The effects of cortical ischemic stroke on auditory processing in humans as indexed by transient brain responses

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Abstract
Objective: To investigate the effects of cortical ischemic stroke and aphasic symptoms on auditory processing abilities in humans as indicated by the transient brain response, a recently documented cortical deflection which has been shown to accurately predict behavioral sound detection.

Methods: Using speech and sinusoidal stimuli in the active (attend) and the passive (ignore) recording condition, cortical activity of ten aphasic stroke patients and ten control subjects was recorded with whole-head MEG and behavioral measurements.

Results: Stroke patients exhibited significantly diminished neuromagnetic transient responses for both sinusoidal and speech stimulation when compared to the control subjects. The attention-related increase of response amplitude was slightly more pronounced in the control subjects than in the stroke patients but this difference did not reach statistical significance.

Conclusions: Left-hemispheric ischemic stroke impairs the processing of sinusoidal and speech sounds. This deficit seems to depend on the severity and location of stroke.

Significance: Directly observable, non-invasive brain measures can be used in assessing the effects of stroke which are related to the behavioral symptoms patients manifest.

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1. Introduction

Stroke is the most common, life-threatening neurologic disease with an annual incidence of approximately six cases in 1000 persons (Wolf, 2004). Although the mortality rate of stroke has declined (Harmsen et al., 1992; Sarti et al., 2000) it can still lead to devastating outcomes among stroke survivors (Elkind, 2009). The early mapping of disabilities is essential for the effective treatment, as it can lead to at least partial prevention of permanent damage. Acute stroke in the left hemisphere often produces aphasic symptoms (Laska et al., 2001) and impairs the processing of linguistic information (Csépe et al., 2001). New, rapid and accurate electrophysiological methods can provide a useful tool for assessing the effects of stroke as they can detect even subtle hearing dysfunctions (Hauser and Levine, 2000), reflect the severity of stroke (Mäkelä et al., 1991), correlate with language comprehension tests (Marchand et al., 2002), and also predict the recovery from aphasic symptoms (Becker and Reinvang, 2007; Sosa Rojas et al., 2009).

Recent studies (Mäkinen et al., 2004; Tiitinen et al., 2005) have introduced a new method for the objective assessment of human sound detection through MEG measurements. When presented with sounds whose intensity increases linearly from inaudible to audible over a period of up to 2 s, subjects display a transient brain response. This response is not time-locked to the onset of the stimulus but, rather, has a latency which increases with shallower intensity slopes and can occur as late as 1 s from the onset of the stimulus (Mäkinen et al., 2004). Importantly, this response predicts behavioral sound detection with almost 100% accuracy: it precedes behavioral reaction time by approximately 200 ms, and can be observed in single subjects already after 3 min of recording time. It is more prominent and spatially constrained over the right hemisphere and is generated in areas which coincide with the auditory-cortex generators of the N1m response elicited by short (~100 ms) stimuli (for a review, see May and Tiitinen, 2010). In essence, the latency fluctuation of the response is highly reminiscent of the behavior of the MMN (Tiitinen et al., 1994), although no
time-consuming oddball paradigm and offline subtraction procedures are needed. The peak amplitude of this response is larger in the active (attended) recording condition and when the intensity slope is increased by shortening the stimulus duration. Previous studies were carried out with healthy young subjects and using sinusoidal sounds only, but the observed brain response could also be useful in clinical settings because it can be obtained rapidly and it provides a direct link to behavioral sound detection (Mäkinen et al., 2004; Tiitinen et al., 2005).

1.1. The effects of stroke

An ischemic stroke can be defined as a syndrome in which clinical symptoms develop rapidly, leading to the loss of cerebral function with no other apparent causes than those of a vascular origin (Davenport and Dennis, 2000; Egan and Bioussé, 2000). Cortical stroke in temporal areas often produces symptoms related to auditory processing and appears as abnormalities in auditory brain responses. For example, the amplitudes of long-latency responses become diminished (Knight et al., 1980, 1988; Rothenberger et al., 1982; Pool et al., 1989) and ERP response latencies shorter (Rothenberger et al., 1982). The diminution of the amplitudes occurs specifically in the acute phase of stroke (Ilvonen et al., 2003) over the damaged hemisphere (Knight et al., 1988; Woods et al., 1993; Sörös et al., 2006). In some cases, no brain responses can be detected (Knight et al., 1988; Leinonen and Joutsiniemi, 1989; Mäkelä et al., 1991; Sörös et al., 2006).

