distinctive targets and standards and the more attention is allocated to the target–standard comparison, the larger the P3a to distractor events. FMRI studies revealed that the brain regions contributing to the P3a (i.e. the "ventral fronto-parietal network, Corbetta and Shulman, 2002) partly overlap with those also contributing to the P300 (Bledowskiet al., 2004b). As the P3a also has an additional contribution from the precentral sulcus including the frontal eyefield, it has been suggested that the latter regions mediate the disengagement of attention and by this serve as a "circuit breaker": As a consequence of orienting towards an unexpected sensory event, the ongoing cognitive activity is interrupted and a new attentional set is adopted (Corbetta and Shulman, 2002).

Among the few studies investigating P3a and P300 in patients with dementia (see Verleger, 2002 for a review), the one by Yamaguchi et al. (2000) is of high relevance in the present context. Using an auditory three-stimulus paradigm, the authors examined the P3a and the P300 in Alzheimer patients and patients with vascular dementia. The P300 was delayed and reduced in amplitude for both patient groups compared to controls. Interestingly, in patients with vascular dementia the P3a was reduced and also showed a longer peak latency as compared to the two other groups. The authors acknowledge that the different aetiology of vascular dementia in Japan and western countries may have contributed to this result. While multiple cortical and subcortical infarcts constitute a main source for vascular dementia in western countries, in Japan small vessel diseases are the main factor causing vascular pathology. By this, the differential response of the P3a in Alzheimer patients and patients with vascular dementia may suggest that the P3a and the cognitive processes reflected in this component are in particular sensitive to small vessel pathology underlying vascular dementia.

A consistent finding in ERP studies examining recognition memory functions is that repeated items elicit more positive going ERPs than non-repeated, new items. These old/new effects start at around 300 ms and show a broad temporal and spatial distribution. Early portions of the old/new effects at frontal recording sites have been associated with an acontextual form of remembering, subjectively reflected by a feeling of familiarity. In contrast, a slightly later and parietally distributed portion of the old/new effects has been associated with the consciously controlled retrieval of information from a prior study episode (see Friedman and Johnson, 2000; Mecklinger, 2000 for overviews). Both portions of the old/new effect have been attenuated by lesions of the medial temporal lobes (Smith and Halgren, 1989; Mecklinger et al., 1998), supporting the view that the ERP old/new effects are correlated with memory functions mediated by a medial temporal lobe circuitry. In the present study the P300 and the P3a together with the old/new effects will be used to examine attention and memory functions in people at risk for vascular dementia.

2. Methods

2.1. Subjects

The study was reviewed by the institutional review boards of both, the Department of Neurology and the Experimental Neuropsychology Unit. All participants gave their informed consent. A group of 30 participants (mean age: 57 years, range 33 to 69 years, 18 male) being treated for arterial hypertension participated in the study. The inclusion criteria were: History of diagnosed essential arterial hypertension (without clinically manifest vascular incidents or secondary disorders) of a minimum of 5 years, possibly already being medicamentously treated, with blood pressure levels of >150 mm Hg (systolic) and >100 mm Hg (diastolic). Exclusion criteria were: Profound cardiac insufficiency, severe cardiac arrhythmia, severe coronary heart disease, a cardiac pacemaker or fresh cardiac infarction. All participants were in good health with no report of neurological or psychiatric disorders. As for some participants only mean blood pressure levels (averaged over several occasions) were available and for other participants blood pressure was measured under different medications no reliable information on the severity of hypertension could be derived.

One participant had to be excluded from the analysis as he/she did not participate in the second session. Due to a large amount of EEG artefacts another participant had to be excluded from the analyses of the ERP data in the three-stimulus task. Three other participants were excluded from the analyses of the old/new effects, due to a combination of low task performance and high amounts of EEG artefacts. A selection of relevant neuropsychological data is displayed in Table 1. The mean general intelligence score (Wechsler Adult Intelligence Scale (WAIS)) was 110 (SD: 15.36) and by this

Table 1
Group data and Neuropsychological measures (mean±SD)

Age:	57 years	(±9.3)
WAIS:	110	(±16)
WMS-R	109	(±18)
WMS-verbal	110	(±17)
WMS-visual	102	(±15)
Digit-Span	15	(±3.6)

WAIS: Wechsler Adult Intelligence Scale; WMS-R: Wechsler Memory Scale—Revised. Digit Span: sum score of the forward and backward versions from the WMS-R.