The effects of brain damage on auditory functions seem to be closely related to the location of the lesion (Alain et al., 1998). Although stroke patients with lesions in the medial or posterior areas of the temporal lobe exhibit marked reductions in auditory brain responses of the damaged hemisphere, patients with lesions in anterior areas of the brain show no decrements even in the damaged hemisphere (Mäkelä et al., 1991; Aaltonen et al., 1993). The location of the damage also has an effect on which specific aspects of the auditory processing system are impaired. In general, temporal-lobe damage affects auditory comprehension performance (Auther et al., 2000) and lesions in the temporoparietal areas result in impaired auditory discrimination (Alain et al., 1998). It has been reported that patients with lesions in the superior part of the temporal lobe have difficulties in detecting brief sounds and auditory rhythms presented at a rapid rate (Nicholls, 1996).

Auditory processing difficulties among stroke patients have been linked to problems in attention (Rothenberger et al., 1982). These problems are reflected in both sustained and selective attention (Stapleton et al., 2001) and disturb the processing of verbal and non-verbal material (Korda and Douglas, 1997). Attentional difficulties of the patients appear, in particular, as slower behavioral reactions (Woods et al., 1993; Saygin et al., 2003) slower processing speeds (Korda and Douglas, 1997; Murray et al., 1997) and higher error rates (Woods et al., 1993; Murray et al., 1997; Ilvonen et al., 2001; Saygin et al., 2003). These difficulties at the behavioral level have also been linked with abnormalities in auditory brain responses (Woods et al., 1993; Ilvonen et al., 2001, 2004) indicating that attentional difficulties impair the auditory processing abilities of stroke patients (Murray et al., 1997).

Stroke in the left hemisphere is associated with impaired linguistic abilities manifesting themselves as aphasic symptoms. Several studies have reported effects of stroke and aphasia on auditory processing abilities, but these results seem to be contradictory. According to some studies the auditory difficulties of the patients are limited to the processing of linguistic information, leaving non-speech processing intact (Sidtis and Volpe, 1988; Aaltonen et al., 1993; Csépe et al., 2001; Ilvonen et al., 2004). In these studies, the disabilities of the patients became evident as diminished brain responses for speech sounds in auditory discrimination tasks compared to those of healthy control subjects, while no differences were found between the subject groups in the processing of nonspeech sounds. This selective deficit of the patients, whereby speech processing is impaired while non-speech processing remains intact, has been explained in terms of aphasic patients having problems already in early stages of speech comprehension, at the level of the acoustic analysis system (Wise et al., 1991). However, in contradiction to these selective-impairment findings, there exists evidence that stroke leads to deficits in non-linguistic domains as well, for example in the recognition of environmental sounds and of intensity and frequency changes of sinusoidal sounds (Clarke et al., 1996; Saygin et al., 2003). These findings could be explained by language sharing some neural mechanisms with non-linguistic processes and by non-speech sounds eliciting early semantic activation (Wise et al., 1991; Démonet et al., 1992).

1.2. The aims of the study

The main objective of this study was to examine whether a newly-discovered transient brain response indexing human sound detection (Mäkinen et al., 2004; Tiitinen et al., 2005) might be used to assess the effects of cortical ischemic stroke on auditory processing and whether these effects manifest themselves in accordance with the findings of previous research. Due to the inconsistencies observed in previous research, the current study aimed to examine whether cortical stroke with aphasic symptoms selectively impairs the auditory processing of linguistic information (e.g. Ilvonen et al., 2004) or, alternatively, disrupts auditory processing more generally, including domains of non-speech processing as well (e.g. Clarke et al., 1996). Based on the findings of previous studies, stroke-related attentional problems were expected to affect the auditory (e.g. Ilvonen et al., 2001) and behavioral (e.g. Saygin et al., 2003) responsiveness of the patients. This study tried to elucidate the effects of cortical stroke at both the group and individual level. Primarily, the group-level differences were examined by comparing the auditory abilities of stroke patients and healthy controls. The individual characteristics of stroke were demonstrated through sub-group analysis and case studies.

2. Methods

2.1. Subjects

Ten patients (Patient Group, mean age 65 years, range 46–82 years, 7 females; see Fig. 1, Left) with radiologically verified stroke in the left hemisphere and 10 age-, gender-, and handedness-matched control subjects (Control Group) with no history of neurological, psychiatric or other serious diseases served as subjects. All the subjects were right-handed native Finnish speakers with no hearing defects. Prior to the measurements, the subjects were informed about the purpose and course of the study and were made aware of the possibility of terminating the experiment at any time. Also, written informed consent was obtained from the subject or from his/her closest relative or spouse. The study was approved by the Ethical Committee of the Helsinki University Central Hospital (HUCH).

The stroke patients were recruited from the Department of Neurology at HUCH. They had suffered their first ischemic stroke with or without hemiplegia, with acute symptoms, no more than 2 weeks before measurement. Based on the assessment of either a neuropsychologist or a logopedist, each patient displayed aphasic or dysphasic symptoms (see Fig. 1, right). According to the neurological examinations, the patients had normal hearing and their co-operation was good. The stroke patients had undergone CT or MRI head scanning in the acute phase of stroke. Patients with multiple in-
farcts, brainstem infarct, intracranial hemorrhage, or brain atrophy were excluded from the study. Patients who had psychiatric diseases, pacemakers, epilepsy, insulin dependent diabetes mellitus, or used medication affecting the CNS were also excluded.

2.2. Stimuli and measurement

The stimuli were created by using a sinusoidal tone and a speech sound as raw material. The production of the stimuli was started by recording a natural utterance (vowel /a/) produced by a native male speaker of Finnish using the fundamental frequency of 113 Hz. The recording was conducted in an anechoic chamber with a high-quality condenser microphone (Bruel and Kjaer 4188). Sound was digitized using a sampling frequency of 22,050 Hz and a resolution of 16 bits. The strongest harmonic, located at 570 Hz in vicinity of the first formant of the vowel /a/, was measured by Fourier transforming the time-domain sound waveform. This frequency value was then used to produce a 570-Hz sinusoidal with a constant amplitude and a duration of 750 ms. By concatenating one fundamental period of the vowel waveform, a speech signal of equal duration was synthesized next. The waveforms of both the tone and the produced speech sound were then multiplied with a 750-ms ramp signal in order to temporally modify their intensity characteristics. The amplitude of the ramp, in dB, rose linearly by 90 dB over its duration. In order to calibrate the stimuli, the A-weighted sound pressure level was measured from the output of the sound delivery system. The levels of both the sinusoidal and speech stimulus were adjusted so that the sound pressure level (SPL) at the end of the stimuli corresponded to 60 dB. Hence, the procedure yielded two stimuli, a tone and a vowel, whose intensity increased linearly from inaudible (−30 dBA) to audible (60 dBA) over a duration of 750 ms. Auditory stimuli were presented binaurally in sequences, with a random inter-stimulus interval (ISI) of 1–4 s. Each sequence contained one stimulus type and the sequences were counterbalanced across subjects with respect to the Latin square design to avoid effects due to habituation, learning, and fatigue.

Measurements and preliminary data analyses were carried out at the BioMag Laboratory at HUCH. Magnetic fields were registered with a whole-head, 306-channel MEG device (Vectorview 4-D, Elekta Neuromag Oy, Finland) with a 600 Hz sampling rate, recording bandpass of 0.03–200 Hz (filter slope 24 dB/octave), and a 1050 ms response averaging period, including a 100 ms baseline. The averaged brain responses, behavioral reaction times, and the raw data were stored for offline analyses. Vertical eye movements were monitored with two electro-oculogram (EOG) electrodes placed below and above the left eye. For controlling horizontal eye movements, two EOG electrodes were positioned at the canthus of each eye. All epochs where the electro-oculogram measurement exceeded |150| μV or the MEG exceeded |3000| fT/cm at any sensor were rejected. To enable the localization of MEG sources, head position with respect to the MEG sensors was determined through the use of head position indicator coils, identified with re-
spect to the three anatomical landmarks of the left and right preauricular points and the nasion. The localization of the indicator coils was carried out with a three-dimensional digitizer (Isotrak 3S1002, Polhemus Navigation Sciences Colchester, VT).