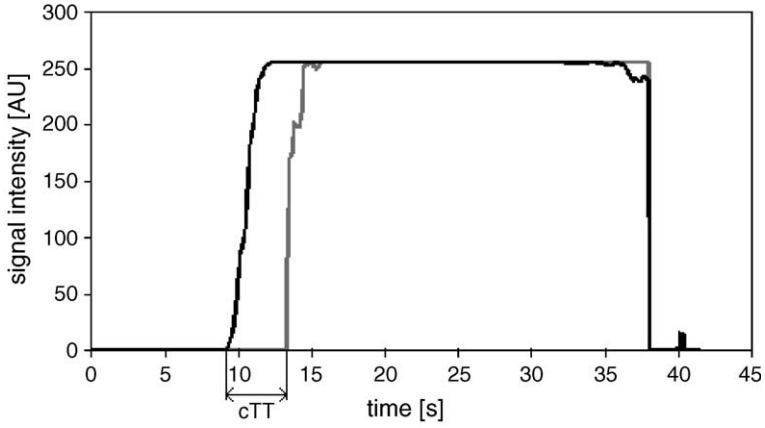

Fig. 1. Signal intensity curves of one randomly selected participant. The black line represents the arterial time–intensity curve; the grey line represents the venous intensity curve. The cTT is illustrated as the difference in signal intensity increase in the artery and the vein. AU: Arbitrary units. For details, see Methods section.

not different from the Wechsler Memory Scale—Revised (WMS-R) score of 109 (SD: 17.7). As the difference of both scores is considered as an index of selective memory impairments, the identity of both scores indicates normal memory functioning across all participants. The digit span (i.e. the combined score for the forward and backward version of the test) is within the normal range.

2.2. Procedure

All participants performed two sessions. The first session took place at the Saarland University Hospital at Homburg and comprised structural MR scanning, transcranial duplex sonography, a medical examination including face-to-face interviews with a standardized questionnaire, blood sampling, and neuropsychological testing (HAWIE, the German version of the WAIS).

The second session comprised a neuropsychological test battery and the EEG recording session and took place in the Neuropsychology Unit at Saarland University. The neuropsychological test battery included the following tests: Wechsler Memory Scale, a verbal memory test including recall and recognition measurements (VGT-16) and the HAWIE mosaic test module. The EEG session consisted of an auditory three stimulus paradigm and a recognition memory test with words. Both sessions lasted approximately 4 h and the minimum duration between both session was 7 days.

2.3. CTT Assessment

For the evaluation of cerebral microcirculation transcranial color coded duplex sonography (TCCS) with ultrasound contrast agents was used. Doppler signals were recorded in the P2 segment of the posterior cerebral artery and the vein of Galen which are lying side by side at this particular insonation site. Sonographic identification of these vessels was verified by pulse-wave Doppler examination that showed typical arterial and venous flow signals. A contrast agent (5 mL Levovist (Schering) 400 mg/mL) was injected into the cubital vein at a constant injection speed (1 mL/s). This agent enhances the ultrasound signal intensity by about 25 dB. The time course of this signal intensity increase is detected by continuous recording the blood flow by means of the intensity weighted power Doppler mode. An example of the resulting

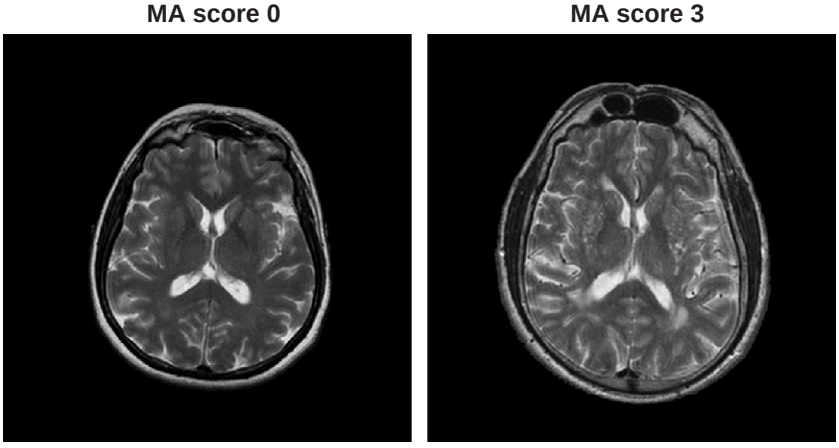

Fig. 2. T2-weighted MR scans of two participants, classified as low (score: 0, left) or high (score: 3 right) on the microangiopathy scale. While there were no small vessel abnormalities in the participant with score 0, the participant with score 3 shows hyperintensity in the periventricular white matter and in subcortical regions. For details, see Methods section.