2.3. Procedure and data analysis

Cortical activity was measured in two recording conditions. In the active condition, the subjects were under instruction to attend to the auditory stimuli and to press a response key with their right-hand index finger when the sounds became audible. In the passive condition, the subjects were instructed to ignore the auditory stimuli and to watch a silent film. The subjects lay in the supine position during the measurement while the auditory stimuli were delivered via plastic tubes and earpieces. The subjects were asked to maintain head position as stable as possible and to avoid eye movements during MEG recording.

Data analyses were based on brain responses collected during four different stimulation sequences (active and passive recording conditions in which either sinusoidal or speech stimulation was used), each containing a minimum of 80 epochs (the actual number of stimuli delivered was in the range of 90–110 per condition, and the overall experimental measurement time per subject was, on the average, 45 min). The peak amplitudes and latencies of the averaged brain responses over the temporal lobes were analyzed separately for each subject and hemisphere by using the planar gradiometer sensor displaying the maximum response amplitude. A 20-Hz lowpass filter was used. Equivalent current dipole (ECD) estimations were carried out by using 44 sensors separately over the left and the right hemisphere. ECD location was calculated in a coordinate system where the x-axis passes horizontally through the middle points of the ears (positive to the right), the y-axis passes through the nasion in the anterior–posterior direction (positive towards nasion), and the z-axis passes vertically through the head (positive upwards). A band-pass filter of 2–20 Hz was used in ECD analyses. The analyses were accomplished with a total of 16 subjects (8 patients and 8 control subjects) as the ECD estimations of two patients (PT7, PT9) were inconclusive due to severe stroke in the left hemisphere.

Reaction times were determined by calculating the delay between the peak amplitude of the transient brain response and the subsequent pressing of the response key. Responses which occurred within the first 2000 ms from stimulus onset were accepted for further analyses. RTs were identified separately for each subject and stimulus type. The RT analyses were performed for a total of 16 subjects (8 patients and 8 control subjects) as the ECD estimations of two patients (PT7, PT9) were inconclusive due to severe stroke in the left hemisphere.

Results

3.1. Differences between the Patient Group and the Control Group

In both subject groups, the auditory stimuli rising in intensity elicited transient brain responses which, however, were systematically smaller in the Patient Group than in the Control Group (F(1, 9) = 7.18, p < 0.05). This was evident in the responses for both stimulus types, recording conditions, and in both hemispheres (see Fig. 2). The brain responses peaked with an average latency of 650 ms with no significant differences between the subject groups (F(1, 9) = 0.02, p = n.s.). In each subject group, neither the amplitude nor the latency of the brain response differed between the hemispheres (F(1, 9) = 0.01–5.01, p = n.s.).

ECDs were estimated separately for each subject group, stimulus type, recording condition and hemisphere. ECDs indicated that the sources of the brain activity were in the vicinity of the auditory cortex in both subject groups (see Fig. 2). In the Patient Group, the mean x/y/z -coordinates of the ECD locations were −44/13/46 mm in the left hemisphere and 52/19/44 mm in the right hemisphere. The corresponding locations in the Control Group were −56/9/44 mm and 50/16/45 mm. There were no significant differences in the x/y/z -coordinates between the subject groups (F(1, 14) = 0.00–4.23, p = n.s.). In the Patient Group, ECD location was unaffected by stimulus complexity, engagement of attention, and hemisphere (F(1, 7) = 0.26–3.13, p = n.s.). However, in the Control Group, the differences between the hemispheres were found to be significant, the source location being 6 mm more lateral in the left hemisphere (F(1, 7) = 13.90, p < 0.01) and 7 mm more anterior in the right hemisphere (F(1, 7) = 7.93, p < 0.05). Neither stimulus type nor attentional engagement had an effect on ECD location in the Control Group (F(1, 7) = 0.07–3.94, p = n.s.).

In the Control Group, the average response amplitude increased by 22% in the active recording condition (73 vs. 60 fT/cm; F(1, 9) = 8.18, p < 0.05 for active vs. passive recording condition, see Fig. 3, left). However, in the Patient Group, no such effect was found (42 vs. 38 fT/cm; F(1, 9) = 1.41, p = n.s., see Fig. 3, right).

No latency differences between the two recording conditions were observed in either subject group (F(1, 9) = 0.00–1.63, p = n.s.).
In the Patient Group, the average behavioral reaction times (RTs) were 363 ms (standard error of the mean, s.e.m. = 66 ms) for the speech and 386 ms (70) for the sinusoidal stimuli. In the Control Group, the RTs were 308 ms (71) for the speech and 319 ms (71) for the sinusoidal stimuli. These latency differences between the two groups, however, did not reach statistical significance ($F(1,7) = 0.71$, $p = n.s.$). No significant differences in the average RTs to the speech and the sinusoidal stimuli were found ($F(1,7) = 0.23–1.15$, $p = n.s.$).

In both groups, the response amplitude increased as a function of stimulus complexity, being larger for the speech than for the sinusoidal stimuli (Patient Group: $F(1,9) = 23.77$, $p < 0.01$; Control Group: $F(1,9) = 30.78$, $p < 0.001$). In addition, stimulus complexity affected the latency of the brain response: in both groups the response latency for the speech stimuli was delayed when compared to that for the sinusoidal stimuli (Patient Group: 31 ms, $F(1,9) = 7.83$, $p < 0.05$; Control Group: 21 ms, $F(1,9) = 9.04$, $p < 0.05$).

There were no significant interactions between the factors in the response amplitudes ($F(1,9) = 0.00–2.49$, $p = n.s.$). In the response latencies, interactions between hemisphere and recording condition ($F(1,9) = 7.80$, $p < 0.05$) and between stimulus type, recording condition and hemisphere ($F(1,9) = 11.39$, $p < 0.01$) were found, indicating that in the right hemisphere, latency was delayed for the response in the passive recording condition (compared to the active condition) and also for the response to the speech sound (compared to the sinusoidal sound). These effects were not observed in the left hemisphere. No other interaction effects were observed ($F(1,9) = 0.00–3.07$, $p = n.s.$). To facilitate comparison, the amplitude and latency results are summarized in Tables 1 and 2.

### 3.2. The effect of stroke severity on auditory processing

When the stroke patients were divided into two sub-groups according to the spatial extent of the stroke (see Methods), it was observed that stroke severity had a marked effect on the transient brain response. Patients with severe left-hemispheric strokes and major damage to the auditory cortical areas exhibited considerably smaller brain responses than patients with mild strokes (Fig. 4). These amplitude differences were statistically significant both in the passive recording condition ($F(1,8) = 32.04$, $p < 0.001$ for sinusoid and $F(1,8) = 34.52$, $p < 0.001$ for speech sounds) and in the active condition ($F(1,8) = 22.06$, $p < 0.01$ for sinusoid and $F(1,8) = 49.07$, $p < 0.001$ for speech sounds). Importantly, the brain responses of the patients with severe strokes were clearly diminished only in the left, damaged hemisphere as no significant amplitude differences between the patient sub-groups were observed in the right, intact hemisphere ($F(1,8) = 0.00–0.99$, $p = n.s.$). In both patient sub-groups, the brain response occurred with an average latency of 650 ms. No latency differences were found between the patient sub-groups in either the left ($F(1,8) = 0.03–2.08$, $p = n.s.$)
p = n.s.) or the right hemisphere (F(1,8) = 0.31–1.89, p = n.s.). There were no amplitude or latency differences between the two hemispheres in either patient sub-group (F(1,4) = 0.49–6.14, p = n.s.).

Unlike with the healthy control subjects, attentional engagement did not significantly increase the amplitude of the brain responses in either patient sub-group (F(1,4) = 0.13–1.28, p = n.s.). Attentional engagement had no observable effect on the latency of the response in either patient sub-group (F(1,4) = 0.57–4.17, p = n.s.). The average RTs of patients with severe stroke were 437 ms (s.e.m. = 114 ms) for the speech and 468 ms (120) for the sinusoidal stimuli. The respective values of the patients with mild stroke were 289 ms (61) and 304 ms (61). Although the average RTs of the patients with severe stroke were considerably longer than those of the patients with mild stroke, these differences were, nevertheless, not significant (F(1,3) = 0.98, p = n.s.).

As with the healthy control subjects, patients with mild left-hemispheric stroke displayed larger responses for the speech than for the sinusoidal stimuli (F(1,4) = 24.80, p < 0.01). However, patients with a severe stroke in the left hemisphere displayed no observable amplitude differences in their responses to the two stimulus types (F(1,4) = 6.49, p = n.s.). Stimulus complexity had no effect on the latency of the brain responses in either patient sub-group (F(1,4) = 2.81–6.00, p = n.s.).