input (P2-segment) and output (vein of Galen) curves is shown in Fig. 1. The arteriovenous cerebral transit time (cTT) was measured as the latency between the rising of the signal intensity increase in the P2-segment and its rising in the vein of Galen. To assess the intraindividual variability two measures were taken in each participant. For details of the procedure, see Puls et al. (1999).

2.4. MR Scanning

All patients underwent a standardized MR protocol including axial T2-weighted images (TR=4010 ms, TE=108 ms, slicethickness 5 mm), FLAIR sequences (TR=7600 ms, TE=119 ms, TI=2300 ms, slicethickness 5 mm), T1-weighted images (TR=464 ms, TE=13 ms, slicethickness 5 mm) and a MR-Spectroscopy. For the MR-Spectroscopy a PRESS sequence with a TR of 1500 ms and a TE of 135 ms was used. The volume was 20 mL. The sample volume was placed within the occipital white matter and the frontal white matter. The spectroscopy data will not be part of this report. For the quantification of microangiopathy, the T2- and FLAIR-images were reviewed from two experienced neuroradiologists due to signal changes within the white matter and periventricular regions. Signal alterations were scored with a 4 point scale: 0=no signal changes, 1=only slight periventricular signal changes, 2=moderate periventricular signal changes, 3=signal alterations periventricular and within the white matter. Fig. 2 shows two participants with low and high MA scores.

2.5. EEG Session

2.5.1. Stimuli and procedure

In the three stimulus task the participants heard standard tones ($p=.80$), deviant tones ($p=.10$) and novel sounds ($p=.10$). The task comprised a total of 500 stimuli. All had a duration of 200 ms and the inter-stimulus-interval (ISI) was 800 ms. The tone frequency of standards and deviants was 600 and 660 Hz, respectively. The novel sounds were selected from commercially available environmental sounds (see Mecklinger et al., 1997, for details). The subject's task was to count the deviant tones.

The recognition memory task was the same as in Experiment 1 of Nessler et al. (2001). In the study phase subjects heard a total of 90 nouns, i.e. 5 nouns from each of 18 semantic categories. The name of the semantic category (e.g. VEGA-TABLES) was presented visually (2400 ms). Next the five category members were played at a rate of one every 2 s. In the test phase, for which ERP averages were computed, the 90 study words were presented together with 90 words from the studied categories not presented in the study phase (LURE words) and 120 new words from non-studied categories. All test words were presented for 200 ms followed by a 2800 ms period in which the subjects indicated by button press whether or not they had heard the word in the study phase. Only ERPs to studied words and categorically new words will be reported here.

2.5.2. EEG Recording and analyses

The EEG activity was recorded with Ag/AgCl electrodes mounted in an elastic cap from 58 scalp sites of the extended