On average, patients with severe stroke exhibited considerably smaller brain responses in the left, damaged hemisphere than patients with mild stroke. Some of the patients with severe stroke were unable to produce any detectable brain responses in the damaged hemisphere although their responses in the right, intact hemisphere were prominent. In contrast, patients with mild strokes produced clearly observable brain responses bilaterally. Stroke severity and the difficulty in processing the rising-intensity sounds was also congruent with the degree of aphasic symptoms the patients displayed (see Fig. 1). To show that these effects are also visible at the single-subject level, two cases are presented.

Patient 2 had a mild stroke in the left hemisphere, in the area of the artery cerebri media (see Fig. 5, top). The patient had only

Table 1
Response amplitudes with standard error of the mean (in parentheses) of the brain responses for the sinusoidal and the speech stimuli, elicited in the active and the passive recording condition in both hemispheres. At the group level stroke patients exhibited smaller-amplitude brain responses when compared to those of the control subjects.

<table>
<thead>
<tr>
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<th>Left hemisphere</th>
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<th>Right hemisphere</th>
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<tbody>
<tr>
<td></td>
<td>Passive</td>
<td>Active</td>
<td>Passive</td>
<td>Active</td>
</tr>
<tr>
<td>Sinusoid</td>
<td>24.3 (7.0)</td>
<td>36.0 (12.5)</td>
<td>36.0 (9.5)</td>
<td>51.4 (12.6)</td>
</tr>
<tr>
<td>Speech</td>
<td>56.0 (12.5)</td>
<td>49.7 (5.1)</td>
<td>51.8 (9.6)</td>
<td>86.0 (15.7)</td>
</tr>
<tr>
<td>Controls</td>
<td>36.7 (3.9)</td>
<td>65.6 (6.4)</td>
<td>49.7 (5.1)</td>
<td>82.6 (7.7)</td>
</tr>
</tbody>
</table>

Table 2
Response latencies with standard error of the mean (in parentheses) of the brain responses for the sinusoidal and the speech stimuli, elicited in the active and the passive recording condition in both hemispheres. No latency differences were observed between the subject groups.

<table>
<thead>
<tr>
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<th>Left hemisphere</th>
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<th>Right hemisphere</th>
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<tbody>
<tr>
<td></td>
<td>Passive</td>
<td>Active</td>
<td>Passive</td>
<td>Active</td>
</tr>
<tr>
<td>Sinusoid</td>
<td>618.3 (17.9)</td>
<td>645.5 (18.4)</td>
<td>644.9 (22.3)</td>
<td>648.3 (11.0)</td>
</tr>
<tr>
<td>Speech</td>
<td>667.1 (16.1)</td>
<td>660.2 (17.6)</td>
<td>676.5 (23.8)</td>
<td>661.5 (9.2)</td>
</tr>
<tr>
<td>Controls</td>
<td>652.6 (10.9)</td>
<td>645.4 (11.1)</td>
<td>648.3 (11.0)</td>
<td>627.9 (10.4)</td>
</tr>
</tbody>
</table>

Fig. 4. Left: averaged amplitudes of the transient brain responses for the sinusoidal and the speech stimuli elicited in the active and the passive recording condition. Stroke severity had a marked effect on the amplitude of the brain response in the left, damaged hemisphere. No such differences were found in the right, intact hemisphere. Right: Grand-averaged brain responses for speech sounds (severe stroke: black curve, mild stroke: gray curve) obtained in the active recording condition in both the left (top) and the right (bottom) hemisphere. Bars indicate standard error of the mean.
slight verbal difficulties occurring mainly in challenging linguistic situations. PT 2 produced prominent brain responses for both stimuli types, in both recording conditions, and in both hemispheres. Patient 9 had a marked stroke, covering almost the entire left hemisphere (see Fig. 5, bottom). The aphasic symptoms were assessed as extensive, dysgraphic symptoms were considerable, and the patient had major difficulties in speaking. Cortical processing of rising-intensity sounds was also appreciably disturbed, there being no detectable brain responses in the left, damaged hemisphere. However, in the right, intact hemisphere this patient showed prominent responses which were larger in amplitude than those produced by PT 2 with mild stroke.