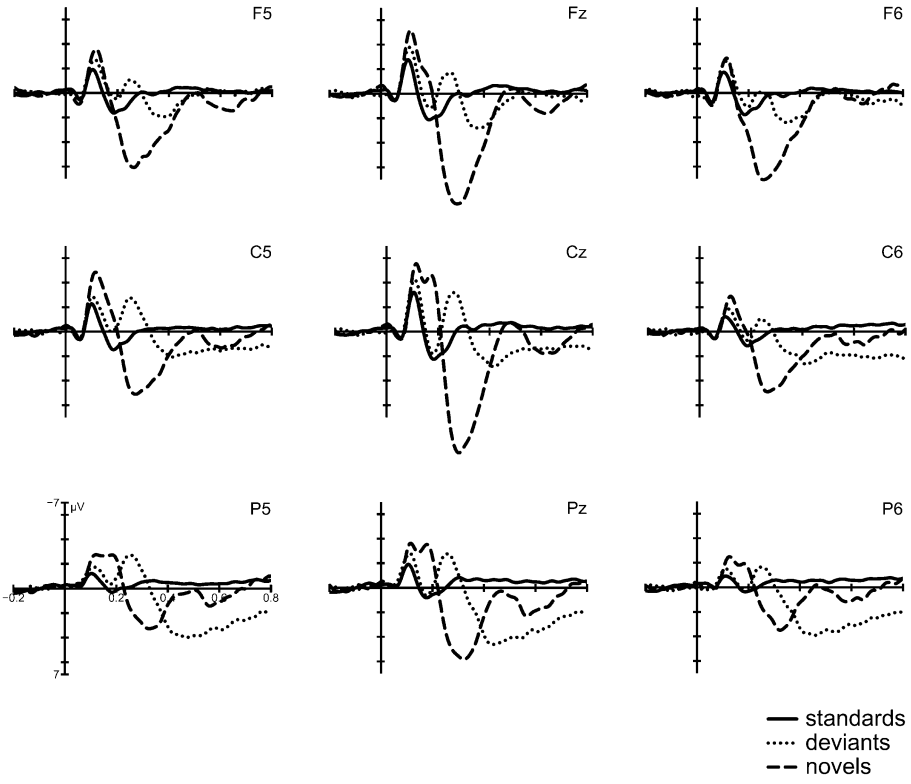

Fig. 3. The ERPs elicited by standards, deviants and novels in the three-stimulus task paradigm at three frontal, central and parietal electrodes. Negative polarity is plotted upwards and the *y*-axes denote the onset of the stimuli. The length of the *x*-axes are 1000 ms (including the 200 ms prestimulus baseline).

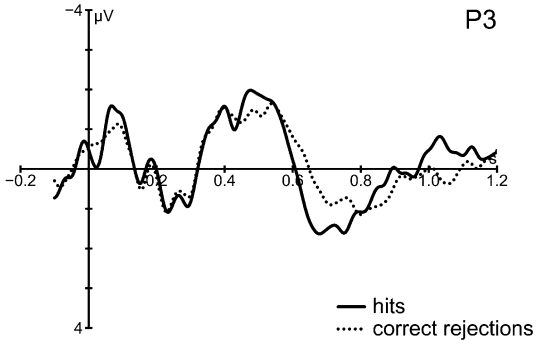

Fig. 4. The ERPs elicited by correct old and new responses at a left parietal electrode (P3). For details, see legend of Fig. 3.

10–20 system. The ground electrode was placed at AFz. The vertical and horizontal EOG was recorded from electrodes placed above and below the right eye and at the outer canthus of each eye. Electrode impedance was kept below 5 kΩ. EEG and EOG were recorded continuously with a band pass from DC to 70 Hz and were sampled at a rate of 500 Hz. ERPs were computed separately for each participant at all recording sites with epochs extending from 200 ms before stimulus onset until 800 (oddball task) or 2000 ms (memory task) thereafter. The 200 ms before stimulus onset served as a baseline. EEG trials with artefacts (criterion: ±40 μV) were rejected. Eye blink artefacts were corrected using a linear regression approach (Gratton et al., 1983).

The P300 component in the oddball task was measured as the mean amplitude in a 100 ms time interval centred around the peak at the Pz recording site. The peak latency was defined as the maximal positive deflection in this time interval. The P3a was measured in a 30 ms time interval centred around the peak at the Fz electrode and its latency was defined as the maximal positive deflection in this period. The time interval was smaller for the P3a because its latency variability is usually lower than the variability in P300. A repeated measure ANOVA with factors electrode (F5, Fz, F6, C5, Cz, C6, P5, Pz, P6) and component (P3a; P300) was used for the statistical evaluation of the ERP data in the three-stimulus task. Effects with two or more degrees of freedom in the numerator were adjusted for violations of sphericity according to the formula of Greenhouse and Geisser (1959).

For the memory task two ERP effects were examined. The early frontal old/new effect was measured in the 350 to 550 ms time window at Fz and the late parietal effect was measured in the 550 to 750 ms time window at the P3 recording site. The time windows for the quantification of the old/new effects were determined by visual inspection of the grand average waveforms and were comparable with those used by Nessler et al. (2001). Only trials with correct responses entered the analysis in the memory task. For statistical quantification of both effects, the Fz and P3 electrode were selected, as prior studies have revealed largest frontal and parietal old/new effects at these two sides (Mecklinger, 2000; Wilding and Rugg, 1996). For all correlation analyses Spearman rank correlation coefficients were used.

3. Results

3.1. Three-stimulus task

The ERP waveforms elicited by target, standard and novel stimuli at frontal, central and parietal recording sites are illustrated in Fig. 3. Target stimuli elicited a large P300 with a parietal maximum and a mean peak latency of 475 ms (SD: 96) at the Pz electrode. For novel sounds an earlier rising P3a with a peak latency of 303 ms (SD: 32) at the Fz electrode and a fronto-central maximum was obtained. At frontal and central recordings sites, the P3a was larger than the P300. These observations were confirmed by statistical analyses. The ANOVA revealed a main effect of component, $F(1,27)=11.09$, $p<.002$, reflecting the P3a>P300 pattern. The differential scalp topography of both components is reflected in a component by electrode interaction, $F(8,216)=28.88$, $p<.0001$, that was still significant when the amplitude measures in both conditions were scaled by vector length (McCarthy and Wood, 1985). Consistent with a large variety of ERP studies using three-stimulus paradigms, this latter result confirms the view, that different neuronal configurations contribute to the P3a and the P300.

3.2. Memory task

3.2.1. Performance measures

The mean reaction times were 1104 ms (SD 256) and 1072 ms (SD 312) for correct old and new responses, respectively, and by this not significantly different ($p>.33$). As an estimate of memory accuracy mean *Pr*-values were calculated by subtracting the false alarm rate from the hit rate. *Pr*-values of 1 indicate perfect memory performance and *Pr*-values of 0 express performance at chance level. The mean *Pr*-value was .52 (SD .20) and by this well above chance level.

3.2.2. ERP measures

The ERP waveforms elicited by hits and correct rejections at the left parietal (P3) recording site are illustrated in Fig. 4. Hit responses elicit more positive going ERP waveforms than

Table 2
The relationship between the ERP measures, neuropsychological measures and the sonographic and MR measures

	cTT	MA
P3a latency	.48 **	.08
P3a amplitude	−.09	−.06
P300 latency	.08	.36°
P300 amplitude	−.18	−.08
Frontal old/new effect	−.11	−.11
Parietal old/new effect	.07	−.17
Pr (memory task)	−.23	−.06
Response time (memory task)	.33°	.25
WAIS	−.09	.33°
WMS-R	.10	−.02
Digit span	.09	.04
Age	.13	.24

CTT: arteriovenous cerebral transit time; MA: microangiopathy, Response time: mean response time collapsed across correct old and new responses in the memory task. **$p<.01$; *$p<.05$; °$p<.10$.

correct rejections in the 600 to 800 ms range. A one-way repeated measure ANOVA with factor responses type, revealed a marginally significant effect, $F(1,25)=3.50$, $p<.07$, whereas at the frontal recording site no reliable effect was obtained ($p<.33$). Consistent with former ERP studies on recognition memory we take the late left parietal old–new effect as an electrophysiological index of successful memory retrieval (Mecklinger, 2000; Friedman and Johnson, 2000). The absence of a frontal old/new effect suggests that familiarity-based recognition was not of high relevance in the present recognition task and that the participants mainly relied on the recollection of the study words in their old/new decisions.

3.3. Correlation analyses

To examine the relationship between the ERP measures, the sonographic measures and the MR measures a series of correlation coefficients were calculated. Microangiopathy (MA) was classified by two experienced neuroradiologists (see Methods section). As illustrated in Table 2 and Fig. 5, among the ERP measures and the neuropsychological measures, the latencies of the P3a and the P300 were the only variables showing reliable correlations with the measures of vascular pathology. The latency of the P3a was positively correlated with the arteriovenous cerebral transit time (cTT) ($p<.01$) and P300 latency was positively correlated by trend with microangiopathy ($p<.057$). No reliable correlation was obtained between microangiopathy (MA) and cerebral transit time (cTT), ($r=.16$). For measures of the frontal and parietal old/new effects no reliable correlation with the MR and sonographic measures were obtained.