4. Discussion

4.1. The effects of stroke on auditory processing

Cortical ischemic stroke appears to have a remarkable effect on the auditory processing abilities reflected both in the transient brain response elicited by stimuli rising slowly in intensity and in consequent behavioral performance. Response amplitudes were significantly smaller in patients than in controls, supporting the findings of previous clinical studies which have shown that stroke in cortical areas causes a considerable diminution of brain responses during both auditory discrimination (e.g. Ilvonen et al., 2001, 2004) and sound detection (Rothenberger et al., 1982; Knight et al., 1988; Pool et al., 1989) especially in the acute phase of stroke (Ilvonen et al., 2003). The fact that cortical stroke impairs the response amplitude while having no effect on latency indicates that auditory problems are at the central level. According to previous studies (Mäkinen et al., 2004; Tiitinen et al., 2005), the peak latency of the transient brain response is time-locked to the moment when the subject detects the auditory stimulus, so it can be seen as an index of hearing threshold. Since no latency differences were observed between patients and control subjects, one could assume that the peripheral auditory processing abilities of the patients were intact (contrasting the currently observed amplitude effects caused by stroke, normal healthy aging appears to cause effects mainly on the latency of brain and behavioral responsiveness, as discussed elsewhere; see Matilainen et al., 2010).

In general, neither patients nor control subjects exhibited hemispheric differences in the amplitude and the latency of the brain response. This finding deviates from previous observations according to which the transient brain response amplitude measured in young and healthy subjects was larger in the right hemisphere (Mäkinen et al., 2004). This discrepancy might be attributable to the age difference between the subject groups and related changes in the interconnections between the two hemispheres. Hemispheric lateralization is reportedly dependent on the subject’s age (Holland et al., 2001; Szaflarski et al., 2006; Naccarato et al., 2006). Furthermore, children and young adults demonstrate a significantly greater degree of temporal lobe asymmetry compared to older subjects (Bellis et al., 2000). In the current study, age-related decrease of lateralization could explain the lack of right-hemispheric dominance in response amplitude, and it might also be one factor behind the current observations that the response amplitudes of the patients were diminished also in the intact hemisphere when compared to those of the control subjects. As the lateralization of cerebral language representation decreases as a result of aging (Szaflarski et al., 2006) and left-hemispheric lesions (Backes et al., 2005), it is not surprising that the impaired language processing abilities of the patients in this study were also reflected in the brain responses of the right, non-dominant hemisphere. This finding could also indicate that pathways from the left ear to the right auditory cortex were affected by the stroke. Future studies in patients with unilateral stroke may provide further information about the possible differences in auditory processing of ipsilateral and contralateral stimulation. Supporting previous studies (Tiitinen et al., 1999; Mäkelä et al., 2002, 2003, 2004), the source location of the brain response in the control subjects was found to differ between the two hemispheres, being more anterior in the right hemisphere. However, in the patients, there were no source location differences between the hemispheres which is consistent with the finding that patients with unilateral brain damage show abnormalities in the ECDs of auditory evoked potentials (Scherg and Von Cramon, 1986).

![Fig. 5](https://example.com/fig5.png) The CT-scans and the transient brain responses in the case studies. PT 2 (top) had a mild stroke in the left hemisphere and the patient exhibited only slight verbal difficulties. PT 2 displayed prominent brain responses in both the healthy and damaged hemisphere. PT 9 (bottom) had a marked stroke covering almost the whole left hemisphere and the aphasic symptoms were assessed as extensive. PT 9 exhibited no detectable brain response in the left, damaged hemisphere while demonstrating prominent brain responses in the right, intact hemisphere.
4.2. The effect of attention on auditory processing

The brain responses of the control subjects increased with the engagement of attention which is in agreement with previous findings indicating that attention is associated with larger-amplitude brain responses (De Chicchis et al., 2002; Mäkinen et al., 2004; Tiitinen et al., 2005). Although attentional engagement did not increase the response amplitudes of the stroke patients as strongly as those of the control subjects, this study found no conclusive evidence of stroke-related attention deficits. Future studies may bring further information on whether stroke impairs the ability to properly allocate voluntary attention (Hyndman et al., 2008) and whether this, in turn, modulates auditory brain responses (Woods et al., 1993; Ivonen et al., 2001, 2004) and behavioral reactions (Woods et al., 1993; Saygin et al., 2003).