The aforementioned results suggest that there is a systematic relationship between the efficiency of cerebral microcirculation (as measured by cTT) and the latency of the P3a. To further examine this pattern of results, we performed a median split of the sample according to the mean cTT measure and contrasted the P3a in both groups of participants. The mean circulation times of the high and low cTT groups were 5.57 and 1.91 s, respectively. As indicated by Fig. 6, showing the P3a for the high and low cTT group, the latency of the P3a is approximately 30 ms shorter in the low cTT group (290 ms, SD 31) than in the high cTT group (318 ms, SD 27), $F(1,23)=5.94$, $p<.02$. Even

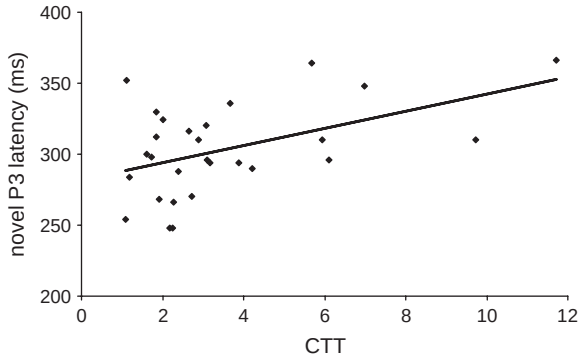

Fig. 5. The correlation between P3a latency and the arteriovenous cerebral transit time (cTT) was $r=.48$, $p<.01$.

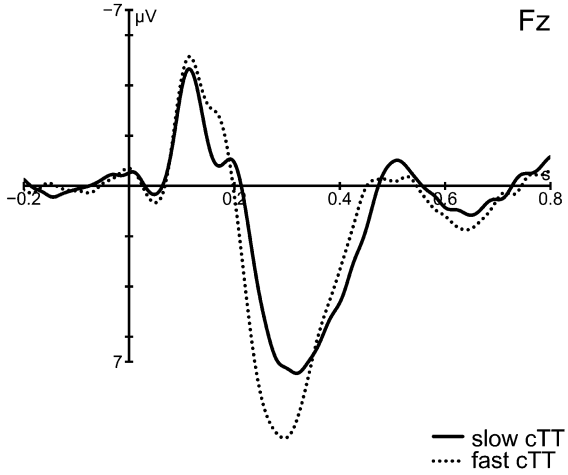

Fig. 6. The ERP waveforms elicited by novel sounds in the three-stimulus task for the groups of participant with long (solid line) and short (dashed line) cTT. For details, see legend of Fig. 3.

though the figure suggests smaller P3a amplitudes in the high cTT group, the statistical analysis did not reveal significant differences ($p<.35$). No significant effects of cTT group were obtained for the other ERP measures.

To examine the relevance of the P3a and P300 measures for the separation of the two cTT groups a linear stepwise discriminant analysis was performed. From the four variables (two latency and two amplitude measures) that entered the analysis, only P3a latency separated the two cTT groups reliably (Wilks–Lambda: .814, $p<.02$). Using this discriminance function with only one depended variable (P3a latency), 62% of the participants were correctly classified in the high cTT group. For the low cTT group the classification accuracy was 68%.

4. Discussion

In this study we examined the relationship between hypertension as one risk factor for vascular dementia and event-related potential indices of attention and memory functions. Previous studies have shown that the arteriovenous cerebral transit time (cTT) can be taken as an estimate of the efficiency of cerebral microcirculation and the amount of small vessel disease in clinical populations. We therefore examined the relationship between cTT and ERP measures of cognitive functions in individuals with arterial hypertension, being at risk for developing vascular dementia. While neuropsychological measures and ERP measures of memory functions (old/new effects) did not show systematic correlations with the cTT and other measures of vascular pathology, a pronounced correlation was obtained between P3a latency and cTT. Participants with long cTT showed a delayed P3a. Notably, such a correlation pattern was neither obtained for P300 latency nor for the response times in the memory task, indicating that the relationship between the P3a and the cTT is not confounded by general cognitive slowing. The results rather show, that the P3a can be considered as a sensitive measure of vascular risk factors even at very early stages of small vessel pathology.

The three stimulus task revealed a pronounced fronto-centrally distributed P3a that was followed by a parietally distributed P300 to target stimuli. The timing and scalp topography of both components is consistent with recent findings by Katayama and Polich (1998). The authors assessed the role of discrimination difficulty between targets and standards on the P3a component. Only when targets and standards were difficult to discriminate, the P3a component did show an earlier peak latency than the P300 and also a fronto-central scalp distribution. With easy target-standard discriminations the P3a displayed a parietal maximum similar to the P300 to targets. According to Polich (2004) the stimulus context, defined as the relative perceptual distinctiveness among stimuli, is the main aspect contributing to P3a generation. When target-standard discrimination is difficult and presumably requires frontal lobe functions for the transient storage of standard stimuli in working memory, the disengagement of attention from target discrimination and the reallocation of attention to distractor or novel stimuli elicits a P3a component. Our results, together with the difficult discrimination task in the present study (600 vs. 660 Hz) are completely consistent with the aforementioned interpretation. In further support of this stimulus context interpretation of the P3a, fMRI studies showed enhanced activation to distractors but not to targets in the lateral premotor cortex including the frontal eye fields (Bledowski et al. 2004a), an area that has been shown to be activated by unattended stimuli that require the interruption of ongoing cognitive activity and the reorientation of attention (Corbetta and Shulman, 2002).

An important issue to be addressed is why the P3a but neither the P300 nor the old/new effects were related to the effectiveness of cerebral microcirculation. The basal ganglia and adjacent areas, deep white areas as well as frontal lobe structures have been show to be highly vulnerable to small vessel diseases. All these vulnerable areas are underlying parts of frontal lobe circuitry. In fact, deficits in frontal lobe functions, as revealed by neuropsychological testing, are more pronounced in patients with vascular dementia than in patients with Alzheimer's disease (Kertesz and Clydesdale, 1994; Verleger, 2002). The severity of white matter lesions in the frontal lobes is correlated with mental deterioration in patients with multiple lacunar infarcts (Fukuda et al., 1990). Thus, it is reasonable to assume that the delayed P3a in individuals with slow cerebral transit time to some extent reflects the selective vulnerability of the frontal lobes to small vessel diseases even at very early stages of vasculopathy as in patients with arterial hypertension.

It is important to note that the majority of studies using ERP measures as indices of mental deterioration in dementia used clinical populations with a clear diagnosis of Alzheimer's disease or vascular dementia (for an overview see Verleger 2002). In the present study, however, a relationship between P3a latency and the integrity of cerebral microcirculations has been obtained in normal individuals with no report of neurological disorders and within-norm values of memory functions (WMS-R) and general mental ability functions (WAIS). This is also confirmed by the finding that the mean cTT in the present study (3.68 s) was comparable in magnitude to the mean cTT obtained in a group of 25 elderly control subjects (3.1 s) in the study by Puls et al. (1999). This suggests that the P3a is a sensitive measure to identify attenuated cognitive functioning that go in parallel with very early forms of small vessel pathology. The P3a by this is a valuable tool for the identification of early vascular risk factors for dementia. An interesting issue is whether the current group of individuals being treated for arterial hypertension already shows some subtle abnormality in P3a latency relative to an age-matched control group. Unfortunatelly, no direct ERP data for this task from controls not being treated for hypertension is available. However, an ERP study examining age differences in P3a latency with a similar auditory three stimulus task (Fabiani and Friedman, 1995) revealed mean P3a latencies of 304 and 349 ms in a group of young (mean age: 25 years) and old participants (mean age: 73 years), respectively. Mean P3a latency of the current study group (mean age: 57 years) was 303 ms and by this closer to the data from the young than the old group in the Fabiani and Friedman study . This observation does not support the view of subtle abnormalities in P3a latency. in our group of participants.

While a systematic relationship was found between the P3a and the integrity of cerebral microcirculation, no such effect was obtained for the ERP indices of memory retrieval, i.e. the old/new effects. In contrast to a prior study with young adults (mean age: 23 years) in which reliable frontal and parietal old/new effects were obtained (Nessler et al., 2001), in the present memory task there was no frontal old/new effect and the parietal effect only approached the significance level. It is conceivable that the attenuated old/new effects result from a combination of lower task performance and different performance strategies in the present group of participants. In fact, mean performance was lower in the present study ($Pr = .52$) than in the aforementioned study ($Pr = .72$) and response times for hits were about 200 ms longer in the present study than in the Nessler et al. study, with no response time differences for correct rejections. The lack of a relationship between the magnitude of the old/new effects and the cTT may indicate that the brain regions contributing to the old/new effects are less vulnerable to small vessel disease than the frontal lobe structures and subcortical structures contributing to the P3a. Alternatively, the recognition memory task may have been not sensitive enough to unravel the subtle brain pathology in the present study group.

Taken together, the present study is exploratory in nature. It nevertheless revealed a remarkable relationship between the integrity of cerebral microcirculation and the P3a in participants being at risk for developing vascular dementia. The P3a can therefore be considered as a sensitive measure even for early and non-clinical stages of cognitive deterioration associated with vascular dementia. Further investigations using longitudinal designs, however, will be required to examine the prognostic validity of the P3a for the functional outcome of vascular dementia.

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