4.3. The processing of speech and non-speech stimuli

Although the auditory problems of aphasics are presumed to be limited to speech sound processing only (Aaltonen et al., 1993; Csépe et al., 2001; Ivonen et al., 2004), the current study impaired the cortical activity of the patients was also evident in the processing of sinusoidal sounds. The causes of this unspecific impairment in processing of speech and non-speech sounds can be related to the properties of the speech stimulus. Previous studies on aphasics (Csépe et al., 2001; Pettigrew et al., 2005) which have indicated selective impairment in speech sound processing only have used syllables. These might be more clearly identified as linguistic stimuli than isolated vowels used, for example, in the current study. Also, the processing of consonants is most often impaired among patients with language difficulties (Csépe et al., 2001). Vowels, in turn, have relatively sustained characteristics both in terms of their temporal and spectral features; they lack fast formant transitions that are present in syllables and they also lack sudden time-domain bursts that occur in the waveforms of some consonants (e.g. unvoiced plosives). It is therefore possible that sustained vowels may not be sufficient for detecting mild problems specific to language processing. However, both the patients and control subjects showed larger brain responses for the spectrally complex speech stimuli than for the sinusoidal sounds, replicating the results of previous studies (Tiitinen et al., 1999; Jaramillo et al., 2001; Palomäki et al., 2002; Mäkelä et al., 2004). Apparently, ecologically more valid speech sounds are processed in a specialized way already in the auditory sensory areas of the human brain (Mäkelä et al., 2002, 2004; Stevens, 2004).

4.4. Stroke severity and auditory processing

One should be cautious with the interpretation of the results concerning the effects of stroke reflected in the transient brain response as the inter-individual variability was considerable. This variability seems to be at least partly due to the highly individual nature of each stroke. Corroborating previous findings, the current study found that the patients with severe stroke in cortical auditory areas produced only minute brain responses or none at all (Leinonen and Jouhtsiniemi, 1989; Mäkelä et al., 1991; Sörös et al., 2006), especially in the damaged hemisphere (Knight et al., 1988; Woods et al., 1993). However, the patients with stroke which only mildly affected the auditory areas produced prominent brain responses in both hemispheres (Knight et al., 1980; Mäkelä et al., 1991; Aaltonen et al., 1993). This difference can be due to the location of the lesion which reportedly has a considerable effect on auditory processing abilities (Alain et al., 1998). Stroke patients with lesions in the medial or posterior areas of the temporal lobe have marked reductions in response amplitudes (Knight et al., 1980, 1988; Alain et al., 1998), whereas patients with lesions located in the anterior areas of the brain show no decrements in auditory brain responses (Mäkelä et al., 1991; Aaltonen et al., 1993). In this study, four of the five patients with mild strokes had lesions located in the anterior areas of the left hemisphere whereas all of the patients with strokes which severely affected auditory processing had lesions located in more posterior areas of the brain.

The above-mentioned amplitude difference between the two patient sub-groups raise questions concerning the sensitivity of the transient brain response in detecting mild problems in auditory processing abilities. Are the observed differences between patients and control subjects only due to the abnormalities observed in patients with severe strokes? Although the amplitude of the transient brain response differentiates patients from controls at the group level, this effect was unambiguous only in the case of severe stroke. This may be attributable to stroke severity, although large inter-individual variability may also have had an effect. Future studies with larger subject groups might be useful in revealing whether the transient brain response is sensitive in distinguishing healthy control subjects both from patients with mild and those with severe strokes. In the current study, stroke severity and location were congruent with the auditory processing abilities of the patients and with the severity of the resulting aphasic symptoms. The patients with strokes located in the anterior areas of the left hemisphere displayed prominent brain responses and most of them exhibited only mild aphasic symptoms. This is in agreement with previous research indicating that brain damage in the anterior part of the left hemisphere causes symptoms which are typical in non-fluent aphasias (von Steinbüchel et al., 1999; Bear et al., 2001) and does not severely disturb the auditory abilities of the patients (Mäkelä et al., 1991; Aaltonen et al., 1993). Then again, in the current study, the patients with severe stroke in the medial temporal areas exhibited serious or at least moderate aphasic symptoms and appreciably disturbed auditory processing. This finding also supports the previous studies showing that damage in more posterior areas of the temporal lobe has a major effect on the auditory and linguistic abilities of the patients (von Steinbüchel et al., 1999; Auther et al., 2000; Bear et al., 2001). It would therefore seem plausible that the problems in cortical auditory processing are related to the severity and location of the lesion and to the aphasic symptoms that the patients manifest.

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References


